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

AMG 785/Romosozumab

Amgen Protocol Number 20110142

EudraCT number 2011-003142-41

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ARCH

(Active-contRolled FraCture Study in Postmenopausal Women With Osteoporosis at High Risk of Fracture)

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NCT Number: 1631214
This NCT number has been applied to the document
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Investigator's Agreement

I have read the attached protocol entitled A Multicenter, International, Randomized, Double-blind, Alendronate-controlled Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis, dated **14 September 2016,** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

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 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: Phase 3

Indication: Treatment of postmenopausal women with osteoporosis

Primary Objectives:

For the primary analysis period (randomization to primary analysis)

- To assess the effect of romosozumab treatment for 12 months followed by alendronate (ALN) treatment compared with ALN treatment alone on the subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) in postmenopausal women with osteoporosis
- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on the subject incidence of new vertebral fracture in postmenopausal women with osteoporosis

Secondary Objectives:

For the primary analysis period

To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on:

- Subject incidence of fractures (all fractures [nonvertebral fractures and new or worsening vertebral fractures], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, multiple new or worsening vertebral fracture**, and clinical vertebral fracture**)
- Percent changes in Dual energy X-ray Absorptiometry (DXA) bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck

For the 12-month double-blind ALN-controlled study period

To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on:

- Subject incidence of fractures (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fractures and new or worsening vertebral fractures] **nonvertebral fracture, hip fracture, clinical vertebral fracture, and major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral]**)
- Percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck

For the overall study period (randomization to end of study)

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of **hip fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip],** nonvertebral fractures

Exploratory Objectives:

For the 12-month double-blind ALN-controlled study period

- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on subject incidence of fractures (new or worsening vertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], and multiple new or worsening vertebral fracture)

- To describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life at 6-month intervals for postmenopausal women with osteoporosis using Patient Reported Outcome (PRO) and Clinician Reported Outcome (ClinRO) questionnaires (Osteoporosis Assessment Questionnaire Short Version [OPAQ SV], EuroQoL-5 Dimensions-5 Levels Health Survey [EQ-5D-5L], Limited Activity Days [LAD] survey, and one item extracted from the Brief Pain Inventory [BPI] assessing the worst pain experienced in the past 24 hours [BPI worst pain])
- To describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life for 3 months at 1-month intervals after experiencing a nonvertebral or clinical vertebral fracture (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain)
- To describe the effect of romosozumab treatment for 12 months compared with ALN treatment on the percent of subjects with a clinically meaningful improvement in worst pain for 3 months at 1-month intervals after experiencing a nonvertebral or clinical vertebral fracture (defined as a 2-point improvement in the BPI worst pain scale compared with the fracture reporting visit)
- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on changes in height

For the primary analysis period

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral)
- To describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life at 6-month intervals for postmenopausal women with osteoporosis using PRO and ClinRO questionnaires (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain)
- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on changes in height

During the Month 12 to 24 ALN study period

- **To assess the effect of one year of romosozumab treatment compared with ALN treatment alone on subject incidence of new vertebral fractures, clinical fracture (nonvertebral fracture and clinical vertebral fracture), nonvertebral fracture, hip fracture, and clinical vertebral fracture during the subsequent year during which all subjects receive ALN treatment.**

Safety Objectives:

For the 12-month double-blind ALN-controlled study period

- To characterize the safety and tolerability of romosozumab treatment for 12 months as determined by a review of reported adverse events, laboratory data, vital signs, and formation of anti-romosozumab antibodies

For the primary analysis period

- To characterize the safety and tolerability of romosozumab treatment for 12 months followed by ALN treatment as determined by a review of reported adverse events, laboratory data, vital signs, and formation of anti-romosozumab antibodies

For the overall study period

- To characterize the safety and tolerability of romosozumab treatment for 12 months followed by ALN treatment as determined by a review of reported adverse events and vital signs

Imaging and Pharmacokinetics (PK) / Bone Turnover Marker (BTM) / Biomarker Sub-study Objectives:

For the 12-month double-blind ALN-controlled study period

- To characterize the serum romosozumab concentration
- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on:
  - Percent changes in bone formation markers Procollagen Type 1 N-telopeptide (P1NP), Bone Specific Alkaline Phosphatase (BSAP), and Osteocalcin (OC) and in bone resorption marker serum Type I collagen C-telopeptide (sCTX)
  - Percent changes in sclerostin and intact Parathyroid Hormone (iPTH)
  - For subjects participating in the imaging components:
    - Percent changes in integral (total) and trabecular volumetric BMD (vBMD) at the lumbar spine by Quantitative Computed Tomography (QCT)
    - Percent changes in lumbar spine strength as assessed by Finite Element Analysis (FEA)
- For subjects participating in the imaging components**:** To assess the effect of romosozumab treatment for 6 months compared with ALN treatment for 6 months on percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck
- To enable exploratory assessments of novel biomarkers through prospective collection of blood samples

For the primary analysis period

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on:
  - Percent changes in bone formation marker P1NP and bone resorption marker sCTX
  - Percent changes in sclerostin and iPTH
  - For subjects participating in the imaging components:
    - Percent changes in integral (total) and trabecular vBMD at the lumbar spine by QCT
    - Percent changes in lumbar spine strength as assessed by FEA
- For subjects participating in the imaging components: To assess the effect of romosozumab treatment for 12 months followed by ALN treatment for 6 months compared with ALN treatment alone on percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck
- To enable exploratory assessments of novel biomarkers through prospective collection of blood samples

Hypotheses: The primary clinical hypotheses are that romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone is effective in reducing the incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) and new vertebral fracture in postmenopausal women with osteoporosis. It is expected that romosozumab treatment for 12 months followed by ALN treatment will reduce the incidence of clinical fractures by 30% and the incidence of new vertebral fractures by 50% compared with the control group (ALN alone).

The primary safety hypothesis is that romosozumab treatment for 12 months is well tolerated in postmenopausal women with osteoporosis.

Primary Endpoints:

During the primary analysis period

- Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) at primary analysis
- Subject incidence of new vertebral fracture through Month 24

Secondary Endpoints:

During the primary analysis period

- Subject incidence of nonvertebral fracture at primary analysis
- Subject incidence of all fractures (nonvertebral fracture and new or worsening vertebral fracture) at primary analysis
- Subject incidence of new or worsening vertebral fracture through Month 24
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) at primary analysis
- Subject incidence of hip fracture at primary analysis
- Subject incidence of multiple new or worsening vertebral fractures through Month 24
- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) through Month 24**
- **Subject incidence of nonvertebral fracture through Month 24**
- **Subject incidence of hip fracture through Month 24**
- **Subject incidence of clinical vertebral fracture through Month 24**
- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Months 24 and 36

During the 12-month double-blind ALN-controlled study period

- Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) through Month 12
- Subject incidence of new vertebral fracture through Month 12
- Subject incidence of all fractures (nonvertebral fracture and new or worsening vertebral fracture) through Month 12
- **Subject incidence of nonvertebral fracture through Month 12**
- **Subject incidence of hip fracture through Month 12**
- **Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12**
- **Subject incidence of clinical vertebral fracture through Month 12**
- Percent change from baseline in BMD at the lumbar spine, total hip and femoral neck at Month 12

During the overall study period

- Subject incidence of nonvertebral fracture at final analysis
- **Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) at final analysis**
- **Subject incidence of hip fracture at final analysis**

Exploratory Endpoints:

During the 12-month double-blind ALN-controlled study period

- Subject incidence of new or worsening vertebral fracture through Month 12
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Month 12
- Subject incidence of multiple new or worsening vertebral fractures through Month 12
- Actual value in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 6 and 12
- Change from baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 6 and 12
- Actual value in PRO and ClinRO measures after experiencing a nonvertebral or clinical vertebral fracture (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at reporting of the nonvertebral or clinical vertebral fracture and at 1, 2, and 3 months after the fracture
- Change from pre-fracture baseline in PRO and ClinRO measures after experiencing a nonvertebral or clinical vertebral fracture (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at reporting of the nonvertebral or clinical vertebral fracture and at 1, 2, and 3 months after the fracture
- Proportion of subjects with a clinically meaningful improvement in worst pain (defined as a 2-point improvement in the BPI worst pain scale compared with the fracture reporting visit) at 1, 2, and 3 months after reporting of a nonvertebral or clinical vertebral fracture
- Change from baseline in height at Month 12

During the primary analysis period

- Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) at primary analysis
- Actual value in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 18, 24, 30, and 36
- Change from baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 18, 24, 30, and 36
- Change from baseline in height at Month 24

During the Month 12 to 24 ALN study period

- **Subject incidence of new vertebral fractures between Month 12 and Month 24**
- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) between Month 12 and Month 24**
- **Subject incidence of nonvertebral fracture between Month 12 and Month 24**
- **Subject incidence of hip fracture between Month 12 and Month 24**
- **Subject incidence of clinical vertebral fracture between Month 12 and Month 24**

Safety Endpoints:

During the 12-month double-blind ALN-controlled study period

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and the shifts from baseline to the worst value between baseline and Month 12
- Changes from baseline in vital signs
- Subject incidence of anti-romosozumab antibodies

During the primary analysis period

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

During the overall study period

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in vital signs

Imaging and PK/BTM/Biomarker Sub-study Endpoints:

During the 12-month double-blind ALN-controlled study period

- Romosozumab serum concentrations at Day 1, Months 1, 3, 6, 9, and 12
- Percent change from baseline in P1NP, BSAP, OC, and sCTX at Months 1, 3, 6, 9, and 12
- Percent change from baseline in iPTH and sclerostin at Months 1, 3, 6, 9, and 12
- For subjects participating in the imaging components:
    - Percent change from baseline in integral (total) and trabecular vBMD at the lumbar spine by QCT at Months 6, and 12
    - Percent change from baseline in lumbar spine strength as assessed by FEA at Months 6, and 12
    - Percent change from baseline in DXA BMD at the lumbar spine, total hip, and femoral neck at Month 6

During the primary analysis period

- Percent change from baseline in P1NP and sCTX at Months 15, 18, 24, and 36
- Percent change from baseline in iPTH and sclerostin at Months 15, 18, 24, and 36
- For subjects participating in the imaging components:
    - Percent change from baseline in integral (total) and trabecular vBMD at the lumbar spine by QCT at Month 24
    - Percent change from baseline in lumbar spine strength as assessed by FEA at Month 24
    - Percent change from baseline in DXA BMD at the lumbar spine, total hip, and femoral neck at Month 18

Study Design:

This is a phase 3 multicenter, international, randomized, double-blind, ALN-controlled study of romosozumab in postmenopausal women with osteoporosis. The study is designed to evaluate if romosozumab treatment for 12 months followed by ALN treatment, compared with ALN treatment alone, is effective in reducing the incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) and new vertebral fracture.

Approximately 4,000 subjects will be randomized 1:1 to receive either 210 mg romosozumab subcutaneous (SC) every month (QM) or 70 mg ALN orally (PO) every week (QW) in a blinded fashion for the duration of the 12-month double-blind ALN-controlled study period. Randomization will be stratified by age (< 75 years, ≥ 75 years). Subjects will also receive matched placebo for either ALN or romosozumab. After the initial 12-month study period, subjects will receive ALN while remaining blinded to their initial treatment assignment (romosozumab or ALN). The primary analysis period will end and the primary analysis will be performed when:

- clinical fracture events (nonvertebral fracture or clinical vertebral fracture) have been confirmed for at least 330 subjects
  AND
- all subjects have had the opportunity to complete the Month 24 study visit

If more than 330 subjects have confirmed clinical fractures at the time each subject has completed her Month 24 visit, the primary analysis will be based on all available data, which may include more than 330 events.

Upon completion of the primary analysis period, subjects will continue to be followed for the secondary endpoint of nonvertebral fractures. Subjects and site personnel will remain blinded to initial treatment assignments. The study will proceed in an event-driven manner. The final analysis (end of study) will be performed when nonvertebral fracture events have been confirmed for at least 440 subjects across the lifetime of the study. The study may be terminated earlier if the primary analysis demonstrates superiority of romosozumab treatment for nonvertebral fracture risk reduction (see Section 10.2 for details on testing strategy). Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture.

The estimated study duration for an individual subject, including the screening period, is 25 to 59 months (if study completion is achieved at primary analysis) or 37 to 71 months (if study completion is achieved when ≥440 subjects have experienced a nonvertebral fracture), based on projected enrollment, and estimated fracture rates. However, actual study duration for individual subjects may be longer, depending on actual enrollment and observed fracture rates.

From screening to end of study, subjects will receive daily calcium and vitamin D supplementation that at a minimum should be 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 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.

Approximately 200 subjects at participating centers will be enrolled in an Imaging and PK/BTM/Biomarker sub-study. Within this sub-study, a subset of approximately 100 subjects will participate in the imaging (DXA, QCT) component of the sub-study.

If there is insufficient enrollment into the blood only portion of the sub-study, additional sub-study sites will be initiated. Subjects already on trial will be invited to participate and consent will be obtained for the use of blood samples from earlier time points for sub-study analyses.

From study start until primary analysis, an external, independent Data Monitoring Committee (DMC) will monitor unblinded safety data on an ongoing basis and consider efficacy data in order to assess the risk/benefit profile of romosozumab.

Sample Size: Approximately 4,000 subjects (approximately 2,000 subjects per arm)

Summary of Subject Eligibility Criteria:

Subjects must be postmenopausal women age 55 to 90 years who meet at least one of the following BMD and fracture criteria:

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

or

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

Subjects with severe metabolic or bone diseases or significant lab abnormalities are not eligible for participation. The use of agents affecting bone metabolism is also exclusionary, however, for selected therapies permissible off-treatment periods prior to randomization are defined in Section 4.2.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration:

During the 12-month double-blind ALN controlled study period, the romosozumab treatment group will receive 210 mg romosozumab SC QM and matched placebo for ALN PO QW in a blinded fashion.

Following the 12-month double-blind ALN controlled study period, the romosozumab treatment group will receive open-label 70 mg ALN PO QW while remaining blinded to their initial treatment assignment (romosozumab).

Non Amgen Investigational Product Dosage and Administration:

During the 12-month double-blind ALN controlled study period, the ALN treatment group will receive 70 mg ALN PO QW and matched placebo for 210 mg romosozumab SC QM in a blinded fashion.

Following the 12-month double-blind ALN controlled study period, the ALN treatment group will receive open-label 70 mg ALN PO QW while remaining blinded to their initial treatment assignment (ALN).

Non Amgen Non-investigational Product Dosage and Administration:

From screening to end of study, subjects will receive daily calcium and vitamin D supplementation that at a minimum should be 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 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.

Control Group: Subjects randomized to receive ALN treatment will serve as the control group.

Procedures: Key procedures will include informed consent, medical, fracture, and medication history, instructions for daily calcium and vitamin D supplementation, physical examination, vital signs, height and weight, laboratory assessments (serum chemistry/ hematology, 25 (OH) vitamin D, and anti-romosozumab antibody), lateral spine x-ray, DXA scans of the lumbar spine and proximal femur, reporting of nonvertebral and suspected clinical vertebral fractures, PROs/ClinROs (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain), adverse event/concomitant medication data collection, investigational product (IP) administration and IP dispensation.

The following assessments will be performed for subjects participating in the Imaging and PK/BTM/Biomarker sub-study: additional blood draws (romosozumab levels, BTMs, sclerostin, iPTH, and for potential biomarker development) and for subjects also participating in the imaging components, QCT scans of the spine and additional DXA scans of the lumbar spine and proximal femur.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

Statistical Considerations: The study is designed to evaluate the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN alone in reducing the subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture), vertebral fracture and nonvertebral fracture. The primary analysis will be performed when clinical fractures have been confirmed for at least 330 subjects and after all subjects have had the opportunity to complete the Month 24 visit. If 330 subjects have confirmed clinical fractures prior to all subjects having completed the Month 24 visit, the analysis will be based on all available data, which may include more than 330 events. The final analysis will be performed when nonvertebral fractures have been confirmed for at least 440 subjects. If superiority of the nonvertebral fracture endpoint is achieved at the primary analysis and the study is stopped after the primary analysis has been performed, all data, including the additional safety and nonvertebral fracture data, collected after the primary analysis will be summarized descriptively and not be included in confirmatory testing. Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture.

In order to maintain the overall significance level at 0.05, the primary endpoints will be assessed using Hochberg's procedure. If both primary endpoints are significant at the 0.05 level, **each of the following secondary DXA BMD endpoints will be tested hierarchically at 0.05 according to the following sequence: percent change from baseline in BMD at lumbar spine at Month 24, percent change from baseline in BMD at total hip at Month 24, percent change from baseline in BMD at femoral neck at Month 24, percent change from baseline in BMD at lumbar spine at Month 12, percent change from baseline in BMD at total hip at Month 12, and percent change from baseline in BMD at femoral neck at Month 12. If all preceding endpoints are significant,** the nonvertebral fracture endpoint will be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test ($\alpha = 0.025$). The Lan-Demets alpha spending function that approximates a Pocock boundary will be used to determine the significance level at the time of the primary analysis.

Subject incidence of clinical fractures will be compared between treatment groups using a Cox proportional hazards model controlling for age (< 75 years, ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. Nonvertebral fractures, major nonvertebral fractures, hip fractures, **clinical vertebral fracture,** and all fractures will be analyzed using the same approach as for clinical fractures. The Kaplan-Meier method will be used to summarize the cumulative fracture incidence at pre-specified time points.

Subject incidence of new vertebral fracture at pre-specified time point**s** will be compared between treatment groups using a logistic regression model adjusting for age (< 75 years, ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. Subject incidence of new or worsening vertebral fractures and multiple new or worsening vertebral fractures will be analyzed using the same approach as for new vertebral fractures. **Subject incidence of new vertebral fractures between Month 12 and Month 24 will be estimated.**

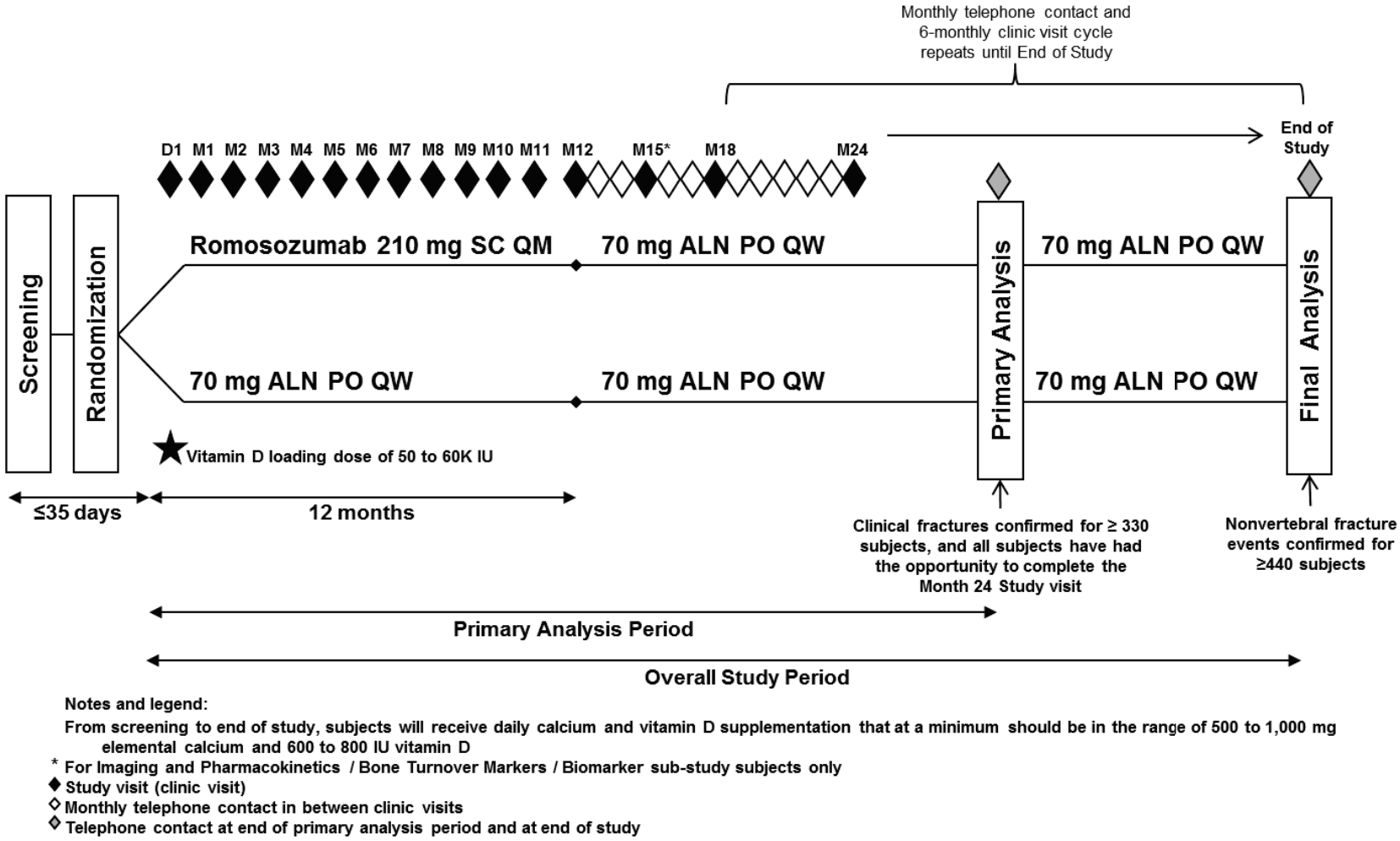
Subject incidence rates of adverse events in the 12-month double-blind ALN-controlled study period will be tabulated by system organ class and preferred term. Summaries of deaths, events of interest, serious adverse events and IP related adverse events, adverse events leading to early discontinuation from IP or study in the 12-month double-blind ALN-controlled study period will also be provided.

The adverse events following the 12-month double-blind study period and in the overall study period will be summarized using the same approach as for the 12-month double-blind ALN-controlled study period.

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

Sponsor: Amgen Inc.

Study Design and Treatment Schema



Notes and legend:

From screening to end of study, subjects will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of 500 to 1,000 mg elemental calcium and 600 to 800 IU vitamin D

* **For Imaging and Pharmacokinetics / Bone Turnover Markers / Biomarker sub-study subjects only**

◆ **Study visit (clinic visit)**

◇ **Monthly telephone contact in between clinic visits**

◈ **Telephone contact at end of primary analysis period and at end of study**

Note: Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALN	Alendronate
ALP	Alkaline Phosphatase
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
AMG 785 (romosozumab)	Anti-human sclerostin antibody, also referred to as hu13C7, h13C7, or Mab-B
ARCH	Active-controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BMD	Bone Mineral Density
BMI	Body Mass Index
BPI	Brief Pain Inventory
BSAP	Bone Specific Alkaline Phosphatase
BTM	Bone Turnover Marker
BUN	Blood Urea Nitrogen
ClinRO	Clinician Reported Outcome; questionnaires completed by physician or site staff using information provided by the subject
CTCAE	Common Terminology Criteria for Adverse Events
Date of Randomization	Date on which the randomization number is assigned; synonymous with enrollment date
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee; term synonymous with Data Safety Monitoring Board
DXA	Dual energy X-ray Absorptiometry
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Electronic Trial Operations System	An electronic system that is used to facilitate the operations of a clinical trial through the collection of study related data. Most common applications of an Electronic Trial Operations system within a clinical trial are: subject randomization and investigational product management. Term synonymous with the industry term IVRS.
End of study for individual subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
End of study (primary completion)	Defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary outcomes
End of study (end of trial)	Defined as when the last subject is assessed or receives an intervention for evaluation in the study
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels Health Survey

Abbreviation or Term	Definition/Explanation
eSAE	Electronic Serious Adverse Event
ET	Early Termination
FDA	Food and Drug Administration
FEA	Finite Element Analysis
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
IPIM	Investigational Product Instruction Manual
iPTH	intact Parathyroid Hormone
IV	Intravenous
Interactive Voice Response System (IVRS)	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
LAD	Limited Activity Days
NHANES	National Health and Nutritional Examination Survey
OC	Osteocalcin
ONJ	Osteonecrosis of the Jaw
OPAQ SV	Osteoporosis Assessment Questionnaire Short Version
Overall study period	Randomization to end of study
P1NP	Procollagen Type 1 N-telopeptide
PD	Pharmacodynamics
PFS	Prefilled Syringe
PK	Pharmacokinetics
PMO	Postmenopausal Osteoporosis
PO	Orally
Primary analysis period	Randomization to primary analysis
PRO	Patient Reported Outcome
PTH	Parathyroid Hormone
QCT	Quantitative Computed Tomography
QM	Every month
QW	Every week
RBC	Red Blood Cell
Romosozumab	International Nonproprietary Name for AMG 785

Abbreviation or Term	Definition/Explanation
RRR	Relative Risk Reduction
SAP	Statistical Analysis Plan
SC	Subcutaneous
Screening Period	Begins when the subject signs the informed consent form and ends on date of randomization
sCTX	Serum Type I collagen C-telopeptide
SERM	Selective Estrogen Receptor Modulator
Source Data	Information from an original record or certified a 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 ID, Randomization ID, and Stratification Value.
SQ0, SQ1, SQ2, SQ3	Visual semiquantitative grading scale for vertebral fractures on lateral spine x-rays: SQ0=no fracture; SQ1=mild fracture; SQ2=moderate fracture; SQ3=severe fracture (Genant et al, 1993)
Study Day 1	Defined as the first day that protocol-specified investigational product is administered to the subject (ie, first injection of romosozumab/placebo)
Study Start Date	Defined as the date on which the first subject is enrolled into the study
Study End Date	Defined as the date on which the last subject completes their final study procedure
TBL	Total Bilirubin
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of Normal
US	United States
vBMD	Volume BMD
WBC	White Blood Cell

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1. OBJECTIVES

1.1 Primary

For the primary analysis period (randomization to primary analysis)

- To assess the effect of romosozumab treatment for 12 months followed by alendronate (ALN) treatment compared with ALN treatment alone on the subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) in postmenopausal women with osteoporosis
- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on the subject incidence of new vertebral fracture in postmenopausal women with osteoporosis

1.2 Secondary

For the primary analysis period

To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on:

- Subject incidence of fractures (all fractures [nonvertebral fractures and new or worsening vertebral fractures], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, multiple new or worsening vertebral fracture, **and clinical vertebral fracture**)
- Percent changes in Dual energy X-ray Absorptiometry (DXA) bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck

For the 12-month double-blind ALN-controlled study period

To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on:

- Subject incidence of fractures (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fractures and new or worsening vertebral fractures], **nonvertebral fracture, hip fracture, clinical vertebral fracture, and major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral]**)
- Percent changes in DXA BMD at the lumbar spine, total hip and femoral neck

For the overall study (randomization to end of study)

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of **hip fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], and** nonvertebral fractures

1.3 Exploratory

For the 12-month double-blind ALN-controlled study period

- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on subject incidence of fractures (new or worsening vertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], and multiple new or worsening vertebral fracture)
- To describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life at 6-month intervals for postmenopausal women with osteoporosis using Patient Reported Outcome (PRO) and Clinician Reported Outcome (ClinRO) questionnaires (Osteoporosis Assessment Questionnaire Short Version [OPAQ SV], EuroQoL-5 Dimensions-5 Levels Health Survey [EQ-5D-5L], Limited Activity Days [LAD] survey, and one item extracted from the Brief Pain Inventory [BPI] assessing the worst pain experienced in the past 24 hours [BPI worst pain])
    - To describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life for 3 months at 1-month intervals after experiencing a nonvertebral or clinical vertebral fracture (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain)
- To describe the effect of romosozumab treatment for 12 months compared with ALN treatment on the percent of subjects with a clinically meaningful improvement in worst pain for 3 months at 1-month intervals after experiencing a nonvertebral or clinical vertebral fracture (defined as a 2-point improvement in the BPI worst pain scale compared with the fracture reporting visit)
- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on changes in height

For the primary analysis period

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral)
- To describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life at 6-month intervals for postmenopausal women with osteoporosis using PRO and ClinRO questionnaires (OPAQ SV), EQ-5D-5L, LAD, and BPI worst pain)
- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on changes in height

During the Month 12 to 24 ALN study period

- **To assess the effect of one year of romosozumab treatment compared with ALN treatment alone on subject incidence of new vertebral fractures, clinical fracture (nonvertebral fracture and clinical vertebral fracture), nonvertebral fracture, hip fracture, and clinical vertebral fracture during the subsequent year during which all subjects receive ALN treatment.**

1.4 Safety

For the 12-month double-blind ALN-controlled study period

- To characterize the safety and tolerability of romosozumab treatment for 12 months as determined by a review of reported adverse events, laboratory data, vital signs, and formation of anti-romosozumab antibodies.

For the primary analysis period

- To characterize the safety and tolerability of romosozumab treatment for 12 months followed by ALN treatment as determined by a review of reported adverse events, laboratory data, vital signs, and formation of anti-romosozumab antibodies

For the overall study

- To characterize the safety and tolerability of romosozumab treatment for 12 months followed by ALN treatment as determined by a review of reported adverse events and vital signs

1.5 Imaging and Pharmacokinetics (PK) / Bone Turnover Marker (BTM) / Biomarker Sub-study

For the 12-month double-blind ALN-controlled study period

- To characterize the serum romosozumab concentration
- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on:
  - Percent changes in bone formation markers Procollagen Type 1 N-telopeptide (P1NP), Bone Specific Alkaline Phosphatase (BSAP), and Osteocalcin (OC), and in bone resorption marker serum Type I collagen C-telopeptide (sCTX)
  - Percent changes in sclerostin and intact Parathyroid Hormone (iPTH)
  - For subjects also participating in the imaging components: Percent changes in integral (total) and trabecular volumetric BMD (vBMD) at the lumbar spine by Quantitative Computed Tomography (QCT)
  - For subjects also participating in the imaging components: Percent changes in lumbar spine strength as assessed by Finite Element Analysis (FEA)
- For subjects participating in the imaging components: To assess the effect of romosozumab treatment for 6 months compared with ALN treatment for 6 months on percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck
- To enable exploratory assessments of novel biomarkers through prospective collection of blood samples

For the primary analysis period

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on
  - Percent changes in bone formation marker P1NP and bone resorption marker sCTX
  - Percent changes in sclerostin and iPTH
  - For subjects participating in the imaging components: Percent changes in integral (total) and trabecular vBMD at the lumbar spine by QCT
  - For subjects participating in the imaging components: Percent changes in lumbar spine strength as assessed by FEA
- For subjects participating in the imaging components: To assess the effect of romosozumab treatment for 12 months followed by ALN treatment for 6 months compared with ALN treatment alone on percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck
- To enable exploratory assessments of novel biomarkers through prospective collection of blood samples

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 $\geq$ 2.5 standard deviations below the mean for normal young adults) (World Health Organization, 1994); the worldwide prevalence of osteoporosis has been estimated as 200 million people (Reginster and Burlet, 2006), including more than 75 million people in the United States (US), Europe, and Japan (World Health Organization, 2007). The morbidity and mortality associated with osteoporotic-related fractures is significant in terms of disability to an individual and cost to the global economy (Cree et al, 2003; Kanis et al, 2001a, Kanis et al, 2001b).

Approved treatments for postmenopausal women with osteoporosis include inhibitors of bone resorption such as selective estrogen receptor modulators (SERMs, eg, raloxifene), bisphosphonates (eg, ALN, risedronate, ibandronate, and zoledronate), calcitonin, denosumab, or agents that stimulate bone formation like teriparatide (the 1-34 fragment of iPTH) (Greenblatt, 2005).

Antiresorptive therapies prevent osteoclasts from resorbing bone, slowing the progression of bone breakdown, increasing BMD, and lowering the risk of vertebral

fractures (relative risk reduction [RRR]: 40% to 70%) and, to a lesser extent, nonvertebral fractures (RRR: 20% to 25%) (Cummings et al, 2009; Black et al, 2007; Chestnut et al, 2004; McClung et al, 2001; Chestnut et al, 2000; Cummings et al, 1998; Ettinger et al, 1999; Harris et al, 1999; Black et al, 1996). Osteoporosis is a chronic disease and despite long-term administration of bisphosphonates, the most commonly prescribed class of antiresorptives, postmenopausal women with severe osteoporosis remain at increased risk of fracture and are in need of therapies with strong efficacy and the potential to reverse their disease condition by increasing bone formation and improving bone structure.

In contrast, bone forming agents can promote larger improvements in bone mass and bone strength 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). Analogs of parathyroid hormone (PTH) (PTH 1-34 [teriparatide] and PTH 1-84) increase bone remodeling by stimulating both bone formation and bone resorption with a net gain in bone mass. As a result, there is a marked improvement in BMD, as well as indices of bone microstructure, that are associated with improved mechanical strength (Borggrefe et al, 2010). Teriparatide shows a RRR of nonvertebral fractures of approximately 35% to 50% and lowers the risk of one or more new vertebral fractures by 65% (Neer et al, 2001).

A novel bone forming agent for the treatment of osteoporosis in postmenopausal women, with a different mechanism of action and the potential to reverse the features of osteoporosis by increasing bone volume and BMD and by improving bone architecture, 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 Romosozumab Background

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

multiple animal models (normal and osteoporotic rats, monkeys) (Li et al, 2009; Li et al, 2007a; Li et al, 2007b; Ominsky et al, 2010a; Ominsky et al, 2010b).

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 markers P1NP, OC, and BSAP, and a decrease in the bone resorption marker sCTX. Increases in BMD at the lumbar spine, total hip and femoral neck have also been demonstrated, by DXA and QCT.

Additional clinical studies have been completed or are currently ongoing:

- A phase 1b ALN-to-romosozumab transition study in postmenopausal women with low bone mass who had been receiving ALN or were treatment naïve
- A phase 1b multiple-dose study using peripheral QCT to evaluate the effect of romosozumab on parameters of bone quality of the forearm in postmenopausal women with low bone mass
- A phase 1 single-dose study in healthy postmenopausal Japanese women
- A phase 2a multiple-dose fracture-healing study in subjects with tibial diaphyseal fractures
- A phase 2 multiple-dose fracture-healing study in subjects with proximal femur fractures

As of 19 April 2011, 417 subjects treated with romosozumab have been tested for anti-romosozumab antibodies. Of these, approximately 20% developed binding antibodies and approximately 5% developed neutralizing antibodies. There were no clinically relevant adverse events associated with binding or neutralizing antibodies.

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

2.3 Justification for Romosozumab Treatment Duration and Dosing Regimen

A 12-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 12 months of romosozumab administration in the phase 2 dose-ranging study. At 12 months, the 210 mg every month (QM) dosing regimen resulted in a BMD increase from baseline of 11.3% at the lumbar spine and 4.1% at the total hip.
- Increases in bone formation as assessed with bone formation markers were not apparent beyond 12 months in the phase 2 dose-ranging study. For the romosozumab 210 mg QM dosing regimen, the median P1NP was 10.2% below baseline 1 week after the Month 12 dose; in contrast to an increase of 82.7% above baseline 1 week after the Day 1 dose. Similarly, median BSAP for the romosozumab 210 mg QM dosing regimen was only 4.0% above baseline at 1 week after the Month 12 dose, compared with 17.9% above baseline 1 week after the Day 1 dose. Median sCTX was 26.3% below baseline at Month 12.
- Based on Month 18 data available for the 210 mg QM treatment group in the phase 2 dose-ranging study, beyond Month 12 the BMD appeared to increase more gradually, likely primarily due to the antiresorptive effect.
- The results of the modeling using a mechanism-based PK/pharmacodynamic (PD) model indicated that the most significant BMD increases occur during the first 12 months of romosozumab treatment.

Thus, the intervention with romosozumab will be limited to 12 consecutive months, and it is essential to administer a dosing regimen that will achieve maximal effect within this 12-month treatment duration.

The 210 mg romosozumab QM dosing regimen was selected based on the following data:

- In the phase 2 dose-ranging study, the 210 mg QM romosozumab dosing regimen resulted in a greater increase in BMD at the lumbar spine and total hip at 12 months compared with other romosozumab dosing groups. Compared with the 140 mg QM romosozumab dosing regimen, the 210 mg QM romosozumab dosing regimen resulted in greater gains in lumbar spine BMD (11.3% vs. 9.3% change from baseline) and total hip BMD (4.1% vs. 3.5% change from baseline). The 210 mg QM dosing regimen also exhibited a greater increase in BMD at the lumbar spine, total hip, and femoral neck compared with the open label active comparators ALN and teriparatide.
- The romosozumab 210 mg QM dosing regimen resulted in the largest and most prolonged increase in markers of bone formation, including BSAP, P1NP, and OC in the phase 2 dose-ranging study. Median P1NP and OC levels remained above baseline up to Months 6 and 9, respectively, and median BSAP levels remained above baseline up to Month 12. In comparison, the 140 mg QM dosing regimen increased markers of bone formation for 3 to 6 months.

- In subjects previously treated with ALN, a 3 mg/kg dose (equivalent to a 210 mg fixed dose) in the phase 1b ALN transition study, suggests greater increases in BMD and bone formation markers than in subjects previously treated with ALN who transitioned to 140 mg QM in the phase 2 dose-ranging study.
- The incidence of adverse events in the phase 2 dose-ranging study was not dose-related, and the incidence of neutralizing antibodies against romosozumab was low (2%) and similar across QM doses. Thus, the safety profile of the 210 mg QM dosing regimen does not appear to be appreciably different from that of lower doses.

In addition to the above considerations of the clinical data, PK/PD modeling and simulations support the choice of the 210 mg QM dosing regimen. Conclusions from the modeling are as follows:

- There is a robust relationship between PK exposure and BMD gains at the lumbar spine; the 210 mg QM dosing regimen is not in the plateau region of the exposure-response curve
- Romosozumab 210 mg QM will result in greater BMD gains at both lumbar spine and total hip compared with 140 mg QM
- Romosozumab 210 mg QM will result in greater increases in P1NP as compared with 140 mg QM
- The rate of BMD increase is greatest during the first 12 months of romosozumab treatment

Based on the above evidence, romosozumab treatments that provide greater systemic exposure are expected to result in greater bone formation response and, consequently, larger BMD gains.

In summary, the proposed treatment regimen of 210 mg romosozumab QM for 12 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 ALN 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 Alendronate Background

Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. ALN (Fosamax®), a bisphosphonate that acts as an inhibitor of osteoclast mediated bone resorption, is indicated for the prevention and treatment of osteoporosis in postmenopausal women. Two trials of three-year duration demonstrated

significant increases in BMD at the lumbar spine, femoral neck and hip trochanter in response to ALN therapy.

Results of those trials and those of the Fracture Intervention Trial three- and four-year studies demonstrated significant reductions in the incidence of one or more new vertebral fractures in women with or without prevalent vertebral fractures at baseline, and incidence of hip fractures, and in the incidence of nonvertebral fractures compared with placebo (Black et al, 1996; Cummings et al, 1998; Fosamax® product insert).

The Fracture Intervention Trial consisted of two placebo-controlled studies in postmenopausal women: a 3-year study of patients with at least one baseline radiographic vertebral fracture and a 4-year study of patients with low bone mass but without a baseline vertebral fracture (Black et al, 1996; Cummings et al, 1998). The 3-year study (in patients with at least one baseline radiographic vertebral fracture) demonstrated that treatment with ALN resulted in statistically significant reductions in fracture incidence compared with placebo. The incidence of at least one new vertebral fracture was decreased from 15.0% to 8.0% (47% RRR). In the 4-year study (in patients with low bone mass but without a baseline vertebral fracture) the incidence of at least one new vertebral fracture was reduced from 3.8% to 2.1% (44% RRR).

Additional information is provided in the ALN package insert.

2.5 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 US Institutes of Medicine for women over the age of 50 years on a western diet is 1,200 mg and 2,000 mg per day respectively. The recommended dietary allowance and tolerable upper intake level of dietary vitamin D for women aged 51-70 years is 600 IU and 4,000 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

4,000 IU per day respectively (IOM 2010; Ross et al, 2011). 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 (administered within 1 week of the study day 1 visit) 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 clinical trials in osteoporosis and are consistent with existing treatment practice and guidelines (Dawson-Hughes et al, 2010, IOM 2010).

2.6 Rationale

This will be a multicenter, international, randomized, double-blind, alendronate-controlled study of romosozumab in postmenopausal women with osteoporosis who have had a previous osteoporotic fracture and now require therapy for secondary prevention.

Choice of control group

Alendronate was chosen as a control because it permits assessment of effects of romosozumab on fracture risk reduction in postmenopausal women with osteoporosis compared with the effects of a commonly used therapy for osteoporosis. Alendronate has shown to be effective in reducing vertebral fractures and its safety profile is well characterized (Black et al, 1996; Cummings et al, 1998; Fosamax® product insert).

However, in postmenopausal women with osteoporosis, fracture risk remains elevated despite continued treatment with alendronate (Black et al, 2006; Schwartz et al, 2010). Therefore an alendronate-controlled trial will provide a relevant comparison with a commonly used therapy for postmenopausal women with osteoporosis.

Endpoints

Primary, secondary, and safety endpoints have been selected to describe the efficacy in fracture risk reduction, and the safety profile of romosozumab. The primary endpoint of subject incidence of clinical fracture captures established markers of efficacy for the treatment of osteoporosis: nonvertebral fractures and clinical vertebral fractures. Nonvertebral fractures and clinical vertebral fractures account for the bulk of significant morbidity and mortality related to osteoporosis. A decrease in the subject incidence of clinical fracture will therefore represent an improvement in the clinical burden from

osteoporosis. The primary endpoint of subject incidence of new vertebral fracture represents an established endpoint for registration of new osteoporosis therapies.

The proposed safety endpoints will permit evaluation of the risk/benefit profile of romosozumab compared to alendronate in postmenopausal women with osteoporosis through the assessment of reported adverse and serious adverse events, vital signs, laboratory data and formation of anti-romosozumab antibodies.

Inclusion criteria

This study will enroll postmenopausal women with osteoporosis who meet at least one of the following BMD and fracture criteria:

- BMD T-score ≤ -2.50 at the total hip or femoral neck and either at least one moderate (SQ2) or severe (SQ3) vertebral fracture or at least 2 mild (SQ1) vertebral fractures

or

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

The risk of fracture in this study population is high, and the subjects are likely to derive significant benefit from a bone forming agent in clinical practice.

Exclusion criteria

Since all patients in the study will receive active treatment (either romosozumab or ALN), there is no lower threshold of BMD T-score as an exclusion criterion, nor is there an exclusion criterion based on higher numbers or severity of prevalent fractures.

The exclusion criteria for disease state, medical and medication history were chosen to minimize the possibility of influencing or confounding the results of the comparative assessment of efficacy and safety of two treatments administered in the study. In addition, subjects who have a contraindication to alendronate or unable to take alendronate oral tablets in accordance with the package insert are to be excluded.

ALN study period

Clinical experience with anabolic agents such as teriparatide and PTH (1-84) strongly support the strategy of consolidating gains from anabolic therapy in new bone matrix that is either mineralized or in the process of being mineralized with a subsequent period of anti-resorptive therapy (Black et al, 2005; Prince et al, 2005). The sequential therapy with ALN following romosozumab treatment for 12 months is justified by the

anti-resorptive mechanism of action of ALN and the established clinical paradigms currently in use with anabolic agents (Black et al, 2005; Rittmaster et al, 2000; National Osteoporosis Foundation 2010).

Final analysis

The study will continue beyond the time of primary analysis to allow following of subjects for the secondary endpoint of nonvertebral fractures.

2.7 Clinical Hypotheses

The primary clinical hypotheses are that romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone is effective in reducing the incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) and new vertebral fracture in postmenopausal women with osteoporosis. It is expected that romosozumab treatment for 12 months followed by ALN treatment will reduce the incidence of clinical fractures by 30% and the incidence of new vertebral fractures by 50% compared with the control group (ALN alone).

The primary safety hypothesis is that romosozumab treatment for 12 months is well tolerated in postmenopausal women with osteoporosis.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3 multicenter, international, randomized, double-blind, ALN-controlled study of romosozumab in postmenopausal women with osteoporosis. The study is designed to evaluate if romosozumab treatment for 12 months followed by ALN treatment, compared with ALN treatment alone, is effective in reducing the incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) and new vertebral fracture.

After signing the informed consent form (ICF), subjects will undergo a screening phase to complete eligibility assessments. Upon confirmation of eligibility, approximately 4,000 subjects will be randomized 1:1 (approximately 2,000 subjects per arm) to receive either 210 mg romosozumab subcutaneous (SC) QM or 70 mg ALN orally (PO) every week (QW) in a blinded fashion for the duration of the 12–month double-blind ALN-controlled study period. Randomization will be stratified by age (< 75 years, ≥ 75 years). Subjects will also receive matched placebo for either ALN or romosozumab. After the initial 12-month study period, subjects will receive ALN while

remaining blinded to their initial treatment assignment (romosozumab or ALN). The primary analysis period will end and the primary analysis will be performed when:

- clinical fracture events (nonvertebral fracture or clinical vertebral fracture) have been confirmed for at least 330 subjects
  AND
- all subjects have had the opportunity to complete the Month 24 study visit.

If more than 330 subjects have confirmed clinical fractures at the time each subject has completed her Month 24 visit, the primary analysis will be based on all available data, which may include more than 330 events.

Upon completion of the primary analysis period, subjects will continue to be followed for the secondary endpoint of nonvertebral fractures. Subjects and site personnel will remain blinded to initial treatment assignments. The study will proceed in an event-driven manner. The final analysis (end of study) will be performed when nonvertebral fracture events have been confirmed for at least 440 subjects across the lifetime of the study. The study may be terminated earlier if the primary analysis demonstrates superiority of romosozumab treatment for nonvertebral fracture risk reduction (see Section 10.2 for details on testing strategy). Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture.

From screening to end of study, subjects will receive daily calcium and vitamin D supplementation that at a minimum should be 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 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.

Approximately 200 subjects at participating centers will be enrolled in an Imaging and PK/BTM/Biomarker sub-study. Within this sub-study, a subset of approximately 100 subjects will participate in the imaging (DXA, QCT) portion of the sub-study.

If there is insufficient enrollment into the blood only portion of the sub-study, additional sub-study sites will be initiated. Subjects already on trial will be invited to participate and consent will be obtained for the use of blood samples from earlier time points for sub-study analyses.

From study start until primary analysis, an external, independent Data Monitoring Committee (DMC) will monitor unblinded safety data on an ongoing basis and consider efficacy data in order to assess the risk/benefit profile of romosozumab.

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

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

Approximately 325 centers in North America, Europe, Central and South America and Asia/Pacific will participate in this trial. Additional regions, countries and/or centers may be added.

Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Approximately 4,000 subjects will be enrolled (approximately 2,000 per arm). An expected annual dropout rate of 10% in the first year and 8% thereafter has been taken into account when determining the sample size (refer to Section 10.2).

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

Study duration is event-driven, ie, the end of study visits will occur when nonvertebral fracture events have been confirmed by the central imaging vendor for at least 440 subjects, unless the primary analysis demonstrates superiority of romosozumab treatment for nonvertebral fracture risk reduction (see Section 10.2 for details on testing strategy). Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture. Enrollment is expected to take approximately 34 months; however, recruitment is competitive and will stop after approximately 4,000 subjects are enrolled.

The estimated study duration for an individual subject, including the screening period, is 25 to 59 months (if study completion is achieved at primary analysis) or 37 to 71 months (if study completion is achieved when at least 440 subjects have experienced a nonvertebral fracture), based on projected enrollment and estimated fracture rate**s**.

However, actual study duration for individual subjects may be longer, depending on actual enrollment and observed fracture rate**s.**

3.4.2 End of Study

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, when clinical fracture events (nonvertebral fracture or clinical vertebral fracture) have been confirmed by the central imaging vendor for at least 330 subjects and all subjects have had the opportunity to complete the Month 24 study visit**.**

End of Trial (end of study): The time when the last subject is assessed or receives an intervention for evaluation in the study. The end of trial will be when nonvertebral fracture events have been confirmed for at least 440 subjects across the lifetime of the study, unless the primary analysis demonstrates superiority of romosozumab treatment for nonvertebral fracture risk reduction (see Section 10.2 for details on testing strategy). Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture.

Early termination (ET) subjects who test positive for neutralizing antibodies to romosozumab at the ET study visit will be asked to return for additional follow-up testing as described in Section 7.8.4.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, demographic information, eligibility). Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 Ambulatory postmenopausal women, age ≥ 55 to ≤ 90 years at randomization. Postmenopausal status is defined as no vaginal bleeding or spotting for 12 consecutive months prior to screening.

4.1.2 Subject meets at least one of the following BMD and fracture criteria

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

or

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

BMD T-scores at the time of screening will be assessed by the central imaging vendor based on DXA scans and using data for Caucasian women from the National Health and Nutritional Examination Survey (NHANES) 1998.

Vertebral fractures at the time of screening will be assessed by the central imaging vendor based on lateral spine x-rays.

History of proximal femur fracture will be assessed by the principal investigator based on discharge summary, radiology report, or comparable documentation of type and date of fracture.

4.1.3 At least one hip is evaluable by DXA, as assessed by the principal investigator

4.1.4 Subject has provided informed consent

4.2 Exclusion Criteria

Use of the following agents affecting bone metabolism (4.2.1 through 4.2.9)

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

4.2.2 Intravenous (IV) bisphosphonates

- Zoledronic acid:
  - any dose received within 3 years prior to randomization
  - more than 1 dose received within 5 years prior to randomization
- IV ibandronate or IV pamidronate:
  - any dose received within 12 months prior to randomization
  - more than 3 years of cumulative use, unless last dose received ≥ 5 years prior to randomization

4.2.3 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

4.2.4 Denosumab or any cathepsin K inhibitor, such as odanacatib (MK-0822): any dose received within 18 months prior to randomization

4.2.5 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

4.2.6 Systemic oral or transdermal estrogen or SERMs: more than 1 month of cumulative use within 6 months prior to randomization

4.2.7 Hormonal ablation therapy: more than 1 month of cumulative use within 6 months prior to randomization

4.2.8 Tibolone, cinacalcet, or calcitonin: any dose received within 3 months prior to randomization

4.2.9 Systemic glucocorticosteroids: ≥ 5 mg prednisone equivalent per day for more than 14 days within 3 months prior to randomization

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

4.2.11 History of solid organ or bone marrow transplants

4.2.12 25 (OH) vitamin D levels < 20 ng/mL**,** as assessed by the central laboratory. Vitamin D repletion will be permitted and subjects may be rescreened once (refer to Section 7.2.2).

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

4.2.14 Current, uncontrolled hyper- or hypothyroidism, per subject report or chart review. Uncontrolled hyperthyroidism is defined as thyroid-stimulating hormone (TSH) and T4 outside the normal range. Uncontrolled hypothyroidism is defined as TSH > 10

4.2.15 Current, uncontrolled hyperparathyroidism or history of hypoparathyroidism, per subject report or chart review. Uncontrolled hyperparathyroidism is defined as: PTH outside the normal range in subjects with concurrent hypercalcemia; or PTH values > 20% above the ULN in normocalcemic subjects

4.2.16 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 prior to signing consent will be acceptable)

4.2.17 Exclusion criteria related to contraindications or possible signs of intolerance to ALN; contraindications and potential signs of intolerance for ALN therapy include:

- Hypocalcemia (as defined in 4.2.13)
- Abnormalities of the esophagus, which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to ALN or other constituents of ALN tablets

- Pregnancy and lactation
- Other contraindications to ALN based on the country-specific product insert applicable to the specific study center
- Significantly impaired renal function (as assessed by the central laboratory based on a derived creatinine clearance of < 35 mL/min using the Modification of Diet in Renal Disease equation [Levey et al, 2006]). The estimated glomerular filtration rate is calculated as follows: estimated glomerular filtration rate (mL/min/1.73m^2) = 175 x [Serum creatinine (mg/dL)]$^{-1.154}$ x [Age]$^{-0.203}$ x [0.742 if subject is female] x [1.212 if subject is black].

General exclusion criteria (4.2.18 through 4.2.28)

4.2.18 Subject is currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)

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

4.2.20 Other investigational procedures are excluded

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

4.2.22 Subject has known sensitivity to any of the products or components to be administered (calcium supplements, vitamin D products, or mammalian cell derived products)

4.2.23 Subject is pregnant or is planning to become pregnant within 3 months after the last dose of investigational product (IP)

4.2.24 Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

4.2.25 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures

4.2.26 Subject is known to have human immunodeficiency virus, hepatitis C virus, or hepatitis B infection

4.2.27 Subject has any condition or illness (acute, chronic, or history), which in the opinion of the Investigator might interfere with the evaluation of the safety of the study product or may otherwise compromise the safety of the subject

4.2.28 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)

4.3 Inclusion Criteria for the Imaging and PK/BTM/Biomarker Sub-study

- Subject is enrolled at a center participating in this sub-study
- Subject has provided informed consent for participation in this sub-study

4.4 Exclusion Criteria for the Imaging and PK/BTM/Biomarker Sub-study

- For subjects participating in the imaging components:
  - Subject has non-evaluable vertebrae in the region of interest for spine QCT scans as assessed by the central imaging vendor at the time of screening, based on lateral spine x-rays
- For all sub-study subjects:
  - Subject has experienced a nonvertebral fracture or clinical vertebral fracture within 6 months prior to enrollment
  - Subject will not be available for protocol-required sub-study procedures, to the best of the subject and investigator's knowledge

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, ICF, and all other subject information and/or recruitment material, as applicable (see Section 11.2). All subjects must personally sign and date the IRB/IEC and Amgen approved ICF before commencement of protocol-specified screening procedures.

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a unique subject identification number from the Interactive Voice Response System (IVRS) before any study procedures are performed. 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. Partial rescreening is permitted for failure to meet the vitamin D entry criteria (refer to Section 7.2.2 for details). Subjects who fail screening for any other reason may enter full rescreening as defined in Section 7.2.3.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or randomization. This number will not be the same as the randomization number assigned to the subject.

PPD

Once all screening procedures have been performed and the subject has been determined to meet all eligibility criteria, the subject will be randomized as described in Section 5.1 to determine their treatment assignment. Treatment assignments are obtained through the IVRS. A subject is considered enrolled upon randomization and treatment assignment. Screen failures are to be entered into the IVRS promptly.

5.1 Randomization

Subjects will be randomized 1:1 in a double-blind manner to either the romosozumab or the ALN treatment group, based on a randomization schedule prepared by the Amgen Central Randomization Group before the start of the study. A subject may only be randomized once, and each randomization number may only be assigned once.

Randomization will be stratified by age (< 75 years, ≥ 75 years). There will be no stratification by or within clinical center.

Every attempt should be made for subjects to receive their first injection of IP on the day of randomization. If this is not possible, subjects must receive the first injection of IP within 72 hours of randomization. Similarly, oral IP must be dispensed within 72 hours of randomization and must be taken within one week of study Day 1.

A subject will be considered enrolled once a randomization number is assigned by the IVRS. It is therefore very important to place the randomization call only after the subject's eligibility and willingness to participate has been confirmed, as the subject cannot be 'unenrolled'.

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. Unblinding at the study site for any other reason will be considered a protocol deviation. 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.

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

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

6. TREATMENT PROCEDURES

Romosozumab, ALN and the respective matched placebo are considered IP in this study. Refer to Section 6.1 and Section 6.2 for details regarding IP and its dosage and administration. Vitamin D and elemental calcium are protocol-required non-investigational therapies. Refer to Section 6.3 for details regarding their dosage and administration.

Refer to the IPIM for further detailed information regarding storage, preparation, and administration of the IP and brief information about the protocol-required non-investigational therapies.

6.1 Romosozumab and Matched Placebo

Romosozumab and matched placebo will be manufactured and packaged by Amgen Inc and distributed using Amgen clinical study drug distribution procedures. Romosozumab will be presented in a single-use 1 mL prefilled syringe (PFS) as a sterile, clear, colorless, and preservative-free liquid containing 70 mg of romosozumab per mL in CCI acetate and CCI calcium, containing CCI sucrose and CCI polysorbate 20 at pH CC. Placebo to romosozumab will be presented in identical containers and stored/packaged the same as romosozumab.

6.1.1 Romosozumab/Placebo Dosage, Administration, and Schedule

During the 12-month double-blind ALN-controlled study period, subjects will receive 3 SC injections of romosozumab (ie, 3 injections of 70 mg romosozumab for a total dose of 210 mg) or matched placebo at each IP dosing visit (ie, Day 1 study visit and monthly study visits thereafter to Month 11). 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. 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 investigational product (IP).

The first dose of romosozumab/placebo 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. Neither the effects of overdose of romosozumab nor an antidote to overdose are known. The maximum amount of romosozumab that can be safely administered in a single dose has not been determined, and there is currently insufficient information to draw any conclusions about the safety of doses higher than those studied in clinical trials. The highest single dose of romosozumab tested in clinical trials is 10 mg/kg SC. Subjects who have received higher than protocol-defined doses should be carefully monitored for adverse events.

6.1.2 Romosozumab/Placebo Dosage Adjustments

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 ± 2 weeks of the target visit date, ie, calculated from the Day 1 visit as described in Section 7.1.1. If romosozumab/placebo cannot be administered ± 2 weeks of the target visit date, the dose has to be considered missed.

6.1.3 Guidance on Hepatotoxicity Stopping and Rechallenge Rules for Romosozumab/Placebo

A US Food and Drug Administration (FDA) Guidance exists for drug-induced liver injury (DILI) (Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009). This guidance is general for all investigational products, and its recommendations can be found in Appendix B. It provides criteria for withholding romosozumab/placebo in the event that a subject develops signs or symptoms of hepatitis during a clinical trial. These guidelines provided in Appendix B apply to all centers in all regions.

6.2 ALN / Matched Placebo and Open-label ALN

ALN and matched placebo will also be used in this study and will be considered non-Amgen investigational products.

Blinded ALN will be manufactured by Merck & Co Inc., packaged by Patheon Inc., and labeled and distributed using Amgen clinical study drug distribution procedures. Blinded ALN will be presented as a blister pack containing 10 tablets.

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

Open-label ALN will be manufactured and packaged by Merck & Co Inc., and labeled and distributed using Amgen clinical study drug distribution procedures. Open-label ALN will be presented as a blister pack containing 4 tablets.

Additional detail regarding these IPs is provided in the IPIM.

6.2.1 ALN/Placebo and ALN Dosage, Administration, and Schedule

During the 12-month double-blind ALN-controlled study period, subjects will be dispensed a 2-month supply (ie, 1 blister pack containing 10 tablets) of ALN or matched placebo at the Day 1, Month 2, Month 4, Month 6, Month 8, and Month 10 visits. One 70 mg tablet will be taken orally once a week and will be self-administered by the subjects. At the Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12 visits, subjects will be asked to bring in all used and unused packages to facilitate collection of unused ALN/placebo and assessment of compliance. The investigational site staff will count the number of returned tablets and capture this information on drug accountability forms and in the electronic case report form (eCRF).

The first 2-month supply of ALN/placebo should be dispensed on the day of randomization. If this is not possible, it must be dispensed within 72 hours of randomization. The first dose of ALN/placebo must be taken within one week of study Day 1.

Following the 12-month double-blind ALN-controlled study period, subjects will be dispensed a 6-month supply (ie, 7 blister packs with 4 tablets each of open-label ALN) at the Month 12 study visit and every 6 months thereafter. One 70 mg tablet will be taken orally once a week and will be self-administered by the subjects. At the Month 18 study visit and every six months thereafter until the end of study, subjects will be asked to bring in all used and unused packages to facilitate collection of unused ALN and assessment of compliance. The investigational site staff will count the number of returned tablets and capture this information on drug accountability forms and in the eCRF. During the end of primary analysis period phone call and the end of study phone

call, subjects will be asked to verbally document their ALN compliance since the last study visit.

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

Unused alendronate at the time of end of study should be returned to the sites (Please refer to study IPIM for details).

ALN is a marketed product. For further information, including information on treatment of overdose, the package insert should be referenced.

6.2.2 Dosage Adjustments

No dosing adjustments for ALN/placebo or ALN will be permitted.

If a subject misses a scheduled dose of the oral investigational product, the dose should be taken as soon as possible as long as it is before the next scheduled dose, and should be resumed at the same dose (70 mg once weekly). Double or extra doses should not be taken.

6.3 Other Protocol-required Therapies

All other protocol-required drugs (ie, vitamin D and calcium supplements) that are commercially available are not provided by Amgen except under special circumstances (eg, if required by local regulation or due to availability issues). The investigator will be responsible for obtaining supplies of these drugs. Sites will be reimbursed for both calcium and vitamin D supplements.

From screening to end of study, subjects will receive daily calcium and vitamin D supplementation that at a minimum should be 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. The initial vitamin D loading dose is to be administered within 1 week of the study day 1 visit. However, if the vitamin D loading dose is missed in this timeframe, it should be given as soon as possible thereafter.

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

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

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

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

Additional details regarding calcium and vitamin D supplements are provided in the IPIM.

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 6.5.

6.5 Excluded Treatments During Study Period

Medications listed below will be proscribed during the study, **including the use of other investigational products and** medications known or suspected to affect bone metabolism:

- Strontium (including strontium ranelate and over-the-counter strontium preparations)
- Fluoride (for treatment of osteoporosis)
- Vitamin K and vitamin K analogs (for treatment of osteoporosis)
- Activated vitamin D (1,25-di(OH) vitamin D or 1-(OH) vitamin D)
- IV bisphosphonates
- Oral bisphosphonates, except ALN as study medication (cumulative dosing regimens of $\leq$ 1 month are acceptable)
- Denosumab
- Teriparatide or any PTH analogs
- Systemic oral or transdermal estrogen (cumulative dosing regimens of $\leq$ 1 month are acceptable, vaginal preparations and estrogen creams will be allowed at any time)
- SERMs (cumulative dosing regimens of $\leq$ 1 month are acceptable)
- Calcitonin (cumulative dosing regimens of $\leq$ 1 month are acceptable)
- Tibolone (cumulative dosing regimens of $\leq$ 1 month are acceptable)
- Cinacalcet

- Prolonged (ie, > 3 months) oral glucocorticoid therapy at a prednisone equivalent dose of ≥ 5.0 mg/day (tapering glucocorticoid courses of < 1 month duration are permitted regardless of dose; inhaled or topical glucocorticoids are permitted)
- Hormonal ablation therapy

If a subject receives any IV bisphosphonate therapy or oral bisphosphonate therapy equivalent to > 1 month of therapy (except ALN as study medication) while being on-study, IP (ie, romosozumab/placebo, blinded ALN/placebo, or open-label ALN) must be discontinued. However, every effort should be made to have the subject continue participation in the study and complete all scheduled assessments.

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

7.1 General Study Procedures

Study assessments and procedures will be performed only after written informed consent is obtained.

During the primary analysis period, PRO/ClinRO questionnaires should preferably be completed before any other study procedure is performed. During the 12-month double-blind ALN-controlled study period, at visits where a nonvertebral or suspected clinical vertebral fracture is reported, the postfracture PRO/ClinRO assessments should be completed immediately after the nonvertebral fracture or suspected clinical vertebral fracture is reported by the subject. During the 3 subsequent monthly study visits, up to the Month 12 study visit, the postfracture PRO/ClinRO assessments should preferably be completed before any other study procedure is performed.

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

Any other procedures that must be performed in a specific order are clearly indicated in Section 7.3.

7.1.1 Study Visit Definitions

The screening date is defined as the date the ICF is signed. The enrollment date is defined as the date of randomization. Randomization must be completed within 35 days of the screening date, or if the subject is rescreened per Section 7.2.2 or Section 7.2.3, within 35 days of the rescreening date.

Day 1 is defined as the day the first dose of romosozumab/placebo is administered. All on-study (post Day 1) visits are to be 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.

7.1.2 Study Windows

Study visit windows differ based on the type of visit and are clearly identified in the description of study visits in Section 7.3. All monthly study visits during the 12-month double-blind ALN-controlled study period have a ± 7-day window (see Section 6.1.2 for romosozumab/placebo dosing window). Following the 12-month double-blind ALN-controlled study period, study visits have a ± 14-day window. The window for the monthly phone contact in between clinic visits throughout the study **is ± 7 days**. **T**he **window for the** end of primary analysis period phone call is **−14** days **to end of primary analysis**. Unscheduled follow-up clinic visits after the monthly phone contact have a + 21-day window. The window for the end of study phone contact is **−14 days to** + 7 days.

Study procedures for a specific visit may be completed on multiple days as long as all the procedures are completed within the visit window.

7.2 Screening and Rescreening

7.2.1 Screening

The screening period begins on the date that the ICF is signed. Screening procedures may be performed on multiple days but must be completed within a 35-day screening window. From start of screening through randomization, all subjects are required to take daily calcium and vitamin D supplementation that at a minimum should be in the range of 500 to 1,000 mg elemental calcium and 600 to 800 IU vitamin D. The screening procedures are:

- Informed consent
- Medical and medication history (including clinical fracture history, and bone-specific medications)
- Assessment of and instructions for daily calcium and vitamin D supplementation
- Physical examination
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood samples for serum chemistry, hematology, and 25 (OH) vitamin D

- Blood sample for serum protein electrophoresis to assess possible diagnosis of multiple myeloma or related lymphoproliferative disorder, performed by the local laboratory (electrophoresis results within 6 months prior to signing consent will be acceptable)
- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit

  Note: To have vertebrae previously treated with vertebroplasty or kyphoplasty included in the eligibility assessment, lateral spine x-rays obtained prior to the procedure must be submitted to the central imaging vendor. The central imaging vendor will use these x-rays to document the presence and severity of the vertebral fracture before vertebroplasty or kyphoplasty. In addition, current lateral spine x-rays, taken after the vertebroplasty or kyphoplasty procedure, must be obtained, either during the screening period or within 35 days prior to the beginning of the screening period as outlined below.
- DXA scan of the proximal femur, submitted to the central imaging vendor as soon as possible following the visit

  Note: To facilitate subject scheduling, the Day 1/baseline lumbar spine DXA scan may be taken with the proximal femur DXA scan performed during screening.

  Note: For screening and Day 1 purposes, lateral spine x-rays and 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:

  a. Images were obtained as part of the routine standard of care, for the purposes of another clinical research study following appropriate informed consent procedures, or as part of community outreach efforts
  b. 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)
  c. DXA images were obtained using the same DXA scanner that will be used for this study
- Serious adverse event reporting

During the screening period, serum calcium levels may be retested once in case of an elevated serum calcium level within 1.1x ULN as assessed by the central laboratory (refer to exclusion criterion 4.2.13). To enroll subjects after retesting of serum calcium levels, an eligible serum calcium level must be confirmed by the central laboratory, and the subject must be randomized within the 35-day screening window.

7.2.2 Partial Rescreening for low Vitamin D

Partial rescreening will be allowed only for subjects who fail to meet the serum 25 (OH) vitamin D criterion. Subjects who fail for any other reason may enter full rescreening as defined in Section 7.2.3.

Informed consent obtained at the beginning of the screening period also covers the partial rescreening for low vitamin D; therefore reconsenting is not required.

Subjects with a serum 25 (OH) vitamin D level < 20 ng/mL may be rescreened according to the following procedure:

- Subject will be logged as a screen failure into the IVRS and immediately entered as a rescreen. Subjects not entered into IVRS as a rescreen will not be eligible for randomization.
- The 35-day rescreening period will commence at this time.
- Subject must be repleted for vitamin D, as confirmed by a serum 25 (OH) vitamin D level ≥ 20 ng/mL assessed by the central laboratory.
- Subject must be randomized within the new 35-day screening window.
- Subject may enter partial rescreening for low vitamin D only once after screening (Section 7.2.1) and only once after full rescreening (Section 7.2.3, if applicable).

During partial rescreening for low vitamin D, blood samples for assessment of serum 25 (OH) vitamin D may be sent to the central laboratory more than once. To enroll subjects after partial rescreening for low vitamin D, an eligible vitamin D level must be confirmed by the central laboratory, and the subject must be randomized within the 35-day rescreening window.

Initial screening assessments performed during the screening period (eg, lateral spine x-rays, DXA scans, or physical examination) may be used for subjects who have been rescreened for low vitamin D, and those assessments do not need to be repeated. However, any lateral spine x-rays obtained prior to the beginning of the screening period (see Section 7.2.1) must be repeated and submitted to the central imaging vendor as soon as possible after rescreening commences.

7.2.3 Full Rescreening

Full rescreening will be allowed for any subject who has previously failed screening if in the opinion of the investigator the reason for the initial screen failure has been resolved or is not applicable anymore. The 35-day rescreening period begins on the date that the ICF is signed. Full rescreening will be performed according to the following procedure:

- Subject informed consent must be obtained.
- Subject will be entered into the IVRS as a full rescreen with the same subject identification number as assigned during the initial screening. Subjects not entered into IVRS as a full rescreen will not be eligible for randomization.
- Subject may only be entered into full rescreening once.

- During full rescreening, all screening procedures have to be performed as defined in Section 7.2.1.
- Subjects who fail to meet the serum 25 (OH) vitamin D criterion during the full rescreening may still enter the partial rescreening for low vitamin D as defined in Section 7.2.2.

7.3 Study Visits

7.3.1 Study Day 1/Baseline

For all subjects

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed)
- Blood sample for serum chemistry, hematology, and anti-romosozumab antibody
- DXA scans of lumbar spine, submitted to the central imaging vendor as soon as possible following the visit

Note: DXA scans of the lumbar spine may also be obtained during the screening period prior to Day 1 to facilitate subject scheduling.

- Adverse event and concomitant medications data collection
- If applicable, vitamin D loading dose of 50,000 to 60,000 IU, preferably by the oral route. The initial vitamin D loading dose is to be administered within 1 week of the study day 1 visit. However, if the vitamin D loading dose is missed in this timeframe, it should be given as soon as possible thereafter.
- Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)
- IP (romosozumab/placebo) injection (must be the last procedure)

Note: If the vitamin D loading dose is given by SC injection, vitamin D and IP should not be administered in the same anatomical location.

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Blood sample for romosozumab levels
- Fasting blood sample for P1NP, sCTX, BSAP, and OC
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development
- For subjects also participating in the imaging components: QCT of the spine, submitted to the central imaging vendor as soon as possible following the visit

7.3.2 Month 1 (± 7 Days)

For all subjects

- Vital signs: blood pressure, temperature, and pulse
- Blood sample for serum chemistry, hematology, and anti-romosozumab antibody
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at this study visit

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Blood sample for romosozumab levels
- Fasting blood sample for P1NP, sCTX, BSAP, and OC
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

7.3.3 Month 2 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)
- Unused oral IP (ALN/placebo) collection (blinded)
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 1 or Month 2 study visit

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.4 Month 3 (± 7 Days)

For all subjects

- Blood sample for serum chemistry, hematology, and anti-romosozumab antibody
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 1, 2, or 3 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Blood sample for romosozumab levels
- Fasting blood sample for P1NP, sCTX, BSAP, and OC
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

7.3.5 Month 4 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)
- Unused oral IP (ALN/placebo) collection (blinded)
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 1 to 4 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.6 Month 5 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 2 to 5 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.7 Month 6 (± 7 Days)

For all subjects

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed)
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry, hematology, and anti-romosozumab antibody
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)
- Unused oral IP (ALN/placebo) collection (blinded)
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Blood sample for romosozumab levels
- Fasting blood sample for P1NP, sCTX, BSAP, and OC
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development
- For subjects also participating in the imaging components:
  - QCT of the spine, submitted to the central imaging vendor as soon as possible following the visit
  - DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit

7.3.8 Month 7 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 4 to 7 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.9 Month 8 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)
- Unused oral IP (ALN/placebo) collection (blinded)
- IP (romosozumab /placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 5 to 8 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.10 Month 9 (± 7 Days)

For all subjects

- Blood sample for serum chemistry and hematology
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 6 to 9 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Blood sample for romosozumab levels
- Fasting blood sample for P1NP, sCTX, BSAP, and OC
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

7.3.11 Month 10 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)
- Unused oral IP (ALN/placebo) collection (blinded)
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 7 to 10 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.12 Month 11 (± 7 Days)

For all subjects

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- IP (romosozumab/placebo) injection (must be the last procedure)

For subjects who have reported nonvertebral or suspected clinical vertebral fractures at the Month 8 to 11 study visits

(PRO/ClinRO questionnaires should preferably be completed before any other study procedures are performed or immediately after a fracture is reported; refer to Section 7.12)

- Postfracture PRO/ClinRO assessments: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain

7.3.13 Month 12 (± 7 Days) / Early Termination for the 12-month Double-blind ALN-controlled Study Period

For all subjects

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed)
- Physical examination
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry, hematology, and anti-romosozumab antibody
- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit
- DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Unused oral IP (ALN/placebo) collection (blinded)
- ALN dispensation (open-label, 6-month supply)

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Blood sample for romosozumab levels
- Fasting blood sample for P1NP, sCTX, BSAP, and OC
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development
- For subjects also participating in the imaging components: QCT of the spine, submitted to the central imaging vendor as soon as possible following the visit

Note: If a subject terminates early from the study between the Day 1 and Month 12 visits, the Month 12 procedures except open-label ALN dispensation are to be completed at that time. DXA scans and lateral spine x-rays should be performed if at least 6 weeks have elapsed since the previous one.

7.3.14 Month 15 (± 14 Days) for Sub-study Subjects Only

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- Fasting blood sample for P1NP and sCTX
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

7.3.15 Month 18 (± 14 Days)

For all subjects

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed)
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry and hematology
- Blood sample for anti-romosozumab antibody
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- ALN dispensation (open-label, 6-month supply)
- Unused ALN collection (open-label)

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Fasting blood sample for P1NP and sCTX
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development
- For subjects participating in the imaging components: DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit

7.3.16 Month 24 (± 14 Days) / Early Termination for Month 12 to Month 24 of the Primary Analysis Period

For all subjects

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed)
- Physical examination
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry, hematology, and anti-romosozumab antibody
- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit
- DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit
- Nonvertebral and suspected clinical vertebral fracture reporting
- Adverse event and concomitant medications data collection
- ALN dispensation (open-label, 6-month supply)
- Unused ALN collection (open-label)

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study

- Fasting blood sample for P1NP and sCTX
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development
- For subjects participating in the imaging components: QCT of the spine, submitted to the central imaging vendor as soon as possible following the visit

Note: If a subject terminates early from the study between the Month 12 and Month 24 visits, Month 24 procedures except ALN dispensation are to be completed at that time. DXA scans and lateral spine x-rays should be performed if at least 6 weeks have elapsed since the previous one.

7.3.17 Month 30 (± 14 Days)

For all subjects

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed) (primary analysis period only)
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry and hematology (to be processed and sent to the central laboratory during the primary analysis period; to be analyzed at local laboratories following the primary analysis period, See Section 7.8.1)
- Nonvertebral fracture reporting
- Suspected clinical vertebral fracture reporting (primary analysis period only)
- Adverse event and concomitant medications data collection
- ALN dispensation (open-label, 6-month supply)
- Unused ALN collection (open-label)

7.3.18 Month 36 and Subsequent Clinic Visits (± 14 Days) to End of Primary Analysis Period

For all subjects, at Month 36 and every 6 months thereafter until the end of the primary analysis period

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed) (primary analysis period only)
- Physical examination
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry and hematology (to be processed and sent to the central laboratory during the primary analysis period)
- Nonvertebral fracture reporting

- Suspected clinical vertebral fracture reporting (primary analysis period only)
- Adverse event and concomitant medications data collection
- ALN dispensation (open-label, 6-month supply)
- Unused ALN collection (open-label)

For all subjects, at Month 36 and every 12 months thereafter **until the end of the primary analysis period**

- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit (primary analysis period only)
- DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit (primary analysis period only)

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study, at Month 36 **or** until end of the primary analysis period**, whichever comes first**

- Fasting blood sample for P1NP and sCTX
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

Note: If a subject terminates early from the study between the Month 24 and the end of the primary analysis period, the Month 36 procedures are to be completed at that time (except ALN dispensation). DXA scans and lateral spine x-rays should be performed if at least 6 weeks have elapsed since the previous one.

7.3.19 Clinical Visits After the Primary Analysis Period to End of Study

For all subjects, at every 6-month clinic visit thereafter

- **Physical examination**
- **Vital signs: blood pressure, temperature, and pulse**
- **Height and weight**
- **Blood sample for serum chemistry and hematology (to be analyzed at local laboratories following the primary analysis period, chloride, bicarbonate, and calculated adjusted calcium assessments are optional after primary analysis. (See Section 7.8.1)**
- **Nonvertebral fracture reporting**
- **Adverse event and concomitant medications data collection**
- **ALN dispensation (open-label, 6-month supply)**
- **Unused ALN collection (open-label)**

7.3.20 Monthly Telephone Contacts in Between Clinic Visits (± 7 Days) Until end of Study

For all subjects

- Nonvertebral fracture reporting
- Adverse event and concomitant medications data collection

Procedure for reporting of nonvertebral fractures during monthly telephone contacts:

When nonvertebral fractures are reported during the monthly telephone contacts, the same process as for nonvertebral fracture reporting at clinic visits should be followed. No unscheduled follow-up clinic visit or further unscheduled assessments will be required. The event should be recorded on the respective eCRF and copies of radiographs or other diagnostic images and/or a copy of the radiology report, surgical report, or discharge summary should be obtained, included in the subject's study records and submitted to the central imaging vendor.

For the primary analysis period only: Procedure for reporting of an adverse event of back pain during monthly telephone contacts:

When back pain is reported during the monthly telephone contacts, the back pain (but not a vertebral fracture) will be recorded as an adverse event, and the subject will be asked to complete an unscheduled follow-up clinic visit as soon as possible but no later than 21 days after reporting of the back pain (refer to Section 7.3.21).

Refer to Section 7.11.1 and Section 7.11.2 for general information about nonvertebral and suspected clinical vertebral fracture reporting procedures.

7.3.21 Unscheduled Follow-up Clinic Visit (+ 21 Days After Monthly Phone Contact) (Primary Analysis Period Only)

For subjects who have reported back pain as an adverse event during the monthly telephone contact:

- Suspected clinical vertebral fracture reporting

For subjects for whom the previously reported back pain is considered to be possibly due to a new or worsening vertebral fracture:

- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit

Procedure for reporting of suspected clinical vertebral fractures during the unscheduled follow-up clinic visit:

Unscheduled follow-up clinic visits will only be completed if back pain is reported during the monthly phone contact. The follow-up clinic visit has to be completed as soon as possible after the phone call but no later than 21 days after reporting of the back pain.

At the unscheduled follow-up clinic visit, the investigator will evaluate if the back pain is possibly due to a new or worsening vertebral fracture, and the respective eCRF will be completed. If the investigator considers the back pain to be possibly due to a new or worsening vertebral fracture, a confirmatory lateral spine x-ray will be taken and submitted to the central imaging vendor as soon as possible following the visit.

7.3.22 Telephone Contact at "End of Primary Analysis Period" (−14 Days to end of Primary Analysis Period)

For all subjects

- Nonvertebral fracture reporting
- Adverse event and concomitant medications data collection
- ALN compliance reporting (open-label)

The procedure for reporting of nonvertebral fractures during the end of primary analysis period telephone contact is the same as for the monthly telephone contacts (refer to Section 7.3.19).

If back pain is reported during the end of primary analysis period telephone contact, the back pain (but not a vertebral fracture) will be recorded as an adverse event. The subject will not be asked to complete an unscheduled follow-up clinic visit.

Note: If all the data required for an end of primary analysis telephone call has already been obtained during the 14 days prior to the end of the primary analysis period, no additional end of primary analysis period telephone call will be necessary.

7.3.23 End of Study Telephone Contact (−14 to + 7 Days)

For all subjects

- Adverse event and concomitant medications data collection
- ALN compliance reporting (open-label)

Note: The end of study telephone contact will not be necessary for subjects who have had a clinic visit or have been contacted during this timeframe if all data required for the end of study telephone contact have been collected. The subjects, however, may be contacted after this time for additional safety information, follow-up, or possible follow on study opportunities.

If a nonvertebral fracture is reported during the end of study telephone contact, the fracture will be recorded as an adverse event. Copies of the radiographs, diagnostic images and/or radiology report, surgical report, clinical notes, or discharge summary need not be obtained.

7.4 Medical History

The subject's complete medical history will be obtained prior to enrollment and recorded in the eCRF. History of fractures after the age of 45 will also be obtained, and will include date of fracture, anatomical site(s) of fracture(s), and degree of trauma involved.

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

7.5 Medication History

Information on all medications administered within the month before study Day 1 will be recorded in the eCRF. For all bone-specific medications, information on administration during the 5 years prior to screening will be recorded.

7.6 Physical Examination

The physical examination will include height (using a stadiometer, to be measured without shoes) and weight. A pelvic, breast, or rectal examination will not be required for the screening or on-study physical examinations unless specific evaluation is deemed necessary by the principal investigator.

7.7 Vital Signs

Vital signs will include temperature, blood pressure, and pulse obtained in the sitting position after the subject has sat quietly for at least 5 minutes.

7.8 Laboratory Assessments

7.8.1 General

All applicable screening and all on-study blood samples during the primary analysis period will be processed and sent to the central laboratory. Depending on the assessment, the central laboratory will be responsible for either performing the assays, or shipping samples to Amgen or a specialty laboratory for assay.

The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, and serum 25 (OH) vitamin D 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 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.

Following the end of primary analysis period, all applicable on-study blood samples will be processed and analyzed at a local laboratory. Local laboratories will use the local laboratory's normal ranges. Local laboratory results will be monitored by the principal investigator and any adverse events supported by local laboratory results should be reported as an adverse event (please see Section 9.1.2).

All blood samples will be obtained by venipuncture before IP administration, when applicable, at the time points outlined in the Schedule**s** of Assessments (Appendix A). The date and time of blood collection will be recorded in the subject's medical record. Samples for assessment of BTMs must be obtained from subjects in the fasted state as indicated in Section 7.8.2.

Table 1 outlines the specific analytes for the serum chemistry and hematology assessments, as well as other assessments to be conducted on blood samples.

Chloride, bicarbonate, and calculated adjusted calcium assessments are optional after primary analysis.

On-study (ie, after baseline/Day 1) laboratory results for serum calcium, albumin-adjusted calcium, phosphorus, and alkaline phosphatase (ALP), will not be reported to any study-related personnel in order to maintain the integrity of the study blind **up until primary analysis. These laboratory results will not be blinded after primary analysis** (refer to Section 10.3 for information on access to individual subject treatment assignments by Amgen). However, in the event of an abnormal value of clinical relevance (panic value) **obtained in the central laboratory during the primary analysis period**, sites will be notified of the unblinded value by the central laboratory. In addition, laboratory results for romosozumab levels, sclerostin, BTMs (P1NP, BSAP, OC, and sCTX), iPTH, and anti-romosozumab antibodies will not be reported to any personnel responsible for study-related management (including the sites). When a panic alert is issued for serum calcium, albumin-adjusted calcium levels, phosphorus, or ALP, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care.

Table 1. Blood Sample Analyte Listing

Serum Chemistry	Hematology	BTMs	Other
Sodium	RBC	P1NP[a]	Romosozumab levels[a]
Potassium	Hemoglobin	sCTX[a]	Sclerostin[a]
Chloride[b]		BSAP[a]	25 (OH) vitamin D
Bicarbonate[b]	Platelets	OC[a]	iPTH[a]
Total Protein	WBC		Anti-romosozumab antibody[a]
Albumin	• Differential		Biomarker sample
Calcium[a]	• Neutrophils		
Magnesium	• Eosinophils		
Phosphorus[a]	• Basophils		
Glucose	• Lymphocytes		
BUN	• Monocytes		
Creatinine			
TBL			
ALP[a]			
ALT (SGPT)			
AST (SGOT)			
Albumin-adjusted Calcium[a,b]			

ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BSAP = bone specific alkaline phosphatase; BTM = bone turnover marker; BUN = blood urea nitrogen; iPTH = intact parathyroid hormone; OC = osteocalcin; P1NP = procollagen type 1 N-telopeptide; RBC = red blood cell; sCTX = serum type-1 collagen C-telopeptide; TBL = total bilirubin; WBC = white blood cell

[a] **Until the end of the primary analysis** period, **r**esults 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 alkaline phosphatase in the event of a panic value.

[b] **Chloride, bicarbonate, and calculated adjusted calcium assessments are optional after primary analysis.**

Any blood or tissue samples collected according to the Schedule of Assessments (Appendix A may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

If informed consent is provided by the subject, Amgen may do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the bone metabolic diseases, the dose response and/or prediction of response to

romosozumab or other protocol-specified therapy, as required, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

Additional subjects will be invited to participate in the blood only portion of the sub-study at the time of enrollment and in the case of insufficient enrollment, additional blood only sub-study sites will be initiated and subjects already on trial will be invited to participate with consent for blood collected earlier in the study to be used for sub-study analyses.

7.8.2 Bone Turnover Markers

Subjects participating in the Imaging and PK/BTM/Biomarker sub-study will have blood drawn at visits specified in Section 7.3 and the Schedule of Assessments (Appendix A) for analysis of BTMs (P1NP, sCTX, BSAP, and OC).

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

Results from BTM assessments are considered potentially unblinding and will not be reported to study-related personnel post Day 1/baseline.

7.8.3 Romosozumab Levels and Sclerostin

Subjects participating in the Imaging and PK/BTM/Biomarker sub-study will have blood drawn at visits specified in Section 7.3 and in the Schedule of Assessments (Appendix A) for analysis of romosozumab and sclerostin levels.

Results from romosozumab and sclerostin assays are considered potentially unblinding and will not be reported to study-related personnel post Day 1/baseline.

7.8.4 Antibody Testing Procedures

Blood samples will be collected from all subjects for anti-romosozumab antibody testing procedures; however only samples from subjects exposed to romosozumab will be analyzed to test for 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.

Subjects who test positive for neutralizing antibodies to romosozumab at the ET visit will be asked to return for additional follow-up testing. This testing should 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) after the last dose of romosozumab. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be 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.

Sites will only be contacted if additional follow-up testing is needed after an ET visit. No notifications will be sent before an ET visit or for subjects testing negative for antibodies to romosozumab.

7.9 Adverse Event Data Collection and Adjudication

Any adverse events occurring after the first dose of IP will be recorded in the subjects' records and on the appropriate eCRFs. Recording of serious adverse events begins after signing of the informed consent form. Refer to Section 9.1 and Section 9.2 for more details.

Additional information will be collected for certain adverse events of interest.

The following events will be adjudicated by independent adjudication committees:

Potential Osteonecrosis of the Jaw (ONJ) Events

Cases of ONJ have been reported in association with anti-resorptive use. ONJ may be associated with pain and/or infection of the jaw bone, teeth or gums resulting in a non-healing area of exposed bone in the mouth. How this happens is poorly understood. One hypothesized mechanism involves interference with bone remodeling as a result of decreased osteoclast activity. In this study all events reported as ONJ, or those coded to pre-specified terms potentially indicative of ONJ, will be reviewed by an independent adjudication committee.

Potential Atypical Femoral Fracture Events

Cases of atypical femoral fracture have been reported in patients with osteoporosis in association with anti-resorptive use. Some case series have reported a possible

association between atypical femoral fracture and long-term alendronate therapy (Odvina et al, 2010; Lenart et al, 2008; Odvina et al, 2005), while others have not (Abrahamsen et al, 2009). All events reported as atypical femoral fractures, or those events relating to pre-specified events potentially indicative of atypical femoral fractures, will be reviewed by an independent adjudication committee.

Potential Cardiovascular Events

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. Serious adverse events with terms mapping to a pre-defined preferred term list potentially indicative of cardiovascular etiology will also be adjudicated.

7.10 Concomitant Medication Data Collection

All concomitant medications, including over-the-counter products, administered while the subject is enrolled in the study must be recorded on the eCRF, listing generic name or trade name, indication, quantity administered, and date(s) of administration.

7.11 Clinical Fracture Recording

7.11.1 Suspected Clinical Vertebral Fractures (Primary Analysis Period)

Information on suspected clinical vertebral fractures will be recorded until clinical fracture events (nonvertebral fracture or clinical vertebral fracture) have been confirmed for at least 330 subjects AND all subjects have had the opportunity to complete the Month 24 study visit. If, during the primary analysis period, a subject reports back pain that is considered by the investigator to be possibly due to a new or worsening vertebral fracture, a confirmatory lateral spine x-ray will be taken and the back pain (but not a vertebral fracture) will be recorded as an adverse event. The lateral spine x-rays as well as copies of other diagnostic images (computerized tomography or magnetic resonance imaging) and/or radiology report, surgical report, or discharge summary will be submitted to the central imaging vendor for confirmation of fracture (refer to Section 7.14). To confirm a clinical vertebral fracture, at least one new or one worsening (ie, change by at least 1 SQ grade) vertebral fracture have to be identified by the central imaging vendor on lateral spine x-rays. The central imaging vendor will inform the sites of any new or worsening vertebral fractures; however x-rays taken upon reporting of back pain may also be read locally if necessary to support subject medical care. Only clinical vertebral fractures confirmed by the central imaging vendor will be included for the statistical analysis.

Postfracture PRO/ClinRO assessments will be triggered by the investigator's decision to order the confirmatory lateral spine x-ray (refer to Section 7.12) after reporting of a suspected clinical vertebral fracture. However, only responses corresponding to clinical vertebral fractures confirmed by the central imaging vendor will be included for the statistical analysis.

7.11.2 Nonvertebral Fractures

Information about any nonvertebral fractures and level of trauma causing the fracture while on study will be recorded. A copy of radiographs or other diagnostic images such as computerized tomography or magnetic resonance imaging confirming the fracture, and/or a copy of the radiology report, surgical report, or discharge summary should be obtained and included in the subject's study records. Copies of the radiographs, diagnostic images and/or radiology report, surgical report, clinical notes, or discharge summary will be submitted to the central imaging vendor for confirmation of fracture. If the radiograph or diagnostic image is not available, then, at minimum, a copy of the radiology report, surgical report, clinical notes, or discharge summary should be submitted to the central imaging vendor. Additional information about nonvertebral fractures will be entered into the eCRF, eg, details regarding the type of fracture and other pertinent data.

Postfracture PRO/ClinRO assessments will be triggered by the reporting of nonvertebral fractures (refer to Section 7.12), except for fractures of the skull, face, fingers, and toes, which are typically not associated with osteoporosis and do not require postfracture PRO/ClinRO assessments. However, only responses corresponding to nonvertebral fractures confirmed by the central imaging vendor will be included for the statistical analysis.

7.12 Patient Reported and Clinician Reported Outcomes

PRO and ClinRO assessments are to be completed before any other study procedures are performed. All subjects will complete the OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain questionnaires every 6 months during the primary analysis period (refer to the Schedule of Assessments, Appendix A). Subjects who have reported a nonvertebral or a suspected clinical vertebral fracture during the 12-month double-blind ALN-controlled study period (ie, up to the Month 12 study visit) will start postfracture PRO/ClinRO assessments. These subjects will be asked to complete the OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain questionnaires. Postfracture PRO/ClinRO assessments will be performed at the visit during which the nonvertebral fracture or suspected clinical

vertebral fracture has been reported and at the 3 consecutive monthly study visits. Subsequent nonvertebral or suspected clinical vertebral fractures will trigger a new cycle of postfracture PRO/ClinRO assessments. Postfracture PRO/ClinRO assessments will only be performed up to the Month 12 study visit; data collection is not required beyond Month 12 even if the fracture has been reported at the Month 10, Month 11, or Month 12 study visits.

7.12.1 OPAQ SV

The OPAQ SV evaluates the impact of vertebral and nonvertebral fractures on physical function, emotional status and back pain. Support for the reliability and validity of the OPAQ SV has been reported in published literature (Silverman, 2000).

7.12.2 EQ-5D-5L

The EQ-5D-5L, developed in 1990, is a widely used generic patient reported health-related quality of life instrument that allows for estimation of utility (Brooks, 1996). The EQ-5D-5L is comprised of 2 components: a health state index and a general health visual analog scale. The EQ-5D-5L health state index is comprised of 5 questions which address the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The responses will be reported as one of five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

7.12.3 Limited Activity day Survey

The LAD is a modification of the Back Pain and LAD questionnaire. The LAD captures subjects' limited activity, hospitalization, and bed rest experience (yes/no), and the number of days of limited activity, hospitalization, and bed rest due to health-related reasons (eg, back pain, fracture) over the last 30 days.

The LAD will be administered as a ClinRO questionnaire.

7.12.4 BPI Worst Pain

The BPI short form is a validated, widely used questionnaire developed to assess the severity of pain and the impact of pain on daily functions (Mendoza et al, 2006). Data in several disease areas, including osteoarthritis, indicate that the modified BPI short form, much like the original scale, was internally reliable, consistent over time, and had good construct, as well as convergent and predictive validity in assessment of patients suffering from conditions of chronic pain. The modified BPI short form, like the parent scale, is a valid and reliable tool for situations in which pain is assessed daily and

minimizes the burden placed on patients to record information necessary for scientific investigations.

To minimize burden for respondents, only one item extracted from the BPI-short form will be used to assess the worst fracture-related pain over the last 24 hours. This item will be referred to as "BPI worst pain". Pain and the limitations due to pain related to day to day osteoporosis will be captured by the OPAQ SV and EQ-5D-5L.

7.13 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.

For all subjects, bone density will be measured at the lumbar spine and the proximal femur. Lumbar spine scans must include L1 through L4. Detailed instructions for scan acquisition can be found in the separate manual provided by the central imaging vendor.

For proximal femur, 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.

7.13.1 Screening BMD Assessment

To determine eligibility based on BMD T-score, proximal femur DXA scans will be analyzed by the central imaging vendor. To facilitate subject scheduling, the Day 1/baseline lumbar spine DXA scan may be taken with the proximal femur DXA scan performed during screening.

Data from the screening DXA scans will be electronically transferred to the central imaging vendor as soon as possible following acquisition. Sites unable to submit data electronically can submit on CD or other media as specified in the DXA Procedural Manual, but electronic submission is preferred.

7.13.2 On-study BMD Assessments

In order to maintain the blind, all DXA scans performed after the baseline assessment must not be analyzed by site staff. All DXA scan data will be submitted electronically to

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

The results from the central imaging vendor will be used as the final data for statistical analysis.

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

DXA BMD data are considered potentially unblinding and will not be reported to study-related personnel (including sites) post Day 1/baseline.

7.13.3 Monitoring of BMD Decreases

BMD changes for individual subjects will be monitored by the central imaging vendor during the primary analysis period. Investigators will be alerted if a subject experiences a BMD loss from baseline of 7% or more at the total hip and/or at the lumbar spine at any time during the study.

7.14 Lateral Spine X-ray Assessments

X-rays of the lateral thoracic and lumbar spine will be acquired according to specific instructions provided by the central imaging vendor per the schedule outlined in Appendix A.

For assessment of prevalent vertebral fractures at screening/baseline, which will be performed by a radiologist at the central imaging center, a visual semiquantitative grading scale will be used (Genant et al, 1993):

- SQ grade 0 (SQ0) = no fracture
- SQ grade 1 (SQ1) = mild fracture, 20 to 25% reduction in vertebral height (anterior, middle, or posterior)
- SQ grade 2 (SQ2) = moderate fracture, 25 to 40% reduction in height
- SQ grade 3 (SQ3) = severe fracture, greater than 40% reduction in height

For assessment of incident vertebral fracture, x-rays will be scored blinded to treatment but not to sequence. The semiquantitative grading scale will be used. New vertebral fractures are defined as fractures in previously undeformed vertebrae. Worsening of pre-existing vertebral fractures will also be assessed. Worsening is defined as an

increase of at least 1 grade on the semiquantitative scale. Investigators will be alerted by the central imaging vendor when a new or worsening vertebral fracture is identified.

If a subject presents with acute back pain likely related to a new vertebral fracture at a time point other than when a scheduled lateral spine x-ray is obtained during the primary analysis period, and occurrence of a vertebral fracture is suspected, unscheduled lateral spinal x-rays will be obtained for submission to the central imaging facility for evaluation (refer to Section 7.11.1). The central imaging vendor will inform the sites if a new or worsening vertebral fracture is identified; however these x-rays may also be read locally if necessary to support the subject's medical care. Only fractures confirmed by the central imaging vendor will be included for the analyses.

7.15 Quantitative Computed Tomography (QCT)

A subset of the subjects participating in the Imaging and PK/BTM/Biomarker sub-study will undergo QCT scans of the spine at visits specified in Section 7.3 and the Schedule of Assessments (Appendix A).

The same QCT scanner must be used for all scans for a particular subject. All QCT scans will be collected by a trained technician and submitted to the central imaging vendor for analysis. QCT data are considered potentially unblinding and will not be reported to study-related personnel (including sites) post Day 1/baseline. Detailed instructions for scan acquisition are provided in a separate manual by the central imaging vendor.

7.16 Biomarker Development

7.16.1 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development may be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop blood tests designed to identify subjects most likely to respond positively or negatively to romosozumab. Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods or ribonucleic acid transcript profiling.

If informed consent is provided by the subject, blood samples will be collected for biomarker development at the time points specified in the Schedule of Assessments (Appendix A).

Refer to the laboratory manual for detailed collection and handling procedures for biomarker development samples.

7.16.2 Sample Storage and Destruction

Biomarker development blood samples and any other components from the cells, as well as any other unused samples may be stored for up to 20 years from the end of the study to research scientific questions related to osteoporosis in postmenopausal women and/or romosozumab. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor will be 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 principal investigator or 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). Following the request from the subject, the principal investigator will provide the sponsor with the required study and subject numbers so that any remaining blood samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have 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. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation; subject data and samples obtained up to withdrawal of consent will be included in the analysis of the study. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Withdrawal of partial consent for a study means that the subject does not wish to take investigational product(s) or other protocol-required therapies any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all

subsequent study visits or procedures). Subjects may decline to continue receiving investigational product(s) or other protocol-required therapies at any time during the study. If this occurs, the investigator will discuss with the subject appropriate procedures for withdrawal from investigational product(s) or other protocol-required therapies. These subjects, as well as those who have stopped receiving investigational product(s) or other protocol-required therapies for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations.

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Reasons for removal from protocol required products or observation might include:

- partial withdrawal of consent
- withdrawal of full consent
- administrative decision by the investigator or Amgen
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix C).
- ineligibility
- significant protocol deviation
- subject noncompliance
- adverse event
- disease progression
- other safety concern by the investigator or Amgen
- death
- lost to follow-up

If a subject experiences BMD reduction of ≥ 7% from baseline at the total hip and/or lumbar spine at any time during the primary analysis period, the investigator is required to discuss implications for individual fracture risk, alternative treatment options and options for continuing in the study with the subject, and to document that discussion. If a decision is made to begin alternative treatment, IP must be discontinued and every effort should be made to complete all remaining study visits, regardless of any alternative treatment chosen by the subject.

8.2 Replacement of Subjects

Subjects will not be replaced on this study.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of 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 the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

9.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of IP through the end of study are reported using the applicable eCRF (eg, Adverse Event Summary eCRF). For subjects who discontinue the study early, adverse events will be reported through 30 days after the last dose of IP.

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,
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to IP, and
- Action taken.

The adverse event toxicity grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The toxicity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to the IP and/or other study drugs. 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 study drugs?

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

The investigator must assess whether the 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 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) should not 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) should be recorded as the adverse event.

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

The investigator's clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject, or subject's parent/legal guardian, may also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject should be encouraged to undergo, at a minimum, an end-of-study assessment.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- 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

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 B for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2.2 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 30 days after the last dose of IP are recorded in the subject's medical record and are submitted to Amgen. For subjects who discontinue the study early, serious adverse events will be reported through 30 days after the last dose of IP. The serious adverse event must be submitted to Amgen within 24 hours following the investigator's knowledge of the event. 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 (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix D for a sample of the Serious Adverse Event Worksheet/eSAE Contingency Report Form. Where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

In addition to the attributes listed in Section 9.1.2, the investigator must also complete the SAE section of the Adverse Event Summary CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. SAEs 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.

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 the investigator's 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 applicable eCRF (eg, Adverse Event Summary eCRF).

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/ECs in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

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

9.3 Pregnancy Reporting

If a pregnancy occurs in a subject while the subject is taking protocol-specified product and for 3 months after end of treatment with romosozumab (ie, 3 months after the Month 11 visit) the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program.

Report pregnancy on the Pregnancy Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Primary Endpoints

During the primary analysis period

- Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) at primary analysis
- Subject incidence of new vertebral fracture through Month 24

10.1.2 Secondary Endpoints

The secondary efficacy endpoints include the following:

During the primary analysis period

- Subject incidence of nonvertebral fracture at primary analysis
- Subject incidence of all fractures (nonvertebral fracture and new or worsening vertebral fracture) at primary analysis
- Subject incidence of new or worsening vertebral fracture through Month 24
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) at primary analysis
- Subject incidence of hip fracture at primary analysis
- Subject incidence of multiple new or worsening vertebral fractures through Month 24
- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) through Month 24**
- **Subject incidence of nonvertebral fracture through Month 24**
- **Subject incidence of hip fracture through Month 24**
- **Subject incidence of clinical vertebral fracture through Month 24**
- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Months 24, and 36

During the 12-month double-blind ALN-controlled study period

- Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) through Month 12
- Subject incidence of new vertebral fracture through Month 12
- Subject incidence of all fractures (nonvertebral fracture and new or worsening vertebral fracture) through Month 12
- **Subject incidence of nonvertebral fracture through Month 12**
- **Subject incidence of hip fracture through Month 12**
- **Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12**
- **Subject incidence of clinical vertebral fracture through Month 12**

- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 12

For the overall study period

- Subject incidence of nonvertebral fractures at final analysis
- **Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) at final analysis**
- **Subject incidence of hip fracture at final analysis**

10.1.3 Exploratory Endpoints

The exploratory endpoints include the following:

During the 12-month double-blind ALN-controlled study period

- Subject incidence of new or worsening vertebral fracture through Month 12
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Month 12
- Subject incidence of multiple new or worsening vertebral fractures through Month 12
- Actual value in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 6 and 12
- Change from baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 6 and 12
- Actual value in PRO and ClinRO measures after experiencing a nonvertebral or clinical vertebral fracture (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at reporting of the nonvertebral or clinical vertebral fracture and at 1, 2 and 3 months after the fracture
- Change from pre-fracture baseline in PRO and ClinRO measures after experiencing a nonvertebral or clinical vertebral fracture (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at reporting of the nonvertebral or clinical vertebral fracture and at 1, 2 and 3 months after the fracture
- Proportion of subjects with a clinically meaningful improvement in worst pain (defined as a 2-point improvement in the BPI worst pain scale compared with the fracture reporting visit) at 1, 2, and 3 months after reporting of a nonvertebral or clinical vertebral fracture
- Change from baseline in height at Month 12

During the primary analysis period

- Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) at primary analysis
- Actual value in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 18, 24, 30, and 36
- Change from baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 18, 24, 30, and 36
- Change from baseline in height at Month 24

During the month 12 to 24 ALN study period

- **Subject incidence of new vertebral fractures between Month 12 and Month 24**
- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) between Month 12 and Month 24**
- **Subject incidence of nonvertebral fracture between Month 12 and Month 24**
- **Subject incidence of hip fracture between Month 12 and Month 24**
- **Subject incidence of clinical vertebral fracture between Month 12 and Month 24**

10.1.4 Safety Endpoints

The safety endpoints include the following:

During the 12-month double-blind ALN-controlled study period

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and the shifts from baseline to the worst value between baseline and Month 12
- Changes from baseline in vital signs
- Subject incidence of anti-romosozumab antibodies

During the primary analysis period

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and the shift from baseline to the worst value between baseline and primary analysis
- Changes from baseline in vital signs
- Subject incidence of anti-romosozumab antibodies

During the overall study period

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in vital signs

10.1.5 Imaging and PK/BTM/Biomarker Sub-study Endpoints

During the 12-month double-blind ALN-controlled study period

- Romosozumab serum concentrations at Day 1, Months 1, 3, 6, 9, and 12
- Percent change from baseline in P1NP, BSAP, OC, and sCTX at Months 1, 3, 6, 9, and 12
- Percent change from baseline in iPTH and sclerostin at Months 1, 3, 6, 9, and 12

- For subjects participating in the imaging components:
  - Percent change from baseline in integral (total) and trabecular vBMD at the lumbar spine by QCT at Months 6, and 12
  - Percent change from baseline in lumbar spine strength as assessed by FEA at Months 6, and 12
  - Percent change from baseline in DXA BMD at the lumbar spine, total hip, and femoral neck at Month 6

During the primary analysis period

- Percent change from baseline in P1NP and sCTX at Months 15, 18, 24, and 36
- Percent change from baseline in iPTH and sclerostin at Months 15, 18, 24, and 36
- For subjects participating in the imaging components:
  - Percent change from baseline in integral (total) and trabecular vBMD at the lumbar spine by QCT at Month 24
  - Percent change from baseline in lumbar spine strength as assessed by FEA at Month 24
  - Percent change from baseline in DXA BMD at the lumbar spine, total hip, and femoral neck at Month 18

10.1.6 Analyses Subsets

10.1.6.1 Primary Efficacy Analysis Set for Vertebral Fracture

This analysis set includes all randomized subjects who have a baseline and ≥ 1 post-baseline evaluation of vertebral fracture at or before the time point under consideration. Subjects in this subset will be analyzed according to their randomized treatment assignments, regardless of treatment received. This analysis set will be used as the primary analysis set for the following endpoints: new, new or worsening, and multiple new or worsening vertebral fractures.

10.1.6.2 Full Analysis Set

This analysis set includes all randomized subjects. Subjects in the full analysis set will be analyzed according to their randomized treatment assignments, regardless of treatment received. The full analysis set will be used as the primary analysis set for the following endpoints: nonvertebral fracture, clinical fracture, major nonvertebral fracture, all fracture, major osteoporotic fracture, and hip fracture.

10.1.6.3 Per-protocol Analysis Set

The per-protocol analysis set will only be used to analyze the following endpoints: subject incidence of clinical fracture, new vertebral fracture through Month 24, and nonvertebral fracture as sensitivity analyses for the primary analysis period and nonvertebral fracture for the overall study period. The per-protocol analysis set includes

subjects who are defined in Section 10.1.6.1 (for new vertebral fractures in the primary analysis period) or Section 10.1.6.2 (for clinical fracture and nonvertebral fracture in the primary or overall **study** analysis period) and receive the active investigational product with no major protocol violations in the corresponding analysis period. The major protocol violations will be defined in the Statistical Analysis Plan (SAP), and will be identified prior to study unblinding. Subjects in the per-protocol set will be analyzed according to their randomized treatment assignments.

10.1.6.4 Primary Efficacy Analysis Set for BMD, Height, and PRO/ClinRO Endpoints for the Double-blind ALN-controlled Study Period and Primary Analysis Period

This analysis set includes all randomized subjects who have a baseline and ≥ 1 post baseline evaluation at or before the time point under consideration. The efficacy analysis set may vary for different endpoints due to missing data. Subjects in the analysis set will be analyzed according to their randomized treatment assignments, regardless of treatment received.

10.1.6.5 Safety Analysis Set for the Double-blind ALN-controlled Study Period, Primary Analysis Period, and Overall Study Period

The safety analysis set includes all randomized subjects who receive ≥ 1 dose of investigational product in the 12-month of double-blind ALN-controlled study period. These subjects will be analyzed according to their actual treatment received, where subjects who received ≥ 1 dose of romosozumab will be analyzed in the romosozumab treatment group regardless of the randomized treatment.

10.1.6.6 Analysis Set for Imaging and PK/BTM/Biomarker Sub-study

The analysis set for BTM/Biomarker includes all randomized subjects who undergo BTM/biomarker sampling during the study. Subjects will be analyzed according to their randomized treatment assignments. The analysis set for imaging includes all randomized subjects who undergo additional imaging procedures during the study. Subjects will be analyzed according to their randomized treatment assignments. The PK analysis set includes all randomized subjects who undergo PK sampling during the study and who have received ≥ 1 dose of romosozumab.

10.1.7 Covariates

All analyses assessing treatment effect of clinical fracture or nonvertebral fracture will include the stratification factor age **(**< 75 or ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score as main covariates in the model. Additional covariates will be analyzed separately and simultaneously, if

appropriate, as exploratory analyses. The additional covariates of interest include the following:

- baseline body mass index (BMI)
- years since menopause at baseline
- prior nonvertebral osteoporotic fracture (yes, no)
- geographic region
- race/ethnicity
- prior use of bone-specific therapeutic agents (yes, no)
- 10-year probability of major osteoporotic fracture with BMD **(as calculated by a third-party vendor)**

All analyses assessing treatment effect on new vertebral fracture endpoints will include the stratification factor age **(**< 75 or ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score as main covariates in the model. The new vertebral fracture endpoint assessed through Month 24 will also be analyzed adjusting for each of the additional covariates, as stated above, separately and simultaneously, if appropriate, as exploratory analyses.

10.2 Sample Size Considerations

The study is designed to evaluate the effectiveness of romosozumab treatment for 12 months followed by ALN (romosozumab/ALN) treatment compared with ALN treatment alone in reducing the subject incidence of clinical fracture (nonvertebral fracture or clinical vertebral fracture), subject incidence of vertebral fracture through Month 24, and subject incidence of nonvertebral fracture in postmenopausal women with osteoporosis. The total sample size of approximately 4,000 subjects (2,000:2,000 equally allocated between the treatment groups) is determined based on the clinical fracture and new vertebral fracture endpoints.

The dropout rate is assumed 10% for the first year and 8% per year thereafter. The enrollment is expected to complete in 34 months.

Because study design requires all subjects to complete the Month 24 visit for the ascertainment of the new vertebral fracture endpoint, the minimum follow-up on an individual subject is at least 24 months. Additionally, all subjects will be followed until at least 440 subjects have confirmed nonvertebral fracture events for the final analysis, unless superiority of the nonvertebral fracture endpoint is achieved at the primary analysis**.** The minimum follow-up time (24 months) and event-driven components of this study add complexity to the sample size calculation and power estimates. To address

this complexity and the added complexity of using Hochberg's method (Hochberg, 1988) to adjust for the multiplicity of the primary endpoints, a simulation was performed to derive the sample size and power for the clinical fracture and nonvertebral fracture endpoints.

New vertebral fracture assumptions

The one-year incidence of new vertebral fractures in untreated subjects in the population defined in this study is expected to be 5.5% (Black et al, 1996; Cummings et al, 2009). Assuming ALN treatment decreases this incidence by 60%, the new vertebral fracture incidence in the ALN group is expected to be 2.2% in one year and 4.4% in two years. Romosozumab/ALN treatment is expected to decrease the incidence of new vertebral fractures by 80%. This represents a risk reduction of 50% compared to ALN treatment alone.

Nonvertebral fracture assumptions

The one-year incidence rate of nonvertebral fractures in the population defined in this study is expected to be 5.5% (Black et al, 2000). Based on the ALN treatment assumption, 25% risk reduction, the one-year nonvertebral incidence rate is expected to be approximately 4% when treated by ALN. Romosozumab/ALN is assumed to reduce the risk by 45% when compared to no treatment. The combination of the 25% assumed reduction for ALN and the 45% assumed reduction for romosozumab /ALN leads to the assumption of a 27% reduction in fracture risk when comparing romosozumab /ALN to ALN.

Clinical fracture assumptions

Clinical fracture is the combination of nonvertebral fractures and clinical vertebral fractures. Clinical vertebral fractures are expected to account for at 1/3 (Black et al, 2000) of new vertebral fractures. In the FREEDOM study, in the untreated population, the one-year incidence rate was 0.5% for clinical vertebral fracture and 3.5% for clinical fracture (Amgen, data on file). Therefore, it is expected that clinical fractures are composed of approximately 85% nonvertebral fractures and 15% clinical vertebral fractures. By pooling the treatment effects of nonvertebral and clinical vertebral fractures in the natural log-scale, with 85% and 15% as weights, then taking the exponential, romosozumab/ALN treatment compared with ALN alone reduces the risk of clinical fractures by approximately 30% (ie, exp(0.15*ln(1-50%) + 0.85*ln(1-27%))=69%, approximately 30% risk reduction). This estimation of risk reduction was further supported in the simulation. Under the assumption that romosozumab/ALN will reduce

the risk by 30% compared to ALN, we would need to follow subjects until the 330th subject had a confirmed clinical fracture to achieve a 90% power to detect the treatment effect using a 2-sided log-rank test at an overall significance level of 0.05. The power calculation was performed using software EAST 5.4.

DXA BMD assumptions

The assumptions of mean percent change in DXA BMD and standard deviation for ALN at Month 12 and Month 24 are summarized in Table 2 (Schnitzer et al, 2000; Greenspan et al, 2002). Using the FRAME study, the assumptions of mean percent change in DXA BMD and standard deviation for romosozumab at Month 12 are summarized in Table 3 (Amgen, data on file). It is further assumed that at Month 24, romosozumab/ALN will maintain the BMD increase achieved at Month 12.

Table 2. Mean Percent Change From Baseline in BMD for Alendronate

	Mean % Change from Baseline	Standard Deviation
Lumbar spine at Month 12	**5.1**	**3.5**
Total hip at Month 12	**2.9**	**3.5**
Femoral neck at Month 12	**2.3**	**4.6**
Lumbar spine at Month 24	**6.3**	**4.9**
Total hip at Month 24[a]	**4.7**	**6.3**
Femoral neck at Month 24	**3.1**	**4.8**

[a] The mean of percent change from baseline at hip trochanter is used as the assumption for total hip.

Table 3. Mean Percent Change From Baseline in BMD at Month 12 for Romosozumab

	Mean % Change from Baseline	Standard Deviation
Lumbar spine at Month 12	**13.1**	**6.0**
Total hip at Month 12	**6.0**	**4.2**
Femoral neck at Month 12	**5.5**	**4.6**

Simulation parameters

The assumed distributions for nonvertebral fractures and new vertebral fractures are exponential with the yearly rates specified previously. A binomial distribution with probability of 1/3 is assumed for the likelihood of a new vertebral fractures being a clinical vertebral fracture. Additionally, the censoring distribution is assumed exponential

with a rate of 10% for the first year and a yearly rate of 8% thereafter. Enrollment is assumed to be completed in 34 months. As stated previously, the minimum follow-up is 24 months and all subjects will be followed until the 330th subject has a clinical fracture. A log-rank test is used for the clinical and nonvertebral fracture endpoints and a X^2 (no continuity correction) test is used for the new vertebral fracture endpoint. Results are based on 10,000 iterations.

Power

The power for the clinical fracture and new vertebral fracture endpoint after accounting for the multiplicity adjustment are 94% and 95%. There is 91% power that both primary endpoints will be significant at the 5% level (2-sided) after accounting for multiplicity. Based on the simulation, the median time of the primary analysis is after the last enrolled subject completes the Month 24 visit. The median number of subjects having clinical fractures in the simulation at the time of the primary analysis is 396. Note that the number of clinical fractures at the time of the primary analysis will exceed 330 when 330 subjects with confirmed clinical fractures occur before the Month 24 analysis.

If both primary endpoints are significant under the Hochberg procedure, **each of the following secondary DXA BMD endpoints will be tested hierarchically at 0.05 according to the following sequence: percent change from baseline in BMD at lumbar spine at Month 24, percent change from baseline in BMD at total hip at Month 24, percent change from baseline in BMD at femoral neck at Month 24, percent change from baseline in BMD at lumbar spine at Month 12, percent change from baseline in BMD at total hip at Month 12, and percent change from baseline in BMD at femoral neck at Month 12. The power for each DXA BMD endpoints is > 99% using the 2-sample *t*-test.**

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

0.0216. Based on the simulation, the power for nonvertebral fracture and both primary endpoints **and DXA BMD endpoints at Month 12 and Month 24** being significant is **approximately** 78% at the primary analysis.

If the significance of nonvertebral fracture is not demonstrated at the time of the primary analysis, the nonvertebral fracture endpoint will be tested again using a 1-sided test at the time of the final analysis. Based on the alpha level spent at the primary analysis, the significance level at final will be determined. For example, if the information fraction is 80% at the primary analysis (ie, the significance level is 0.0216 at primary), the significance level at the final analysis will be 0.0119 using software EAST 5.4 or R gsDesign package. Based on the simulation, the power for nonvertebral fracture being significant at the primary or final analysis and both primary endpoints **and DXA BMD endpoints at Month 12 and Month 24** being significant at primary analysis is **approximately** 84%.

Monitoring of Blinded Fracture Rates
The sponsor will monitor the pooled clinical fracture rate; if it is lower than expected, the sample size may be modified.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Staff from Amgen's Biological Sample Management, Pharmacokinetics & Drug Metabolism, and Clinical Immunology and Molecular Sciences departments perform analyses during this double-blind study. Therefore, the staff will not be blinded to the treatment assignments in this study. However, these individuals will not have access to subject level clinical data apart from the samples they are assaying and analyzing during the course of the study. They will ensure potentially unblinding data are not distributed to blinded individuals until the primary analysis. Roles and/or groups authorized to access restricted data elements during study (including at primary analysis) will be pre-specified to ensure the integrity of the trial.

10.4 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study prior to the evaluation of the primary endpoints.

An external, independent DMC will monitor unblinded safety data on an ongoing basis throughout the study and consider efficacy data in order to assess the risk/benefit profile of romosozumab. No type I error adjustment is necessary for the evaluation of primary endpoints. The DMC will not stop the trial early for efficacy or futility. DMC members will

have access to treatment assignments if knowledge of treatment assignment at the individual level is essential to evaluate safety. To minimize the potential introduction of bias, these individuals will not have direct contact with the study site personnel or subjects. An independent statistical service provider will generate unblinded reports for review by the DMC. If at any time there are safety concerns, the DMC will communicate the concerns to a representative from Amgen senior management. The DMC will convene approximately every 3 to 6 months. The start date will depend on subject accrual rates. Roles and groups requiring access to restricted and interim data at the time of the primary analyses and any time before initial database lock will be pre-specified to ensure the integrity of the trial.

10.5 Planned Methods of Analysis

10.5.1 General Approach/Considerations

The analytical approach for this study will be to use inferential testing to evaluate the following:

- the effect of romosozumab treatment for 12 months followed by ALN treatment on fracture outcome as compared with ALN alone
- the effect of romosozumab treatment for 12 months on fracture outcome as compared with ALN alone

All efficacy analyses will be performed by randomized treatment, regardless of treatment received.

At primary analyses, to maintain the overall significance level of 0.05, Hochberg's method will be used to evaluate the primary endpoints:

- Subject incidence of clinical fracture at primary analysis
- Subject incidence of new vertebral fracture through Month 24

If both the primary endpoints are significant at the 0.05 level (2-sided), **each of the following secondary DXA BMD endpoints will be tested hierarchically at 0.05 (2-sided). If all preceding endpoints are significant,** the nonvertebral fracture at the primary analysis will be evaluated based on a 1-sided test at the significance level determined by the alpha spending function specified in Section 10.2. All remaining secondary and exploratory efficacy endpoints will be tested at significance level of 0.05. If superiority of the nonvertebral fracture endpoint is achieved at the primary analysis and the study is stopped after the primary analysis has been performed, all data, including the additional safety and nonvertebral fracture data, collected after the primary analysis will be summarized descriptively and not be included in confirmatory testing.

Study completion constitutes either completion of primary analysis if superiority is proven for nonvertebral fractures or when at least 440 subjects have experienced a nonvertebral fracture.

Continuous parameters will be summarized using descriptive statistics, which include the mean, standard deviation, minimum, 25th percentile, median (50th percentile), 75th percentile, maximum, and number of non-missing observations (n). Nominal and ordinal categorical variables will be summarized using frequencies and percentages. For time-to-event parameters, the event rate at particular time point will be estimated using Kaplan-Meier method.

10.5.2 Analysis of Key Study Endpoints

10.5.2.1 Efficacy Endpoints

Clinical Fractures

Clinical fractures include nonvertebral fractures and clinical vertebral fracture (with $\geq$ 1 grade increase from the previous grade in any vertebra from T4 to L4) that are associated with signs and/or symptoms indicative of a fracture. All nonvertebral fractures confirmed by the central imaging vendor, except those of the skull, face, fingers, and toes, which are typically not associated with osteoporosis, will be included in analyses. However, fractures associated with high trauma severity or pathologic fractures will be excluded.

Subject incidence of clinical fracture at pre-specified time points will be estimated for each treatment group using Kaplan-Meier method. The treatment effect on clinical fractures will be assessed based on the hazard ratio, corresponding 95% confidence interval, and the p-value of the score test from a Cox proportional hazards model controlling for stratification factor age **(**< 75 or $\geq$ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. For subjects who have one or more clinical fractures from randomization to a pre-specified time point, the first event is used to define time to first clinical fracture. Subjects who do not have clinical fractures from randomization to a pre-specified time point will be censored at the date of last evaluation for clinical fractures prior to the pre-specified time point. Graphical representations of the clinical fracture incidence over time will also be displayed using Kaplan-Meier curves.

Vertebral Fracture Endpoints

Lateral spine x-rays will be obtained at screening (baseline) then annually, until primary analysis, and at visits when a clinical vertebral fracture is suspected. A new vertebral fracture is identified when there is ≥ 1 grade increase from the previous grade of 0 in any vertebra from T4 to L4.

The subject incidence of new vertebral fracture will be calculated as the ratio of the number of subjects experiencing at least one new vertebral fracture during the time period of interest to the number of subjects evaluable for new vertebral fracture during the time period of interest (See Section 10.1.6.1). The number of subjects reporting at least one new vertebral fracture and the incidence rates will be summarized by treatment group.

Subject incidence of new vertebral fracture at pre-specified time point**s** will be compared between treatment groups using a logistic regression model adjusting for stratification factor age **(**< 75 or ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. The odds ratio of vertebral fracture for subjects randomized to romosozumab as compared with subjects randomized to ALN, the corresponding 95% confidence interval, and the p-value using a score test will be reported.

The subject incidence of new or worsening vertebral fractures and subject incidence of multiple new or worsening vertebral fractures will be analyzed using the same approach as described for subject incidence of new vertebral fractures.

Nonvertebral Fractures

Nonvertebral fractures will be analyzed using the same approach as described for clinical fractures.

Other Fractures Endpoints at Specific Time Points

Major nonvertebral fractures, all fractures, major osteoporotic fractures, **clinical vertebral fractures,** and hip fractures **at specific time points** will be analyzed using the same approach as described for clinical fractures.

Fracture Endpoints Between Month 12 and Month 24

Subject incidence of new vertebral fractures between Month 12 and Month 24 will be described.

Subject incidence of clinical fracture, nonvertebral fracture, hip fracture, and clinical vertebral fracture between Month 12 and Month 24 will be summarized descriptively as for the clinical fracture endpoint.

Bone Mineral Density by DXA

For a body site (lumbar spine, total hip and femoral neck), percent changes of BMD from baseline to Month 12 will be compared between treatment groups using an ANCOVA model with treatment group, stratification factor (age), presence or absence of severe vertebral fracture at baseline, baseline BMD at the same body site as the endpoint, machine type, interaction of baseline BMD and machine type as independent variables. Any missing BMD value at Month 12 will be imputed by the last post-baseline BMD value that is prior to Month 12.

Percent changes of BMD from baseline to Month 24 and 36 during the primary analysis period will be analyzed using the same ANCOVA approach. Any missing values at Months 24 or 36 will be imputed by the last post-Month 12 value that is prior to the time point of interest.

Patient and Clinician Reported Outcome

The actual values and changes from baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) will be summarized by visit within each treatment group for all subjects. The change from baseline in PRO and ClinRO measures at Months 6 and 12 will be described and compared between treatment groups using non-parametric methods.

After experiencing an on-study clinical fracture during the primary analysis period, the actual values and the changes from the pre-fracture baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) will be summarized by visit since the reporting of the clinical fracture within each treatment group and both treatment groups combined. The change from pre-fracture baseline in PRO measures will be compared between treatment groups by visit since the reporting of the clinical fracture using regression model**s** adjusting for fracture location and potentially other factors impacting the PRO as per the statistical analysis plan. Pre-fracture baseline is defined as the last PRO or ClinRO measurement before the reporting of the clinical fracture.

The proportion of subjects with a clinically meaningful improvement in worst pain (defined as a 2-point improvement in the BPI worst pain scale compared with the fracture reporting visit) at months 1, 2 and 3 after experiencing a clinical fracture will be

analyzed using a logistic regression model adjusting for fracture location and potentially other factors impacting the pain score as per the statistical analysis plan.

Change from Baseline in Height

The changes from baseline in height at Months 12 and 24 will be summarized by visit within each treatment group using the full analysis set and analyzed using a non-parametric method.

BTM and Biomarkers in the Sub-study

The changes from baseline in BTMs and biomarkers will be summarized by visit within each treatment group using the analysis set for the Imaging and PK/BTM/Biomarker sub-study and will be analyzed using a non-parametric method.

Lumbar Spine BMD by DXA and BMD and estimated bone strength by QCT in the Sub-study

Lumbar spine BMD and estimated bone strength measured in the sub-study will be summarized by visit using the same approach as described for the main study.

10.5.2.2 Safety Endpoints

Adverse Events

Subject incidence rates of adverse events in the 12-month double-blind study period will be tabulated by system organ class and preferred term. Summaries of deaths, events of interest, serious, and investigational product related adverse events, adverse events leading to early withdrawals from investigational product or study in the 12-month double-blind study period, will also be provided.

The adverse events in the primary analysis period and in the overall study period will be summarized using the same approach as described for the 12-month double-blind study period.

Laboratory Assessments

The actual values and changes from baseline by visit will be summarized descriptively for each laboratory parameters in the 12-month double-blind study period. Laboratory parameters will also be summarized showing the shift in CTCAE toxicity grades from baseline to the ‘worst’ on-study value in the 12-month double-blind ALN-controlled study period.

The actual values and changes from baseline by visit will be summarized descriptively for each laboratory parameters for the primary analysis period. Laboratory parameters

will also be summarized showing the shift in CTCAE toxicity grades from baseline to the 'worst' on-study value in the primary analysis period. Graphical representation showing central tendency and dispersion of the actual values and/or changes from baseline of laboratory parameters over time will be provided.

Vital Signs

The actual values and changes from baseline in vital signs by visit will be summarized descriptively in the 12-month double-blind study period, the primary analysis period**,** and the overall study period.

Anti-romosozumab Antibodies

The frequencies and percentages of subjects exhibiting anti-romosozumab antibodies at any time in the 12-month double-blind study period will be tabulated. This analysis will be repeated to further include all testing results from samples collected during the rest **of** the primary analysis period.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should 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 investigational products are 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 her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall 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 should document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be

signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject.

If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB 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 will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- On the eCRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with a complete and accurate date of birth on the demographics eCRF.
- For Serious Adverse Events reported to Amgen, subjects should be identified by their initials, date of birth, and a subject identification number.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/International Conference on Harmonization (ICH) GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB 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 named representatives to have access to her study-related records, including personal information, without violating the confidentiality of the subject.

11.4 Investigator Signatory Obligations

Each clinical study report should be signed by the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- 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 IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB 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 should notify the IEC/IRB 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 investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

12.2 Study Documentation and Archive

The investigator should 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 eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF 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 Electronic Trial Operations System captures the following data points and these are considered source data: protocol number, site number, subject ID, gender, date of birth, date informed consent was signed, sub-study participation, treatment group assignment, screen failure reason, randomization date, randomization number and IP box ID assignment.

eCRF entries may be considered source data if the eCRF 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 should include:

- Subject files containing informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the IEC/IRB and Amgen
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

In addition, all original source documents supporting entries in the eCRFs 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 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the eCRFs 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 monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, 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, drug 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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the EDC system database for site resolution and closed by Amgen reviewer.
- The principal investigator signs only the Investigator Verification Form for this EDC study. This signature will indicate that the principal investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, 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 early termination) 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 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.5 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), 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**;** (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 should meet conditions 1, 2, 3, and 4.
- 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.

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

12.6 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. If permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

13. REFERENCES

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14. APPENDICES

Appendix A. Schedule of Assessments

Procedure	12-month double-blind ALN-controlled study period																			Rest of Study			
																				Monthly contact [13]			
	SCR & Full Rescreening [1]	D1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15[39]	M18	M24	M30	M36 [7]	Phone call	Follow-up clinic visit	End o Primary Analysis Period Phone Contact [8]	End of Study Phone Contact [8]
Informed Consent	X																						
History	X																						
Instructions for daily vitamin D and calcium supplementation	X																						
Physical Examination	X													X			X		X				
Vital Signs (blood pressure, temperature, pulse)	X		X					X						X		X	X	X	X				
Height & Weight	X							X						X		X	X	X	X				
Vitamin D status	X																						
Serum protein electrophoresis to assess multiple myeloma or related lymphoproliferative disorder	X[10]																						
Serum Chemistry and Hematology	X	X	X		X			X			X			X		X	X	X[17]	X[17]				
Anti-romosozumab antibody [3]		X	X		X			X						X		X	X						
Lateral Spine X-Rays (lumbar and thoracic) [5]	X													X			X		X[18,19]		X[14, 18]		
DXA (proximal femur)	X[15]													X			X		X[18,19]				
DXA (lumbar spine)		X[15]												X			X		X[18,19]				
PROs and ClinROs (OPAQ SV, EQ-5D-5L, LAD, BPI worst pain) [2]		X						X						X		X	X	X[18]	X[18]				
Reporting of nonvertebral fractures			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Reporting of suspected clinical vertebral fractures			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[18]	X[18]		X[18]		
OPAQ SV, EQ-5D-5L, LAD, BPI worst pain [6]			X	X	X	X	X		X	X	X	X	X										
Adverse Event[12] and Concomitant Medication data collection	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
If applicable: Vitamin D loading dose (50,000 to 60,000 IU)		X[4]																					
Oral IP (ALN/placebo) dispensation (blinded, 2-month supply)		X		X		X		X		X		X											
Unused Oral IP (ALN/placebo) collection (blinded)				X		X		X		X		X		X									

IP (Romosozumab/placebo) Injection[2]		X	X	X	X	X	X	X	X	X	X	X	X									
ALN dispensation (open-label, 6-month supply)														X		X	X	X	X			
Unused ALN collection (open-label)																X	X	X	X			
ALN compliance reporting (open-label)																					X	X
Imaging and/or PK/BTM/Biomarker Sub-study (subset of approximately 200 subjects, of which approximately 100 will participate in the imaging assessments)																						
Romosozumab levels		X	X		X			X			X			X								
P1NP, sCTX, Sclerostin, iPTH, blood sample for novel biomarker development (serum and plasma sample)[11]		X	X		X			X			X			X	X	X	X		X[18]			
BSAP, OC[11]		X	X		X			X			X			X								
QCT of the spine[16]		X						X						X			X					
DXA (lumbar spine/proximal femur)[16]								X								X						

1. During Screening and Full Rescreening, serious adverse event reporting only; no adverse event reporting or concomitant medication data collection.
2. PROs/ClinROs should preferably be the first procedure at each applicable visit, IP injection must be the last procedure at each applicable visit.
3. Blood draws will continue approximately every three months for subjects testing positive for neutralizing antibodies at ET visit.
4. The initial vitamin D loading dose is to be administered within 1 week of the study day 1 visit. However, if the vitamin D loading dose is missed in this timeframe, it should be given as soon as possible thereafter.
5. Additional lateral spine X-rays may be taken in cases of a suspected clinical vertebral fracture.
6. Post-fracture Month 12. Data collection will occur only up to the Month 12 study visit and is not required after Month 12 even if the fracture has been reported at the Month 10, Month 11, or Month 12 study visits.
7. Following Month 36, clinic visits will continue every 6 months until end of study (440 nonvertebral fractures) including all assessments listed unless otherwise noted.
8. End of primary analysis period phone contacts will occur when clinical fracture events (nonvertebral fracture or clinical vertebral fracture) have been confirmed by the central imaging vendor for at least 330 subjects and all subjects have had the opportunity to complete their Month 24 study visit.
9. End of study telephone contacts will be performed after nonvertebral fracture events have been confirmed for at least 440 subject.
10. Performed by local laboratory; electrophoresis results within 6 months prior to signing consent will be acceptable.
11. Blood draws for BTMs must be obtained from subjects in fasting stage and before noon. Fasting stage is defined as overnight fasting. If overnight fasting is not feasible, at a minimum 8 hours is required.

[12] SAE reporting to continue through 30 days after the last dose of IP.
[13] Monthly contacts begin at M13. Contact will be initiated by a phone call. During the primary analysis period, if back pain is reported during the phone call, it will be recorded as an adverse event and the subject will be asked to complete an unscheduled follow-up clinic visit as soon as possible but no later than 21 days after reporting of the back pain for evaluation of a suspected clinical vertebral fracture.
[14] Lateral spine x-ray will only be taken at the unscheduled follow-up clinic visit if the investigator considers the back pain previously reported during the monthly phone contact to be possibly due to a new or worsening vertebral fracture.
[15] To facilitate subject scheduling, the Day 1/baseline lumbar spine DXA scan may be taken with the proximal femur DXA scan performed during screening. For Screening and Day 1 purposes, lateral spine x-rays and 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 criteria outlined in Section 7.2.1 are met.
[16] In a subset of subjects.
[17] To be processed and sent to the central laboratory during the primary analysis period; to be analyzed at local laboratories following the primary analysis period.
[18] To be performed in the primary analysis period only.
[19] To be performed at month 36 and then every 12 months thereafter during the primary analysis period only.
[20] For subjects in the sub-study only.

Notes:

a) To maintain the blind of the study, the following on-study (after Day 1/baseline) data will not be reported to any study-related personnel: serum calcium, albumin-adjusted calcium, phosphorus, alkaline phosphatase, romosozumab levels, Sclerostin, BTMs, iPTH, anti-romosozumab antibodies, and DXA results. However, in the case of a panic value for either serum calcium, albumin-adjusted calcium, phosphorus or alkaline phosphatase the central laboratory will notify the study site. When a panic alert is issued for serum calcium, albumin-adjusted calcium levels, phosphorus, or ALP, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care. After primary analysis, the chemistry and hematology labs will be unblinded as these will be done by local lab.
b) Phone contact to occur monthly in between clinic visits following the 12-month, double-blind, ALN-controlled study period **un**til **the** end of study. When a nonvertebral fracture is reported: Event to be recorded in eCRF, copies of radiographs or other diagnostic images and/or a copy of the radiology report, surgical report, or discharge summary should be obtained, included in the subject's study records and submitted to the central imaging vendor. When back pain is reported (until clinical fracture events have been confirmed by the central imaging vendor for at least 330 subjects and all subjects have had the opportunity to complete their Month 24 study visit): back pain (but not a vertebral fracture) will be recorded as an adverse event. The subject will be asked to complete an unscheduled follow-up clinic visit as soon as possible but no later than 21 days after reporting of the back pain. If at the unscheduled clinic visit, the investigator considers the back pain to be possibly due to a new or worsening vertebral fracture, a confirmatory lateral spine x-ray will be taken.
c) Visit windows are ±7 days for the monthly study visits during the 12-month double-blind ALN-controlled study period, ± 14 days for clinic visits during the rest of the study. The window for the monthly phone contact in between clinic visits and the end of primary analysis period phone contact is ± 7 days. The window for the end of study contact is **-14 to** +7 days.
d) If a subject terminates early from the study between Day 1 and Month 12, the Month 12 procedures (except ALN dispensation) are to be completed at that time. If a subject terminates early between Month 12 and Month 24, the Month 24 procedures (except ALN dispensation) are to be completed at that time. If a subject terminates early from the study between Month 24 and the end of the primary analysis period, the Month 36 procedures are to be completed at that time (except ALN dispensation; DXA scans and lateral spine x-rays should be performed if at least 6 weeks have elapsed since the previous one). If a subject terminates early from the study following the end of primary analysis period, the end of primary analysis period phone contact procedures are to be completed at that time.
e) Study visits and phone contacts after Month 24 are required until the end of study phone contact has been completed.

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

For grading of adverse events, the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 is to be used.

Grade	CTCAE version 3.0
1	MILD ADVERSE EVENTS
2	MODERATE ADVERSE EVENTS
3	SEVERE ADVERSE EVENTS
4	LIFE-THREATENING OR DISABLING ADVERSE EVENTS
5	DEATH RELATED to ADVERSE EVENTS

Go to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf to access a full version of CTCAE version 3.0

United States FDA Guidance on Hepatotoxicity Stopping and Rechallenge Rules

As noted in Section 6.1.3 an FDA Guidance exists for DILI (Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009). This guidance is general for all investigational and marketed products, and is synopsized here as a reference. It provides criteria for reporting and withholding investigational product in the event that a subject develops signs or symptoms of hepatotoxicity during a clinical trial. For the purpose of this study, these FDA guidelines apply to all centers in all countries.

Criteria for Permanent Withholding of IP due to Potential Hepatotoxicity

IP should be discontinued permanently and the subject should be followed for possible DILI, if ALL of the criteria below are met:

- TBL>2x ULN or international normalized ratio >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 laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic Steatohepatitis (NASH) or other "fatty liver disease"

It should be noted that some of the circumstances above may nevertheless warrant discontinuation of romosozumab (Section 8) without requiring assessment for drug-induced liver injury.

Criteria for Conditional Withholding of IP due to Potential Hepatotoxicity

For subjects that do not meet the criteria for permanent withholding of investigational product outlined above, IP should be withheld if ANY of the following criteria are met, and the subject should be evaluated for DILI:

- 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

- OR: clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3x ULN, investigational product should be withheld.
- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

IP should be withheld pending investigation into alternative causes of DILI. If IP is withheld, the subject should be followed according to recommendations above for possible DILI. Rechallenge may be considered if an alternative cause, such as acute Hepatitis B infection, is discovered and the laboratory abnormalities resolve to normal or baseline.

Criteria for Rechallenge of IP after Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then IP should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation should never be rechallenged.

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation that require permanent withholding of IP require the following:

- The event should 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, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities should be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI should be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.

Additional Clinical Assessments and Observation

All subjects in whom IP is withheld (either permanently or conditionally) due to potential DILI or who experience AST/ALT elevations >3x ULN should undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that should be performed during this period include:

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL >2x ULN or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours
  - Subjects should be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the investigational product has been discontinued AND the subject is asymptomatic
- Obtain PT/international normalized ratio, fractionated bilirubin and any other potentially relevant laboratory evaluations of liver function or disease

- Obtain complete blood count with differential to assess for eosinophilia
- Obtain appropriate blood sampling for PK analysis if this has not already been collected
- 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 medications (including non-prescription medicines & herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A,B,C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of DILI including but not limited to: Nonalcoholic Steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation that require permanent withholding of investigational product
- Follow the subject until all laboratory abnormalities return to baseline or normal. The "close observation period" should continue for a minimum of 4 weeks after drug discontinuation.

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

Appendix C. Pregnancy Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20110142

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:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

Appendix D. eSAE Contingency Report Form

AMGEN Study # *20110142* *AMG 785*	Serious Adverse Event Report Form for eSAE Studies For Restricted Use

Complete either Section A or Section B and follow the instructions provided:

Section A

☐ **Rave is active for this study but has not been accessible for at least one business day. I am submitting (check/complete all that apply):**

- ☐ An event that applies to a specialty CRF page titled _____ (e.g. VTE, clinical fracture)
- ☐ Screening event (as defined by the protocol) | **OR** | ☐ On-study (as defined by the protocol)

– *Complete ONLY Sections 1, 2 and 3 (page 1)*
– *Sign and date the signature section following Section 3*
– *Fax completed page of the form to the number noted in the header above Section 1*

Section B

☐ **Access to Rave has either not begun or has ended for this study. I am submitting (check all that apply):**

- ☐ Screening event (as defined by the protocol)
  - ☐ This is a new event report
  - ☐ This is follow-up information for a previously reported event
- **OR**
- ☐ Event after access to Rave has ended (*provide subject's End of Study date in Section 2*)
  - ☐ This is a new event report
  - ☐ This is follow-up information for a previously reported event

– *Complete ALL sections of the form (all 3 pages)*
– *Sign and date the signature section at the end of the form*
– *Fax completed form (all 3 pages) to the number noted in the header above Section 1*

<<For completion by Amgen 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	Date of birth Day Month Year	Sex ☐F ☐M	Race	If applicable, provide End of Study date

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

3. SERIOUS ADVERSE EVENT

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? No ✓ Yes ✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure e.g. biopsy

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

If you temporarily cannot access Rave, sign below and submit ONLY this page to the number noted in the header above Section 1.

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

AMGEN Study # *20110142* *AMG 785*	Serious Adverse Event Report Form for eSAE Studies For Restricted Use

If* access to Rave has either not begun or has ended for this study, *complete the remainder of this form.

Site Number	Subject ID Number

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP_____ ☐✓Blinded ☐✓Open Label	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld

6. RELEVANT CONCOMITANT MEDICATIONS (e.g. chemotherapy) Any Relevant Medications? ☐ No ☐ Yes, If yes, please complete:

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

Test Unit Date Day Month Year											

AMGEN Study # *20110142* *AMG 785*	Serious Adverse Event Report Form for eSAE Studies For Restricted Use

Site Number | Subject ID Number

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

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 -	Title	Date
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.		

Amendment 5

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

Amgen Protocol Number AMG 785 (Romosozumab) 20110142

Amendment Date: 14 September 2016

Rationale:

In response to regulatory agency feedback, BMD endpoints at months 12 and 24 have been added as intermediate steps in the sequence of endpoints to be multiplicity adjusted. These endpoints will be tested after the primary endpoint testing and prior to testing of subject incidence of nonvertebral fractures at primary analysis. In addition, fracture endpoints at additional specified time points have been added to the secondary endpoints based on feedback from key opinion leaders. The addition of clinical vertebral fractures as an additional fracture endpoint was added based on the advice of regulatory authorities.

To accommodate high enrolling sites, the end of primary analysis phone call window has been extended (7 days to 14 days) and noted that if the information has otherwise been acquired from the subject (during a monthly phone call or study visit) during this time period an additional phone call is not necessary. In addition, since it has become clear that 330 fractures will have occurred before the last subject reaches Month 24, the date of the end of primary analysis period will be determined and sites will be notified several months in advance. Thus the window will begin 2 weeks before the end of the primary analysis extending to the end of primary analysis period.

The protocol is also being amended to include the following:

- Added clarification that the alendronate (ALN) should be returned to the site for destruction at the completion of the study
- Added clarification that the investigator should contact the subjects after the end of study for additional safety information and follow-up as well as follow on opportunities
- Added clarification that chloride, bicarbonate, and calculated adjusted calcium will not be required after the primary analysis period if these results are unavailable from the local laboratory

- Clarified that laboratory results will not be blinded after the primary analysis period
- Administration, typographical, and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

Description of Changes:

Section: Global

Change:

Minor corrections throughout (eg, correcting typographical and formatting errors)

Section: Global

Replace:

17 August 2015

With:

14 September 2016

Section: Title Page

Replace:

PPD

Clinical Study Manager (Global)

Amgen Inc

One Amgen Center Drive,

Thousand Oaks, CA 91320-1799 USA

Phone: PPD Fax: PPD

PPD

Clinical Study Manager (Regional)

Amgen Limited

240 Cambridge Science Park

Cambridge UK CB4 0WD

Phone: PPD

Fax: PPD

With:

PPD

Global **Clinical Trial Manager**

Amgen Inc

One Amgen Center Drive,

Thousand Oaks, CA 91320-1799 USA

Phone: PPD Fax: PPD

PPD

Global Clinical Trial Manager

Amgen Inc

1 Uxbridge Business Park,

Sanderson Road

Uxbridge UB8 1DH

England

Telephone: PPD

Section: Title Page

Add:

Amendment 5: 14 September 2016

Section: Synopsis, Secondary Objectives

For the primary analysis period

Replace:

- Subject incidence of fractures (all fractures [nonvertebral fractures and new or worsening vertebral fractures], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, and multiple new or worsening vertebral fracture)

With:

- Subject incidence of fractures (all fractures [nonvertebral fractures and new or worsening vertebral fractures], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, multiple new or worsening vertebral fracture**, and clinical vertebral fracture**)

Section: Synopsis, Secondary Objectives

For the 12-month double-blind ALN-controlled study period

Replace:

- Subject incidence of fractures (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fractures and new or worsening vertebral fractures])

With:

- Subject incidence of fractures (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fractures and new or worsening vertebral fractures] **nonvertebral fracture, hip fracture, clinical vertebral fracture, and major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral]**)

Section: Synopsis, Secondary Objectives

For the overall study period (randomization to end of study)

Replace:

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of nonvertebral fractures

With:

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of **hip fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip],** nonvertebral fractures

Section: Synopsis, Exploratory Objectives

For the 12-month double-blind ALN-controlled study period

Replace:

- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on subject incidence of fractures (new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral]~~,~~ and multiple new or worsening vertebral fracture)

With:

- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on subject incidence of fractures (new or worsening vertebral fracture, ~~nonvertebral fracture,~~ major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], ~~hip fracture, major osteoporotic fracture~~

~~[hip, forearm, humerus, and clinical vertebral],~~ and multiple new or worsening vertebral fracture)

Section: Synopsis, Exploratory Objectives

Add:

During the Month 12 to 24 ALN study period

- **To assess the effect of one year of romosozumab treatment compared with ALN treatment alone on subject incidence of new vertebral fractures, clinical fracture (nonvertebral fracture and clinical vertebral fracture), nonvertebral fracture, hip fracture, and clinical vertebral fracture during the subsequent year during which all subjects receive ALN treatment.**

Section: Synopsis, Secondary Endpoints

During the primary analysis period

Add:

- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) through Month 24**
- **Subject incidence of nonvertebral fracture through Month 24**
- **Subject incidence of hip fracture through Month 24**
- **Subject incidence of clinical vertebral fracture through Month 24**

Section: Synopsis, Secondary Endpoints

During the 12-month double-blind ALN-controlled study period

Add:

- **Subject incidence of nonvertebral fracture through Month 12**
- **Subject incidence of hip fracture through Month 12**
- **Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12**
- **Subject incidence of clinical vertebral fracture through Month 12**

Section: Synopsis, Secondary Endpoints

During the overall study period

Add:

- **Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) at final analysis**
- **Subject incidence of hip fracture at final analysis**

Section: Synopsis, Exploratory Endpoints

During the 12-month double-blind ALN-controlled study period

Replace:

- Subject incidence of new or worsening vertebral fracture through Month 12
- Subject incidence of nonvertebral fracture through Month 12
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Month 12
- Subject incidence of hip fracture through Month 12
- Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12
- Subject incidence of multiple new or worsening vertebral fractures through Month 12

With:

- Subject incidence of new or worsening vertebral fracture through Month 12
- ~~Subject incidence of nonvertebral fracture through Month 12~~
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Month 12
- ~~Subject incidence of hip fracture through Month 12~~
- ~~Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12~~
- Subject incidence of multiple new or worsening vertebral fractures through Month 12

Section: Synopsis, Exploratory Endpoints

Add:

During the Month 12 to 24 ALN study period

- **Subject incidence of new vertebral fractures between Month 12 and Month 24**
- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) between Month 12 and Month 24**
- **Subject incidence of nonvertebral fracture between Month 12 and Month 24**
- **Subject incidence of hip fracture between Month 12 and Month 24**
- **Subject incidence of clinical vertebral fracture between Month 12 and Month 24**

Section: Synopsis, Statistical Considerations

Replace:

In order to maintain the overall significance level at 0.05, the primary endpoints will be assessed using Hochberg's procedure. If both primary endpoints are significant at the

0.05 level, the nonvertebral fracture endpoint will be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test ($\alpha = 0.025$). The Lan-Demets alpha spending function that approximates a Pocock boundary will be used to determine the significance level at the time of the primary analysis.

Subject incidence of clinical fractures will be compared between treatment groups using a Cox proportional hazards model controlling for age (< 75 years, ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. Nonvertebral fractures, major nonvertebral fractures, hip fractures, and all fractures will be analyzed using the same approach as for clinical fractures. The Kaplan-Meier method will be used to summarize the cumulative fracture incidence at pre-specified time points.

Subject incidence of new vertebral fracture at a pre-specified time point will be compared between treatment groups using a logistic regression model adjusting for age (< 75 years, ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. Subject incidence of new or worsening vertebral fractures and multiple new or worsening vertebral fractures will be analyzed using the same approach as for new vertebral fractures.

With:

In order to maintain the overall significance level at 0.05, the primary endpoints will be assessed using Hochberg's procedure. If both primary endpoints are significant at the 0.05 level, **each of the following secondary DXA BMD endpoints will be tested hierarchically at 0.05 according to the following sequence: percent change from baseline in BMD at lumbar spine at Month 24, percent change from baseline in BMD at total hip at Month 24, percent change from baseline in BMD at femoral neck at Month 24, percent change from baseline in BMD at lumbar spine at Month 12, percent change from baseline in BMD at total hip at Month 12, and percent change from baseline in BMD at femoral neck at Month 12. If all preceding endpoints are significant,** the nonvertebral fracture endpoint will be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test ($\alpha = 0.025$). The Lan-Demets alpha spending function that approximates a Pocock boundary will be used to determine the significance level at the time of the primary analysis.

Subject incidence of clinical fractures will be compared between treatment groups using a Cox proportional hazards model controlling for age (< 75 years, ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. Nonvertebral fractures, major nonvertebral fractures, hip fractures, **clinical vertebral fracture,** and all fractures will be analyzed using the same approach as for clinical fractures. The Kaplan-Meier method will be used to summarize the cumulative fracture incidence at pre-specified time points.

Subject incidence of new vertebral fracture at ~~a~~ pre-specified time point**s** will be compared between treatment groups using a logistic regression model adjusting for age (< 75 years, ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score. Subject incidence of new or worsening vertebral fractures and multiple new or worsening vertebral fractures will be analyzed using the same approach as for new vertebral fractures. **Subject incidence of new vertebral fractures between Month 12 and Month 24 will be estimated.**

Section: 1.2 Secondary

For the primary analysis period

Replace:

- Subject incidence of fractures (all fractures [nonvertebral fractures and new or worsening vertebral fractures], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, and multiple new or worsening vertebral fracture)

With:

- Subject incidence of fractures (all fractures [nonvertebral fractures and new or worsening vertebral fractures], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, ~~and~~ multiple new or worsening vertebral fracture, **and clinical vertebral fracture**)

Section: 1.2 Secondary

For the 12-month double-blind ALN-controlled study period

Replace:

- Subject incidence of fractures (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fractures and new or worsening vertebral fractures])

With:

- Subject incidence of fractures (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fractures and new or worsening vertebral fractures], **nonvertebral fracture, hip fracture, clinical vertebral fracture, and major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral]**)

Section: 1.2 Secondary

For the overall study (randomization to end of study)

Replace:

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of nonvertebral fractures

With:

- To assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of **hip fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], and** nonvertebral fractures

Section: 1.3 Exploratory

For the 12-month double-blind ALN-controlled study period

Replace:

- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on subject incidence of fractures (new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal

tibia, ribs, proximal humerus, forearm, and hip], hip fracture, major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral],and multiple new or worsening vertebral fracture)

With:

- To assess the effect of romosozumab treatment for 12 months compared with ALN treatment on subject incidence of fractures (new or worsening vertebral fracture, ~~nonvertebral fracture,~~ major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], ~~hip fracture, major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral],~~and multiple new or worsening vertebral fracture)

Section: 1.3 Exploratory

Add:

During the Month 12 to 24 ALN study period

- **To assess the effect of one year of romosozumab treatment compared with ALN treatment alone on subject incidence of new vertebral fractures, clinical fracture (nonvertebral fracture and clinical vertebral fracture), nonvertebral fracture, hip fracture, and clinical vertebral fracture during the subsequent year during which all subjects receive ALN treatment.**

Section: 6.2.1 ALN/Placebo and ALN Dosage, Administration, and Schedule

Add:

Unused alendronate at the time of end of study should be returned to the sites (Please refer to study IPIM for details).

ALN is a marketed product. For further information, including information on treatment of overdose, the package insert should be referenced.

Section: 6.5 Excluded Treatments During Study Period

Replace:

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

With:

Medications listed below will be proscribed during the study, **including the use of other investigational products and**~~as these~~ medications ~~are~~ known or suspected to affect bone metabolism:

Section: 7.1.2 Study Windows

Replace:

Study visit windows differ based on the type of visit and are clearly identified in the description of study visits in Section 7.3. All monthly study visits during the 12-month double-blind ALN-controlled study period have a ± 7-day window (see Section 6.1.2 for romosozumab/placebo dosing window). Following the 12-month double-blind ALN-controlled study period, study visits have a ± 14-day window. The window for the monthly phone contact in between clinic visits throughout the study and the end of primary analysis period phone call is ± 7-days. Unscheduled follow-up clinic visits after the monthly phone contact have a + 21-day window. The window for the end of study phone contact is + 7 days.

With:

Study visit windows differ based on the type of visit and are clearly identified in the description of study visits in Section 7.3. All monthly study visits during the 12-month double-blind ALN-controlled study period have a ± 7-day window (see Section 6.1.2 for romosozumab/placebo dosing window). Following the 12-month double-blind ALN-controlled study period, study visits have a ± 14-day window. The window for the monthly phone contact in between clinic visits throughout the study **is ± 7 days**. ~~and~~ ~~t~~**T**he **window for the** end of primary analysis period phone call is **−14** days **to end of primary analysis**. Unscheduled follow-up clinic visits after the monthly phone contact have a + 21-day window. The window for the end of study phone contact is **−14 days to** + 7 days.

Section: 7.3.18

Replace:

7.3.18 Month 36 and Subsequent Clinic Visits Until End of Study (± 14 days) / Early Termination for the Month 24 to End of Primary Analysis Period

With:

7.3.18 Month 36 and Subsequent Clinic Visits ~~Until End of Study~~ (± 14 days)~~ / Early Termination for the Month 24~~ to the End of Primary Analysis Period

Section: 7.3.18, Month 36 and Subsequent Clinic Visits to the End of Primary Analysis Period

Replace:

For all subjects, at Month 36 and every 6 months thereafter

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed) (primary analysis period only)
- Physical examination
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry and hematology (to be processed and sent to the central laboratory during the primary analysis period; to be analyzed at local laboratories following the primary analysis period)

With:

For all subjects, at Month 36 and every 6 months thereafter **until the end of the primary analysis period**

- PRO/ClinRO questionnaires: OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain (should preferably be completed before any other study procedures are performed) (primary analysis period only)
- Physical examination
- Vital signs: blood pressure, temperature, and pulse
- Height and weight
- Blood sample for serum chemistry and hematology (to be processed and sent to the central laboratory during the primary analysis period~~; to be analyzed at local laboratories following the primary analysis period~~)

Section: 7.3.18, Month 36 and Subsequent Clinic Visits to the End of Primary Analysis Period

Replace:

For all subjects, at Month 36 and every 12 months thereafter

- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit (primary analysis period only)
- DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit (primary analysis period only)

With:

For all subjects, at Month 36 and every 12 months thereafter **until the end of the primary analysis period**

- Lateral spine x-rays (lumbar and thoracic), submitted to the central imaging vendor as soon as possible following the visit (primary analysis period only)
- DXA scans of lumbar spine and proximal femur, submitted to the central imaging vendor as soon as possible following the visit (primary analysis period only)

Section: 7.3.18, Month 36 and Subsequent Clinic Visits to the End of Primary Analysis Period

Replace:

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study, at Month 36 and every 12 months thereafter until end of the primary analysis period

- Fasting blood sample for P1NP and sCTX
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

With:

For subjects participating in the Imaging and PK/BTM/Biomarker sub-study, at Month 36 ~~and every 12 months thereafter~~ **or** until end of the primary analysis period**, whichever comes first**

- Fasting blood sample for P1NP and sCTX
- Blood sample for sclerostin and iPTH
- Blood sample (serum and plasma) for novel biomarker development

Section: 7.3.19

Add:

7.3.19 Clinical Visits after the Primary Analysis Period to End of Study

For all subjects, at every 6-month clinic visit thereafter

- **Physical examination**
- **Vital signs: blood pressure, temperature, and pulse**
- **Height and weight**
- **Blood sample for serum chemistry and hematology (to be analyzed at local laboratories following the primary analysis period, chloride, bicarbonate, and calculated adjusted calcium assessments are optional after primary analysis. (See Section 7.8.1)**
- **Nonvertebral fracture reporting**
- **Adverse event and concomitant medications data collection**
- **ALN dispensation (open-label, 6-month supply)**
- **Unused ALN collection (open-label)**

Section: 7.3.20

Replace:

7.3.21 Telephone Contacts in Between Clinic Visits (± 7 days)

With:

7.3.20 Telephone Contacts in Between Clinic Visits (± 7 days) **Until End of Study**

Section: 7.3.22

Replace:

7.3.21 Telephone Contact at "End of Primary Analysis Period" / "Early Termination" Telephone Contact Following the Primary Analysis Period (+ 7 days)

With:

7.3.22 Telephone Contact at "End of Primary Analysis Period" (**−14 days to End of Primary Analysis Period)** ~~/ "Early Termination" Telephone Contact Following the Primary Analysis Period (+ 7 days~~)

7.23.21 Telephone Contact at "End of Primary Analysis Period" (−14 days to End of Primary Analysis Period)

Add:

Note: If all the data required for an end of primary analysis telephone call has already been obtained during the 14 days prior to the end of the primary analysis period, no additional end of primary analysis period telephone call will be necessary.

Section: 7.3.22

Replace:

7.3.22 End of Study Telephone Contact (+ 7 days)

With:

7.3.23 End of Study Telephone Contact (**−14 to** + 7 days)

Section: 7.3.23, End of Study Telephone Contact (−14 to + 7 days)

Add:

Note: The end of study telephone contact will not be necessary for subjects who have had a clinic visit or have been contacted during this timeframe if all data required for the end of study telephone contact have been collected. The subjects, however, may be contacted after this time for additional safety information, follow-up, or possible follow on study opportunities.

Unused alendronate at the time of end of study should be returned to the site (Please refer to the study IPIM for additional details).

Section: 7.8.1 General

Replace:

Table 1 outlines the specific analytes for the serum chemistry and hematology assessments, as well as other assessments to be conducted on blood samples.

On-study (ie, after baseline/Day 1) laboratory results for serum calcium, albumin-adjusted calcium, phosphorus, and alkaline phosphatase (ALP), will not be reported to any study-related personnel in order to maintain the integrity of the study blind (refer to Section 10.3 for information on access to individual subject treatment assignments by Amgen). However, in the event of an abnormal value of clinical relevance (panic value), sites will be notified of the unblinded value by the central laboratory. In addition, laboratory results for romosozumab levels, sclerostin, BTMs

(P1NP, BSAP, OC, and sCTX), iPTH, and anti-romosozumab antibodies will not be reported to any personnel responsible for study-related management (including the sites). When a panic alert is issued for serum calcium, albumin-adjusted calcium levels, phosphorus, or ALP, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care.

With:

Table1 outlines the specific analytes for the serum chemistry and hematology assessments, as well as other assessments to be conducted on blood samples.

Chloride, bicarbonate, and calculated adjusted calcium assessments are optional after primary analysis.

On-study (ie, after baseline/Day 1) laboratory results for serum calcium, albumin-adjusted calcium, phosphorus, and alkaline phosphatase (ALP), will not be reported to any study-related personnel in order to maintain the integrity of the study blind **up until primary analysis. These laboratory results will not be blinded after primary analysis** (refer to Section 10.3 for information on access to individual subject treatment assignments by Amgen). However, in the event of an abnormal value of clinical relevance (panic value) **obtained in the central laboratory during the primary analysis period**, sites will be notified of the unblinded value by the central laboratory. In addition, laboratory results for romosozumab levels, sclerostin, BTMs (P1NP, BSAP, OC, and sCTX), iPTH, and anti-romosozumab antibodies will not be reported to any personnel responsible for study-related management (including the sites). When a panic alert is issued for serum calcium, albumin-adjusted calcium levels, phosphorus, or ALP, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care.

Section: 7.8.1 General

Table 1

Replace

Chloride		BSAP[a]	25 (OH) vitamin D
Bicarbonate	Platelets	OC[a]	iPTH[a]
Albumin-adjusted Calcium[a]			

[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 alkaline phosphatase in the event of a panic value.

With:

Chloride[b]		BSAP[a]	25 (OH) vitamin D
Bicarbonate[b]	Platelets	OC[a]	iPTH[a]
Albumin-adjusted Calcium[a,b]			

[a] **Until the end of the primary analysis** period, 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 alkaline phosphatase in the event of a panic value.
[b] **Chloride, bicarbonate, and calculated adjusted calcium assessments are optional after primary analysis.**

Section: 7.8.1 General

Replace:

If informed consent is provided by the subject, Amgen may do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the bone metabolic diseases, the dose response and/or prediction of response to 103 romosozumab or other protocol-specified therapy, as required, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

With:

If informed consent is provided by the subject, Amgen may do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the bone metabolic diseases, the dose response and/or prediction of response to ~~103~~ romosozumab or other protocol-specified therapy, as required, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

Section: 10.1.2 Secondary Endpoints

During the Primary Analysis Period

Add:

- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) through Month 24**
- **Subject incidence of nonvertebral fracture through Month 24**
- **Subject incidence of hip fracture through Month 24**
- **Subject incidence of clinical vertebral fracture through Month 24**

Section: 10.1.2 Secondary Endpoints

During the 12-month double-blind ALN-controlled study period

Add:

- **Subject incidence of nonvertebral fracture through Month 12**
- **Subject incidence of hip fracture through Month 12**
- **Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12**
- **Subject incidence of clinical vertebral fracture through Month 12**

Section: 10.1.2 Secondary Endpoints

For the overall study period

Add:

- **Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) at final analysis**
- **Subject incidence of hip fracture at final analysis**

Section: 10.1.3 Exploratory Endpoints

During the 12-month double-blind ALN-controlled study period

Replace:

- Subject incidence of new or worsening vertebral fracture through Month 12
- Subject incidence of nonvertebral fracture through Month 12
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Month 12
- Subject incidence of hip fracture through Month 12
- Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12
- Subject incidence of multiple new or worsening vertebral fractures through Month 12
- Actual value in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 6 and 12

With:

During the 12-month double-blind ALN-controlled study period

- Subject incidence of new or worsening vertebral fracture through Month 12
- ~~Subject incidence of nonvertebral fracture through Month 12~~
- Subject incidence of major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Month 12

- ~~Subject incidence of hip fracture through Month 12~~
- ~~Subject incidence of major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral) through Month 12~~
- Subject incidence of multiple new or worsening vertebral fractures through Month 12
- Actual value in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at Months 6 and 12

Section 10.1.3 Exploratory Endpoints

Add:

During the month 12 to 24 ALN study period

- **Subject incidence of new vertebral fractures between Month 12 and Month 24**
- **Subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) between Month 12 and Month 24**
- **Subject incidence of nonvertebral fracture between Month 12 and Month 24**
- **Subject incidence of hip fracture between Month 12 and Month 24**
- **Subject incidence of clinical vertebral fracture between Month 12 and Month 24**

Section: 10.1.6.3 Per-protocol Analysis Set

Replace:

The per-protocol analysis set includes subjects who are defined in Section 10.1.6.1 (for new vertebral fractures in the primary analysis period) or Section 10.1.6.2 (for clinical fracture and nonvertebral fracture in the primary or overall analysis period) and receive the active investigational product with no major protocol violations in the corresponding analysis period.

With:

The per-protocol analysis set includes subjects who are defined in Section 10.1.6.1 (for new vertebral fractures in the primary analysis period) or Section 10.1.6.2 (for clinical fracture and nonvertebral fracture in the primary or overall **study** analysis period) and receive the active investigational product with no major protocol violations in the corresponding analysis period.

Section: 10.1.7 Covariates

Replace:

The additional covariates of interest include the following:

- baseline body mass index (BMI)
- years since menopause at baseline
- prior nonvertebral osteoporotic fracture (yes, no)
- geographic region
- race/ethnicity
- prior use of bone-specific therapeutic agents (yes, no)
- 10-year probability of major osteoporotic fracture with BMD

With:

The additional covariates of interest include the following:

- baseline body mass index (BMI)
- years since menopause at baseline
- prior nonvertebral osteoporotic fracture (yes, no)
- geographic region
- race/ethnicity
- prior use of bone-specific therapeutic agents (yes, no)
- 10-year probability of major osteoporotic fracture with BMD **(as calculated by a third-party vendor)**

Section: 10.2 Sample Size Considerations

Add:

DXA BMD assumptions

The assumptions of mean percent change in DXA BMD and standard deviation for ALN at Month 12 and Month 24 are summarized in Table 2 (Schnitzer et al, 2000; Greenspan et al, 2002). Using the FRAME study, the assumptions of mean percent change in DXA BMD and standard deviation for romosozumab at Month 12 are summarized in Table 3 (Amgen, data on file). It is further assumed that at Month 24, romosozumab/ALN will maintain the BMD increase achieved at Month 12.

Table 2. Mean Percent Change From Baseline in BMD for Alendronate

	Mean % Change from Baseline	Standard Deviation
Lumbar spine at Month 12	**5.1**	**3.5**
Total hip at Month 12	**2.9**	**3.5**
Femoral neck at Month 12	**2.3**	**4.6**
Lumbar spine at Month 24	**6.3**	**4.9**
Total hip at Month 24[a]	**4.7**	**6.3**
Femoral neck at Month 24	**3.1**	**4.8**

[a] **The mean of percent change from baseline at hip trochanter is used as the assumption for total hip.**

Table 3. Mean Percent Change From Baseline in BMD at Month 12 for Romosozumab

	Mean % Change from Baseline	Standard Deviation
Lumbar spine at Month 12	**13.1**	**6.0**
Total hip at Month 12	**6.0**	**4.2**
Femoral neck at Month 12	**5.5**	**4.6**

Section: 10.2, Sample Size Considerations

Power

Replace

If both primary endpoints are significant under the Hochberg procedure, the nonvertebral fracture endpoint will be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test (α = 0.025). The Lan-DeMets alpha spending function (Lan and DeMets,1983) that approximates a Pocock boundary (Pocock, 1977), (0.025*LN(1+(EXP(1) -1)*information fraction)), will be used to determine the significance level at the time of the primary analysis. Based on the number of subjects with nonvertebral fractures at the time of the primary analysis out of the total 440 planned, which represents the information fraction in the alpha spending function, the significance level will be calculated at the time of primary analysis. For example, if the information fraction is 80% at time of the primary analysis, the significance level is 0.0216. Based on the simulation, the power for nonvertebral fracture and both primary endpoints being significant is 78% at the primary analysis.

If the significance of nonvertebral fracture is not demonstrated at the time of the primary analysis, the nonvertebral fracture endpoint will be tested again using a 1-sided test at

the time of the final analysis. Based on the alpha level spent at the primary analysis, the significance level at final will be determined. For example, if the information fraction is 80% at the primary analysis (ie, the significance level is 0.0216 at primary), the significance level at the final analysis will be 0.0119 using software EAST 5.4 or R gsDesign package. Based on the simulation, the power for nonvertebral fracture being significant at the primary or final analysis and both primary endpoints being significant at primary analysis is 84%.

With

If both primary endpoints are significant under the Hochberg procedure, **each of the following secondary DXA BMD endpoints will be tested hierarchically at 0.05 according to the following sequence: percent change from baseline in BMD at lumbar spine at Month 24, percent change from baseline in BMD at total hip at Month 24, percent change from baseline in BMD at femoral neck at Month 24, percent change from baseline in BMD at lumbar spine at Month 12, percent change from baseline in BMD at total hip at Month 12, and percent change from baseline in BMD at femoral neck at Month 12. The power for each DXA BMD endpoints is > 99% using the 2-sample *t*-test.**

If all preceding endpoints are significant, the nonvertebral fracture endpoint will be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test (α = 0.025). The Lan-DeMets alpha spending function (Lan and DeMets,1983) that approximates a Pocock boundary (Pocock, 1977), (0.025*LN(1+(EXP(1) -1)*information fraction)), will be used to determine the significance level at the time of the primary analysis. Based on the number of subjects with nonvertebral fractures at the time of the primary analysis out of the total 440 planned, which represents the information fraction in the alpha spending function, the significance level will be calculated at the time of primary analysis. For example, if the information fraction is 80% at time of the primary analysis, the significance level is 0.0216. Based on the simulation, the power for nonvertebral fracture and both primary endpoints **and DXA BMD endpoints at Month 12 and Month 24** being significant is **approximately** 78% at the primary analysis.

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

80% at the primary analysis (ie, the significance level is 0.0216 at primary), the significance level at the final analysis will be 0.0119 using software EAST 5.4 or R gsDesign package. Based on the simulation, the power for nonvertebral fracture being significant at the primary or final analysis and both primary endpoints **and DXA BMD endpoints at Month 12 and Month 24** being significant at primary analysis is **approximately** 84%.

Section: 10.5.1 General Approach/Considerations

Replace:

If both the primary endpoints are significant at the 0.05 level (2-sided), the nonvertebral fracture at the primary analysis will be evaluated based on a 1-sided test at the significance level determined by the alpha spending function specified in Section 10.2. All remaining secondary and exploratory efficacy endpoints will be tested at significance level of 0.05 without multiplicity adjustment~~t~~. If superiority of the nonvertebral fracture endpoint is achieved at the primary analysis and the study is stopped after the primary analysis has been performed, all data, including the additional safety and nonvertebral fracture data, collected after the primary analysis will be summarized descriptively and not be included in confirmatory testing.

With:

If both the primary endpoints are significant at the 0.05 level (2-sided), **each of the following secondary DXA BMD endpoints will be tested hierarchically at 0.05 (2-sided). If all preceding endpoints are significant,** the nonvertebral fracture at the primary analysis will be evaluated based on a 1-sided test at the significance level determined by the alpha spending function specified in Section 10.2. All remaining secondary and exploratory efficacy endpoints will be tested at significance level of 0.05 ~~without multiplicity~~ ~~adjustment~~. If superiority of the nonvertebral fracture endpoint is achieved at the primary analysis and the study is stopped after the primary analysis has been performed, all data, including the additional safety and nonvertebral fracture data, collected after the primary analysis will be summarized descriptively and not be included in confirmatory testing.

Section: 10.5.2.1 Efficacy Endpoints

Vertebral Fracture Endpoints

Replace:

Subject incidence of new vertebral fracture at a pre-specified time point will be compared between treatment groups using a logistic regression model adjusting for stratification factor age **(**< 75 or ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score.

With:

Subject incidence of new vertebral fracture at ~~a~~ pre-specified time point**s** will be compared between treatment groups using a logistic regression model adjusting for stratification factor age **(**< 75 or ≥ 75 years), presence or absence of severe vertebral fracture at baseline, and baseline total hip BMD T-score.

Section: 10.5.2.1 Efficacy Endpoints

Replace:

Other Fractures Endpoints

Major nonvertebral fractures, all fractures, major osteoporotic fractures, and hip fractures will be analyzed using the same approach as described for clinical fractures.

With:

Other Fractures Endpoints **at Specific Time Points**

Major nonvertebral fractures, all fractures, major osteoporotic fractures, **clinical vertebral fractures,** and hip fractures **at specific time points** will be analyzed using the same approach as described for clinical fractures.

Section: 10.5.2.1 Efficacy Endpoints

Add:

Fracture Endpoints Between Month 12 and Month 24

Subject incidence of new vertebral fractures between Month 12 and Month 24 will be described.

Subject incidence of clinical fracture, nonvertebral fracture, hip fracture, and clinical vertebral fracture between Month 12 and Month 24 will be summarized descriptively as for the clinical fracture endpoint.

Section: 10.5.2.1 Efficacy Endpoints

Patient and Clinician Reported Outcome
Replace

The change from pre-fracture baseline in PRO measures will be compared between treatment groups by visit since the reporting of the clinical fracture using regression model adjusting for fracture location and potentially other factors impacting the PRO as per the statistical analysis plan.

With

The change from pre-fracture baseline in PRO measures will be compared between treatment groups by visit since the reporting of the clinical fracture using regression model**s** adjusting for fracture location and potentially other factors impacting the PRO as per the statistical analysis plan.

Section: 10.5.2.1 Efficacy Endpoints

BTM and Biomarkers in the Substudy

Add:

Lumbar Spine BMD by DXA and BMD and estimated bone strength by QCT in the Sub-study

Lumbar spine BMD and estimated bone strength measured in the sub-study will be summarized by visit using the same approach as described for the main study.

Section: 13 References

Add

Greenspan SL, Schneider DL, McClung MR, et al. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2002;136:742-746.

Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging Clin Exp Res*. 2000;12:1-12.

Section: Appendix A Schedule of Assessments

Replace:

	12-month double-blind ALN-controlled study period														**Rest of Study**								
Procedure	**SCR & Full Rescreening [1]**	**D 1**	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**M 7**	**M 8**	**M 9**	**M 10**	**M 11**	**M 12**	**M 15[20]**	**M 18**	**M 24**	**M 30**	**M 36 [7]**	**Monthly contact [13]**		**End of Primary Analysis Period Phone Contact [8]**	**End of Study Phone Contact [9]**
																				Phone call	**Follow-up clinic visit**		
Lateral Spine X-Rays (lumbar and thoracic) [5]	X													X			X		X[18,]		X[14, 18]		

With:

	12-month double-blind ALN-controlled study period														**Rest of Study**								
Procedure	**SCR & Full Rescreening [1]**	**D 1**	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**M 7**	**M 8**	**M 9**	**M 10**	**M 11**	**M 12**	**M 15[20]**	**M 18**	**M 24**	**M 30**	**M 36 [7]**	**Monthly contact [13]**		**End of Primary Analysis Period Phone Contact [8]**	**End of Study Phone Contact [9]**
																				Phone call	**Follow-up clinic visit**		
Lateral Spine X-Rays (lumbar and thoracic) [5]	X													X			X		X[18,19]		X[14, 18]		

Replace

b) Phone contact to occur monthly in between clinic visits following the 12-month, double-blind, ALN-controlled study period. When a nonvertebral fracture is reported: Event to be recorded in eCRF, copies of radiographs or other diagnostic images and/or a copy of the radiology report, surgical report, or discharge summary should be obtained, included in the subject's study records and submitted to the central imaging vendor. When back pain is reported (until clinical fracture events have been confirmed by the central imaging vendor for at least 330 subjects and all subjects have had the opportunity to complete their Month 24 study visit): back pain (but not a vertebral fracture) will be recorded as an adverse event. The subject will be asked to complete an unscheduled follow-up clinic visit as soon as possible but no later than 21 days after reporting of the back pain. If at the unscheduled clinic visit, the investigator considers the back pain to be possibly due to a new or worsening vertebral fracture, a confirmatory lateral spine x-ray will be taken.

With

b) Phone contact to occur monthly in between clinic visits following the 12-month, double-blind, ALN-controlled study period **unti**l **the end of study**. When a nonvertebral fracture is reported: Event to be recorded in eCRF, copies of radiographs or other diagnostic images and/or a copy of the radiology report, surgical report, or discharge summary should be obtained, included in the subject's study records and submitted to the central imaging vendor. When back pain is reported (until clinical fracture events have been confirmed by the central imaging vendor for at least 330 subjects and all subjects have had the opportunity to complete their Month 24 study visit): back pain (but not a vertebral fracture) will be recorded as an adverse event. The subject will be asked to complete an unscheduled follow-up clinic visit as soon as possible but no later than 21 days after reporting of the back pain. If at the unscheduled clinic visit, the investigator considers the back pain to be possibly due to a new or worsening vertebral fracture, a confirmatory lateral spine x-ray will be taken.

Replace

c) Visit windows are ±7 days for the monthly study visits during the 12-month double-blind ALN-controlled study period, ± 14 days for clinic visits during the rest of the study. The window for the monthly phone contact in between clinic visits and the end of primary analysis period phone contact is ± 7 days. The window for the end of study contact is -14 to +7 days.

With

c) Visit windows are ±7 days for the monthly study visits during the 12-month double-blind ALN-controlled study period, ± 14 days for clinic visits during the rest of the study. The window for the monthly phone contact in between clinic visits and the end of primary analysis period phone contact is ± 7 days. The window for the end of study contact is **-14 to** +7 days.