# Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Postmenopausal South Korean Women With Osteoporosis

Romosozumab (AMG 785)

Amgen Protocol Number 20150242

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**Investigator's Agreement**

I have read the attached protocol entitled A Multicenter, Randomized, Double-blind, Placebo-controlled, Study to compare the Efficacy and Safety of Romosozumab with placebo in postmenopausal South Korean women with osteoporosis, dated **13 November 2017**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one 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)

## Protocol Synopsis

**Title:** A Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Compare the Efficacy and Safety of Romosozumab with Placebo in Postmenopausal South Korean women with Osteoporosis

**Study Phase:** 3

**Indication:** Osteoporosis in postmenopausal women

**Primary Objective:** To evaluate the effect of treatment with romosozumab for 6 months compared with placebo on percent changes in bone mineral density (BMD) at the lumbar spine as assessed by dual-energy x-ray absorptiometry (DXA) in postmenopausal women with osteoporosis.

**Secondary Objective:** To evaluate the effect of treatment with romosozumab for 6 months compared with placebo on the percent changes in DXA BMD at the total hip and femoral neck.

**Exploratory Objective:** To evaluate the effect of treatment with romosozumab for 6 months compared with placebo on percent changes in bone turnover markers (BTM): bone formation marker procollagen type 1 N-telopeptide (P1NP) and bone resorption marker serum type I collagen C-telopeptide (CTX).

**Safety Objective:** To characterize the safety and tolerability of treatment with romosozumab for 6 months compared with placebo as determined by a review of reported adverse events, laboratory data, vital signs, and the formation of anti-romosozumab antibodies over the 6-month treatment period, and adverse events and the formation of anti-romosozumab antibodies for the overall study period (6-month treatment period followed by the 3-month follow-up period).

**Pharmacokinetics (PK):** To characterize the serum romosozumab concentration

**Hypotheses:** The primary clinical hypothesis is that in South Korean postmenopausal women with osteoporosis, the mean percent change in lumbar spine BMD in subjects receiving romosozumab will be superior to that of those receiving placebo at month 6. It is hypothesized that changes in BMD at the lumbar spine in subjects receiving romosozumab will be at least 6.6% greater than in subjects receiving placebo. The safety hypothesis is that romosozumab treatment for 6 months is well tolerated in South Korean women with osteoporosis.

**Primary Endpoint:** Percent change from baseline in DXA BMD at the lumbar spine at month 6

**Secondary Endpoint:** Percent change from baseline in DXA BMD at the femoral neck and total hip at month 6.

**Exploratory Endpoints:** Percent changes from baseline in bone turnover markers (BTM): bone formation marker procollagen type 1 N-telopeptide (P1NP) and bone resorption marker serum type I collagen C-telopeptide (CTX) at months 1, 3, and 6

**Safety Endpoints:**

For the 6-month treatment period:

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value between baseline and month 6
- Changes from baseline in vital signs
- Incidence of subjects with anti-romosozumab antibodies at months 1, 3, and 6

For the overall study period (6-month treatment period followed by the 3-month follow-up period):

- Subject incidence of adverse events by system organ class and preferred term
- Subject incidence of the formation of anti-romosozumab antibodies

**Pharmacokinetic Endpoint:** Romosozumab serum concentration at months 1, 3, and 6

**Study Design:** This is a multicenter, randomized, double-blind, placebo-controlled study in approximately 60 South Korean postmenopausal women with osteoporosis. The study is designed to evaluate if treatment with romosozumab once a month (QM) for 6 months compared with placebo is effective in increasing BMD at the lumbar spine. In addition, the study will assess the effect of treatment with romosozumab QM for 6 months compared with placebo on BMD at the femoral neck and total hip.

Approximately 60 subjects will be randomized in a 1:1 ratio to receive 210 mg romosozumab subcutaneous (SC) QM (approximately 30 subjects) or matched placebo SC QM (approximately 30 subjects), respectively, in a blinded fashion for the duration of the 6-month treatment period.

Upon completion of the 6-month treatment period, subjects will be followed for an additional 3 months to ensure appropriate follow-up for anti-romosozumab antibody formation.

From screening to end of study (EOS), subjects will receive daily calcium and vitamin D supplementation. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of vitamin D after randomization.

Approximately 10 sites in South Korea will participate in this study. Sites that do not enroll subjects within 2 months of site initiation may be closed.

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**Sample Size:** Approximately 60 subjects will be enrolled in the study.

**Summary of Subject Eligibility Criteria:** The study will enroll ambulatory postmenopausal Korean women, ≥ 55 to ≤ 90 years of age at randomization with a DXA BMD T-score ≤ -2.50 at the lumbar spine, total hip or femoral neck. Subjects must have at least 2 vertebrae in the L1 through L4 region and at least 1 proximal femur evaluable by DXA. Subjects with a BMD T-score ≤ -4.0 at the lumbar spine, total hip or femoral neck and subjects with a history of hip fracture are ineligible for the study. For a full list of eligibility criteria, please refer to Section 4.1.

**Investigational Product:** Romosozumab or matching placebo administered by prefilled syringe (PFS).

**Amgen Investigational Product Dosage and Administration**: Romosozumab 210 mg or matching placebo will be administered QM for 6 months as an SC injection via PFS at day 1, month 1, month 2, month 3, month 4, and month 5. All dosing with be administered in-clinic.

**Non-Amgen Non-investigational Product Dosage and Administration:** From screening to EOS, subjects will receive daily calcium and vitamin D supplementation that at a minimum is in the range of 500 to 1 000 mg elemental calcium and 600 to 800 IU vitamin D. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of 50 000 to 60 000 IU vitamin D after randomization, preferably by the oral route. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion.

**Procedures:** Informed consent; demographics; medical, medication, fracture, tobacco, alcohol, and substance use history; physical examination; physical measurements (height and weight); vital signs (blood pressure, heart rate, respiratory rate, and temperature); concomitant medications; serious adverse event reporting; adverse event reporting; laboratory assessments (serum chemistry, hematology, serum protein electrophoresis, hepatitis B and C testing, serum 25 (OH) vitamin D, intact parathyroid hormone (iPTH), pharmacokinetics, anti-romosozumab antibody, BTMs; DXA scan of the lumbar spine and proximal femur; IP administration; daily calcium and vitamin D supplementation; and if applicable, vitamin D loading dose administration.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 1).

**Statistical Considerations:**

Primary Efficacy Endpoint:

The analysis to assess the percent change from baseline in lumbar spine DXA BMD at month 6 will employ an analysis of covariance (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 independent 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% confidence interval (CI) and associated p-value will be provided for the difference between the least-squares means for romosozumab and placebo.

Conclusions for the primary efficacy hypothesis of different efficacy of romosozumab compared with placebo at lumbar spine BMD will be made using a 2-sided test with type 1 error rate of 0.05.

Secondary Efficacy Endpoints:

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 independent 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 romosozumab and placebo.

Exploratory Efficacy Endpoints:

For P1NP and CTX, descriptive statistics will be presented by treatment group at each visit for both actual values and the percent change from baseline values. Graphs depicting median and interquartile ranges by treatment group for percent change over time will be provided.

Safety Endpoints:

Safety analyses will include assessments of treatment-emergent adverse events, IP exposure, clinical laboratory assessments, vital signs, and anti-romosozumab antibodies. The safety analysis set will be used for these analyses. There is no planned inferential statistical testing in the safety analyses. All categorical endpoints will be summarized using the number and percent of subjects. All continuous endpoints will be summarized using descriptive statistics including mean, standard deviation, minimum, quartiles, maximum, and number of subjects.

Pharmacokinetic Endpoint:

Trough serum concentration values determined from subjects may be summarized in tabular form and presented graphically. Additional pharmacokinetic analyses will be performed as appropriate.

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

**Sponsor:** Amgen, Inc.

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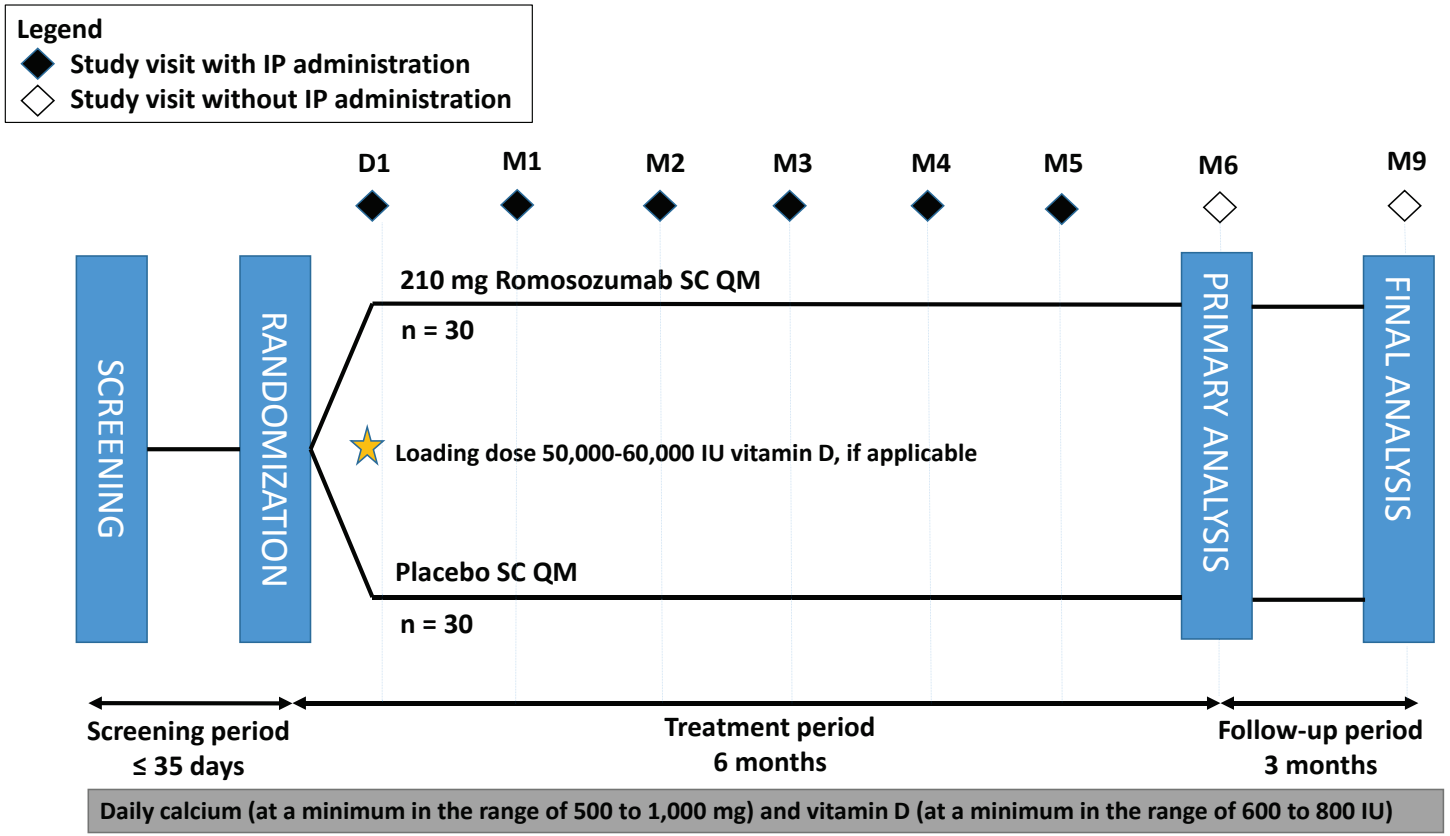
|---|---|
| Data Element Standards Version(s)/Date(s): | Version 5/20 March 2015 |

**Study Design and Treatment Schema**




Abbreviations: D=day; IP=investigational product; M=month; n=number; QM=once monthly; SC=subcutaneous;

## Study Glossary

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ALP | alkaline phosphatase |
| ALT | alanine transferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| BMD | bone mineral density |
| BMI | body mass index |
| BP | blood pressure |
| BTM | bone turnover markers |
| 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 when the last subject is assessed or receives an intervention for evaluation in the study |
| 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 |
| **EOI** | **Event of Interest** |
| EOS | end of study |
| ET | early termination |
| GCP | Good Clinical Practice |
| HepBcAb | total hepatitis B core antibody |
| HepBsAg | Hepatitis B Surface Antigen |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| INR | international normalized ratio |
| 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. |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| IP | investigational product |
| IPIM | Investigational Product Instruction Manual |
| iPTH | intact parathyroid hormone |
| IRB/IEC | institutional review board/independent ethics committee |
| IV | intravenous |
| NHANES | National Health and Nutritional Examination Survey |
| P1NP | procollagen type 1 N-telopeptide |
| PCR | polymerase chain reaction |
| PFS | prefilled syringe |
| PMO | postmenopausal osteoporosis |
| PTH | parathyroid hormone |
| QM | once a month |
| SC | subcutaneous |
| 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. |
| T4 | thyroxine |
| TBL | total bilirubin |
| TSH | thyroid stimulating hormone |
| ULN | upper limit of normal |

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# 1. OBJECTIVES

## 1.1 Primary

To evaluate the effect of treatment with romosozumab for 6 months compared with placebo on percent changes in bone mineral density (BMD) at the lumbar spine as assessed by dual-energy x-ray absorptiometry (DXA) in postmenopausal women with osteoporosis.

## 1.2 Secondary

To evaluate the effect of treatment with romosozumab for 6 months compared with placebo on the percent changes in DXA BMD at the total hip and femoral neck.

## 1.3 Exploratory

To evaluate the effect of treatment with romosozumab for 6 months compared with placebo on percent changes in bone turnover markers (BTM): bone formation marker procollagen type 1 N-telopeptide (P1NP) and bone resorption marker serum type I collagen C-telopeptide (CTX).

## 1.4 Safety

To characterize the safety and tolerability of treatment with romosozumab for 6 months compared with placebo as determined by a review of reported adverse events, laboratory data, vital signs, and the formation of anti-romosozumab antibodies over the 6-month treatment period, and adverse events and the formation of anti-romosozumab antibodies for the overall study period (6-month treatment period followed by the 3-month follow-up period).

## 1.5 Pharmacokinetics

To characterize the serum romosozumab concentration.

# 2. BACKGROUND AND RATIONALE

## 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, based on the World Health Organization's current definition of osteoporosis (BMD T-score ≥ 2.5 standard deviations below the mean for young healthy 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, Europe, and Japan

(World Health Organization, 2007). In Korea, at the age of 50 years, the residual lifetime probabilities of osteoporosis-related fractures are 59.5% for women (Park, 2011). 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).

Osteoporosis is a chronic disease and despite long-term administration of bisphosphonates, the most commonly prescribed class of antiresorptives, some postmenopausal women with 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. Bone forming agents can promote larger improvements in bone mass and bone strength compared with 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). 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, ultimately resulting in increased bone strength and reduced risk for fracture, would be a welcome new therapeutic option particularly for subjects with significantly compromised bone strength at high risk of fracture.

### 2.2 Amgen Investigational Product Background

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 (non-osteopenic and osteopenic rats and monkeys) (Ominsky et al, 2015; Li et al, 2014; Li et al, 2010; Ominsky et al, 2010).

Romosozumab is a humanized monoclonal antibody that is designed to bind and inhibit sclerostin, thereby promoting osteoblast differentiation and activity, leading to an increase in bone formation, BMD, and bone 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 marker P1NP and a decrease in the bone resorption marker serum CTX. Increases in BMD at the lumbar spine, total hip and femoral neck have also been demonstrated, by DXA, and quantitative computed tomography.

The ability of romosozumab to prevent fractures in postmenopausal women with osteoporosis is currently being evaluated in the following phase 3 studies:

- Placebo-controlled study designed to evaluate if treatment with romosozumab for 12 months is effective in reducing the risk of new vertebral and nonvertebral fractures
- Alendronate-controlled study designed to evaluate if treatment with romosozumab for 12 months followed by alendronate treatment, is effective in reducing the incidence of clinical fractures and new vertebral fractures

Refer to the specific sections of the Romosozumab Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation.

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

### 2.3 Calcium and Vitamin D Background

Calcium and vitamin D are important in the formation of bone matrix and for its subsequent mineralization where calcium found as calcium hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) provides bones and teeth tissue with its strength. Calcium and vitamin D are therefore considered key components of therapy in the management of postmenopausal osteoporosis (PMO) (Dawson-Hughes et al, 2010) and have been required as background therapies in all contemporary therapeutic trials in PMO. Because of the active bone formation and mineralization that is expected with romosozumab, calcium and vitamin D supplementation will be necessary in order to achieve and maintain positive bone balance. The recommended dietary allowance and tolerable upper intake level of dietary calcium recommended by the United States Institutes of Medicine for women over the age of 50 years on a western diet is 1,200 mg and 2000 mg per day respectively. The recommended dietary allowance and tolerable upper intake level of dietary vitamin D for women aged 51 to 70 years is 600 IU and 4000 IU per day respectively while the recommended dietary allowance and tolerable upper intake level of dietary vitamin D for women over the age of 70 years is 800 IU and

4000 IU per day respectively (Ross et al, 2011; IOM, 2010). This is consistent with 2015 Position Statement of the Korean Society for Bone and Mineral Research which recommends a daily calcium intake of 800 to 1 000 mg/day and a minimum intake of 800 IU per day of vitamin D in South Korea (Kim, 2015). The initial loading dose of 50 000 to 60 000 IU of vitamin D for subjects with vitamin D levels of ≥ 20 ng/mL and ≤ 40 ng/mL at screening is necessary to provide a sufficient calcium pool for the expected and significant increase in bone mass and needed for bone mineralization in the first several months after initiation of treatment with romosozumab. This dose has been shown to be safe and well tolerated (Giusti et al, 2010; Tucci, 2009). The daily supplementation required in this study, that at a minimum should be in the range of 500 to 1 000 mg elemental calcium and 600 to 800 IU of vitamin D, is safe and represents commonly used and accepted doses for PMO clinical trials and are consistent with existing treatment practice and guidelines (Dawson-Hughes et al, 2010; IOM 2010).

### 2.4 Rationale

A 6-month romosozumab treatment duration is supported by the following considerations:

Substantial increases in BMD at the lumbar spine, total hip and femoral neck were observed during 6 months of romosozumab administration in the phase 2 dose-ranging study. At 6 months, the 210 mg once a month (QM) dosing regimen resulted in a BMD increase from baseline of 8.2 % with 95% confidence interval (CI) (7.3%, 9.2%) at the lumbar spine and 2.9 % with 95% CI (2.3%, 3.4%) at the total hip.

The 210-mg romosozumab QM dosing regimen is the same dosing regimen used in the other phase 3 trials including the 2 fracture trials mentioned above.

In summary, the proposed treatment regimen of 210 mg romosozumab QM for 6 months is expected to achieve optimal increases in BMD and bone formation markers in subjects who are treatment-naïve and in those who have previously received alendronate without negatively impacting the safety profile of romosozumab. Thus, a 210 mg QM dosing regimen is expected to provide the best risk-benefit profile and enable evaluation of the safety, tolerability, and efficacy of romosozumab to prevent fractures in postmenopausal women with osteoporosis.

Refer to the Investigator's Brochure for a detailed description of data from the phase 2 dose-ranging study.

### 2.4.1 Choice of Control Group

A placebo-controlled study was chosen because it permits a minimally confounded demonstration of efficacy and safety of romosozumab in the treatment of postmenopausal women with osteoporosis. The use of a placebo control is also consistent with regulatory guidance in South Korea. The following measures have been taken to minimize risk for subjects who will receive placebo:

- Subjects with a history of hip fractures and those with BMD T-score ≤ -4.0 at the lumbar spine, total hip or femoral neck are excluded.
- Subjects are eligible for a loading dose of vitamin D (50 000 to 60 000 IU) at the start of the study, and all subjects will receive supplemental vitamin D and calcium throughout the study. These supplements have been shown to have a protective effect on the skeleton.
- Exposure to placebo is minimized by the short study duration (6 months).

### 2.4.2 Study Population

The target population for this study is postmenopausal South Korean women with osteoporosis, defined as:

- BMD T-score ≤ -2.50 at the lumbar spine, total hip, or femoral neck.

These inclusion criteria approximate those used in the romosozumab phase 3 global fracture studies in postmenopausal women with osteoporosis. Key exclusion criteria are metabolic bone disease, uncorrected vitamin D insufficiency, current uncontrolled hyper-or hypoparathyroidism, current uncontrolled hyperparathyroidism or history of hypoparathyroidism, and current hyper- or hypocalcemia. These and other criteria have been selected to align with the eligibility criteria used in the global romosozumab phase 3 fracture studies in postmenopausal women with osteoporosis.

## 2.5 Clinical Hypotheses

The primary clinical hypothesis is that in South Korean postmenopausal women with osteoporosis, the mean percent change in lumbar spine BMD at month 6 in subjects receiving romosozumab will be superior to that of those receiving placebo. It is hypothesized that changes in BMD at the lumbar spine in subjects receiving romosozumab will be at least 6.6% greater than in subjects receiving placebo.

The safety hypothesis is that romosozumab treatment for 6 months is well tolerated in South Korean women with osteoporosis.

# 3. EXPERIMENTAL PLAN

## 3.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study in approximately 60 South Korean postmenopausal women with osteoporosis. The study is designed to evaluate if treatment with romosozumab QM for 6 months compared with placebo is effective in increasing BMD at the lumbar spine. In addition, the study will assess the effect of treatment with romosozumab QM for 6 months compared with placebo on BMD at the femoral neck and total hip.

Approximately 60 subjects will be randomized in a 1:1 ratio to receive 210 mg romosozumab subcutaneous (SC) QM (approximately 30 subjects) or matched placebo SC QM (approximately 30 subjects), respectively, in a blinded fashion for the duration of the 6-month treatment period.

Upon completion of the 6-month treatment period, subjects will be followed for an additional 3 months to ensure appropriate follow-up for anti-romosozumab antibody formation.

The overall study design is described by a study schema at the end of the protocol synopsis section.

From screening to end of study (EOS), subjects will receive daily calcium and vitamin D supplementation, which at a minimum should be in the range of 500 to 1000 mg elemental calcium and 600 to 800 IU vitamin D. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of 50 000 to 60 000 IU vitamin D after randomization (administered within 1 week of the study day 1 visit), preferably by the oral route. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion.

The study endpoints are defined in Section 10.1.1.

## 3.2 Number of Sites

Approximately 10 sites in South Korea will participate in this study. Sites that do not enroll subjects within 2 months of site initiation may be closed.

## 3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects". Approximately 60 South Korean postmenopausal women with osteoporosis will be enrolled, including

approximately 30 subjects randomized to receive 210 mg romosozumab SC QM and 30 subjects randomized to receive matched placebo SC QM.

The rationale for the number of subjects required is outlined in Section 10.2.

### 3.4 Replacement of Subjects

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

### 3.5 Estimated Study Duration

#### 3.5.1 Study Duration for Subjects

After signing the informed consent form (ICF), subjects should be randomized within 35 days.

Following 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 early termination (ET) visit will be asked to return for anti-romosozumab antibody testing after EOS for up to 1 year after the last investigational product (IP) administration.

#### 3.5.2 End of Study

**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 purpose of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.**

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis, ie, after all subjects have had the opportunity to complete the month 6 visit.

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study, ie, when the last subject completes the month 9 visit.

**If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination 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).**

## 4. SUBJECT ELIGIBILITY

The study population is South Korean postmenopausal women with osteoporosis.

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).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

## 4.1 Inclusion and Exclusion Criteria

### 4.1.1 Inclusion Criteria

101 Subject has provided informed consent/assent prior to initiation of any study-specific activities/procedures.

102 Ambulatory postmenopausal Korean women, ≥ 55 to ≤ 90 years of age at enrollment.

103 Postmenopause is defined as no spontaneous vaginal bleeding or spotting for 12 or more consecutive months prior to screening.

104 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 and using data for Caucasian women from the National Health and Nutritional Examination Survey (NHANES) 1998.

105 At least 2 vertebrae in the L1 through L4 region and at least one hip are evaluable by DXA, as assessed by the principal investigator.

### 4.1.2 Exclusion Criteria

201 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). Other investigational procedures while participating in this study are excluded.

202 Subject has known sensitivity to any of the products to be administered during dosing (calcium supplements, vitamin D products, or mammalian cell derived products).

203 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.

204 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.

205 Subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment and within 3 months after the last dose of IP.

206 BMD T-score ≤ -4.0 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 and using data for Caucasian women from the NHANES 1998.

207 History of hip fracture.

208 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.

209 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).

210 History of solid organ or bone marrow transplant.

211 History of osteonecrosis of the jaw and/or atypical femoral fracture.

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

213 Current, uncontrolled hyper- or hypothyroidism, Uncontrolled hyperthyroidism is defined as thyroid stimulating hormone (TSH) and thyroxine (T4) outside the normal range. Uncontrolled hypothyroidism is defined as TSH > 10.

214 Current, uncontrolled hyperparathyroidism or history of hypoparathyroidism, per subject report or chart review. 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.

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

216 Subject previously has entered this study or has previously participated in a study with a sclerostin antibody product.

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

218 Possible diagnosis of multiple myeloma or related lymphoproliferative disorder, as assessed by serum protein electrophoresis performed by the local laboratory (electrophoresis results within 6 months of signing consent will be acceptable).

221 Positive results for human immunodeficiency virus, per subject report or chart review.

222 Use of 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

223 Use of 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, IV pamidronate, or IV alendronate:
  - 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

224 Use of 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

225 Use of strontium ranelate, or fluoride (for osteoporosis):

- more than 1 month of cumulative use within 5 years prior to randomization

226 Use of denosumab or any cathepsin K inhibitor, such as odanacatib (MK-0822):

- any dose received within 18 months prior to randomization

227 Use of tibolone, cinacalcet or calcitonin:

- any dose received within 3 months prior to randomization

228 Use of systemic oral or transdermal estrogen or selective estrogen receptor modulators (SERMs):

- more than 1 month of cumulative use within 6 months prior to randomization

229 Use of activated vitamin D3, vitamin K2, more than 1 month of cumulative use within 6 months prior to randomization

230 Use of hormonal ablation therapy:

- more than 1 month of cumulative use within 6 months prior to randomization

231 Use of systemic glucocorticosteroids: ≥ 5 mg prednisone equivalent per day for more than 14 days within 3 months prior to randomization

232 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.

## 5. 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 Section 11.2). All subjects must personally sign and date the ICF before commencement of study specific activities/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 (defined as the point at which the subject signs the ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVR/IWR. 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.

Only subjects who do not meet the serum 25 (OH) vitamin D eligibility criterion (ie, subjects with a serum 25 (OH) vitamin D level < 20 ng/mL) (see Section 4.1.1) will be permitted to rescreen one time.

## 5.1 Randomization/Treatment Assignment

Subjects who meet all eligibility requirements (Section 4.1) will be randomly assigned in a 1:1 allocation ratio to the 2 treatment groups (romosozumab and placebo) in a double-blind manner.

Randomization will be based on a schedule prepared by the Amgen Central Randomization Group before the start of the study. Randomization will be performed by IVRS, and the randomization number will be provided through the IVRS. A subject may be randomized only once, and each randomization number will be assigned only once.

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

### 5.2 Site Personnel Access to Individual Treatment Assignments

The identity of IP assigned to subject numbers or to individual packages of IP will be contained in the IVRS. Authorized site staff will be provided with a unique Personal Identification Number to access the IVRS to obtain unblinding information. This Personal Identification Number is unique to the individual and must not be shared.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation.

The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Refer to the Investigational Product Instruction Manual (IPIM) for instructions on how to access treatment information in the event the blind needs to be broken.

## 6. TREATMENT PROCEDURES

### 6.1 Classification of Products and Medical Device

The Amgen IPs used in this study are romosozumab and matching placebo. The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of romosozumab and placebo.

The non-Amgen non-IPs used in this study are elemental calcium and vitamin D.

The medical device used in this study is a prefilled syringe (PFS).

### 6.2 Investigational Product

#### 6.2.1 Amgen Investigational Product

Romosozumab and matching placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Romosozumab will be supplied in a single-use PFS as a sterile, clear, colorless or slightly colored, and preservative-free solution for SC injection. Each PFS contains 70 mg of romosozumab per mL in C CI mM acetate and C CI mM calcium containing CCI % w/v sucrose and CCI % w/v polysorbate 20 at pH CC I with a deliverable volume of 1 mL. The 3 romosozumab 70 mg/mL PFSs to be administered at each dosing visit will be packaged together in a single box.

Placebo will be presented in identical containers and stored/packaged the same as romosozumab.

#### 6.2.1.1 Dosage, Administration, and Schedule

The IP will be administered in accordance with instructions in the IPIM.

The IP (romosozumab/placebo) will be administered SC via PFS on day 1, month 1, month 2, month 3, month 4, and month 5. All doses will be administered at the study site.

Subjects will receive 3 SC injections of romosozumab (ie, 3 injections of 70 mg romosozumab for a total dose of 210 mg) or matching placebo QM. A separate PFS will be used for each injection; however, all 3 PFS to be used at a specific visit will be supplied in a single box, as assigned by the IVRS.

Injections will be administered by a healthcare professional into different sites on the subject's anterior abdominal wall, upper thigh, or upper arm. The injection should not be administered in the same arm from which blood is drawn. The romosozumab/placebo SC injection must be administered as the last procedure after all other study visit procedures have been completed.

The volume, start date/time, each administration site, and box number of romosozumab/placebo are to be recorded on each subject's CRF.

A physician must be available during administration of romosozumab/placebo. It is recommended that all subjects be closely observed for approximately 30 minutes after dosing with IP.

The first dose of IP should be administered on the day of randomization. If this is not possible, it must be administered within 72 hours of randomization.

Refer to specific instructions provided by the IVRS vendor for additional information on box assignment and to the IPIM for additional information regarding storage and preparation of IP.

Overdose with this product has not been reported. The effects of overdose of this product are not known. An antidote to overdose of this product is not 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.

#### 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

No dosing adjustments for romosozumab/placebo will be permitted.

All efforts should be made to administer romosozumab/placebo within the defined study visit windows (refer to Section 7). In case of an out-of-window visit, romosozumab/placebo can be administered within ± 2 weeks of the target visit date (ie, calculated from the day 1 visit as described in Section 7). If romosozumab/placebo cannot be administered within ± 2 weeks of the target visit date, the dose has to be considered missed.

### 6.2.2 Non-Amgen Non-investigational Products

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

The dose, start date, stop date, and frequency for calcium and vitamin D are to be recorded on each subject's CRF. At screening, the investigator or designee will instruct subjects on daily calcium and vitamin D supplementation.

Additional details regarding the non-Amgen non-IPs are provided in the IPIM.

#### 6.2.2.1 Calcium

Subjects will receive daily calcium supplementation orally from screening to EOS, which at a minimum should be in the range of 500 to 1 000 mg elemental calcium.

#### 6.2.2.2 Vitamin D

Where available, vitamin $D_3$ preparations should be used; if vitamin $D_3$ is not available, use of vitamin $D_2$ preparations is acceptable.

Subjects will receive daily vitamin D supplementation orally from screening to EOS, which at a minimum should be in the range of 600 to 800 IU vitamin D. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of 50 000 to 60 000 IU of vitamin D after randomization, preferably by the oral route. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion.

#### 6.2.2.3 Non-Amgen Non-investigational Products Dose Adjustments

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 dosage lowered. The intolerance as well as the resolution (ie, change in formulation or dosage) should be documented in the subject chart.

### 6.3 Hepatotoxicity Stopping and Rechallenge Rules

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 IP or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation, July 2009).

#### 6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Amgen IP (romosozumab/placebo) should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible DILI, if ALL of the criteria below are met:

- TBL > 2x ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

| Baseline AST or ALT value | AST or ALT elevation |
|---|---|
| < ULN | > 3x ULN |

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; 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-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

### 6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen IP outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen IP and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

| Baseline AST or ALT value | AST or ALT elevation |
|---|---|
| Any | > 8x ULN at any time |
| Any | > 5x ULN but < 8x ULN for ≥ 2 weeks |
| Any | > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule |
| Any | > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice). |

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Romosozumab/placebo should be withheld pending investigation into alternative causes of DILI. If IP(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. 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 (Section 6.3.3).

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

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

If signs or symptoms recur with rechallenge, then romosozumab/placebo should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.

## 6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

Concomitant therapies are to be collected in the CRF from the signing of the ICF through the EOS visit. For concomitant therapies affecting bone metabolism, collect therapy name, indication, dose, unit, frequency, start date, and stop date. For all other concomitant therapies, collect therapy name, indication, start date, and stop date.

## 6.5 Medical Devices

The PFS used in this study will be provided by Amgen. The PFS will be used for administration of IP for all subjects. Additional details for the PFS is to be provided in the IPIM.

Other medical devices (eg, syringes, sterile needles, alcohol prep pads), which are not considered test articles, may be used in the conduct of this study as part of standard care. These 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.

## 6.6 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. Drugs or devices include romosozumab/placebo and PFS.

This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes IP. Any product complaint(s) associated with an

IP(s) or non-IP(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

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

The following treatments are not permitted during the study:

- 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)
- Intravenous bisphosphonates
- Oral bisphosphonates (cumulative dosing regimens of ≤ 1 month are acceptable)
- Denosumab
- Teriparatide or any PTH analogs
- Systemic oral or transdermal estrogen (cumulative dosing regimens of ≤ 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
- 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)
- Any cathepsin K inhibitor, such as odanacatib (MK-0822):
- Hormonal ablation therapy
- Cinacalcet

If a subject discontinues IP 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 8.1).

## 7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 1 can only be performed after obtaining informed consent. Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

### 7.1 Schedule of Assessments

## Table 1. Schedule of Assessments

| Period | Screening | Treatment Period | | | | | | | Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8/ET | 9/EOS |
| Day/Month | Within 35 days of 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 -7/+3 days | Month 9 -7/+3 days |
| General and safety assessments | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Fracture history | X | | | | | | | | |
| Medication history | X | | | | | | | | |
| Smoking and ethanol use history | X | | | | | | | | |
| Substance use history | X | | | | | | | | |
| Instructions for daily vitamin D & calcium supplementation | X | | | | | | | | |
| Physical examination | X | | | | | | | X | |
| Physical measurements | X | | | | | | | X | |
| Vital signs | X | | X | | | | | X | |
| Concomitant medications | X | X | X | X | X | X | X | X | X |
| Record serious adverse events | X---------- | | | | | | | | ----------X |
| Record adverse events | | X---------- | | | | | | | ----------X |
| Record disease-related events | | X---------- | | | | | | | ----------X |
| Laboratory Assessments | | | | | | | | | |
| Serum chemistry | X | X | X | | X | | | X | |
| Hematology | X | X | X | | X | | | X | |
| Serum protein electrophoresis | X | | | | | | | | |
| Hepatitis B & Hepatitis C testing | X | | | | | | | | |
| Serum 25 (OH) vitamin D | X | X | | | | | | | |
| iPTH | | X | X | | X | | | X | |
| Pharmacokinetics | | X | X | | X | | | X | |
| Anti-romosozumab antibody | | X | X | | X | | | X | X |
| Bone turnover markers | | X | X | | X | | | X | |



Footnotes defined on next page of the table

## Table 1. Schedule of Assessments

| Period | Screening | Treatment Period | | | | | | | Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8/ET | 9/EOS |
| Day/Month | Within 35 days of 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 -7/+3 days | Month 9 -7/+3 days |
| Imaging Assessments | | | | | | | | | |
| DXA scan - Lumbar spine | X | | | | | | | X | |
| DXA scan - Proximal femur | X | | | | | | | X | |
| IP Administration | | | | | | | | | |
| In-clinic IP injection[a] | | X | X | X | X | X | X | | |
| vitamin D loading dose[b] | | X | | | | | | | |

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DXA = dual-energy x-ray absorptiometry; EOS = end of study; ET = early termination; iPTH = Intact Parathyroid Hormone.

[a] Must be the last procedure at each dosing visit.

[b] Vitamin D loading dose of at least 50 000 to 60 000 IU, preferably by oral route is required for all subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion.

## 7.2 General Study Procedures

Study assessments and procedures will be performed only after written informed consent is obtained. During the study, every effort should be made to keep subjects on the study schedule of procedures.

The procedures performed at each study visit are outlined Table 1.

Details regarding each type of procedure are provided in subsequent sub-sections. Refer to the applicable supplemental central laboratory, IVRS, IPIM, and study manuals for detailed collection and handling procedures.

IP administration must be the last procedure after all other study visit procedures have been completed at each applicable visit.

### 7.2.1 Screening Enrollment and/or Randomization

Informed consent must be obtained before completing any other screening procedure or discontinuation of standard therapy for any disallowed therapy. After signing the written ICF, site will register the subject in the IVRS and screen the subject in order to assess eligibility for participation. Screening procedures may be performed on multiple days but must be completed within the 35-day screening window. If a subject has not met all eligibility criteria at the end of the 35-day window, the subject will be registered as a screen fail. Subjects who screen fail only the serum 25 (OH) vitamin D eligibility criterion may be eligible for rescreening once as described in Section 7.2.2.

The screening procedures to be completed are designated in the Schedule of Assessments (Table 1).

During the screening period, albumin-adjusted serum calcium levels may be retested once in case of an elevated albumin-adjusted serum calcium level within 1.1x ULN as assessed by the central laboratory. To enroll subjects after retesting of albumin-adjusted serum calcium levels, an eligible albumin-adjusted serum calcium level must be confirmed by the central laboratory, and the subject must be randomized within the original 35-day screening window. These subjects should not be screen failed.

A blood sample will be collected during the screening period for serum protein electrophoresis to assess possible diagnosis of multiple myeloma or related lymphoproliferative disorder; the analysis will be performed by the local laboratory. Electrophoresis results within 6 months prior to signing informed consent will be acceptable.

At screening, laboratory assessments will be conducted to determine hepatitis B and C status as follows:

- If hepatitis B and/or hepatitis C status is known to be positive by serology, no additional laboratory testing procedures are required
- If hepatitis B and/or hepatitis C status is not known to be positive by serology, the following laboratory testing is required:
  - Hepatitis B Surface Antigen (HepBsAg) and total hepatitis B core antibody (HepBcAb)
    - If results are HepBcAb positive and HepBsAg positive, no additional testing is necessary
    - If results are HepBcAb positive and HepBsAg negative, additional testing for Hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary
  - Hepatitis C virus antibody
    - If results are hepatitis C virus antibody positive, additional testing for hepatitis C virus RNA by PCR is necessary.

### 7.2.2 Rescreening

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. To initiate rescreening, subjects must first be registered as screen failed in IVRS and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Subjects not entered into IVRS as a rescreen will not be eligible for randomization. Rescreening date is defined as the date of IVRS entry, and a 35-day rescreening window will commence at this time. Subjects are not required to reconsent for the rescreening period.

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 can 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.

The following procedures are to be completed during the rescreening period as designated in the Schedule of Assessments (Table 1):

- Laboratory assessments (vitamin D only)
- Serious adverse event reporting

- Documentation of concomitant medications
- Registration in IVRS
- Randomization via IVRS

Any other procedures already performed during the screening period (eg, imaging assessments, or laboratory assessments other than vitamin D status) do not need to be repeated during the rescreening period.

### 7.2.3 Treatment Period

Visits will occur per the Schedule of Assessments (Table 1) during the treatment period from day 1 through month 6. Romosozumab is to be administered as the last procedure of each applicable visit.

Day 1 is defined as the day the first dose of IP 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.

If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. The procedures for the month 6/ET visit should be completed at the time of withdrawal (Table 1).

### 7.2.4 End of Study Visit

At month 9, subjects will return to the site for the EOS visit for the procedures specified in the Schedule of Assessments (Table 1).

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 after EOS for up to 1 year after the last IP administration.

## 7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures, which are conducted at the timepoints specified in the Schedule of Assessments (Table 1).

### 7.3.1 Informed Consent

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

### 7.3.2 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. Additionally demographic data may be used to study the impact on BTMs variability and pharmacokinetics of the protocol-required therapies.

### 7.3.3 Medical History

The investigator or designee will collect a complete medical history starting within 5 years prior to screening through administration of the first dose of IP. In addition, osteoporosis history must date back to the original diagnosis. Medical history will include information on the subject's concurrent medical conditions. All findings are to be recorded on the medical history CRF.

Detailed information will also be collected about the history of hearing disorders and cancer history.

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 IP. 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.

### 7.3.4 Fracture History

will be collected from the age of 45 through administration of the first dose of IP. Fracture history will include date of fracture, anatomical site(s) of fracture(s), and degree of trauma involved. All findings are to be recorded on the fracture history CRF.

### 7.3.5 Medication History

The investigator or designee will collect a detailed history of prior therapies affecting bone metabolism that were taken from 5 years prior to screening through randomization. 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.

### 7.3.6 Substance use History

The investigator or designee will collect information about the prior and/or current use of tobacco and alcohol and substance use. All findings are to be recorded on the CRF.

### 7.3.7 Physical Examination

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

### 7.3.8 Height and Weight

Body weight should be measured in kilograms without shoes, and height should be measured in centimeters without shoes.

### 7.3.9 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure (BP), 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 BP assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same throughout the study and documented on the vital sign CRF. The arm with the highest systolic reading at screening will then be used for further BP readings throughout study. The appropriate sized cuff should be used.

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

If abnormalities are found and they are considered an adverse event, they are to be recorded on the Event CRF.

### 7.3.10 Concomitant Medications

Concomitant therapies are to be collected in the CRF from the signing of the ICF through the EOS visit. For concomitant therapies affecting bone metabolism, collect therapy name, indication, dose, unit, frequency, start date, and stop date. For all other concomitant therapies, collect therapy name, indication, start date, and stop date.

### 7.3.11 Adverse Events, Serious Adverse Events, and Adverse Device Effects

Any serious adverse events occurring after the signing of the ICF through the EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is longer) will be recorded. Any adverse events, adverse device effects, and disease-related events observed by the investigator or reported by the subject occurring after randomization through the EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is longer) will be recorded in the subjects' records and on the appropriate CRFs. Refer to Section 9.2 for more details.

In order to fully evaluate certain events of interest during the study, the following events will be submitted to an independent committee for adjudication:

- potential osteonecrosis of the jaw events
- potential atypical femoral fracture **events**
- **injection site reaction**
- **potential events of serious cardiovascular adverse events**

Further, in order to carefully evaluate cardiovascular events during the trials, all deaths and serious adverse events that are deemed by the investigator to be of potential cardiovascular origin or etiology will be submitted to an independent committee for adjudication, as described in the Clinical Events Classification Charter for Study 20150242. Serious adverse events with terms mapping to a pre-defined preferred term list potentially indicative of cardiovascular etiology will also be adjudicated.

### 7.3.12 Pharmacokinetic Assessment

Samples for pharmacokinetic assessments will be collected from all subjects enrolled.

Blood samples for pharmacokinetic testing are to be collected at the time points outlined in the Schedule of Assessments (Table 1). At study visits where pharmacokinetic samples are to be collected and IP is also to be administered, blood samples for pharmacokinetic testing are to be collected prior to administration of IP.

Results from pharmacokinetic assays are considered potentially unblinding and will not be reported to study-related personnel.

### 7.3.13 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 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 compact disc 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 study site must comply with the requests from the central imaging vendor. Repeat scans must be performed as soon as possible after the request is received.

#### 7.3.13.1 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 evaluable lumbar vertebrae and at least 1 evaluable proximal femur (as determined by the principal investigator or designee).

#### 7.3.13.2 On-study Bone Mineral Density Assessments

DXA BMD data are considered potentially unblinding. In order to maintain the blind, all DXA scans performed after the screening assessment must not be analyzed by site staff. DXA BMD data obtained after screening will not be reported to study-related personnel, including sites. The results from the central imaging vendor will be used as the final data for statistical analysis.

### 7.4 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the local and central laboratories, as applicable. Depending on the assessment, the central laboratory will be responsible either for performing the assays, or for shipping samples to Amgen or a specialty laboratory for assay.

The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, hepatitis B and C, serum 25 (OH) vitamin D, and intact-parathyroid (iPTH) tests. 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 either will 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 IP administration. Blood samples for the assessments of BTMs must be obtained from subjects in fasting state and before noon. Fasting state is defined as overnight fasting. If overnight fasting is not feasible, a minimum 8 hours of fasting is required. The date and time of sample collection will be recorded in the source documents at the site.

Specific analytes for serum chemistry, hematology, and other testing to be conducted on blood and urine samples are shown in Table 2. Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

**Table 2. Analyte Listing**

| Serum chemistry | Hematology | BTM | Other analytes |
|---|---|---|---|
| Sodium | Red blood cell | CTX[a] | Romosozumab levels[a] |
| Potassium | Hemoglobin | P1NP[a] | 25 (OH) vitamin D |
| Chloride | Platelets | | iPTH[a] |
| Bicarbonate | White blood cell | | Anti-romosozumab[a] antibody |
| Total protein | -Differential | | HepBsAg |
| Albumin | -Neutrophils | | HepBcAb |
| Calcium[a] | -Eosinophils | | Hepatitis C virus antibody |
| Albumin-adjusted calcium[a] | -Basophils | | |
| Magnesium | -Lymphocytes | | |
| Phosphorus[a] | -Monocytes | | |
| Glucose | | | |
| Blood urea nitrogen | | | |
| Creatinine | | | |
| TBL | | | |
| ALP[a] | | | |
| ALT (SGPT) | | | |
| AST (SGOT) | | | |
| TSH | | | |
| Free T4 | | | |

ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BTM = bone turnover marker; HepBsAg = hepatitis B surface antigen; HepBcAb = total hepatitis B core antibody; iPTH = intact-parathyroid hormone; T4 = thyroxine; TBL = total bilirubin; TSH=thyroid stimulating hormone.

[a] Results of post-day 1 assessments will be blinded to any study-related personnel (including the sites) except for serum calcium, albumin-adjusted calcium, phosphorus, or ALP in the event of a panic value.

Results of laboratory assessments for serum calcium, albumin-adjusted calcium, phosphorus, ALP, P1NP, CTX, iPTH, romosozumab levels, and anti-romosozumab antibodies are considered potentially unblinding and will not be reported to any study-related personnel after day 1 in order to maintain the integrity of the study blind. However, in the event of an abnormal value of clinical relevance (panic value) for serum calcium, albumin-adjusted calcium, phosphorus, or ALP, sites will be notified of the unblinded value by the central laboratory. After such notification is issued, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care. Notifications will also be issued for subjects who test positive for neutralizing anti-romosozumab antibodies at the final scheduled study visit (refer to Section 7.3 for details).

### 7.5 Antibody Testing Procedures

All subjects will have samples assayed for binding, and if positive, neutralizing antibodies. Blood samples for antibody testing are to be collected at the timepoints indicated in the Schedule of Assessments (Table 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 for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-romosozumab antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to romosozumab detected at the final scheduled visit. If results are not provided, no neutralizing antibodies to romosozumab have been detected at the final scheduled study visit.

Subjects who test positive for neutralizing antibodies to romosozumab at the final scheduled study 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, QM) 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 Assessments (Table 1), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

### 7.6 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to romosozumab.

For all subjects in the study, blood samples will be collected according to the Schedule of Assessments (Table 1) for determination of BTMs (CTX and P1NP).

### 7.7 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 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 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, 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 blood 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 Section 11.3 for subject confidentiality.

# 8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

## 8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving IP 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 IP or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

## 8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen IP(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 Section 12.1.

### 8.3 Reasons for Removal From Treatment or Study

#### 8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required IP or procedural assessments might include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- death
- lost to follow-up
- decision by sponsor or investigator (other than subject request, safety concern, lost to follow-up)

In the event a subject experiences a clinical fracture during the study period, the investigator is required to discuss the subject's individual fracture risk and alternative treatment options with the subject and to note the discussion in the subject's records. If a decision is made to begin an alternative approved therapy, the subjects must discontinue IP and every effort should be made to have the subject complete the remaining study visits and assessments, regardless of the alternative therapy chosen by the subject.

#### 8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study might include:

- decision by sponsor or investigator
- withdrawal of consent from study
- death
- lost to follow-up

## 9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

### 9.1 Definition of Safety Events

#### 9.1.1 Disease-related Events

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Fractures (serious or non-serious) are

anticipated to occur in the study population due to the underlying disease. Such events do not meet the definition of an adverse event unless:

- assessed to be more severe than expected for the subject's condition or
- if the investigator believes there is a causal relationship between the IP(s)/study treatment protocol required therapies and disease worsening.

If one of these criteria are met, the disease-related event must be reported as an adverse event or serious adverse event; otherwise, it will be reported as a disease-related event.

Disease-related events and/or disease-related outcomes that do not qualify as 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.
- Death due to the disease under study is to be recorded on the Event CRF.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP(s)/study treatment protocol required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

### 9.1.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

An adverse device effect is any adverse event related to the use of a 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.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

### 9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a disease-related event as defined in Section 9.1.1):

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A disease-related event is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

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 Safety Event Reporting Procedures

### 9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after first dose of IP through the EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is longer) are reported using the Event CRF. Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.

Events assessed by the investigator to be related to the IP/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

### 9.2.2 Adverse Events

#### 9.2.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is longer) are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (or toxicity defined below),
- Assessment of relatedness to IP (romosozumab/placebo and/or the PFS), or other protocol-required therapies/protocol-required procedure or activity, and
- Action taken.

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

The investigator must assess whether the adverse event is possibly related to the IP and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the IP and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of IP, protocol-required therapies, device[s] and/or procedure including any screening procedure[s]). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of IP, protocol-required therapies, device[s]), and/or procedure?"

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.

The investigator is responsible for reviewing laboratory test results and determining 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.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

#### 9.2.2.2 Reporting Procedures for 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 the EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is longer) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?"

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

In addition to the attributes listed in Section 9.2.2.1, the investigator must also complete the serious adverse event section of the Event CRF.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and GCP.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

#### 9.2.2.3 Reporting 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. 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 for the purposes of expedited reporting.

### 9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a subject, while the subject is taking protocol-required therapies, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 3 months after the end of treatment with romosozumab/placebo.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Study Endpoints, Analysis Sets, and Covariates

#### 10.1.1 Study Endpoints

##### 10.1.1.1 Primary Endpoint

- Percent change from baseline in DXA BMD at the lumbar spine at month 6

##### 10.1.1.2 Secondary Endpoint

- Percent change from baseline in DXA BMD at the femoral neck and total hip at month 6

##### 10.1.1.3 Exploratory Endpoints

- Percent changes from baseline in BTMs: P1NP and CTX at months 1, 3, and 6

#### 10.1.1.4 Safety Endpoints

For the 6-month treatment period:

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value between baseline and month 6
- Changes from baseline in vital signs
- Incidence of subjects with anti-romosozumab antibodies at months 1, 3, and 6

For the overall study period (6-month treatment period followed by the 3-month follow-up period):

- Subject incidence of adverse events by system organ class and preferred term
- Subject incidence of the formation of anti-romosozumab antibodies

#### 10.1.1.5 Pharmacokinetic Endpoint

- Romosozumab serum concentration at months 1, 3, and 6

### 10.1.2 Analysis Sets

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.

The BMD efficacy analysis set for each BMD endpoint will include all randomized subjects who have a baseline DXA BMD measurement and at least 1 postbaseline DXA BMD measurement for the skeletal site (lumbar spine, femoral neck, or total hip) being evaluated. Data from subjects in this set will be analyzed according to randomized treatment groups, regardless of actual treatment received.

The BTM efficacy analysis set will include all randomized subjects who have a baseline measurement and at least 1 postbaseline measurement for the endpoint of interest (CTX, P1NP). Data from subjects in this set will be analyzed according to randomized treatment groups, regardless of actual treatment received.

The safety analysis set will include all randomized subjects who receive at least 1 dose of IP. These subjects will be analyzed according to their actual treatment received.

The pharmacokinetic set will include all subjects in the safety set who have evaluable serum romosozumab concentration. This set will be used in all PK analyses.

### 10.1.3 Covariates and Subgroups

All analyses assessing BMD endpoints at the lumbar spine, femoral neck, and total hip will include treatment group, baseline value of BMD, machine type and interaction of baseline BMD value, and machine type as independent covariates.

No subgroup analysis is planned.

## 10.2 Sample Size Considerations

The sample size is based on comparison of romosozumab to placebo on percent change in lumbar spine BMD at month 6. From earlier Study 20060326, the estimated mean percentage differences in lumbar spine BMD between romosozumab versus placebo at month 6 were 7.9 with 95% CI (6.6, 9.3). The standard deviations (romosozumab vs. placebo) of mean percentage change in lumbar spine BMD at month 6 were 3.9 vs. 3.8. A sample size of 30 subjects per treatment arm will provide >99% power to detect significant treatment difference (romosozumab vs. placebo) in percent change in lumbar spine BMD at month 6 assuming a mean percent difference of 6.6 and a standard deviation of 3.9 with two-sided type 1 error of 5% and 10% dropout rate under the two sample t-test.

## 10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators, or subjects prior to the study being formally unblinded (eg, the formal unblinding at the final analysis) except as specified (eg, Section 5.2 and Section 9.2.2.2).

In order to perform limited planned analyses (eg, exposure-response analyses, PK analyses) or other key evaluations, certain functions may be unblinded to individual treatment assignments prior to the formal unblinding of the study. If such analyses will be performed during the conduct of the study, consider listing the functions and when they will become unblinded (eg, study milestone, percentage of study data availability).

## 10.4 Planned Analyses

### 10.4.1 Interim Analysis

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

### 10.4.2 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 effect of treatment with romosozumab for 6 months compared with placebo on percent changes in BMD at the lumbar spine as assessed by DXA in South Korean women with osteoporosis. Formal statistical testing will be conducted to evaluate the following hypothesis: in South Korean women with osteoporosis, the mean percent change in lumbar spine BMD in subjects receiving romosozumab will be different to that of those receiving placebo at month 6.**

**Secondary objectives of the primary analysis include the evaluation of the effect of treatment with romosozumab compared with placebo on the following:**

- **Percent change from baseline in DXA BMD at the femoral neck and total hip at month 6**

**Exploratory objectives of the primary analysis include the evaluation of the effect of treatment with romosozumab for 6 months compared with placebo on the following:**

- **Percent changes from baseline in BTMs P1NP and CTX**

**For the exploratory objectives, all inferential statistics will be considered exploratory in nature.**

**Safety objectives of the primary analysis include the comparison of the safety and tolerability for 6-month treatment with 210 mg romosozumab QM to placebo in South Korean women with osteoporosis on the following:**

- **Subject incidence of adverse events, including Event of Interest (EOI)**
- **Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value**
- **Changes from baseline in vital signs**
- **Incidence of subjects with anti-romosozumab antibodies**

### 10.4.3 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.

**Final analysis will include the analysis of primary, secondary, exploratory efficacy endpoints, as well as the safety endpoints through 6-month treatment period and the analysis of safety endpoints (adverse events and formation of anti-romosozumab antibodies) for the 9-month study period.**

The primary objective of the **final analysis** is the safety objective (ie**,** the comparison of the safety and tolerability following **9**-month treatment with 210 mg romosozumab QM to placebo in **South Korean** women with osteoporosis).

**In the final analysis, data from the overall 9-month study period (6-month treatment period plus 3-month follow-up period) will be analyzed.**

## 10.5 Planned Methods of Analysis

### 10.5.1 General Considerations

For computation of change from baseline endpoints, baseline will be taken as the observation recorded just prior to first dose of IP. In the case where 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.

### 10.5.2 Primary Efficacy Endpoint

The analysis to assess the percent change from baseline in lumbar spine DXA BMD at month 6 will employ an analysis of covariance (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 independent 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 romosozumab and placebo.

Conclusions for the primary efficacy hypothesis of different efficacy of romosozumab compared with placebo at lumbar spine BMD will be made using a 2-sided test with

type 1 error rate of 0.05. The BMD efficacy analysis set will be used to for these analyses.

### 10.5.3 Secondary Efficacy Endpoints

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 independent 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 romosozumab and placebo. The BMD efficacy analysis set will be used for these analyses.

### 10.5.4 Exploratory Efficacy Endpoints

For P1NP and CTX, descriptive statistics will be presented by treatment group at each visit for both actual values and the percent change from baseline values. Graphs depicting median and interquartile ranges by treatment group for percent change over time will be provided. The BTM efficacy analysis set will be used for these analyses.

### 10.5.5 Safety Endpoints

Safety analyses will include assessments of treatment-emergent adverse events, IP exposure, clinical laboratory assessments, vital signs, and anti-romosozumab antibodies.

The safety analysis set will be used for these analyses.

There is no planned inferential statistical testing in the safety analyses. All categorical endpoints will be summarized using the number and percent of subjects. All continuous endpoints will be summarized using descriptive statistics including mean, standard deviation, minimum, quartiles, maximum, and number of subjects.

#### 10.5.5.1 Adverse Events

For the 6-month treatment period, 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, **events of interest (including positively adjudicated osteonecrosis of the jaw, positively adjudicated atypical femoral fracture, injection site reaction, and positively adjudicated serious cardiovascular adverse events),** adverse events leading to withdrawal from IP or other

protocol-required therapies, and treatment-emergent adverse events will also be provided. Subject incidence of disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term. The treatment-emergent adverse events in the overall 9-month study period (6-month treatment period followed by a 3-month follow-up period) will be summarized using the same approach as for the 6-month treatment period. In addition, adverse events reported between month 6 and month 9 (no treatment phase) will be listed by subject number and treatment received in the first 6 months.

#### 10.5.5.2 Exposure to Investigational Product

The exposure to IP will be summarized using descriptive statistics.

#### 10.5.5.3 Laboratory Assessments

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.

#### 10.5.5.4 Vital Signs

The analyses of vital signs will include summary statistics (actual value and change from baseline for blood pressure, pulse and temperature) over time by visit for the 6-month treatment period.

#### 10.5.5.5 Anti-romosozumab Antibodies

The incidence and percentage of subjects who develop anti-romosozumab antibodies (binding, and if positive, neutralizing) at months 1, 3, 6 and 9 will be tabulated by treatment group. For subjects who develop anti-romosozumab antibodies, romosozumab serum concentrations may also be analyzed. Additionally, exploratory analyses may be performed to assess any impact on safety or efficacy.

### 10.5.6 Pharmacokinetic Endpoint

Trough serum concentration profiles determined from subjects may be summarized in tabular form and presented graphically. Additional pharmacokinetic analyses will be performed as appropriate. The pharmacokinetic set will be used for these analyses.

# 11. REGULATORY OBLIGATIONS

## 11.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IP is administered.

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. 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 and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

## 11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A

copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

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 is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for 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.

### 11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- 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 date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) 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.

### 11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center 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

## 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or ET and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen IP(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 IP(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

### 12.2 Study Documentation and Archive

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 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.

In this study, the IVR/IWR system captures the following data points and these are considered source data: subject identification number, randomization date, randomization number, and treatment group assignment.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data.

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.

Elements to include:

- Subject files containing completed CRFs, ICFs, 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, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

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

### 12.3 Study Monitoring and Data Collection

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.

The Amgen Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing 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.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and ET) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

### 12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publically 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.

### 12.5 Language

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

### 12.6 Publication Policy

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), which states:

- Authorship credit should 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 should 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.

### 12.7 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.

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# 14. APPENDICES

## Appendix A. Additional Safety Assessment Information

### Adverse Event Grading Scale

For grading of adverse events, CTCAE version 3.0 is to be used. The CTCAE version 3.0 is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

### Drug-induced Liver Injury Reporting & 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 Section 6.3 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 the 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 Section 9.2.2.2.

### Additional Clinical Assessments and Observation

All subjects in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.3.1 and 6.3.2 or who experience AST or ALT elevations > 3 x 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 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(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:
  - Obtain complete blood count with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain 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
  - Obtain viral serologies
  - Obtain creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all IP(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 corresponding CRFs.

## Appendix B. Sample Serious Adverse Event Report Form

| AMGEN<br>Study # 20150242<br>AMG 785 | **Electronic Serious Adverse Event Contingency Report Form**<br>**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<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*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<br>Day Month Year | Date Ended<br>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? Romosozumab No | Romosozumab Yes | Prefilled syringe No | Prefilled syringe Yes | <Device> No | <Device> Yes | <Device> No | <Device> Yes | Outcome of Event<br>Resolved<br>Not resolved<br>Fatal<br>Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Yes<br>No | | | | | | | | | | | |
| | | | | Yes<br>No | | | | | | | | | | | |
| | | | | Yes<br>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<br>Day Month Year | Date Discharged<br>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<br>Day Month Year | Prior to, or at time of Event: Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| Romosozumab/prefilled syringe | ☐ blinded ☐ open label | | | | | | | Lot # _____<br>☐ Unknown<br>Serial #<br>_____<br>☐ Unavailable / Unknown |
| | ☐ blinded ☐ open label | | | | | | | Lot # _____<br>☐ Unknown<br>Serial #<br>_____<br>☐ Unavailable / Unknown |

*FORM-056006* *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

| AMGEN<br>Study # 20150242<br>AMG 785 | **Electronic Serious Adverse Event Contingency Report Form**<br>**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<br>Study # 20150242<br>AMG 785 | Electronic Serious Adverse Event Contingency Report Form<br>**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 -<br>*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 C. Pregnancy and Lactation Notification Worksheets

## 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:** _____

**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

## Amendment 2

**Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Postmenopausal South Korean Women With Osteoporosis**

Amgen Protocol Number Romosozumab (AMG 785) 20150242

Amendment Date: 13 November 2017

**Rationale:**

This study is being conducted to support registration of romosozumab in Korea.

A primary analysis at 6 months is being added in this protocol amendment. Conducting a primary analysis in addition to a final analysis allows evalalution of the efficacy and safety data in the most expedited manner to support registrational activities.

Importantly, the primary analysis is being added to maintain consistency with what was done in previous studies with a similar design in the romosozumab development program.

Additional updates include:

- Align End of Study and Publication Policy language to new template text
- Update schema to include primary and final analysis, and add month 5 visit to align with protocol
- Clarify adverse events of interest to include injection site reactions and potential events of serious cardiovascular adverse events
- Make editorial and administrative edits

**Description of Changes:**

Section: Global

Change: Date updated throughout from 09 June 2017 to **13 November** 2017.

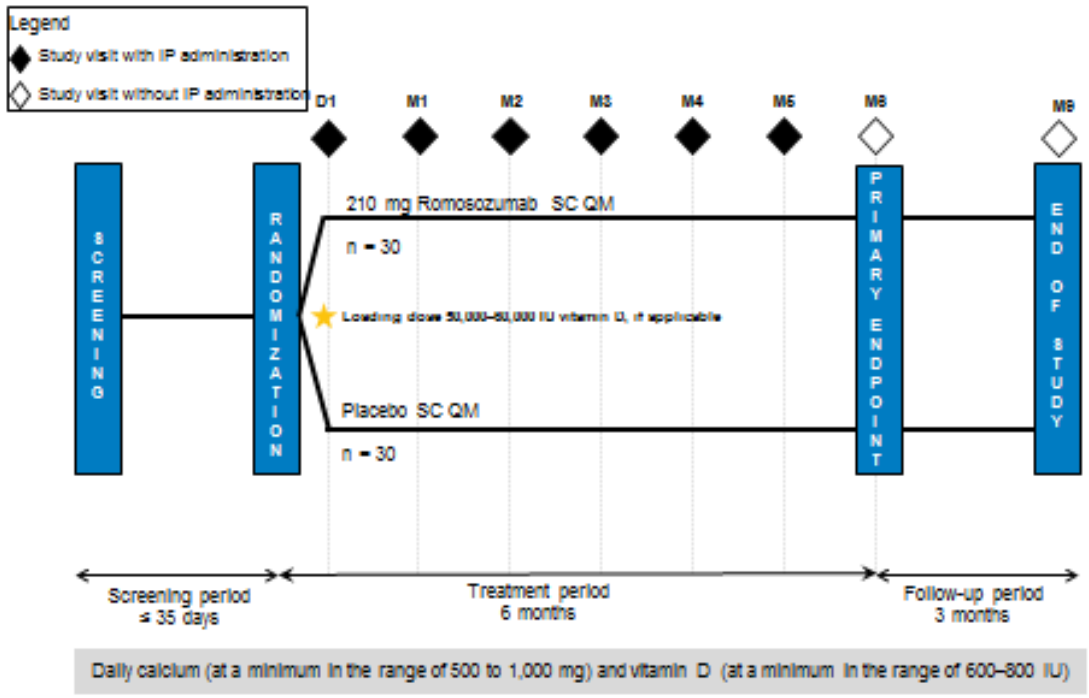
Section: Title Page

Add:

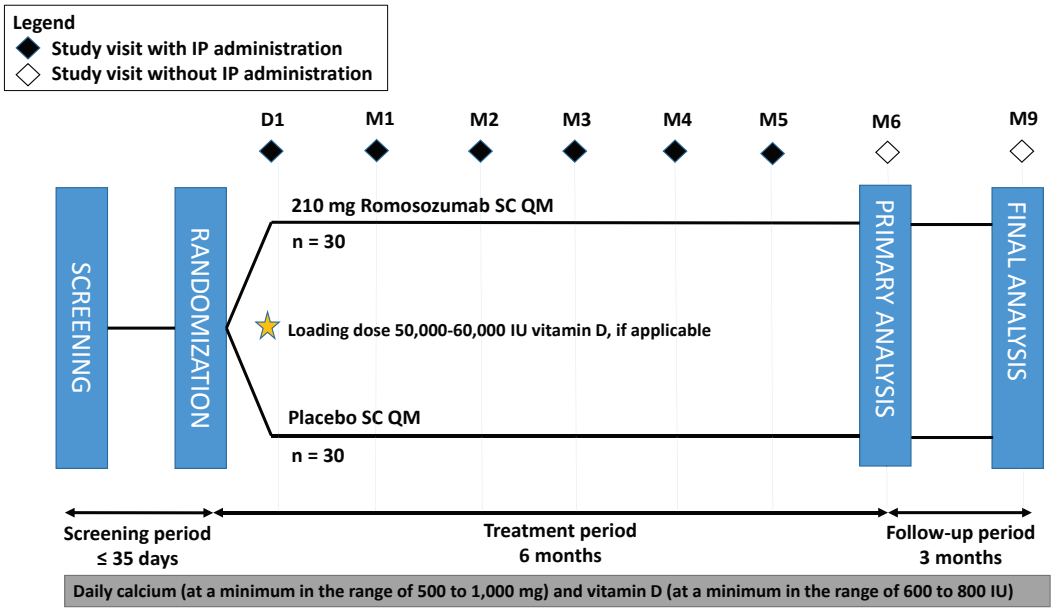
**Amendment 02 Date** **13 November 2017**

Section: Study Design and Treatment Schema

Replace:



With:




Section: Study Glossary

Add:

| EOI | Event of Interest |
|---|---|

Section: 3.5.2 End of Study paragraph 1

Add:

**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 purpose of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.**

Section: 3.5.2 End of Study paragraph 4

Add:

**If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination 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).**

Section: 7.3.11 Adverse Events, Serious Adverse Events, and Adverse Device Effects

Replace:

- potential osteonecrosis of the jaw events
- potential cases of atypical femoral fracture

With:

- potential osteonecrosis of the jaw events
- potential atypical femoral fracture **events**
- **injection site reactions**
- **potential events of serious cardiovascular adverse events**

Section: 10.4.1 Interim Analysis

Add:

**10.4.1 Interim Analysis**

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

Section: 10.4.2 Primary Analysis

Add:

**10.4.2 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 effect of treatment with romosozumab for 6 months compared with placebo on percent changes in BMD at the lumbar spine as assessed by DXA in South Korean women with osteoporosis. Formal statistical testing will be conducted to evaluate the following hypothesis: in South Korean women with osteoporosis, the mean percent change in lumbar spine BMD in subjects receiving romosozumab will be different to that of those receiving placebo at month 6.**

**Secondary objectives of the primary analysis include the evaluation of the effect of treatment with romosozumab compared with placebo on the following:**

- **Percent change from baseline in DXA BMD at the femoral neck and total hip at month 6**

**Exploratory objectives of the primary analysis includes the evaluation of the effect of treatment with romosozumab for 6 months compared with placebo on the following:**

- **Percent changes from baseline in BTMs P1NP and CTX**

**For the exploratory objectives, all inferential statistics will be considered exploratory in nature.**

**Safety objectives of the primary analysis include the comparison of the safety and tolerability for 6-month treatment with 210 mg romosozumab QM to placebo in South Korean women with osteoporosis on the following:**

- **Subject incidence of adverse events, including Event of Interest (EOI)**
- **Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value**
- **Changes from baseline in vital signs**
- **Incidence of subjects with anti-romosozumab antibodies**

Section: 10.4.3 Final Analysis

Replace:

10.4.1 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 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 additional 3 months is the safety objective (ie the comparison of the safety and tolerability following 6 -month treatment with 210 mg romosozumab QM to placebo in postmenopausal women with osteoporosis)

With:

**10.4.3** 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.

**Final analysis will include the analysis of primary, secondary, exploratory efficacy endpoints, as well as the safety endpoints through 6-month treatment period and the analysis of safety endpoints (adverse events and formation of anti-romosozumab antibodies) for the 9-month study period.**

The primary objective of the **final analysis** is the safety objective (ie**,** the comparison of the safety and tolerability following **9**-month treatment with 210 mg romosozumab QM to placebo in **South Korean** women with osteoporosis).

**In the final analysis, data from the overall 9-month study period (6-month treatment period plus 3-month follow-up period) will be analyzed.**

Section: 10.5.5.1 Adverse Events

Add:

For the 6-month treatment period, 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, **events of interest (including positively adjudicated osteonecrosis of the jaw, positively adjudicated atypical femoral fracture, injection site reaction, and positively adjudicated serious cardiovascular adverse events),** adverse events leading to withdrawal from IP or other protocol-required therapies, and treatment-emergent adverse events will also be provided.

Section: 12.6 Publication Policy

Replace:

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), which states:

- Authorship credit should 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. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should 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 should qualify for authorship, and all those who qualify should be listed.

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

With:

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), which states:

- Authorship credit should 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 should 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.

## Amendment 1

**Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Postmenopausal South Korean Women With Osteoporosis**

Romosozumab (AMG 785) 20150242

Amendment Date: 09 June 2017

**Rationale:**

The protocol is amended to:

- Add independent committee adjudication for deaths and serious adverse events to be of potential cardiovascular origin or etiology
- Revise Hepatitis B and C exclusion criteria to clarify the circumstances under which PCR should be performed to determine active disease
- Add a superscript “a” to CTX and P1NP in Table 2 (Analyte Listing) to indicate that post-day 1 assessments are blinded
- Make minor administrative changes and edits throughout the protocol