Statistical Analysis Plan

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

Abbreviation or Term	Definition/Explanation
AI/Pen	autoinjector/pen
AFF	atypical femoral fracture
ANCOVA	analysis of covariance
BMD	bone mineral density
BTM	bone turnover marker
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DXA	dual-energy x-ray absorptiometry
eGFR	estimated glomerular filtration rate
EOI	event of interest
HCP	healthcare provider
IP	investigational product
IPDs	Important Protocol Deviations
IVRS	interactive voice response system, telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
LLOQ	lower limit of quantitation
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
ONJ	osteonecrosis of the jaw
P1NP	procollagen type 1 N-telopeptide
PK	pharmacokinetic
PFS	prefilled syringe
QM	once a month
SC	subcutaneous
sCTX	serum type-1 collagen C-telopeptide
SMQ	standardized MedDRA queries
ULN	upper limit of normal
ULOQ	upper limit of quantification

1. Introduction

The purpose of this Statistical Analysis Plan is to provide details of the statistical analyses that have been outlined within the protocol for Study 20150120, Romosozumab dated 10 August 2017. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

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

Objectives	Endpoints
Exploratory	
[redacted]	

2.2 Hypotheses and/or Estimations

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

3. Study Overview

3.1 Study Design

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

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

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

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

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

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

3.2 Sample Size

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

[redacted]

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

4. Covariates and Subgroups

4.1 Planned Covariates

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

4.2 Subgroups

No subgroups will be evaluated in this study.

5. Definitions

5.1 Basic Definitions

Investigational Product (IP)

Romosozumab 210 mg QM

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.

Treatment-emergent Adverse Events

Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to the end of study date.

Serious adverse events (SAEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to the end of study date.

5.2 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 taken on the same day, the baseline is obtained as the average of the measurements.

Note: If baseline result from DXA assessment is not available, the result assessed on or before Study Day 14 will be considered baseline.

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:

Study Day = (Date of Interest – Date of Study Day 1) + 1

For days prior to Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1)

Analysis Visit

To allow for variations in scheduling study visits, the analysis visit windows defined in Appendix A will be used to assign evaluations to the most appropriate nominal visit for analysis and summarization.

5.3 Study Dates

Enrollment (Randomization) Date

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

First Dose Date

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

Last Dose Date

The date of administration of last dose of IP

Study Day 1

Study day 1 is defined as the first dose date. For subjects who did not receive IP, study day 1 is defined as the randomization date.

End of the 6-Month Treatment Period Date

The end of the 6-month treatment period date is defined as the date of the last assessment at the Month 6 visit. For subjects who discontinue from the study before completing the Month 6 visit, the end of study date is used for the end of the 6-month treatment period end date. For those subjects who missed the Month 6 visit but did not terminate the study early, the target day (Day 183) for Month 6 plus 3 days will be used as the end of the 6-month treatment period date.

Start of the Follow-up Period Date

The start of the follow-up period date is defined as the end of the 6-month treatment period date plus one day.

End of the Follow-up Period Date

For subjects with non-missing start of the follow-up period date, the end of the follow-up period date is defined as the end of study date as recorded on the electronic case report form (CRF).

5.4 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 the 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.

5.5 Subject Disposition

Enrolled

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

Exposed to IP

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

5.6 Arithmetic Calculations

Percent Change from Baseline

The change from baseline value divided by the baseline value and multiplied by 100: ((value at date of interest – baseline value) / 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 at least 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.

6. Analysis Sets

6.1 Full Analysis Set

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

6.1.1 Primary Efficacy Analysis Subset

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

6.1.2 Hip Bone Mineral Density Efficacy Analysis Subset

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

6.1.3 Bone Turnover Marker Analysis Subset

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

6.2 Safety Analysis Subset

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, such that subjects who received at least 1 dose of the romosozumab self-administration by AI/Pen will be analyzed in the romosozumab self-administration by AI/Pen treatment group, regardless of the randomized treatment.

6.3 Per Protocol Analysis Subset

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

6.4 Pharmacokinetic Analysis Subset

The pharmacokinetic analysis subset includes all randomized subjects who received at least 1 dose of IP and have at least 1 reported pharmacokinetic concentration result. Subjects will be analyzed according to their actual treatment received.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

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

7.2 Primary Analysis

The primary analysis will be performed after all subjects have had the opportunity to complete the Month 6 visit. Only data from the 6-month treatment period will be summarized for the primary analysis. The primary objective of the primary analysis is to evaluate the noninferiority of the effect of self-administering 210 mg romosozumab QM via AI/Pen compared with the effect of 210 mg romosozumab QM administered by HCP via PFS in postmenopausal women with osteoporosis with respect to percent change from baseline in DXA BMD of lumbar spine at Month 6. Formal statistical testing will be conducted to evaluate the following hypothesis: the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects self-administering 210 mg romosozumab QM with AI/Pen is not inferior to that in subjects receiving 210 mg

romosozumab QM by HCP administration with PFS using a margin of -2 percentage points. The lower bound of the 1-sided 97.5% CI from mean treatment difference (self-administration with AI/pen minus HCP administration with PFS) for the treatment arms will be compared with the noninferiority margin of -2% for assessing noninferiority.

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

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

[redacted]

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

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

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

7.3 Final Analysis

The final analysis will be performed after all subjects have had the opportunity to complete the Month 9 visit, ie, after all subjects have had the opportunity to complete the 3-month follow-up study period. Cumulative safety data from the 6-month treatment and follow up periods will be summarized for the final analysis. The 3-month follow-up period will provide the opportunity to monitor all subjects for adverse events and formation of anti-romosozumab antibodies.

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

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

8. Data Screening and Acceptance

8.1 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.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

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

8.3.1 DXA BMD Endpoints

Lumbar spine scans at screening and Month 6 will be acquired in duplicate. The average of the duplicate scans on the same day will be used for analyses. For proximal femur DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study.

For the primary analysis, 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 analysis of covariance (ANCOVA) models. If a subject has BMD values from different DXA machine types (ie, Hologic and Lunar) only those BMD values that are collected from the same machine type as the baseline BMD will be used for analyses. For proximal femur scans that are measured on different body sides (i.e., left and right), only those BMD values that are collected from the same body site as the baseline BMD will be used for analyses.

A sensitivity analysis will be performed using multiple imputation to evaluate the primary and secondary endpoint analyses. In this analysis, the missing baseline or Month 6 DXA values will be imputed separately resulting in 5 complete sets by Markov Chain Monte Carlo (MCMC) method for each endpoint. The imputation model will include the baseline value, machine type, and treatment group.

8.3.2 Bone Turnover Markers

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

8.3.3 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 8-1 and Table 8-2. 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.

Table 8-1. 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 Study Day 1
	Month	JAN	Default to Study Day 1 if the event started in the same year as Study Day 1
	Day / Month / Year	First Dose Date	Use randomization date for subjects who did not receive investigational product

Table 8-2. Imputation Rules on Partial Start Date of IP Administration in AI/Pen Arm

	Missing		Impute
Start Date	Day		Dispensed date (If the month and year of start date is the same with the month and year of dispensed date) 01 (If the month of start date is different with month of dispensed date)
	Day / Month		Dispensed date
	Month	If the year is the same with the year of dispensed date	Month of dispensed date (if the day is larger or equal to the day of dispensed date) Month of dispensed date plus one (if the day is less than the day of dispensed date)
		If the year is different with the year of dispensed date	Month of dispensed date plus one

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.

8.3.4 Laboratory Parameters

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

8.4 Detection of Bias

Not Applicable.

8.5 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 may be conducted to evaluate the influence of extreme values in the data. These analyses will be documented in the clinical study report.

8.6 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.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.
Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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

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

9.2 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 investigational product administration, completing the 6-month treatment period (Primary Analysis), and completing the study (Final Analysis) will be included. The disposition of subjects will also include the number (%) of subjects who withdrew from the IP and their reasons for withdrawal.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline disease characteristics as listed below will be summarized by treatment group based on the Full Analysis Set defined in Section 6.1.

- Race
- Ethnicity (Hispanic, non-Hispanic)
- Age at randomization
- Age groups (< 65, ≥ 65 years; < 75, ≥ 75 years; ≥ 18 - < 65 years, ≥ 65 - < 75 years, ≥ 75 - < 85 years, ≥ 85 years)

- Body composition (height [cm], weight [kg], BMI [kg/m^2])
- BMD T-score at the lumbar spine, total hip and femoral neck
- Bone turnover markers (sCTX, P1NP)
- Years since menopause
- Fracture history (Yes, No)
- Laboratory parameters (calcium corrected by albumin, phosphorus, creatinine, serum 25(OH) vitamin D, eGFR)
- Prior osteoporosis medication use (Yes, No)
- Substance use, including tobacco use (never, former, current)
- Baseline use of vitamin D (Yes, No)
- Baseline use of calcium (Yes, No)
- Parental fracture (Yes, No, Unknown)

9.5 Efficacy Analyses

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 absolute values at baseline by machine type. Additionally, absolute values, change from baseline, and percent change from baseline at Month 6 will be provided by machine type.

9.5.1 Analyses of Primary Efficacy Endpoint

The primary analysis to assess the percent change from baseline in DXA BMD at lumbar spine at Month 6 will employ an analysis of covariance (ANCOVA) model using observed data. The ANCOVA model will include randomized treatment, baseline value of BMD, machine type, and interaction of baseline BMD value and machine type as prognostic variables. Summaries for the results will include least-squares means point estimates of the percent change from baseline for each treatment arm. The model will allow for heterogeneity between treatments. The 2-sided 95% CI and associated p-value will be provided for the difference between the least-squares means for HCP-administered 210 mg romosozumab by PFS and self-administered 210 mg romosozumab by AI/Pen.

Conclusions for the primary efficacy hypothesis of efficacy of self-administration of romosozumab by AI/Pen compared with HCP-administered romosozumab by PFS at lumbar spine BMD at Month 6 will be made using a 1-sided test with type 1 error rate of 0.025 and noninferiority margin of -2.0%. The primary efficacy analysis set will be used

for the primary analysis. Sensitivity analyses using the per protocol analysis subset and multiple imputation as described in Section 8.3.1 will be performed.

9.5.2 Analyses of Secondary Efficacy Endpoints

For the secondary efficacy BMD endpoints (total hip and femoral neck at Month 6), the percent change from baseline in DXA BMD will employ an ANCOVA model as described in Section 9.5.1. The hip BMD efficacy analysis subset will be used to for these analyses.

A sensitivity analysis using multiple imputation as described in Section 8.3.1 will be performed.

9.5.3 Analyses of Exploratory Efficacy Endpoints

[redacted] 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 Van Elteren rank-sum test (Van Elteren, 1960).

9.6 Safety Analyses

9.6.1 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

Treatment-emergent adverse events are events with an onset on or after the administration of the first dose of investigational product and will include events reported as disease-related events.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, fatal adverse events, and adverse events of interest. Events of interested are described in Section 9.6.1.1.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

In addition, summaries of treatment-emergent adverse events occurring in at least 5% of the subjects and serious adverse events occurring in at least 0.1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events and fatal disease-related events by system organ class and preferred term.

The subject incidence of treatment-emergent adverse device effects will also be summarized.

9.6.1.1 Events of Interest

Subject incidence of events of interest (EOI; standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term. 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, and osteoarthritis will be identified using Amgen-defined MedDRA search strategies. Adjudicated-positive adverse events of atypical femoral fracture (AFF), osteonecrosis of the jaw (ONJ), and serious cardiovascular adverse events will also be summarized as EOIs as described in Sections 9.6.1.1.2, 9.6.1.1.3, and 9.6.1.1.4, respectively.

9.6.1.1.1 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.

9.6.1.1.2 Atypical Femoral Fracture

The events of AFF which occurred on 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.

9.6.1.1.3 Osteonecrosis of the Jaw

The events of ONJ which occurred on 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.

9.6.1.1.4 Adjudicated-positive Serious Cardiovascular Adverse Events

The following baseline cardiovascular risk factors will be summarized descriptively:

- Age and age groups (<75 and ≥ 75 years)
- Smoking history (Current/former, never, unknown)
- History of cardiovascular-related medical history
  - History of hypercholesterolemia (Yes, No)
  - History of hypertension (Yes, No)
  - History of diabetes (Yes, No)
  - History of cardiovascular disease (Yes, No)
  - History of central nervous system vascular disorder (Yes, No)
- Narrowly-defined history of cardiovascular disease:
  - History of ischemic heart disease (Yes, No)
  - History of coronary artery disease (Yes, No)
- History of cerebrovascular disease/event, atrial fibrillation, or atrial flutter:
  - History of central nervous system haemorrhages and cerebrovascular conditions (Yes, No)
  - History of cerebrovascular disease (Yes, No)
  - History of ischemic stroke or TIA (Yes, No)
  - History of atrial fibrillation/atrial flutter (Yes, No)
- History of cardiovascular or cerebrovascular event:
  - History of stroke, myocardial infarction or revascularization (Yes, No)
  - History of stroke or myocardial infarction (Yes, No)
  - History of stroke (Yes, No)
  - History of myocardial infarction (Yes, No)
  - History of revascularization (Yes, No)
  - History of heart failure (Yes, No)

Cardiovascular medical history risk identification strategy is defined in Appendix C.

All deaths and potential cardiovascular-related serious adverse events 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-positive serious

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.

9.6.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics (actual value and change or percent change from baseline for each laboratory parameter) over time by visit for the 6-month treatment period. Shifts in grades based on Common Terminology Criteria for Adverse Events (CTCAE) v3.0 of safety laboratory values between the baseline and the worst on-study value through Month 6 will be tabulated. Subject incidence of worst postbaseline calcium corrected by albumin CTCAE grades decreases will also be summarized. The percentages of subjects with laboratory toxicities ≥ 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 aspartate transaminaseor alanine transaminase > 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 may explain the elevation in laboratory analytes in order to assess whether these cases are true Hy's law cases.

9.6.3 Vital Signs

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

9.6.4 Physical Measurements

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

9.6.5 Antibody Formation

The incidence and percentage of subjects who develop anti-romosozumab antibodies (binding and, if positive, neutralizing) at any time through Month 6 will be tabulated by treatment group for primary analysis. This analysis will be repeated to further include all

testing results from samples collected during the 3-month follow-up period at the time of the final analysis.

The subject incidence of injection site reaction, adverse events potentially associated with hypersensitivity, and adverse events corresponding to the MedDRA high level group term of autoimmune disorders will be provided by binding and neutralizing anti-romosozumab antibody status.

9.6.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment group. A partial dose will be counted as one dose in the summary of exposure to investigational product.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

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 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 pharmacokinetic analyses will be provided. These analyses will be performed by the Clinical Pharmacology Modeling and Simulation group.

10. Changes From Protocol-specified Analyses

Table 10-1 of protocol version 1.0 dated 10 August 2017 states that the non-inferiority margin is based on the treatment difference:

$(\mu_{\text{romosozumab HCP PFS}} - \mu_{\text{romosozumab self-administration AI/Pen}})$.

However, the noninferiority margin will be based on:

$(\mu_{\text{romosozumab self-administration AI/Pen}} - \mu_{\text{romosozumab HCP PFS}})$

This is reflected in Table 3-1 of this statistical analysis plan and in Section 7.2.

According to the Schedule of Activities in Protocol version 1.0 (Table 2-1) physical measurements (height and weight) will be assessed at baseline, month 3, and month 6. However, physical measurements at month 3 were not collected. Therefore, summaries of physical measurements will not include month 3.

11. Literature Citations / References

Van Elteren P.H. (1960) On the combination of independent two-sample test of Wilcoxon, Bulletin of the International Statistical Institute, 37, 351-361.

12. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

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. If more than one evaluation on the same date, the average of the results will be used. Only laboratory results collected from the central laboratory will be averaged in the case of duplicate results.

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, Physical Measurements[b]

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.
[b] Protocol indicates physical measurements will be assessed at month 3, however the data is not collected at month 3.

Serum Romosozumab Levels and Laboratory Assessments (Chemistry)

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

[a] Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 1.

Vital Signs, and Laboratory Assessments (Hematology)

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

BTMs (sCTX and P1NP)

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[a]	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	≥ Study Day 230

[a] Any antibody assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 1.

Appendix B. 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/ctcaev3.pdf.

Appendix C. Cardiovascular Medical History Risk Group Identification Strategy

Cardiovascular Medical History Risk Group	Search Strategy
Hypercholesterolemia	Dyslipidemia SMQ (narrow)
Hypertension	Hypertension SMQ (narrow)
Diabetes	Hyperglycaemia SMQ (narrow)
Cardiovascular Disease	Cardiac Disorders SOC and Vascular Disorders SOC
Central Nervous System Vascular Disorder	Central Nervous System Vascular Disorders HLGT
Ischemic heart disease	Ischemic heart disease SMQ (narrow)
Central nervous system haemorrhages and cerebrovascular conditions	Central nervous system haemorrhages and cerebrovascular conditions SMQ (narrow)
Atrial fibrillation or atrial flutter	Preferred terms
Stroke	Stroke AMQ (see Appendix D)
Myocardial infarction	Myocardial infarction SMQ (narrow)
Coronary artery disease	Coronary artery disorders HLGT
Revascularization	Coronary revascularization AMQ (see Appendix E; narrow)
Cerebrovascular disease	Central nervous system vascular disorders SMQ (narrow)
Heart Failure	Cardiac failure SMQ (narrow)
Ischemic stroke or TIA	Ischaemic central nervous system vascular conditions SMQ (narrow)

Appendix D. Search Terms for History of Stroke

Basal ganglia haemorrhage
Basal ganglia infarction
Basal ganglia stroke
Basilar artery occlusion
Brain stem embolism
Brain stem haemorrhage
Brain stem infarction
Brain stem microhaemorrhage
Brain stem stroke
Brain stem thrombosis
Central nervous system haemorrhage
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar embolism
Cerebellar haemorrhage
Cerebellar infarction
Cerebellar microhaemorrhage
Cerebellar stroke
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery thrombosis
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral infarction
Cerebral infarction foetal
Cerebral microembolism
Cerebral microhaemorrhage
Cerebral septic infarct
Cerebral thrombosis
Cerebral vascular occlusion
Cerebrovascular accident
Embolic cerebral infarction
Embolic stroke
Haemorrhage intracranial
Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Intracranial tumour haemorrhage
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Lacunar stroke
Migrainous infarction
Perinatal stroke
Periventricular haemorrhage neonatal
Pituitary haemorrhage
Post procedural stroke

Post stroke depression
Putamen haemorrhage
Stroke in evolution
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subdural haemorrhage
Subdural haemorrhage neonatal
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke
Transverse sinus thrombosis
Vertebral artery occlusion
Vertebral artery thrombosis

Appendix E. Search Terms for History of Revascularization

Preferred Term	Scope
Aortic aneurysm repair	Narrow
Aortic bypass	Narrow
Aortic stent insertion	Narrow
Endarterectomy of aorta	Narrow
Intra-thoracic aortic aneurysm repair	Narrow
Arterectomy	Narrow
Arterectomy with graft replacement	Narrow
Arterial aneurysm repair	Narrow
Arterial bypass operation	Narrow
Arterial graft	Narrow
Arterial stent insertion	Narrow
Carotid angioplasty	Narrow
Carotid artery bypass	Narrow
Carotid artery stent insertion	Narrow
Carotid endarterectomy	Narrow
Carotid revascularisation	Narrow
Cerebral endovascular aneurysm repair	Narrow
Cerebral revascularisation	Narrow
Coronary angioplasty	Narrow
Coronary arterial stent insertion	Narrow
Coronary artery bypass	Narrow
Coronary endarterectomy	Narrow
Coronary revascularisation	Narrow
Endarterectomy	Narrow
Intra-cerebral aneurysm operation	Narrow
Mesenteric artery stent insertion	Narrow
Percutaneous coronary intervention	Narrow
Peripheral artery angioplasty	Narrow
Peripheral artery bypass	Narrow
Peripheral artery stent insertion	Narrow
Peripheral endarterectomy	Narrow
Pulmonary endarterectomy	Narrow
Renal artery angioplasty	Narrow
Renal artery stent placement	Narrow
Aneurysm repair	Narrow
Aneurysmectomy	Narrow
Angioplasty	Narrow
Arteriovenous graft	Narrow
Peripheral revascularisation	Narrow
Thrombectomy	Narrow
Thromboembolectomy	Narrow
Vascular graft	Narrow
Vascular stent insertion	Narrow

SAP Amendment 1

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

AMG 785/Romosozumab Amgen Protocol Number 20150120

Protocol Date:	10 August 2017
SAP Version Number	2.0
SAP Amendment Date	08 May 2019

The statistical analysis plan for this study was amended to clarify analyses to be performed during the upcoming primary analysis for this study (snapshot planned for 20 June 2019).

Editorial changes were also implemented throughout the document.

Description of Changes:

Global

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

Header date was replaced with 08 May 2019.

Document version was replaced with v2.0.

5.1 Basic Definitions

Add:

Treatment-emergent Adverse Events

Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to the end of study date.

Serious adverse events (SAEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to the end of study date.

5.2 Study Points Reference

Replace:

Baseline

The baseline measurement is defined as the last measurement prior to the first dose of investigational product. 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 investigational product. If a subject does not receive investigational product, 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 investigational product. Note: If baseline result from lateral spine x-ray, DXA, or QCT assessment is not available, the result assessed on or before Study Day 14 will be considered baseline.

With:

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 taken on the same day, the baseline is obtained as the average of the measurements.

Note: If baseline result from DXA assessment is not available, the result assessed on or before Study Day 14 will be considered baseline.

5.2 Study Points Reference

Replace:

Study Day

The number of days from Study Day 1, inclusive:

Study Day = (Date of Interest – Date of Study Day 1) + 1.

With:

Study Day

The number of days from Study Day 1, inclusive:

Study Day = (Date of Interest – Date of Study Day 1) + 1

For days prior to Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1)

5.3 Study Dates

Add:

Last Dose Date

The date of administration of last dose of IP

5.6 Arithmetic Calculations

Remove:

eGFR (mL/min/1.73 m^2) = 175 × (Serum creatinine [mg/dL])$^{-1.154}$ x (Age [years])$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

6.1.3 Bone Turnover Marker Analysis Subset

Replace:

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

With:

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

6.3 Per Protocol Analysis Subset

Replace:

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

With:

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

7.2 Primary Analysis

Replace:

The primary analysis will be performed after all subjects have had the opportunity to complete the Month 6 visit. The primary objective of the primary analysis is to evaluate the noninferiority of the effect of self-administering 210 mg romosozumab QM via AI/Pen compared with the effect of 210 mg romosozumab QM administered by HCP via PFS in

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

With:

The primary analysis will be performed after all subjects have had the opportunity to complete the Month 6 visit. Only data from the 6-month treatment period will be summarized for the primary analysis. The primary objective of the primary analysis is to evaluate the noninferiority of the effect of self-administering 210 mg romosozumab QM via AI/Pen compared with the effect of 210 mg romosozumab QM administered by HCP via PFS in postmenopausal women with osteoporosis with respect to percent change from baseline in DXA BMD of lumbar spine at Month 6. Formal statistical testing will be conducted to evaluate the following hypothesis: the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects self-administering 210 mg romosozumab QM with AI/Pen is not inferior to that in subjects receiving 210 mg romosozumab QM by HCP administration with PFS using a margin of -2 percentage points. The lower bound of the 1-sided 97.5% CI from mean treatment difference (self-administration with AI/pen minus HCP administration with PFS) for the treatment arms will be compared with the noninferiority margin of -2% for assessing noninferiority.

7.3 Final Analysis

Replace:

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

With:

The final analysis will be performed after all subjects have had the opportunity to complete the Month 9 visit, ie, after all subjects have had the opportunity to complete the 3-month

follow-up study period. Cumulative safety data from the 6-month treatment and follow up periods will be summarized for the final analysis. The 3-month follow-up period will provide the opportunity to monitor all subjects for adverse events and formation of anti-romosozumab antibodies.

8.3 Handling of Missing and Incomplete Data

8.3.1 DXA BMD Endpoints

Replace:

Both lumbar spine and proximal femur scans at Month 6 will be acquired in duplicate. The average of the duplicate scans on the same day will be used for analyses.

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. If a subject has BMD values from different DXA machine types (ie, Hologic and Lunar) only those BMD values that are collected from the same machine type as the baseline BMD will be used for analyses. For proximal femur scans that are measured on different body sides (i.e., left and right), only those BMD values that are collected from the same body site as the baseline BMD will be used for analyses.

A sensitivity analysis will be performed using multiple imputation to evaluate the primary and secondary endpoint analyses. In this analysis, the missing Month 6 DXA values will be imputed separately resulting in 5 complete sets by Markov Chain Monte Carlo (MCMC) method for each endpoint. The imputation model will include the baseline value, machine type, and treatment group.

With:

Lumbar spine scans at screening and Month 6 will be acquired in duplicate. The average of the duplicate scans on the same day will be used for analyses. For proximal femur DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study.

For the primary analysis, 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 analysis of covariance (ANCOVA) models. If a subject has BMD values from different DXA machine types (ie,

Hologic and Lunar) only those BMD values that are collected from the same machine type as the baseline BMD will be used for analyses. For proximal femur scans that are measured on different body sides (i.e., left and right), only those BMD values that are collected from the same body site as the baseline BMD will be used for analyses.

A sensitivity analysis will be performed using multiple imputation to evaluate the primary and secondary endpoint analyses. In this analysis, the missing baseline or Month 6 DXA values will be imputed separately resulting in 5 complete sets by Markov Chain Monte Carlo (MCMC) method for each endpoint. The imputation model will include the baseline value, machine type, and treatment group.

8.3 Handling of Missing and Incomplete Data

Add:

8.3.3 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 8-1 and Table 8-2. 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.

Table 8-1. 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 Study Day 1
	Month	JAN	Default to Study Day 1 if the event started in the same year as Study Day 1
	Day / Month / Year	First Dose Date	Use randomization date for subjects who did not receive investigational product

Table 8-2. Imputation Rules on Partial Start Date of IP Administration in AI/Pen Arm

	Missing		Impute
Start Date	Day		Dispensed date (If the month and year of start date is the same with the month and year of dispensed date) 01 (If the month of start date is different with month of dispensed date)
	Day / Month		Dispensed date
	Month	If the year is the same with the year of dispensed date	Month of dispensed date (if the day is larger or equal to the day of dispensed date) Month of dispensed date plus one (if the day is less than the day of dispensed date)
		If the year is different with the year of dispensed date	Month of dispensed date plus one

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. Laboratory Parameters

9.4 Demographic and Baseline Characteristics

Replace:

Subject demographic and baseline disease characteristics as listed below will be summarized by treatment group based on the Full Analysis Set defined in Section 6.1.

- Race
- Ethnicity (Hispanic, non-Hispanic)
- Age at randomization
- Age groups (< 65, ≥ 65 years; < 75, ≥ 75 years)
- Body composition (height [cm], weight [kg], BMI [kg/m2])
- BMD T-score at the lumbar spine, total hip and femoral neck
- Bone turnover markers (sCTX, P1NP)
- Years since menopause
- Fracture history (Yes, No)

- Laboratory parameters (calcium corrected by albumin, phosphorus, serum 25(OH) vitamin D, eGFR)
- Prior osteoporosis medication use (Yes, No)
- Substance use in the last 5 years, including tobacco use (never, former, current) and alcoholic use (none, < 3 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)

With:

Subject demographic and baseline disease characteristics as listed below will be summarized by treatment group based on the Full Analysis Set defined in Section 6.1

- Race
- Ethnicity (Hispanic, non-Hispanic)
- Age at randomization
- Age groups (< 65, ≥ 65 years; < 75, ≥ 75 years**;** ≥ 18 - < 65 years, ≥ 65 - < 75 years, ≥ 75 - < 85 years, ≥ 85 years)
- Body composition (height [cm], weight [kg], BMI [kg/m^2])
- BMD T-score at the lumbar spine, total hip and femoral neck
- Bone turnover markers (sCTX, P1NP)
- Years since menopause
- Fracture history (Yes, No)
- Laboratory parameters (calcium corrected by albumin, phosphorus, creatinine**,** serum 25(OH) vitamin D, eGFR)
- Prior osteoporosis medication use (Yes, No)
- Substance use, including tobacco use (never, former, current)
- Baseline use of vitamin D (Yes, No)
- Baseline use of calcium (Yes, No)
- Parental fracture (Yes, No, Unknown)

9.6.1 Adverse Events and Disease-related Events

Replace:

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, fatal adverse events, and adverse events of interest. Events of interested are described in Section 9.6.1.1.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

In addition, summaries of treatment-emergent and serious adverse events occurring in at least 5% of the subjects and serious adverse events occurring in at least 2% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events and fatal disease-related events. Adverse device effects will also be summarized.

The subject incidence of treatment-emergent adverse events and adverse device effects will be summarized by actual treatment received.

With:

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

Treatment-emergent adverse events are events with an onset on or after the

administration of the first dose of investigational product and will include events reported as disease-related events.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, fatal adverse events, and adverse events of interest. Events of interested are described in Section 9.6.1.1.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

In addition, summaries of treatment-emergent adverse events occurring in at least 5% of the subjects and serious adverse events occurring in at least 0.1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events and fatal disease-related events by system organ class and preferred term.

The subject incidence of treatment-emergent adverse device effects will also be summarized.

9.6.1.1.4 Adjudicated-positive Serious Cardiovascular Adverse Events

Replace:

Baseline cardiovascular risk factors will be summarized descriptively. These risk factors are defined as age (≥ 75, < 75), smoking history, and other clinical history including hypertension, diabetes, cardiovascular disease, hypercholesterolemia, and central nervous system vascular disorders. The cardiovascular risk factors of history of hypertension, diabetes, cardiovascular disease, hypercholesterolemia, and central nervous system vascular disorders will be identified based on the Medical & Surgical History eCRF based on MedDRA version 20.1. The SMQ for Hypertension, the SMQ for Hyperglycaemia, the System Organ Classes of Cardiac Disorders and Vascular Disorders, and the Central Nervous System Vascular Disorders High Level Group Term will be used to identify preferred terms associated with hypertension, diabetes,

cardiovascular disease and central nervous system vascular disorders, 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.

All deaths and potential cardiovascular-related serious adverse events 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-positive serious 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, odds ratios and 95% confidence intervals. No statistical tests will be performed.

With:

The following baseline cardiovascular risk factors will be summarized descriptively:

- Age and age groups (<75 and ≥ 75 years)
- Smoking history (Current/former, never, unknown)
- History of cardiovascular-related medical history
  - History of hypercholesterolemia (Yes, No)
  - History of hypertension (Yes, No)
  - History of diabetes (Yes, No)
  - History of cardiovascular disease (Yes, No)
  - History of central nervous system vascular disorder (Yes, No)
- Narrowly-defined history of cardiovascular disease:
  - History of ischemic heart disease (Yes, No)
  - History of coronary artery disease (Yes, No)
- History of cerebrovascular disease/event, atrial fibrillation, or atrial flutter:
  - History of central nervous system haemorrhages and cerebrovascular conditions (Yes, No)
  - History of cerebrovascular disease (Yes, No)
  - History of ischemic stroke or TIA (Yes, No)
  - History of atrial fibrillation/atrial flutter (Yes, No)

- History of cardiovascular or cerebrovascular event:
  - History of stroke, myocardial infarction or revascularization (Yes, No)
  - History of stroke or myocardial infarction (Yes, No)
  - History of stroke (Yes, No)
  - History of myocardial infarction (Yes, No)
  - History of revascularization (Yes, No)
  - History of heart failure (Yes, No)

Cardiovascular medical history risk identification strategy is defined in Appendix C.

All deaths and potential cardiovascular-related serious adverse events 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-positive serious 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.

9.6.6 Exposure to Investigational Product

Add:

A partial dose will be counted as one dose in the summary of exposure to investigational product.

10. Changes From Protocol-specified Analyses

Replace:

Table 10-1 of protocol version 1.0 dated 10 August 2017 states that the non-inferiority margin is based on the treatment difference:

$(\mu_{\text{romosozumab self-administration AI/Pen}} - \mu_{\text{romosozumab HCP PFS}})$

However, the noninferiority margin will be based on:

$(\mu_{\text{romosozumab HCP PFS}} - \mu_{\text{romosozumab self-administration AI/Pen}})$.

This is reflected in Table 3-1 of this statistical analysis plan and in Section 7.2.

With:

Table 10-1 of protocol version 1.0 dated 10 August 2017 states that the non-inferiority margin is based on the treatment difference:

$(\mu_{romosozumab\ HCP\ PFS} - \mu_{romosozumab\ self\text{-}administration\ AI/Pen})$.

However, the noninferiority margin will be based on:

$(\mu_{romosozumab\ self\text{-}administration\ AI/Pen} - \mu_{romosozumab\ HCP\ PFS})$

This is reflected in Table 3-1 of this statistical analysis plan and in Section 7.2.

According to the Schedule of Activities in Protocol version 1.0 (Table 2-1) physical measurements (height and weight) will be assessed at baseline, month 3, and month 6. However, physical measurements at month 3 were not collected. Therefore, summaries of physical measurements will not include month 3.

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Replace:

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 Laboratory Assessments (Chemistry)

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

Physical Measurements, Vital Signs, and Laboratory Assessments (Hematology)

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

BTMs (sCTX and P1NP)

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

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

With:

Spine and Hip DXA Scans, Physical Measurements[b]

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.
[b]Protocol indicates physical measurements will be assessed at month 3, however the data is not collected at month 3.

Serum Romosozumab Levels and Laboratory Assessments (Chemistry)

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

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 1.

Vital Signs, and Laboratory Assessments (Hematology)

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

BTMs (sCTX and P1NP)

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[a]	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	≥ Study Day 230

[a]Any antibody assessment done on Study Day 1 but after the administration of the investigational product will be classified into Month 1.

Appendix B

Remove:

Appendix B. Code Fragment

[redacted]

[redacted]

Appendix C, D and E

Add:

Appendix C. Cardiovascular Medical History Risk Group Identification Strategy

Cardiovascular Medical History Risk Group	Search Strategy
Hypercholesterolemia	Dyslipidemia SMQ (narrow)
Hypertension	Hypertension SMQ (narrow)
Diabetes	Hyperglycaemia SMQ (narrow)
Cardiovascular Disease	Cardiac Disorders SOC and Vascular Disorders SOC
Central Nervous System Vascular Disorder	Central Nervous System Vascular Disorders HLGT
Ischemic heart disease	Ischemic heart disease SMQ (narrow)
Central nervous system haemorrhages and cerebrovascular conditions	Central nervous system haemorrhages and cerebrovascular conditions SMQ (narrow)
Atrial fibrillation or atrial flutter	Preferred terms
Stroke	Stroke AMQ (see Appendix D)
Myocardial infarction	Myocardial infarction SMQ (narrow)
Coronary artery disease	Coronary artery disorders HLGT
Revascularization	Coronary revascularization AMQ (see Appendix E; narrow)

Cerebrovascular disease	Central nervous system vascular disorders SMQ (narrow)
Heart Failure	Cardiac failure SMQ (narrow)
Ischemic stroke or TIA	Ischaemic central nervous system vascular conditions SMQ (narrow)

Appendix D. Search Terms for History of Stroke

Basal ganglia haemorrhage
Basal ganglia infarction
Basal ganglia stroke
Basilar artery occlusion
Brain stem embolism
Brain stem haemorrhage
Brain stem infarction
Brain stem microhaemorrhage
Brain stem stroke
Brain stem thrombosis
Central nervous system haemorrhage
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar embolism
Cerebellar haemorrhage
Cerebellar infarction
Cerebellar microhaemorrhage
Cerebellar stroke
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery thrombosis
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral infarction
Cerebral infarction foetal

Cerebral microembolism

Cerebral microhaemorrhage

Cerebral septic infarct

Cerebral thrombosis

Cerebral vascular occlusion

Cerebrovascular accident

Embolic cerebral infarction

Embolic stroke

Haemorrhage intracranial

Haemorrhagic cerebral infarction

Haemorrhagic stroke

Haemorrhagic transformation stroke

Intracranial tumour haemorrhage

Intraventricular haemorrhage

Intraventricular haemorrhage neonatal

Ischaemic cerebral infarction

Ischaemic stroke

Lacunar infarction

Lacunar stroke

Migrainous infarction

Perinatal stroke

Periventricular haemorrhage neonatal

Pituitary haemorrhage

Post procedural stroke

Post stroke depression

Putamen haemorrhage

Stroke in evolution

Subarachnoid haemorrhage

Subarachnoid haemorrhage neonatal

Subdural haemorrhage

Subdural haemorrhage neonatal

Thalamic infarction

Thalamus haemorrhage

Thrombotic cerebral infarction

Thrombotic stroke

Transverse sinus thrombosis

Vertebral artery occlusion

Vertebral artery thrombosis

Appendix E. Search Terms for History of Revascularization

Preferred Term	Scope
Aortic aneurysm repair	Narrow
Aortic bypass	Narrow
Aortic stent insertion	Narrow
Endarterectomy of aorta	Narrow
Intra-thoracic aortic aneurysm repair	Narrow
Arterectomy	Narrow
Arterectomy with graft replacement	Narrow
Arterial aneurysm repair	Narrow
Arterial bypass operation	Narrow
Arterial graft	Narrow
Arterial stent insertion	Narrow
Carotid angioplasty	Narrow
Carotid artery bypass	Narrow
Carotid artery stent insertion	Narrow
Carotid endarterectomy	Narrow
Carotid revascularisation	Narrow
Cerebral endovascular aneurysm repair	Narrow
Cerebral revascularisation	Narrow
Coronary angioplasty	Narrow
Coronary arterial stent insertion	Narrow
Coronary artery bypass	Narrow
Coronary endarterectomy	Narrow
Coronary revascularisation	Narrow
Endarterectomy	Narrow
Intra-cerebral aneurysm operation	Narrow
Mesenteric artery stent insertion	Narrow
Percutaneous coronary intervention	Narrow
Peripheral artery angioplasty	Narrow
Peripheral artery bypass	Narrow

Peripheral artery stent insertion	Narrow
Peripheral endarterectomy	Narrow
Pulmonary endarterectomy	Narrow
Renal artery angioplasty	Narrow
Renal artery stent placement	Narrow
Aneurysm repair	Narrow
Aneurysmectomy	Narrow
Angioplasty	Narrow
Arteriovenous graft	Narrow
Peripheral revascularisation	Narrow
Thrombectomy	Narrow
Thromboembolectomy	Narrow
Vascular graft	Narrow
Vascular stent insertion	Narrow