
STATISTICAL ANALYSIS PLAN

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

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AFF	Atypical femoral fracture
ANCOVA	Analysis of covariance
BMD	Bone Mineral density
BMI	Body mass index
BTM	Bone turnover marker
BP	Blood pressure
CI	Confidence interval
CTCAE	Common terminology criteria of adverse events
CTX	Serum Type 1 Collagen C-Telopeptide
DRE	Disease Related Events
DXA	Dual X-ray absorptiometry
eCRF	Electronic case report form
EDC	Electronic data capture
End of Study (end of trial)	Defined as when the last subject is assessed or receives an intervention for evaluation in the study
End of Study (primary completion)	Defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	End of study
FAS	Full analysis set
GCP	Good clinical practice
IP	Investigational Product
IPD	Important protocol deviation
iPTH	Intact parathyroid hormone
IVRS	Interactive voice response system
LLOQ	Lower limit of qualification
MedDRA	Medical dictionary for regulatory activities
MACE	Major Adverse Cardiac Events
ONJ	Osteonecrosis of the jaw
P1NP	Procollagen type 1 N-terminal peptide
PFS	Prefilled syringe

Abbreviation or Term	Definition/Explanation
PMO	Postmenopausal osteoporosis
QM	Every month
Romosozumab	International nonproprietary name for AMG 785
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA query
ULOQ	Upper limit of qualification
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for romosozumab Study 20150242 **Amendment 2 dated 13 November 2017**. The scope of this plan includes all analyses that are planned and will be executed by the Biostatistics department or designee unless otherwise specified eg, standard PK tables may be provided by the Clinical Pharmacology, and Modeling and Simulation Group.

2. Objectives

2.1 Primary

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

2.2 Secondary

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

2.3 Exploratory

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

2.4 Safety

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

2.5 Pharmacokinetics (PK)

To characterize the serum romosozumab concentration at selected time points.

3. Study Overview

3.1 Study Design

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

Approximately 60 subjects will be randomized in a 1:1 ratio to receive 210 mg romosozumab subcutaneous (SC) QM (approximately 30 subjects) or matched placebo SC QM (approximately 30 subjects), respectively, in a blinded fashion for the duration of the 6-month treatment period. Upon completion of the 6-month treatment period, subjects will be followed for an additional 3 months to ensure appropriate follow-up for assessing anti-romosozumab antibody formation and safety.

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

The primary analysis of the study will be performed after all subjects have had the opportunity to complete the Month 6 visit. The final analysis will be performed after all subjects have had the opportunity to complete the Month 9 end of study visit. The overall study design is described by a study schema at the end of the protocol synopsis section.

3.2 Sample Size

The sample size is based on comparison of romosozumab to placebo on percent change from baseline in lumbar spine BMD at month 6. From an earlier Study 20060326, the estimated mean percentage differences in lumbar spine BMD between romosozumab versus placebo at month 6 were 7.9 with 95% CI (6.6, 9.3). The standard deviations (romosozumab vs. placebo) of mean percentage change in lumbar spine BMD at month 6 were 3.9 vs. 3.8. A sample size of 30 subjects per treatment arm will

provide >99% power to detect significant treatment difference (romosozumab vs. placebo) in percent change in lumbar spine BMD at month 6 assuming a mean percent difference of 6.6 and a standard deviation of 3.9 with two-sided type 1 error of 5% and 10% dropout rate under the two sample t-test.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

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

4.1.2 Secondary Endpoints

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

4.1.3 Exploratory Endpoints

- Percent changes from baseline in BTM: CTX and P1NP at Months 1, 3, and 6

4.1.4 Safety Endpoints

For the 6-month treatment period:

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

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

- Subject incidence of AEs by system organ class and preferred term
- Subject incidence of the formation of anti-romosozumab antibodies
- **Subject incidence of adjudicated positive cardiovascular serious adverse events**

4.1.5 Pharmacokinetic Endpoint

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

4.2 Planned Covariates

All analyses assessing BMD endpoints at the lumbar spine, femoral neck, and total hip will include treatment, baseline DXA BMD value, machine type (Hologic or Lunar), and the machine type-by-baseline DXA BMD value interaction as independent variables.

5. Hypotheses

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

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

6. Definitions

6.1 Basic Definitions

Investigational Product (IP)

Romosozumab or placebo.

Interactive Voice Response System (IVRS)

The system used to assign eligible subjects to randomized treatment as well as to manage IP supply at the site and track subjects' study termination data.

6.2 Study Points of Reference

Baseline

The baseline measurement is defined as the last measurement prior to the first dose of IP. If the measurement is taken on the same day as the first dose and the exact measurement time relative to the first dose is unknown, it will be assumed to have been taken prior to the first dose of IP. If a subject does not receive IP baseline is the closest recorded measurement on or prior to the randomization date. For baseline duplicate BMD, the baseline is obtained as the average of the measurements taken prior to the first dose of IP.

Study Day 1

The first day of IP administration or the day of randomization for subjects who do not receive any dose of IP.

Study Day

The number of days from Study Day 1, inclusive:

$$\text{Study Day} = (\text{Date of Interest} - \text{Date of Study Day 1}) + 1.$$

Analysis Visit Windows

Based on protocol, all monthly study visits up to month 5 have a -/+7 day window. The study visits at month 6 and month 9 have a -7/+ 3 day window. Study procedures for a specific visit may be completed on multiple days as long as all the procedures are completed within the visit window. To allow for variations in scheduling study visits, the analysis visit windows defined in [Appendix 13.1.2](#) will be used to assign evaluations to the most appropriate nominal visit for analysis and summarization.

6.3 Study Dates

Informed Consent Date

The date on which a subject signs the informed consent.

Screening Date

Screening date is defined as the date of the first screening visit if there is more than one screening visit.

Enrollment (Randomization) Date

The date on which a subject is assigned to one of the treatments through the IVRS.

First Dose Date

The date of administration of first dose of IP; this date may or may not be the same as the randomization date.

Last Dose Date

The date of administration of last dose of IP.

End of Study Date

End of study date is defined as the date of the last assessment for the Month 9 visit for subjects who completed the study; or the date of the last assessment for the early termination visit for subjects who discontinued the study.

End of 6-Month Treatment Period Date

End of treatment period date is defined as the date of the last assessment of Month 6 visit. For subjects who discontinued from the study before completing Month 6 visit, the end of study date is used for the end of treatment period date. For those subjects who

missed Month 6 visit and did not early terminate, the target day (Day 183) for Month 6 plus 3 days will be used as the end of treatment period.

Start of Follow-up Period Date

End of 6-month treatment period date plus one day.

6.4 Study Time Intervals

Screening Period

The time period between the date of informed consent and first dose of IP or randomization date for subjects who do not receive IP.

Treatment Period

The time period from the first dose date to the end of 6-month treatment period date inclusive.

Follow-up Period

For subjects entering in the 3-month follow-up period: the time period from the start of follow-up period date to the end of study date.

6.5 Subject Disposition

Enrolled (Randomized)

Individuals are considered enrolled if they have been assigned a randomization number. Enrolled individuals are referred to as “subjects”.

Exposed to IP

Subjects are defined as exposed to IP if they have a value for the sum of IP volume that exceeds zero.

6.6 Arithmetic Calculations

Age at Randomization Date

Number of whole years from a subject’s birthdate to the randomization date as recorded on the eCRF.

Estimated Glomerular Filtration Rate (eGFR)

$eGFR(mL/min/1.73 m^2)=175 \times (S_{cr, std})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

where $S_{cr, std}$ is serum creatinine in standard unit (mg/mL)

Percent Change From Baseline

The change from baseline value divided by baseline value and multiplied by 100:

$((\text{value at date of interest} - \text{baseline value}) / \text{baseline value}) * 100.$

Subject Incidence for AEs

The subject incidence for a given event in a given time period is defined as the number of subjects with ≥ 1 reported occurrence of the event divided by the number of subjects who are at risk for having the event at the beginning of the given time period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

BMD Value for Duplicate Scans

For DXA scans of spine and femur where duplicate measurements are taken, the mean of duplicate records will be used for analysis.

6.7 Study Analyses

6.7.1 Primary Analysis

The analysis of primary, secondary, exploratory, as well as the safety endpoints through Month 6 is considered the primary analysis. The primary analysis will be performed when all subjects have had the opportunity to complete the treatment period (Month 6 visit).

6.7.2 Final Analysis

Final analysis will include the analysis of primary, secondary, exploratory efficacy endpoints, as well as the safety endpoints through 6-month treatment period and the analysis of safety endpoints (adverse events and formation of anti-romosozumab antibodies) for the 9-month study period. The final analysis will be performed when all subjects have completed the 6-month treatment period and the 3-month followup period.

7. Analysis Subsets

7.1 Full Analysis Set

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

7.2 BMD Efficacy Analysis set

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

7.3 BTM Efficacy Analysis set

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

7.4 Safety Analysis Set

The safety analysis subset will include all randomized subjects who receive at least 1 dose of IP. These subjects will be analyzed according to their actual treatment received, where subjects who receive at least 1 dose of romosozumab will be analyzed in the romosozumab treatment group regardless of the randomized treatment.

7.5 Pharmacokinetic Set

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

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

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

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

All data for this study will be received from Amgen's data management department and will be housed within the Electronic Data Capture (EDC) database, Rave. All screening and on-study blood samples will be processed by the central laboratory and will be electronically transferred to the Amgen database. All imaging data will be submitted to the central imaging vendor for analysis. The results from the central imaging vendor analysis will be electronically transferred to the Amgen database. All other data will be captured on the eCRF.

An Analysis Dataset for PK Concentrations (ADPC) will be provided to CPMS from Biostatistics.

9.3 Handling of Missing and Incomplete Data

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

9.3.1 BMD by DXA

Missing baseline BMD by DXA at any anatomical site will not be imputed. For purposes of the primary efficacy endpoint analysis and secondary efficacy analyses, observed BMD data at month 6 will be used in the ANCOVA models. **Lumbar spine scans at Month 6 will be acquired in duplicate and the average, when both duplicate values are available, will be used. For proximal femur scans, the left side should be used for all scans at all visits. If the right side must be used or is inadvertently used at baseline, then it must be used consistently throughout the study.** Only BMD values collected from the same body site as the baseline BMD will be used for analyses.

9.3.2 Bone Turnover Markers

Missing BTM (either baseline or post-baseline values) and PK data will not be imputed. Any values below the lower limit of quantification will be imputed using the lower limit of quantification for analysis **for BTM and 0 for serum romosozumab concentrations.**

9.3.3 Dates

No imputation will be done on incomplete stop date of an AE or a concomitant medication. The imputation rules for incomplete start dates of AEs or concomitant medications are provided in [Table 1](#). AEs with a partially missing start date that occur prior to Study Day 1 will be considered pre-treatment AEs and excluded from safety analyses. Missing years will not be imputed under any condition. Partial dates will be listed as is on the listings

Table 1. Imputation Rules on Partial Start Date of AE or Concomitant Medication

	Missing	Impute	Exception
Start Date	Day	01	Default to Study Day 1 Date if the event started in the same year and month as Day 1
	Day / Month	01JAN	Default to Study Day 1 Date if the event started in the same year as Day 1

If a death date is incomplete and missing only the day field, it will be imputed as the first day of the month if the latest date from other data is before the month of the death.

However, if the latest date is during the same month as the death, the partial death date will be imputed using the latest date.

For dates of last menstrual period, the imputation rules for partial dates are as follows: if the day is missing, default to day 15; if both month and day are missing, default to July 1st. If the imputed date is on or after the randomization date, default to randomization date minus 1. Missing years will not be imputed under any conditions.

9.3.4 Lab Parameters

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

9.4 Outliers

Observations found to be due to data entry errors will be corrected by the study team before final database lock. Potential outliers that are not due to data entry error will be included in the primary analysis. The validity of any questionable values will be confirmed. No valid measurement will be purposely excluded from descriptive or inferential analyses. However, sensitivity analyses **excluding the outliers** may be conducted to evaluate the influence of extreme values in the data. These analyses will be documented in the clinical study report.

9.5 Distributional Characteristics

The assumptions underlying the parametric models analyzed for continuous data will be checked. In cases where residuals indicate marked departures from the assumptions, additional sensitivity analyses will be performed using transformations or alternate methods such as nonparametric or robust procedures.

9.6 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified according to processes described in procedures or technical manuals about the "Configuration

Management of Statistical Analysis and Reporting Systems”, “Statistical Analysis and Reporting System Development and Validation”, and “Development of Statistical Analysis and Reporting Systems”.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment consists of Amgen-supported versions of The SAS System running on the Sun Solaris operating system. Because it is common for multiple versions of SAS to be available during the study period, the SAS version used to produce analyses will be documented in the validation documentation and the clinical study report.

10. Statistical Methods of Analysis

10.1 General Principles

The hypotheses will be tested and the romosozumab treatment effects will be estimated using statistical models and summary statistics.

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

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

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

10.2 Subject Accountability

The disposition of all randomized subjects will be tabulated by randomized treatment group. Subject enrollment and disposition for the number (%) of subjects randomized, successfully completing IP administration, completing the 6 month treatment period, and completing the 9 month study period will be included. The disposition of subjects will also include the number (%) of subjects who withdrew from the IP and their reasons for withdrawal, study completion, and the number of subjects who withdrew from study and their reasons for withdrawal.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list is used to produce the summary of IPDs table and the list of subjects with IPDs.

Eligibility deviations are defined in the protocol. A summary table and a list of deviations from eligibility criteria will also be generated.

10.4 Demographic and Baseline Characteristics

Subject demographic and baseline disease characteristics as listed below will be summarized by treatment group based on the FAS defined in [Section 7.1](#).

- demographics (race, sex, ethnicity, age at study entry [year], age groups [<65 , ≥ 65 to <75 , and ≥ 75])
- body composition (height [cm], weight [kg], BMI [kg/m²])
- BMD T-score at lumbar spine, total hip and femoral neck
- BMD (g/cm²) by machine type at lumbar spine, total hip and femoral neck
- bone turnover markers (CTX, P1NP)
- years since menopause (year)
- fracture history (Y/N) (**including historic fracture, historic fracture at age ≥ 45 , historic fracture at age ≥ 55 , time since the most recent fracture in months**)
- laboratory parameters (calcium corrected by albumin, phosphorus, **creatinine, estimated glomerular filtration rate (eGFR), eGFR [< 15 , 15 to < 30 , 30 to < 60 , 60 to < 90 , and ≥ 90 mL/min/1.73m²]**), serum 25 (OH) vitamin D level and iPTH)
- glucocorticoid use (Yes, No)
- substance use in the past 5 years including tobacco use (never, former, current); alcoholic beverages (none, ≤ 2 per day, ≥ 3 per day);
- baseline use of vitamin D (Yes, No)
- baseline use of calcium (Yes, No)
- parental hip fracture (Yes, No, Unknown)
- secondary osteoporosis (Yes, No)
- rheumatoid arthritis (Yes, No)
- **cardiovascular risk factors (age ≥ 75 , < 75], smoking history and other clinical history including hypertension, diabetes, cardiovascular disease, and hypercholesterolemia)**

The cardiovascular risk factors of history of hypertension, diabetes, cardiovascular disease, central nervous system vascular disorder and hypercholesterolemia will be identified based on the Medical & Surgical History eCRF based on MedDRA version 20.0 or later. The SMQ for Hypertension, the SMQ for Hyperglycaemia, and the SOC of Cardiac Disorders and Vascular Disorders will be used to identify preferred terms associated with hypertension, diabetes and cardiovascular disease, respectively. The Dyslipidaemia SMQ will be used to identify history of hypercholesterolemia, excluding terms associated with conditions of low cholesterol or increased high-density lipoprotein. The preferred terms utilized are listed in [Appendix 13.4](#).

Summary tables of prior and concomitant medication will also be generated by treatment group using FAS.

Subject demographic and history of cardiovascular risk factors will be summarized using all subjects in FAS.

10.5 Dose of Calcium Supplement and Vitamin D Loading Dose Administration at Baseline

Calcium supplement dose and Vitamin loading dose will be summarized by baseline vitamin D level (< 20 ng/mL, ≥ 20 ng/mL and ≤ 40 ng/mL, and > 40 ng/mL) and randomized treatment group.

10.6 Efficacy Analyses

All statistical testing will be 2-sided. The baseline value of BMD and machine type will be included in the statistical model for primary and secondary efficacy analyses. For each of the efficacy BMD endpoints (lumbar spine, total hip, and femoral neck at Month 6), descriptive statistics will be provided for **actual** values and percent change from baseline at post-baseline visit by machine type and visit.

10.6.1 Primary Analysis of Primary Efficacy Endpoint

The primary analysis to assess the percent change from baseline in lumbar spine DXA BMD at Month 6 will employ an ANCOVA model. The ANCOVA model will include treatment, baseline DXA BMD value as main effects. Additional covariates of machine type (Hologic or Lunar) and machine type by baseline DXA BMD value interaction will also be included in the model to adjust for the effect of machine type on baseline DXA BMD value. SAS procedure PROC MIXED is to be used to obtain the least squares means (LSM) point estimates of the percent change from baseline for each treatment

arm. Model based adjusted treatment difference of LSM with associated 95% CI and corresponding p-value will be presented. SAS code fragments are provided in Appendix 13.2.1.

Conclusion for the primary efficacy hypothesis of different efficacy of romosozumab compared with placebo at lumbar spine BMD at 6 months will be made using a 2 sided test with type 1 error rate of 0.05.

The primary analysis will use the BMD efficacy analysis set.

10.6.2 Primary Analysis of Secondary Efficacy Endpoints

For each of the secondary efficacy BMD endpoints (total hip and femoral neck percent change from baseline at Month 6), the analysis approach follows that specified in [Section 10.6.1](#).

10.6.3 Analyses of Exploratory Efficacy Endpoints

For P1NP and CTX, descriptive statistics will be presented by treatment group at each visit for both absolute values, change from baseline and the percent change from baseline values. Graphs depicting median and interquartile ranges by treatment group for percent change over time will be provided. The significance of the treatment difference for the percentage change from baseline at each visit will be assessed using a Wilcoxon Rank-Sum test. SAS code fragments are provided in Appendix 13.2.2.

The BTM efficacy analysis subset will be used for these analyses.

10.7 Safety Analyses

Safety data will be summarized by the actual treatment received in the treatment period (any subject randomized to placebo who incorrectly receives ≥ 1 dose of romosozumab will be analyzed as receiving romosozumab and any subject randomized to romosozumab who incorrectly only receives placebo doses will be analyzed as receiving placebo).

Safety data for the 6-months of treatment period and the 9-month study period will be summarized using safety analysis set defined in [Section 7.4](#).

10.7.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all AEs to a system organ class and a preferred term. AEs will be summarized in the 6-month treatment period and in the 9-month study period for all subjects who receive at least one dose of IP in the treatment period, ie, safety analysis

set. The subject incidence rates for the 9-month study period will include all events that occurred in the 6-month treatment period, and in addition, all events that occurred in the additional 3 month follow-up period. In addition, AEs reported between month 6 and month 9 (no treatment phase) will be listed by subject number and treatment received in the first 6 months.

All AE tables will be summarized by treatment group. The subject incidence of AEs will be summarized for all treatment emergent, serious, treatment related, serious treatment related, leading to withdrawal of IP, fatal, and of special interest. Subject incidence of special interest adverse events will also be summarized according to their categories.

Subject incidence of all treatment emergent, , serious, those leading to withdrawal of IP, related to IP adverse events will be tabulated by system organ class (SOC) and preferred term in descending order of frequency in the romosozumab arm. Fatal adverse events will be tabulated by preferred term in descending order of frequency in the romosozumab arm.

Disease related events (DRE) will be indicated in the AE listing and only tabulated with sufficient data.

10.7.1.1 Events of Interest (EOIs)

Events of interest of hypersensitivity and malignancy will be identified using a narrow search/scope in standardized MedDRA queries (SMQ). Event of interest of hypocalcemia, injection site reaction, hyperostosis, and osteoarthritis will be identified using Amgen-defined MedDRA search strategies. Subject incidence rates of these events will be provided.

Adjudicated positive cardiovascular serious adverse events, adjudicated AEs of osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) will also be summarized as EOIs.

10.7.1.1.1 Osteonecrosis of the Jaw Adjudication

The events of ONJ which occurred in the study will be adjudicated and summarized. All potential events of ONJ identified through a pre-defined search of the MedDRA terms will be submitted to the ONJ Adjudication committee for review and adjudication. The committee will determine whether the event meets the case definition criteria for ONJ.

Number of adjudicated positive ONJ events will be summarized.

10.7.1.1.2 Atypical Femoral Fracture Adjudication

The events of AFF which occurred in the study will be adjudicated and summarized. All potential events of AFF identified through a pre-defined search of the MedDRA terms will be submitted to the AFF Adjudication committee for review and adjudication. The committee will determine whether the event meets the case definition criteria for AFF.

Number of adjudicated positive AFF events will be summarized.

10.7.1.1.3 Injection Site Reaction

The duration, severity and nature (concomitant, recurrent) of the injection site reactions will be summarized. The time (in days) to first injection site reaction will also be summarized descriptively.

10.7.1.1.4 Adjudicated Positive Serious Cardiovascular Events

All deaths and potential cardiovascular-related serious AEs will be submitted to an external independent committee comprised of experienced cardiologists for adjudication. The committee will adjudicate the events and determine whether the event is cardiovascular in nature.

Only events confirmed positive by the adjudication committee to meet cardiovascular event definition criteria will be included for analysis. Adjudicated cardiovascular events of death, cardiac ischemic event, cerebrovascular event, non-coronary revascularization, heart failure and peripheral vascular events not requiring revascularization will be summarized using subject incidence rates. No statistical tests will be performed

10.7.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics (absolute value, change from baseline and percent change from baseline) over time by visit for the 6-month treatment period for selected analytes (hemoglobin, lymphocytes, total neutrophils, white blood cell, phosphorus, alkaline phosphatase, calcium corrected by albumin, magnesium, glucose, alanine amino transferase [ALT], aspartate amino transferase [AST], eosinophil, total bilirubin, and creatinine). Of note, these summaries will also be provided in conventional units for: hemoglobin, phosphorus, magnesium, total bilirubin, creatinine and calcium corrected by albumin.

Laboratory shift tables based on Common Terminology Criteria for Adverse Events v3.0 (CTCAE) will also be provided to compare baseline laboratory values with the most extreme post-baseline values through 6 months. Subject incidence of worst

post-baseline calcium corrected by albumin CTCAE grades decreases will also be summarized. The percentages of subjects with laboratory toxicities \geq grade 3 CTCAE will be summarized.

Graphs showing central tendency and dispersion of the absolute values and percent changes from baseline by visit will also be provided for the following laboratory parameters: calcium corrected by albumin, phosphorus and alkaline phosphatase.

Drug-induced liver injury will be assessed by evaluating subjects for Hy's Law. Hy's law laboratory criteria are defined as AST or ALT $>$ 3 times upper limit of normal (ULN), total bilirubin $>$ 2 times ULN, and alkaline phosphatase $<$ 2 times ULN assessed within 7 days. Subjects who meet these Hy's law laboratory criteria on study will be further evaluated to assess whether there exist underlying conditions or concomitant medications which can explain the elevation in laboratory analytes in order to assess whether these cases are true Hy's law cases.

All these analyses will be performed using the safety analysis set.

10.7.3 Vital Signs, Body Weight, and BMI

Descriptive statistics of actual values and changes from baseline in vital signs (systolic and diastolic blood pressure, heart rate, and temperature), body weight, and BMI will be presented by scheduled visit. These analyses will be performed using the safety analysis set.

10.7.4 Antibody Formation

The incidence and percentage of subjects who develop anti-romosozumab antibodies (binding, and if positive, neutralizing) at months 1, 3, and 6 will be tabulated by treatment group for primary analysis **and repeated for the final analysis to include all testing results from samples collected during the 3-month follow-up period (at month 9)**.

For subjects who develop anti-romosozumab antibodies, romosozumab serum concentrations may also be analyzed. Subjects who test positive for binding antibodies against romosozumab will be interpreted as transient positive if the binding antibody status was negative at the subject's last time point tested within the study period. Subjects who test positive for neutralizing antibodies against romosozumab will be interpreted as transient positive if the neutralizing antibody status was negative at the subject's last time point tested within study period.

10.7.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by randomized treatment group. The number of days on study, the number of doses received, and the cumulative exposure to IP will be summarized using the full analysis set.

10.8 Pharmacokinetic Analyses

Individual and mean serum romosozumab concentration-time data will be tabulated and presented graphically using nominal times. Descriptive statistics will be provided for romosozumab serum concentrations at each time point. The data set will be analyzed using the current version of Phoenix WinNonlin within the Pharsight Knowledgebase System (PKS) data repository. Romosozumab serum concentrations with values below the lower limit of quantification will be set to zero for analysis. Reasons for excluding any data from the PK analyses will be provided. These analyses will be performed by the **CPMS** group.

11. Changes From Protocol-specified Analyses

12. Literature Citations / References

13. Appendices

13.1 Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

13.1.1 Dates

All dates should be converted to SAS dates prior to their use in any calculation.

13.1.2 Analysis Visit Windows

For the baseline assessment (excluding DXA), regardless of the width of the visit window, if there are multiple records within a Baseline window, the record that is the closest to and on or prior to Study Day 1 will be considered as the baseline value.

For the post-baseline assessment, if more than 1 visit falls within the defined window, the result from the visit closest to the target day will be used. If 2 evaluations are of the same distance from the target day, the result from the later visit will be used.

To allow for variations in scheduling, the following visit windows will be used to assign evaluations to a most appropriate nominal visit for analysis and summarization.

Furthermore, there will be no gaps between visit windows in order to include as many data points as possible for summarization.

Spine and Hip DXA Scans

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline ^a	1	Last evaluation prior to or on Study Day 1
Month 6	183	≥ Study Day 2

^a If results from baseline DXA are not available, the results from scans taken on or before Study Day 14 will be considered baseline values and not the Month 6 values.

Serum Romosozumab Levels and BTMs (serum CTX and P1NP) and Laboratory Assessments

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to or on Study Day 1
Month 1	31	Study Day 2 to 61
Month 3	92	Study Day 62 to 137
Month 6	183	≥ Study Day 138

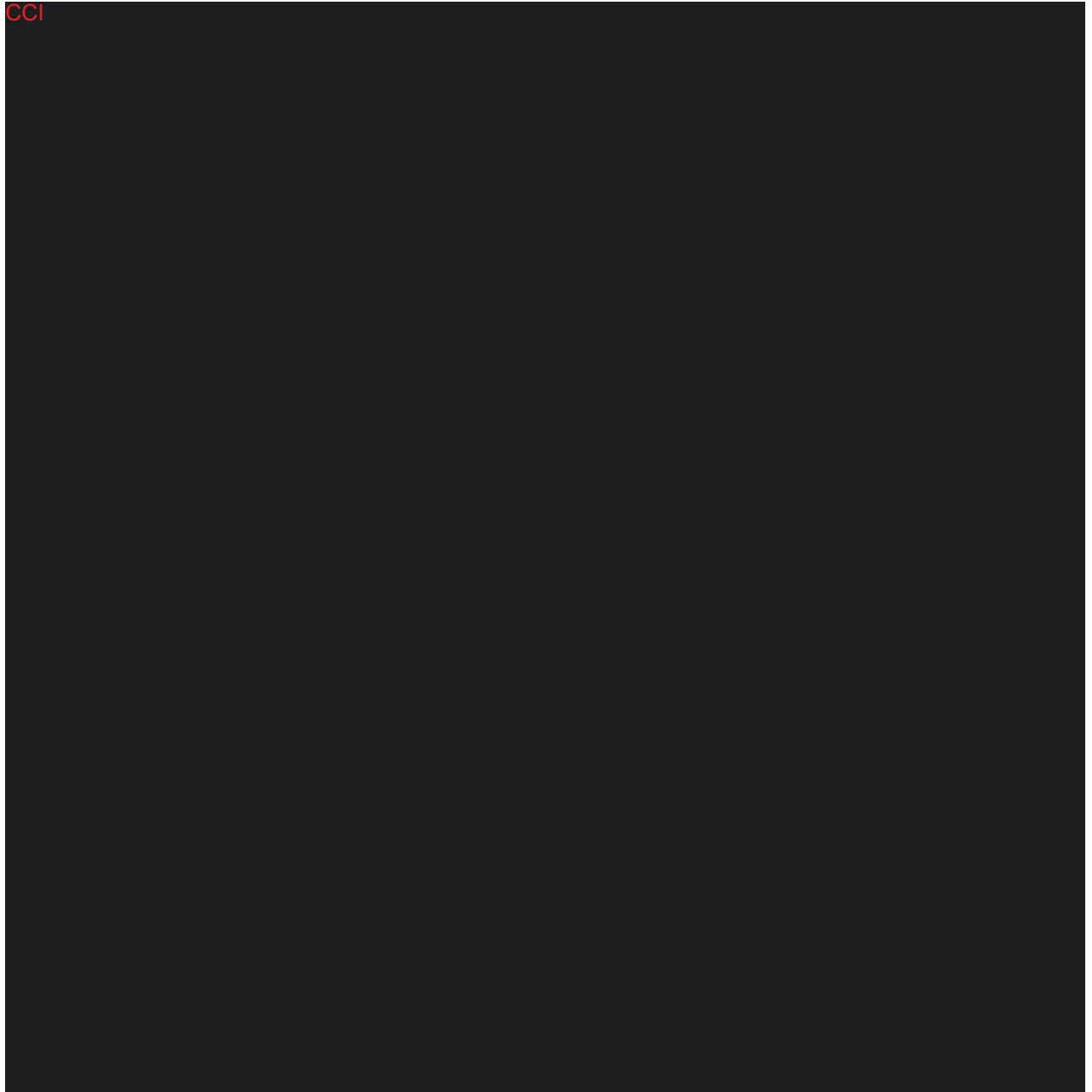
Vital Signs

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to or on Study Day 1
Month 1	31	Study Day 2 to 61
Month 6	183	≥ Study Day 62

Antibody Assessments

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to or on Study Day 1
Month 1	31	Study Day 2 to 61
Month 3	92	Study Day 62 to 137
Month 6	183	Study Day 138 to 229
Month 9	275	≥ 229

CCI



CCI



13.3 Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) are available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf.

13.4 Cardiovascular Medical History Risk Factor Preferred Terms

<u>Risk Factor</u>	<u>Preferred Terms^a</u>
<u>Hypercholesterolemia</u>	<u>Acquired lipoatrophic diabetes</u> <u>Acquired mixed hyperlipidaemia</u> <u>Apolipoprotein B/Apolipoprotein A-1 ratio increased</u> <u>Autoimmune hyperlipidaemia</u> <u>Blood cholesterol abnormal</u> <u>Blood cholesterol esterase increased</u> <u>Blood cholesterol increased</u> <u>Blood triglycerides abnormal</u> <u>Blood triglycerides increased</u> <u>Diabetic dyslipidaemia</u> <u>Dyslipidaemia</u> <u>Familial hypertriglyceridaemia</u> <u>Fat overload syndrome</u> <u>High density lipoprotein abnormal</u> <u>High density lipoprotein decreased</u> <u>Hypercholesterolaemia</u> <u>Hyperlipidaemia</u> <u>Hypertriglyceridaemia</u> <u>Hypo HDL cholesterolaemia</u> <u>Intermediate density lipoprotein increased</u> <u>LDL/HDL ratio increased</u> <u>Lipid metabolism disorder</u> <u>Lipids abnormal</u> <u>Lipids increased</u> <u>Lipoprotein (a) abnormal</u> <u>Lipoprotein (a) increased</u> <u>Low density lipoprotein abnormal</u> <u>Low density lipoprotein increased</u> <u>Non-high-density lipoprotein cholesterol increased</u> <u>Remnant hyperlipidaemia</u> <u>Remnant-like lipoprotein particles increased</u> <u>Total cholesterol/HDL ratio abnormal</u> <u>Total cholesterol/HDL ratio decreased</u> <u>Type I hyperlipidaemia</u> <u>Type II hyperlipidaemia</u> <u>Type III hyperlipidaemia</u> <u>Type IIa hyperlipidaemia</u> <u>Type IIb hyperlipidaemia</u> <u>Type IV hyperlipidaemia</u> <u>Type V hyperlipidaemia</u> <u>Very low density lipoprotein abnormal</u> <u>Very low density lipoprotein increased</u>

^a Preferred terms were identified based on the dyslipidaemia SMQ by eliminated preferred terms indicative of low cholesterol or increased high-density lipoprotein coded based on MedDRA version 20.0 or later