STATISTICAL ANALYSIS PLAN

Study: OP0002

Product: Romosozumab

A MULTICENTER RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY AND TOLERABILITY OF ROMOSOZUMAB TREATMENT IN POSTMENOPAUSAL CHINESE WOMEN WITH OSTEOPOROSIS

SAP/Amendment Number	Date
Final SAP	28 May 2019
SAP Amendment 1	04 Aug 2020
SAP Amendment 2	03 Mar 2023

Confidentiality Statement

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LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AFF	atypical femoral fracture
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AUC	area under the curve
BMD	bone mineral density
BP	blood pressure
BTM	bone turnover marker
BW	body weight
CCBR	Chinese Conference on Biometric Recognition
CI	confidence interval (s)
CV	Coefficient of variance
CRO	contract research organization
DBPC	Double-Blind, Placebo-Controlled
DCM	Data cleaning meeting
DEM	Data evaluation meeting
DMC	Data Monitoring Committee
DXA	dual-energy x-ray absorptiometry
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic Case Report form
EOS	End of Study
ES	Enrolled Set
ET	Early Termination
FSH	follicle-stimulating hormone
FU	Follow-up
ICE	intercurrent events
ICF	Informed Consent form
ICH	International Council for Harmonisation

IMP	investigational medicinal product
iPTH	intact parathyroid hormone
iv	intravenous(ly)
LLOQ	lower limit of quantification
LS	least squares
MedDRA®	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model with repeated measures
MSR	minimum significant ratio
NAb	neutralizing antibodies
OH	hydroxy
OL	open-label
ONJ	osteonecrosis of the jaw
P1NP	procollagen type 1 N-telopeptide
PD	pharmacodynamic(s)
PD-PPS	Pharmacodynamic Per Protocol Set
PDF	Portable Document Format
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PT	preferred term
PTH	parathyroid hormone
QM	every month
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
sCTX	type I collagen C-telopeptide
SD	standard deviation(s)
SOC	system organ class
SQ0, SQ1, SQ2, SQ3	visual semiquantitative grading scale for vertebral fractures on lateral spine x-rays: SQ0=no fracture; SQ1=mild fracture; SQ2=moderate fracture; SQ3=severe fracture (Genant et al, 1993)
SS	Safety Set

T4	thyroxine
TEAE	treatment-emergent adverse event
TFLs	Tables, Figures and Listings
TPTD	teriparatide
TSH	thyroid-stimulating hormone
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 OP0002 dated 23 Mar 2022. The scope of this SAP includes all analyses that are planned and will be conducted by the Biostatistics department or designee unless otherwise specified.

Changes in the statistical methodology will be documented in a SAP amendment. Amendments to this document will be finalized prior to database lock.

This SAP has been written in consideration of the guidelines International Council for Harmonisation (ICH) E9.

2 PROTOCOL SUMMARY

2.1 Objectives for the Double-Blind, Placebo-Controlled Period

2.1.1 Primary objective

The primary objective is to evaluate the effect of treatment with romosozumab for 6 months compared with placebo on the percent change in BMD at the lumbar spine in postmenopausal Chinese women with osteoporosis.

2.1.2 Secondary objective

The secondary objective is to evaluate the effect of treatment with romosozumab for 6 months compared with placebo on the percent change in BMD at the total hip and femoral neck in postmenopausal Chinese women with osteoporosis.

2.1.3 Other objectives

The other objectives are as follows:

- To evaluate the effect of treatment with romosozumab for 3 months compared to placebo on the percent change in BMD at the lumbar spine, total hip, and femoral neck in postmenopausal Chinese women with osteoporosis.
- To evaluate the effect of treatment with romosozumab at 1-, 3-, and 6-month time points compared with placebo on the percent changes in BTMs in postmenopausal Chinese women with osteoporosis. The BTMs include the bone formation marker P1NP and the bone resorption marker sCTX.
- To characterize serum concentrations of romosozumab in postmenopausal Chinese women with osteoporosis who are randomized to romosozumab treatment.

2.1.4 Safety objective

The safety objective is to characterize the safety and tolerability of romosozumab treatment for 6 months compared with placebo in postmenopausal Chinese women with osteoporosis.

2.2 Objectives for the Open-Label Treatment Period

2.2.1 Secondary objective

The secondary objective is to describe the percent change in BMD at the lumbar spine, total hip, and femoral neck in postmenopausal Chinese women with osteoporosis who are continuing with

6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled (DBPC) Period (a total of 12 months of romosozumab treatment).

2.2.2 Other objectives

The other objectives are as follows:

- To describe the percent change in BMD at the lumbar spine, total hip, and femoral neck in postmenopausal Chinese women with osteoporosis who transition to 6 months of romosozumab treatment after initially being randomized to placebo in the DBPC Period.
- To describe the percent changes in BTMs in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment). The BTMs include bone formation marker P1NP and bone resorption marker sCTX.
- To describe the percent changes in BTMs in postmenopausal Chinese women with osteoporosis who transition to 6 months of romosozumab treatment after initially being randomized to placebo in the DBPC Period. The BTMs include bone formation marker P1NP and bone resorption marker sCTX.
- To describe area under the curve (AUC) for the entire 12-month treatment for P1NP in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).
- To characterize the serum concentrations of romosozumab in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).
- To characterize the serum concentrations of romosozumab in postmenopausal Chinese women with osteoporosis who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment.

2.2.3 Safety objectives

The safety objectives will be presented for the Open-Label (OL) Treatment Period (up to Month 12) and for the overall study period that includes the 3-month Follow-Up (FU) Period (for a total of 15 months) as follows:

- To characterize the safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).
- To characterize the safety and tolerability of romosozumab treatment in postmenopausal Chinese women with osteoporosis who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment.

2.3 Study variables for the Double-Blind, Placebo-Controlled Period

2.3.1 Efficacy variables

2.3.1.1 Primary efficacy variable

The primary efficacy variable is percent change from baseline in BMD at the lumbar spine at the end of the DBPC Period (Month 6) as assessed by DXA.

2.3.1.2 Secondary efficacy variables

The secondary efficacy variables are as follows:

- Percent change from baseline in BMD at the total hip at the end of the DBPC Period (Month 6) as assessed by DXA.
- Percent change from baseline in BMD at the femoral neck at the end of the DBPC Period (Month 6) as assessed by DXA.

2.3.1.3 Other efficacy variables

The other efficacy variables are percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 3 as assessed by DXA.

2.3.2 Pharmacokinetic and pharmacodynamic variables

2.3.2.1 Other pharmacokinetic variables

The other PK variables are serum trough concentrations of romosozumab at Day 1 (baseline) and at Months 1, 3, and 6.

2.3.2.2 Other pharmacodynamic variables

The other PD variables are percent changes from baseline in P1NP and sCTX at Months 1, 3, and 6.

2.3.3 Safety variables

2.3.3.1 Primary safety variable

The primary safety variable is the overall incidence of treatment-emergent adverse events (TEAEs)

2.3.3.2 Other safety variables

The other safety variables are as follows:

- 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.
- Changes from baseline in electrocardiogram (ECG) parameters.
- Clinically significant physical examination findings from baseline through Month 6.
- Incidence of subjects with antiromosozumab antibodies at Day 1 (baseline) and at Months 1, 3, and 6.

2.4 Study variables for the Open-Label Treatment Period

2.4.1 Efficacy variables

2.4.1.1 Secondary efficacy variables

The secondary efficacy variables are as follows:

- Percent change from baseline in BMD at the lumbar spine at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).
- Percent change from baseline in BMD at the total hip at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).
- Percent change from baseline in BMD at the femoral neck at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).

2.4.1.2 Other efficacy variables

The other efficacy variables are percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months.

2.4.2 Pharmacokinetic and pharmacodynamic variables

2.4.2.1 Other pharmacokinetic variables

The other PK variables are as follows:

- Serum trough concentrations of romosozumab at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab in the DBPC Period (a total of 12 months of romosozumab treatment).
- Serum trough concentrations of romosozumab at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months.

2.4.2.2 Other pharmacodynamic variables

The other PD variables are as follows:

- Percent changes from baseline in P1NP and sCTX at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC (a total of 12 months of romosozumab treatment).
- Percent changes from baseline in P1NP and sCTX at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months.
- AUC for the entire 12-month treatment period for P1NP in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the DBPC Period (for a total of 12 months of romosozumab treatment).

2.4.3 Safety variables

The safety variables listed below will be assessed during the OL Treatment Period, including some selected safety variables that will be followed up to Month 15, in subjects who are initially randomized to 6 months of romosozumab treatment in the DBPC Period and continue with romosozumab for 6 months (for a total of 12 months of romosozumab treatment) and in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months.

2.4.3.1 Primary safety variable

The primary safety variable is the overall incidence of TEAEs.

2.4.3.2 Other safety variables

The other safety variables are as follows:

- Changes from baseline in laboratory assessments (serum chemistry and hematology) and shifts from baseline to the worst value between baseline and Month 12.
- Changes from baseline in vital signs.
- Changes from baseline in ECG parameters.
- Clinically significant physical examination findings from baseline through Month 12.
- Incidence of subjects with antiromosozumab antibodies at Months 7, 9, and 12, and at the EOS Visit.

2.5 Study design and conduct

This is a Phase 3 multicenter randomized, DBPC study followed by OL Treatment Period in postmenopausal Chinese women with osteoporosis to evaluate the efficacy, safety and tolerability of romosozumab treatment. The study consists of 4 study periods: Screening Period (Day -35 to Day -1), 6-month DBPC period, 6-month OL Treatment Period, and 3-month FU Period. The overall study design including treatment assignments is depicted in the schematic diagram in Figure 1. For each individual subject, the study will last approximately 16 months. A

subject's participation in the study may be extended up to 1 year after the final IMP administration if the subject tests positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit.

In the DBPC Period, after screening, approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years) , in a 2:1 ratio to receive either 210 mg romosozumab subcutaneous (sc) treatment every month (QM) (200 subjects) or matched placebo sc QM (100 subjects) in a blinded manner for 6 months to evaluate if romosozumab treatment for 6 months, compared with placebo, is effective in increasing BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck. The primary analysis will be performed using the data obtained from the DBPC Period.

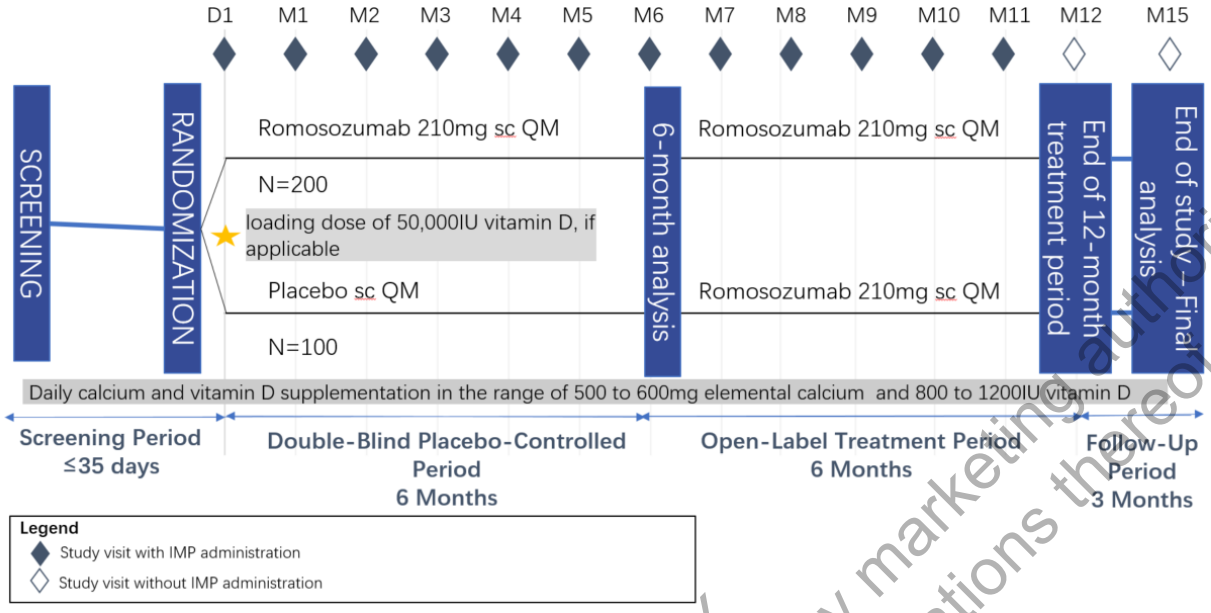
Upon completion of the 6-month DBPC Period, subjects will enter the 6-month OL Treatment Period and receive 210mg romosozumab sc QM for 6 months in an open-label fashion. During this period, all subjects will receive active treatment (romosozumab), 12 months exposure for subjects randomised to romosozumab and 6 months exposure for those randomized to placebo.

After completing the OL Treatment period, subjects will be followed up for an additional 3 months (FU Period) and will complete the EOS Visit (Month 15). Subject participation in the study is concluded after the EOS Visit. Subjects who test positive for neutralizing antibodies to romosozumab at the EOS Visit or ET Visit will be asked to return for additional follow-up testing for up to 1 year after final administration of investigational medicinal product (IMP).

BMD will be measured by DXA using same machine at screening, at 3 months, at the end of DBPC period (6 month), and at the end of 6 months OL Treatment Period (12 month). Only Lunar or Hologic densitometers will be allowed in the study. All DXA scans will be submitted to and analyzed by the central imaging vendor. To maintain the blind, all BMD data will be analyzed by the central imaging vendor and these results will not be reported to the investigator and study-related personnel after the first administration of IMP in the DBPC period, and to minimize the introduction of any bias during the OL Treatment Period, once the investigator is unblinded to individual treatment assignments.

The end of the study is defined as the date of the last visit of the last subject in the study.

Figure 1: Overall study design for OP0002



D=day; IMP=investigational medicinal product; IU=international unit; M=month; N=number of subjects in each treatment arm; QM=every month; sc=subcutaneous(ly)

Note: Final analysis will include the remaining efficacy and safety analyses for Month 12 and the safety analyses for the overall study period, ie, the period from the start of double-blind treatment to the Month 15 Visit for each subject will be evaluated.

2.6 Determination of sample size

The sample size calculations were done using historical BMD data of all 3 anatomical sites taken into account from the romosozumab studies 20070337 and 20120156.

- Assumptions for BMD of the lumbar spine:

Postmenopausal women with osteoporosis in 20120156 showed a treatment difference of 8.4 with 95% CI: 6.9 to 9.9 when compared with placebo BMD response at lumbar spine. Furthermore, postmenopausal women with osteoporosis in 20070337 showed a treatment difference of 9.4 (95% CI: 7.9 to 10.8). Taking the minimum of the lower confidence bound (conservative approach) results in an assumption of 6.9 for the treatment difference in percentage change from baseline at Month 6.

For postmenopausal women with osteoporosis in 20120156, the upper bounds of the SDs were 4.94 for the romosozumab group and 3.93 for the placebo group; in 20070337, the upper bounds of the SDs were 6.10 and 3.32, respectively. This indicates that SDs were differing between romosozumab and placebo necessitating a statistical test accounting for differing SDs. To merge the SDs of 20070337 and 20120156, the pooled common SDs were calculated separately for romosozumab and placebo taking the upper bound in each study and each arm (conservative approach). As a result, the assumptions for the SDs are 5.26 for the romosozumab arm and 3.34 for the placebo arm.

- Assumptions for BMD of the total hip

Studies 20070337 and 20120156 showed a minimum treatment difference on total hip BMD of 3.5 (95% CI: 2.5 to 4.4) when compared with placebo. The combined upper bounds of the SDs for 20070337 and 20120156 were 3.80 for the romosozumab group and 3.03 for the placebo group.

- Assumptions for BMD of the femoral neck:

Studies 20070337 and 20120156 showed a minimum treatment difference on femoral neck BMD of 3.2 (95% CI: 2.0 to 4.3) when compared with placebo. The combined upper bounds of the SDs for 20070337 and 20120156 were 4.39 for the romosozumab group and 4.10 for the placebo group.

- Resulting sample size:

For the sample size calculations, a 2-group Satterthwaite t-test will be assumed (2-sided on a 5% significance level) which allows for unequal SDs and unequal sample size ratios. Taking into account the upper bounds pooled common SDs and the minimum effect size as assumptions (BMD of the femoral neck outlined above), the sample size of 146 subjects for romosozumab and 73 subjects for placebo would preserve at least 90% power for the percent change from baseline in BMD of the lumbar spine, total hip and femoral neck at Month 6.

To give a reasonable chance to show significance, at least 90% power for all 3 anatomical sites, following a hierarchical testing procedure (see Section 4.5) with safety objectives and dropout taken into account, a total sample size of 300 subjects (ie, 200 subjects in the romosozumab group and 100 subjects in the placebo group) seemed appropriate.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by the biostatistics department at UCB and/or Parexel. All computations will be performed using SAS® version 9.4 or later (SAS Institute, NC, USA).

Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, SD, minimum and maximum, coefficient of variance (CV) [where applicable]) will be tabulated. Data may be summarized by treatment group and in addition, may be summarized by time (using defined analysis visit windows, referring to section 3.2.3).

Unless otherwise noted, all summaries will be displayed by randomized treatment group (placebo, romosozumab 210mg sc QM) regardless of the treatment individual subjects actually received. A summary with all treatment groups combined (ie, total column) will be presented for the demographic and Baseline characteristics, for the prior medications, as well as for the medical, procedure history and risk factors.

Decimal places for descriptive statistics will always apply the following rules:

- "n" or "N" will be an integer.
- Percentage values will be presented with 1 decimal place. No percentage will be displayed for zero counts and no decimal will be displayed when percentage is 100%.
- Mean, SD, and median will use 1 additional decimal place compared to the original data.

- CV (%) will be presented with 1 decimal place.
- Minimum and maximum will have the same number of decimal places as the original value.
- Categorical missing data will be summarized in a separate category.

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 3 decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999." The multiple testing issues for the primary and secondary efficacy analyses are handled with a fixed sequence testing procedure as described in Section 4.5.

The SAS outputs supportive of any statistical model (ie. all excluding the descriptive analyses) will be provided as a separate Portable Document Format (PDF) document in addition to Tables, Figures and Listings (TFLs). These outputs will be included in the "Documentation of Statistical Methods" section of the clinical study report.

The order of treatment groups to be presented in tables from left to right will be:
Outputs including only data of the DBPC Period for 6-Month Analysis:

- Placebo
- Romosozumab 210mg

Outputs including also data of the OLE Treatment Period and FU Period for Final Analysis:

- Placebo / Romosozumab 210mg (subjects receive Placebo during 6-month DBPC Period and then receive Romosozumab during OLE Period)
- Romosozumab 210mg / Romosozumab 210mg (subjects receive Romosozumab during 6-month DBPC Period and then receive Romosozumab during OLE Period)

Data listings will be prepared for subjects with available data including the calculated data [Enrolled Set (ES), Randomized Set (RS), Safety Set (SS), Full Analysis set (FAS), Per-Protocol Set (PPS), Pharmacokinetic Per-Protocol Set (PK-PPS) and Pharmacodynamic Per-Protocol Set (PD-PPS)], depending on the domain.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 6-month analysis

The 6-month analysis of efficacy and safety will be performed after all subjects have completed the 6-month DBPC Period. After the last subject last visit of the 6-month DBPC Period and after data cleaning, a database snapshot will be taken for the 6-month analysis. Following the snapshot, the study will be unblinded to the individuals of the dedicated team from sponsor and CRO involved in conducting the statistical analysis and in the compilation of the statistical analysis report and the CSR. The names of members of the dedicated team will be documented before the database snapshot. The investigators and other sponsor staff initially remain blinded. Upon finalization of the CSR (6-month analysis), investigators will remain blinded to treatment assignments for study participants in their sites. The leading Principal Investigator (PI) involved in the sign-off of the CSR (6-month analysis) will be unblinded at the aggregate level (tables and

figures) but will remain blinded to treatment assignment for individual study participants. Other investigators will remain blinded at the aggregate level to the 6-month results until the final analysis of the data. Note this is a change from the protocol as regulatory requirements now only require the leading PI to sign-off the CSR. Subjects will remain blinded to the DBPC Period treatment assignment throughout the study.

The primary variable of the 6-month analysis is the evaluation of the effect of treatment with romosozumab compared with placebo on the percent change in BMD at the lumbar spine in postmenopausal Chinese women with osteoporosis. Formal statistical testing will be performed (see Section 4.5).

The secondary variables of the 6-month analysis are to evaluate the effects of treatment with romosozumab compared with placebo on the percent change in BMD at the total hip and femoral neck. For these endpoints, confirmatory testing will be performed as outlined in Section 4.5.

Other variables of the 6-month analysis include the evaluation of the effect of treatment with romosozumab compared with placebo at 3 months on the percent change in BMD at the lumbar spine, total hip and femoral neck, the evaluation of the effect of treatment with romosozumab compared with placebo at 1-, 3-, and 6-month time points on the percent changes in BTMs, and to characterize serum concentrations of romosozumab in subjects who are randomized to romosozumab for 6 months. For the other variables, statistical testing will be performed in an exploratory manner.

The safety analyses of the 6-month analysis will compare the safety of romosozumab treatment with placebo in postmenopausal Chinese women with osteoporosis. The safety analyses in the 6-month analysis will include all available data collected up to the time of 6-month data snapshot. The safety variables to be analyzed in the 6-month analysis are presented in Section 2.3.3.

3.2.1.2 Final analysis

After all subjects have the opportunity to complete the Month 15 Visit, the database lock will be executed. Based on these data, the remaining efficacy and safety analyses for Month 12 and the safety analyses for the overall study period (treatment start through Month 15) will be performed.

3.2.2 Relative day

Days on or after the day of first dose of IMP and prior to or on the day of last IMP:

Relative day will be calculated as the current date minus the date of first dose of IMP + 1 (eg. the day of first dose will be Day 1).

Days prior to the first dose of IMP:

Relative day will be calculated as date of first dose of study drug minus the current date (the day prior to first dose will be Day -1).

Days after the last dose of IMP:

Relative day will be calculated as the current date minus the date of last dose of study drug including a "+" to denote posttreatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

3.2.3 Analysis visit windows

For the Baseline assessment and definition, please refer to Section 3.3 for details. For the post-baseline assessment, if more than 1 visit measurement falls within the defined visit window, the result from the visit closest to the target day will be used for analysis and summarization. If 2 evaluations are of the same distance from the target day, the result from the later visit will be used. Scheduled and unscheduled visits/measurements are considered for this purpose. 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.

DXA Scans

Nominal visit	Target study day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to first dose of IMP
Month 3	90	Day 2 – 135
Month 6	180	Day 136 - End of DBPC period + 14 days
Month 12	360	≥ Day End of DBPC period + 15

BTMs (serum CTX and P1NP), PK samples, antibodies samples and laboratory tests

Nominal visit	Target study day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to or on Study Day 1 and prior to the first IMP
Month 1	30	Day 2 – 60
Month 3	90	Day 61 – 135
Month 6	180	Day 136 – End of DBPC period (note: M6 IMP will belong to OL)
Month 7	210	Day End of DBPC period + 1 – 240
Month 9	270	Day 241-315
Month 12	360	≥ Day 316

Vital signs

Nominal visit	Target study day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to or on Study Day 1 prior to the first IMP
Month 1	30	Day 2 – 105
Month 6	180	Day 106 – End of DBPC period
Month 7	210	Day End of DBPC period + 1 – 285
Month 12	360	≥ Day 286

ECG

Nominal visit	Target study day	Window Definition (Study Day)
Baseline	1	Last evaluation prior to or on Study Day 1 prior to the first IMP
Month 1	30	Day 2 – 60
Month 3	90	Day 61 – 135
Month 6	180	Day 136 – End of DBPC period
Month 9	270	Day End of DBPC period + 1 - 315
Month 12	360	≥ Day 316

The definition for End of Study, End of DBPC period, End of OL Period and End of Follow-Up Period are specified in Section 3.2.4.

3.2.4 Timing of analysis cut-offs

3.2.4.1 End of study date

End of study (EOS) date is defined as the date of the last contact; or the date of the last assessment for the early termination (ET) visit for subjects who discontinued the study if no last contact date in EDC CRF form.

3.2.4.2 End of DBPC Period date

End of DBPC Period date is defined as the last date of the assessments of the Month 6 visit or start date of OL visits if Month 6 visit is missed. For subjects who discontinued from the study before completing Month 6, the ET date is used for the end of DBPC period date. ~~204g4~~

3.2.4.3 Start of Open-Label Period

For subjects entering in the open-label period, the end of double-blind period date is the beginning of the open-label period date. All scheduled assessments occurring on this date are attributed to the double-blind period. The month 6 dose of ROMO is considered as occurring in the open-label period.

3.2.4.4 End of Open-Label Treatment Period date

End of OL Treatment Period date is defined as the date of the last assessment of the Month 12 visit. For subjects who discontinued from the study before completing Month 12, the ET date is used for the end of 12-month OL Treatment Period date. For those subjects who remained on study but missed the month 12 visit, last OL Treatment + 30 days will be used as the end of 12-month treatment period date.

3.2.4.5 End of Follow-Up Period date

End of FU Period date is defined as the date of the last assessment of the FU visit. For subjects who discontinued from the study before completing FU visit, the last contact date is used for the end of FU period date. For those subjects who remained on study but missed the FU, the final visit + 3 month or final administration of IMP + 4 month will be used as the end of FU period date.

3.3 Definition of Baseline values

A Baseline value for a subject is defined as the latest measurement for that subject up to and including the day of administration of first IMP, unless otherwise stated. If there is evidence that measurements taken on the same day as administration of first study medication were actually taken after this administration, then only values strictly prior to that date should be considered for that subject for baseline. If multiple measurements within the baseline period were done, the record that is the closest to and prior to or on the date of first IMP administration will be considered as the Baseline value. If a Baseline measurement is missing or not collected, and a Screening value (within 35 days prior to day 1) is available, the Screening value will be utilized as Baseline instead.

For computation of change from Baseline BMD of lumbar spine endpoint, Baseline will be identified as the average number of values (averaging is dedicated to the duplicate BMD values taken on the same day) obtained prior to the first dose of IMP (assuming that any observation on the same day as the first dose is prior to dosing, unless evidence stated). For computation of change from Baseline BMD of femoral neck and total hip, also other change from Baseline endpoints, the Baseline will be identified as the last observation prior to the first dose of IMP (assuming that any observation on the same day as the first dose is prior to dosing, unless evidence stated).The randomization date will be used as reference for subjects who did not receive any dose of IMP but who had non-missing observations on study.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy (effectiveness), key safety, or PK/PD outcomes for an individual subject. The criteria for identifying important protocol deviations will be pre-defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to unblinding to confirm exclusion of subjects from analysis sets.

Since the PPS will be used for a sensitivity analysis of the primary endpoint which is assessed at Month 6, the exclusion from PPS is limited to the double-blind period, ie only study participants with IPD prior to Month 6 can be excluded from the PPS. Study participants with IPD after Month 6 will not be excluded from the PPS, but might be excluded from PK-PPS and PD-PPS during OLE Period.

3.5 Analysis sets

3.5.1 Enrolled Set

Enrolled Set (ES) will consist of subjects who signed the Informed Consent form (ICF).

3.5.2 Randomized Set

Randomized Set (RS) will consist of subjects who have been randomized. Disposition data are based on the ES and the RS.

3.5.3 Safety Set

Safety Set (SS) will consist of all randomized subjects who received at least 1 dose of IMP. These subjects will be analyzed according to the 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.

Data on safety and exposure will be based on the SS.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of IMP and provided at least 1 Baseline and post-baseline BMD measurement. In the case of dosing administration error, analyses of the FAS will be conducted according to randomized treatment. This will be the primary efficacy analysis set.

The FAS will be used for demographics, disease characteristics and BMD efficacy analysis.

3.5.5 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of subjects in the FAS who have completed a minimal exposure of 6 months of a treatment regimen without any important protocol deviations that may influence the validity of the data for the primary and selected secondary BMD efficacy variables. ~~Post-baseline deviations will not necessarily lead to exclusion of a subject from PPS analysis but may lead to exclusion of data~~.

The PPS will be used as supportive analyses for BMD efficacy analysis.

3.5.6 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will include all subjects in the SS who have at least one evaluable serum romosozumab concentration measurement with no further PK related important protocol deviations. This analysis set will be used in the PK analyses.

3.5.7 Pharmacodynamic Per-Protocol Set

The Pharmacodynamic Per-Protocol Set (PD-PPS) will include all subjects in the SS who have at least 1 evaluable BTM measurement with no further PD-related important protocol deviations.

This analysis set will be used in the analyses of the BTMs.

3.6 Treatment assignment and treatment groups

It is expected that subjects will receive treatment as randomized; hence safety analyses will be based on the SS as randomized. However, if after unblinding it is determined that subjects received treatment other than what they were randomized to, then for safety analyses purposes subjects will be allocated to the actual treatment they received.

Treatment assignment for all other analysis sets will be according to randomization and not actual treatment received.

3.7 Center pooling strategy

Based on the clusters of the sites with considerations of geographical and climate differences, the pooling strategy will consider the following 3 regions: North, East and South. The detail of site and corresponding region is listed in Appendix 13.9.

3.8 Coding dictionaries

The latest version of Medical Dictionary for Regulatory Activities (MedDRA®) will be used to code all adverse events, medical histories, and concomitant diseases to a SOC and a PT.

World Health Organization (WHO) Drug dictionary will be used to code and classify all Prior / Concomitant Medications at the Anatomical Therapeutic Chemical Classification (ATC) level according to their indication and/or formulation.

3.9 Changes to protocol-defined analyses

Section 13.6 of the protocol amendment 3 describes the primary and secondary analysis to be used in this study. More specifically, the protocol describes primary analysis using last observation carried forward (LOCF) as the method for handling missing data. This SAP has been modified such that the missing or out of window data due to COVID-19 impact will be imputed by multiple imputation and other missing data (rather than due to COVID-19 impact) will be imputed by LOCF. The original LOCF method will be also applied in sensitivity analysis. The modification is provided in this SAP.

Section 3.2.2 and Section 4.2.2.2 of the protocol amendment 3 describe the area under the curve through Month 12 in P1NP will be produced by treatment group (AUC). This SAP has removed AUC for other objectives.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

All model-based analyses will include treatment, age strata group (stratification factor), Baseline DXA BMD value, baseline machine type (Hologic or Lunar), region, the baseline machine type-by-baseline DXA BMD value interaction as independent variables, if applicable.

4.2 Handling of dropouts or missing data

In general, even if the IMP is discontinued, the subjects will be encouraged to continue the study schedule up to the planned final visit. For all subjects, all available data will be included in analyses, regardless of whether the data are collected before or after the subject discontinues IMP or before or after the subject takes alternative osteoporosis therapy (licensed drugs only) (see Appendix 13.1) or prohibited medication. This principle is as close as possible to the Intention to treat (ITT) principle and is currently accepted from a regulatory perspective as a conservative approach. Since this approach reflects effectiveness and real-world application rather than efficacy, it is in line with the late development stage of romosozumab within the clinical program.

If not otherwise specified, any missing data will not be imputed.

Supplementary analyses will be performed on the primary and secondary efficacy endpoints to assess the treatment effect of romosozumab when considering any subsequent or concomitant prohibited and/or alternative osteoporosis therapy (licensed drugs only).

Potentially, deaths could occur during this study. However, these events most likely will not be linked to the study indication of postmenopausal osteoporosis in China so that data which would have been collected after date of death will not be imputed.

In the data evaluation meetings (DEM), the following blinded overall incidences will be monitored since they have the potential to affect the interpretation or the existence of the BMD measurements:

- Incidence of subjects who discontinued IMP
- Incidence of subjects who discontinued IMP by reasons
- Incidence of subjects who received prohibited medication during ongoing IMP treatment
- Incidence of subjects who received alternative osteoporosis therapy during ongoing IMP treatment
- Incidence of subjects who received alternative osteoporosis therapy after early termination of IMP
- Incidence of subjects who died

For those sites which show strong deviations from the average of all sites during the DEM, appropriate measures such as re-training, following-up with corrective actions etc. would be considered. Further analyses including time to various discontinuation events (Kaplan-Meier plots), events by Baseline characteristics and events by efficacy endpoints may be conducted to explore the cause and impact of the discontinuations.

All the missing visit or missing data related to COVID-19 will be listed. Additional listings will be provided for the patients' assessments with COVID-19 impact. Additional summary and sensitivity analyses will be provided if deems necessary.

4.2.1 Dates

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment in the study or not. For the purposes of imputing missing date or missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

- Missing start day, but month and year present:

  If study start date (Day 1) occurred in the same month and year as the occurrence of the AE/medication, the start day of the event/medication will be assigned to the day of study start day.

  Otherwise the start day will be set to the 1st day of the month.

- Missing start day and month, but year present:

  If the study start date (Day1) occurred in the same year as the occurrence of the AE/medication, the start day and month will be assigned to the date of study start day.

  Otherwise the start day and month will be set to 01 Jan.

- Missing end day, but month and year present:

  If the date of last contact occurred in the same year and month as the occurrence of the AE/medication, the end day will be assigned to the date of the last contact.

  Otherwise the end day will be set to the last day of the month.

- Missing end day and month, but year present:

  If the day of last contact occurred in the same year as the occurrence of the AE/medication, the end day and month will be assigned to the date of last contact.

- Completely missing start date:

  An AE will be considered as occurring during treatment.

  Medications with an unknown stop date or a stop date after the date of the first IMP application will be considered as concomitant medication but not as prior medication. Medications with a stop date prior to first IMP application will be considered as prior medication but not as concomitant medication.

- Completely missing stop date:

  Adverse events with a completely missing stop date will be considered ongoing.

  Medications with a completely missing stop date will be considered as concomitant medications.

4.3 Interim analyses and data monitoring

No interim analysis is planned for this study.

An external, independent Data Monitoring Committee (DMC) will monitor unblinded safety and efficacy data on an ongoing basis throughout the study. DMC members will have access to treatment assignments if knowledge of treatment assignment at the individual level is essential to evaluate safety. To minimize the potential introduction of bias, these individuals will not have direct contact with the study site personnel or subjects. An independent statistical service provider will generate unblinded reports for review by the DMC. If at any time there are safety concerns, the DMC will communicate the concerns to a representative from UCB senior management. The actual dates and the conduct of the DMC meetings are outlined in the DMC Charter.

4.4 Multicenter studies

For the purpose of the summaries and analyses, the term 'Site' will be used to define each center. The primary efficacy variable will be presented by treatment groups and region to explore interactions between treatment and regions according to Section 3.7.

4.5 Multiple comparisons/multiplicity

For addressing multiplicity issues, a hierarchical testing procedure will be implemented which consists of 3 steps.

(1) Lumbar spine BMD percent change from Baseline at 6 months

(2) Total hip BMD percent change from Baseline at 6 months

(3) Femoral neck BMD percent change from Baseline at 6 months

The statistical test of the treatment effects in the second step will be made in a confirmatory manner only when the treatment effect on the primary efficacy endpoint is statistically significant using a 2-sided type I error rate of 0.05. Likewise, the third step will be made only when the treatment effect tested in step1 and step 2 are statistically significant using a 2-sided type I error rate of 0.05.

4.6 Examination of subgroups

To assess the consistency and robustness of the treatment effect on lumbar spine BMD, the primary analysis and selected secondary analyses will be performed for the following subgroups:

- age group (< 75 years, ≥ 75 years)
- region defined in section 3.7 (South, East, and North China)
- Baseline lumbar spine BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5; for lumbar spine BMD analysis only)
- Baseline total hip BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5; for total hip BMD analysis only)
- Baseline femoral neck BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5; for femoral neck BMD analysis only)
- Baseline Vitamin D (≤ 40 ng/mL, > 40 ng/mL) and loading dose of vitamin D (Yes, No)

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The numbers and percentages of subjects who were screened with screen failure reason for the ES. The number of subjects who did not meet study eligibility criteria will be listed for the ES.

The numbers and percentages of subjects that were randomized, completed, prematurely discontinued from IMP, withdraw from study, reason for premature discontinuation from IMP and study, and successfully completing IMP and study will be summarized by the treatment groups and study periods (through Month 6, through OL period, Safety follow-up period, and through Month 15) for the RS. The number of subjects who completed each visit (as captured in the CRF) will also be listed. The number of subjects who withdrawal due to AE will be summarized and listed for the RS. In addition, the disposition of subjects into treatments groups and analysis sets (RS, FAS, SS, and PPS) will also be summarized on the RS.

5.2 Protocol deviations

Important protocol deviations (IPD) will be identified at data cleaning meetings (DCMs) prior to taking a snapshot from the database for the analysis. The identified important protocol deviations will be classified by predefined items (eg., inclusion criteria, exclusion criteria, incorrect treatment, prohibited medication, treatment non-compliance and procedural non-compliance) and summarized by the treatment groups and study periods for the RS. In addition, the number of subjects with at least 1 IPD will be displayed by site.

IPD related to COVID-19 protocol deviations will be summarized for treatment non-compliance and procedural non-compliance.

5.3 Impact of COVID-19

A summary table of visits and reasons affected by COVID-19 will be presented based on the Randomized set.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The demographics and other Baseline characteristics will be summarized descriptively based on FAS. In case FAS and SS are different, the demographics will also be summarized based on SS.

6.1 Demographics

The continuous demographic variables:

- Age at study entry (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

BMI (kg/m^2) will be calculated as:

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$$

The categorical demographic variables:

- Gender
- Race
- Ethnicity
- Region
- Country
- EudraCT age categories (18-<65, 65 to <85, and ≥85)
- Clinicaltrials.gov age categories (≤18, 19 to <65, and ≥65)
- Age class (<65, ≥ 65 to <75, and ≥75)
- Age class (<75, ≥75)
- Age strata group from IVRS (<75, ≥75)
- BMI (kg/m^2) (<18.5, 18.5 to <23, 23 to <27.5, ≥27.5)

6.2 Other Baseline disease characteristics

- BMD T-score at lumbar spine, total hip and femoral neck
- BMD T-score categories at lumbar spine (≤ -3.0, > -3.0 to < -2.5, and ≥ -2.5), total hip (≤ -2.5 and > -2.5) and femoral neck (≤ -2.5 and > -2.5)
- BMD (g/cm^2) by machine type (Hologic vs. Lunar) at lumbar spine, total hip and femoral neck
- bone turnover markers (sCTX [ng/L], P1NP [ug/L])
- years since menopause (year)
- laboratory parameters [calcium corrected by albumin, phosphorus, creatinine, serum 25 hydroxy (OH) vitamin D level, thyroid-stimulating hormone (TSH), and intact parathyroid hormone (iPTH) Total cholesterol, low-density Lipoprotein (LDL), high-density Lipoprotein (HDL), triglycerides]
- prior osteoporosis medication use (Yes, No)
- type of osteoporosis medication use (eg. oral bisphosphonate, IV bisphosphonate, denosumab, teriparatide (TPTD), parathyroid hormone (PTH), calcitonin, strontium, fluoride, hormone replacement therapy, traditional herbal medication, activated vitamin D, SERM, vitamin K, other)
- Loading dose of vitamin D (Yes, No)
- Baseline use of calcium (Yes, No)

- 10 year probability of major osteoporotic and hip fractures based on WHO risk factor criteria (FRAX, see in Appendix 13.3) calculated with femoral neck BMD T-score
- 10 year probability of major osteoporotic and hip fractures based on WHO risk factor criteria (FRAX) calculated without femoral neck BMD T-score
- parental hip fracture (Yes, No, Unknown)
- glucocorticoid use (Yes, No)
- secondary osteoporosis (Yes, No)
- rheumatoid arthritis (Yes, No)
- alcohol use (Yes, No, Unknown)
- tobacco (Yes, No, Unknown)
- caffeinated beverage use (Yes, No, Unknown)

6.2.1 Cardiovascular risk factors:

- history of diabetes (type1, type2, No, Unknown)
- history of hypertension (Yes, No, Unknown)
- history of hyperlipidemia
- history of hypercholesterolemia (Yes, No)
- history of renal impairment (Yes, No, Unknown)
- history of atherosclerosis (Yes, No, Unknown)
- prior heart failure (Yes, No, Unknown)
- prior transient ischaemic attack (Yes, No, Unknown)
- prior angina pectoris (Yes, No, Unknown)
- other prior cardiovascular ischaemic events (Yes, No, Unknown)

6.3 Medical history and concomitant diseases

Previous and ongoing medical history will be summarized by MedDRA® SOC and PT. Medical procedures are not coded. The analysis will be performed based on FAS.

Prior fracture profiles will be summarized:

- fracture history (Yes, No, Unknown)
- prevalent vertebral fracture as assessed by the central imaging vendor based on the lateral spine x-ray (Yes, No, Unknown)
- number of prevalent vertebral fractures (0, 1, 2, ≥3, not readable/missing) and incidences of the grade of prevalent vertebral fracture (SQ0, SQ1, SQ2, SQ3)
- historical fracture at or after age of 45 (Any historical fracture, historical osteoporotic fracture, historical nonvertebral fracture, historical major nonvertebral fracture)

- historical fracture at or after age of 55 (Any historical fracture, historical osteoporotic fracture, historical nonvertebral fracture, historical major nonvertebral fracture)
- time since the most recent fracture (years)
- time since the most recent fracture (< 12 months, ≥ 12 months)

6.3.1 Prevalent vertebral fracture

A subject has a prevalent vertebral fracture if any vertebra from T4 to L4 has a grade of ≥ 1 at baseline assessed by the central imaging vendor based on the lateral spine x-ray. A subject does not have a prevalent vertebral fracture when all 13 grades from T4 to L4 are 0. Otherwise, the subject will have an unknown status for prevalent vertebral fracture.

6.3.2 Any historical fracture

Any Historical fracture is defined as any fracture recorded on the Subject Fracture History eCRF regardless of trauma severity or vertebral fracture based on baseline spinal radiograph.

6.3.3 Historical osteoporotic fracture

Historical osteoporotic fracture is defined as any nonvertebral fracture recorded on the Subject Fracture History eCRF not including skull, facial bones, fingers, toes, spine and tailbone and not associated with known high trauma severity or pathologic fractures, or vertebral fracture based on baseline spinal radiograph

6.3.4 Historical nonvertebral fracture

Historical nonvertebral fracture is defined as any fracture recorded on the Subject Fracture History eCRF not including skull, facial bones, fingers, toes, spine, and tailbone and not associated with known high trauma severity or pathologic fractures

6.3.5 Historical major nonvertebral fracture

A subset of historical nonvertebral fractures including the following locations: pelvis (not hip), hip, lower leg (not knee or ankle), ribs, shoulder, forearm, and wrist and not associated with known high trauma severity or pathologic fractures

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of IMP. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first dose of IMP. Any treatment other than IMP administered from the time of signing the ICF to the EOS Visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study. If study medications with missing start date and end date without ongoing status, the medications will regard as both prior and concomitant medication. The analysis will be performed based on Randomized Set.

Medications will be summarized by WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

The IMP will be administered at the study site by staff trained in the injection technique. Date and time of IMP administration during double-blind period and open-label period will be recorded in the subject's eCRF.

Drug accountability must be recorded on the Drug Accountability form.

The expected day of administration will be based upon (1) the date of first IMP administration and (2) the previous injection date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be computed based upon the actual and expected days for each of the 2 methods. The ratios of compliance will also be summarized as a continuous variable and categorically (<80% and ≥80%). The general formula for the compliance ratio is given as follows for double-blind period and overall period:

Compliance Ratio (CR) during double-blind period= {[Study Duration (days) during double-blind period] - [Cumulative Difference (days) during double-blind]} ÷ {Study Duration (days) during double-blind period}

Compliance Ratio (CR) during overall period = {[Study Duration (days) during Romosozumab treatment period] - [Cumulative Difference (days) during Romosozumab treatment period]} ÷ {Study Duration (days) during Romosozumab treatment period}

Compliance will be summarized as the number of doses received relative to the number of doses expected. Percent compliance will be calculated as:

Percent compliance during double-blind period = 100 x number of doses received during double-blind period ÷ number expected during double-blind period.

Percent compliance during overall period = 100 x number of doses received during Romosozumab treatment period ÷ number expected during Romosozumab treatment period.

Treatment compliance will be presented for SS.

8 EFFICACY ANALYSES

The BMD efficacy analyses will be performed based on the FAS. The results from the central imaging vendor will be used in the FAS. PPS will also be utilized for sensitivity analyses. Statistical testing will be conducted as outlined in Section 4.5. For all confirmatory testing, both adjusted and unadjusted p-values will be provided. The derivation rules for the adjusted p-values are provided in Appendix 13.2. For each efficacy BMD endpoint, descriptive statistics will be provided for absolute values, change from baseline and percent change from baseline at post-baseline visit by machine-type and visit. In addition, mean (±SE) plot by visit will be presented for primary endpoint and observed case.

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Primary analysis of primary efficacy variable

Primary analysis of Primary efficacy endpoint

Estimands's attributes to be considered for the evaluation of the primary endpoint

(1) Target Population: Postmenopausal Chinese women with osteoporosis meet the inclusion and exclusion criteria

(2) Treatment: Romosozumab or PBO for 6 months

(3) Endpoint: percentage change from baseline in BMD at lumbar spine at end of DBPC period (month 6).

(4) Intercurrent Events (ICEs) and strategies to handle ICEs:

(a) ICE #1: treatment discontinuation not due to COVID-19 will be handled by treatment policy strategy

(b) ICE #2: alternative osteoporosis therapy will be handled by treatment policy strategy.

(c) ICE #3: treatment interruption and impacted BMD data (missing or out of visit window) due to COVID-19 will be handled by hypothetical strategy

(5) Population level outcome: difference of least square (LS) means for Romosozumab and PBO

ICE #1 Treatment discontinuation not due to COVID-19 and ICE#2 use of alternative osteoporosis therapy is rare (not expected to happen frequently). They will follow treatment policy strategy which align with ITT principle. The treatment policy strategy will include all available data observed at Month 6 regardless of the occurrence of intercurrent events. This means the analysis includes on- and off-treatment values collected after study participants prematurely discontinued study treatment but agreed to remain on the study and continued to attend visits and provide assessments at those visits or data after alternative/prohibited medication administrated. Those observed values will be analyzed according to the study participant's randomized treatment.

During COVID-19 pandemic, study procedures (i.e. IMP administration and BMD assessment) are heavily impacted by sites close, participants quarantined or partially lock down. Thus, treatment was interrupted, or BMD assessment could not be performed or performed out of window. Treatment interruption and impacted BMD data (missing or out of visit window) due to COVID-19 will be considered as ICE #3. Hypothetical strategy, in which the interest is in the treatment effect if the ICE did not occur, is a recommended option for most pandemic-related ICEs (R. Daniel Meyer, et al., 2020).

The data after ICE#1 and ICE#2 will be handled by treatment policy strategy and will use the observed data to do analysis. COVID-19 impacted data after ICE#3, then it will be setting to missing and imputed by multiple imputation (MI) under missing at random (MAR) assumption (MI-MAR). Details of this multiple imputation analysis are outlined in Appendix 13.4. This COVID-19 impacted data includes any BMD data after treatment interrupted (exceed 70 days since previous IMP, based on PK modeling which demonstrated that BMD loss begins after 70 days without dosing) and any missing data or out of window (exceed 70 days since previous IMP) data due to Covid-19 (other than actual COVID-19 infection). Missing data other than due to COVID-19 impacted will be imputed by LOCF.

Missing baseline BMD by DXA at any anatomical site will not be imputed and evaluated for the BMD analysis. Missing postbaseline BMD will be imputed using the LOCF approach (by carrying forward the last non-missing postbaseline value prior to the missing value from the same anatomical site) in the 6-month analysis.

In all visits and including the screening visit, if duplicated DXA assessment were performed on the same visit the mean of the duplicated BMD values will be used for analysis. The corresponding

T-score at baseline will be converted using the mean of the duplicated BMD (checking missing DXA assessment during DEMs in section 4.2).

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 and imputation. For anatomical sites that can be measured on different body sides (ie, left and right), only those BMD values that are collected from the same body side as the Baseline BMD will be used for analyses and imputation.

The comparison of the percent change from Baseline in lumbar spine DXA BMD at Month 6 between treatment groups will be evaluated using an analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group, age strata group (stratification factor), Baseline BMD value, machine type at baseline, region, and interaction of Baseline BMD value and machine type at baseline as independent variables. Summaries for the results will include least squares (LS) means point estimates of the percent change from Baseline for each treatment arm.. Summaries including the LS mean, standard error, 2-sided 95% CI and associated p-values (unadjusted p-value and adjusted p-value) will be provided for the difference between the LS means for romosozumab and placebo.

8.1.2 Sensitivity and Supplementary analyses of the primary efficacy variable(s)

- Sensitivity and supplementary analyses of the primary efficacy endpoint will be conducted:

Approach	Analysis Set	ICE/ICE Strategy	Missing Data Strategy
Sensitivity analysis 1	PPS	NA	Same with primary analysis
Sensitivity analysis 2 MMRM	FAS	Same with primary analysis	Data after ICE#3 will be setting to missing and leave it missing before running MMRM. No other imputation before MMRM.
Sensitivity 3	FAS	Same with primary analysis	Observed

Supplementary analysis 1	FAS	ICE#1, ICE#2, and ICE#3 from the primary estimand will all be handled by treatment policy strategy in this supplemental analysis.	LOCF
Supplementary analysis 2	FAS	ICE #1: treatment discontinuation (BMD data collected >70 days after last IMP) will be handled by hypothetical strategy. ICE #2: alternative osteoporosis therapy will be handled by hypothetical strategy.	Data after ICEs will be setting to missing and replaced with LOCF
Supplementary analysis 3	FAS	Same with Supplementary analysis 2	Data after ICEs will be setting to missing and replaced with MI-MAR

For sensitivity analysis 2, a mixed effects model with repeated measures model (MMRM) will be fit with the percent change from Baseline at Months 3 and 6 in BMD of the lumbar spine as the dependent variable, and Baseline BMD, machine type at baseline, interaction of Baseline BMD and machine type at baseline, visit (categorical), treatment (categorical), interaction of treatment and visit, region and interaction of treatment and region as the independent variables. The MMRM analysis will include subject as a random effect, treatment, age strata group (stratification factor), region, visit, and treatment-by-visit interaction as fixed effects, with adjustment for baseline BMD value. The variance structure will allow for heteroskedasticity of variance between treatment groups. The FAS will be used for the repeated measurement model. If model cannot be estimated, region will be excluded from MMRM model.

A blinded data review process will be implemented in which the missingness of data, statistical assumptions, eligibility of definition of categorical variables/thresholds will be assessed. If it turns out that the number of randomized subjects without Baseline and/or without BMD measurement at an on-treatment visit is high, then a sensitivity analysis will be pre-specified under blinded conditions using multiple imputation strategies under the “missing at random” assumption. Depending on the amount of missingness, additional sensitivity analyses under “missing not at random” assumptions may be defined. If the need of such analysis is indicated during the blinded data review process, the method of these analyses will be prespecified in the final SAP before unblinding and database lock.

Further sensitivity analyses will be investigated in DEM of certain critical events listed in Section 4.2 which will be monitored throughout the blinded data review process.

Due to the exploratory nature of these analyses, even though the p-values will be computed for each analysis in an exploratory manner, formal significance testing will not be conducted.

8.2 Statistical analysis of the secondary efficacy variables

For the secondary efficacy BMD endpoints during the DBPC Period (at total hip and femoral neck at Month 6), will be performed following the same analyses that for the primary endpoints. The main analysis and sensitivity/supplementary analyses of key secondary endpoints will follow same estimands than the primary endpoint except attribute of "Endpoint". COVID-19 related intercurrent event is also added to the estimand of key secondary endpoints and same strategy in each analysis.

- Percent change from baseline in BMD at the total hip at the end of the DBPC (Month 6) as assessed by DXA
- Percent change from baseline in BMD at the femoral neck at the end of the DBPC Period (Month 6) as assessed by DXA
- Percent change from baseline in BMD at the lumbar spine at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment)
- Percent change from baseline in BMD at the total hip at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment)
- Percent change from baseline in BMD at the femoral neck at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab treatment in the Double-Blind, Placebo-Controlled Period (for a total of 12 months of romosozumab treatment)
  The derivation rules specified in Section 8.1.1 will be applied for the calculation of the secondary BMD endpoints as well.

8.2.1 Secondary efficacy variables - DBPC Period

For the secondary efficacy BMD endpoints during the DBPC Period (at total hip and femoral neck at Month 6), a percent change from Baseline in DXA BMD will employ an ANCOVA model. The ANCOVA model will include the same independent variables and interactions as described in Section 8.1.1. The FAS will be used for this analysis. This analysis will be performed with adjustment for multiplicity as described in Section 4.5. Nominal (unadjusted) p-values will be provided as well for exploratory purposes.

A sensitivity analysis will be performed on the analysis of the secondary efficacy variable as described in the above paragraph based the PPS. In addition, a MMRM will be fit with the percent change from Baseline at Months 3 and 6 in BMD of the total hip and femoral neck with

the same independent variables and interactions as described in Section 8.1.1.The FAS will be used for these analyses.

For the secondary efficacy BMD endpoints at total hip and femoral neck, the following 2 further sensitivity analyses will be conducted:

Only those values are included in analysis, which were assessed during the period when subjects received IMP and does not apply to any alternative osteoporosis therapy (licensed drugs only). In particular, all values which were assessed more than 70 days after last dose of IMP or were assessed after the first intake of alternative osteoporosis therapy (licensed drugs only) will be considered as missing data and will not be imputed. For one analysis, missing data imputation via LOCF will be applied, and for the other analysis via multiple imputation according to missing at random assumption will be applied.

8.2.2 Secondary efficacy variables - OL Treatment Period

For the OL Treatment Period, only the post Month 6 value will be used for imputation, the values in the DBPC Period will not be carried forward into the OL Treatment Period.

For the OL Treatment Period analyses, the secondary efficacy variables are the percent change from Baseline in BMD at lumbar spine, total hip, and femoral neck at the end of OL Period (at 12 months) as assessed by DXA in subjects initially randomized to romosozumab only. The descriptive statistics will be performed for 12 months analysis.

8.3 Statistical analysis of other efficacy variable

The other efficacy variables are defined as:

- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 3 as assessed by DXA – DBPC Period
- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at the end of OL Treatment Period (Month 12) as assessed by DXA in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months – OL Treatment Period

The derivation rules specified in Section 8.1.1 and Section 8.2.2 will be applied for the calculation of the other efficacy variables as well.
The ANCOVA method described in Section **Error! Reference source not found.** for the primary efficacy variable will be performed. For Month 12 analysis, Only descriptive statistics will be summarized.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Missing PK or PD values (either Baseline or postbaseline values) will not be imputed. Measurement values that are below the lower limit of quantification (BLQ) will be considered equal to the LLOQ/2 for all analyses. If more than 1/3 of the samples are BLQ at a particular visit no summary statistics will be calculated and only minimum and maximum values will be reported.

9.1 Pharmacokinetics

Pharmacokinetic variables will be analyzed for all subjects in the PK-PPS at both Month 6 and final analysis. The serum trough concentrations of romosozumab will be summarized based on the PK-PPS using descriptive statistics (n, geometric mean, 95% confidence interval for geometric mean, geometric CV%, mean, standard deviation, median, minimum value, maximum value) for the below analyses:

- Month 1-6 of romosozumab/romosozumab treatment group at 6-month analysis
- Month 1-12 of romosozumab/romosozumab treatment group at final analysis
- Month 1-6 of romosozumab/romosozumab group pooled with month 6-12 of placebo/ romosozumab treatment group at final analysis

Geometric mean (geometric coefficient of variation) and GeoMean (±95% CI) romosozumab serum concentration time profiles will be displayed graphically on a linear scale and semi-logarithmic scale.

Spaghetti plots of concentration-time profiles will be displayed graphically on a linear scale and semi-logarithmic scale.
A population PK analyses will be conducted. Details of the analysis will be described in a separated data analysis plan and results will be reported separately.

9.2 Pharmacodynamics

Pharmacodynamic variables will be analyzed for all subjects in the PD-PPS at both Month 6 and final analysis.

For the BTMs (P1NP and sCTX), descriptive statistics (n, geometric mean, 95% confidence intervals, geometric CV%, mean, standard deviation, median, interquartile range, minimum value, maximum value) will be presented by treatment group. The following list of endpoints will be analysed:

- observed values, change from Baseline and percent change from Baseline at all planned visits
- maximum on-treatment observed values, change from Baseline and percent change from Baseline (P1NP only)
- minimum on-treatment observed values, change from Baseline and percent change from Baseline (sCTX only)

Pharmacodynamic-time plots in P1NP and sCTX with median+/-interquartile range will be generated for the actual value and percent change from Baseline for each PD parameter at each visit for both the romosozumab and placebo group and these plots will be displayed on a linear scale.

For all PD endpoints, the following analyses are performed at:

- romosozumab treatment group vs. placebo group for month 1-6 at Month 6 analysis

- romosozumab/romosozumab treatment group vs. placebo/romosozumab treatment group for month 1-12 at final analysis
- romosozumab/romosozumab treatment group for month 1-6 vs. placebo/romosozumab treatment group for month 6-12 at final analysis

10 SAFETY ANALYSES

Safety will be presented by treatment groups for the SS.

10.1 Extent of exposure

The number of doses received will be summarized categorically (eg., 1, 2, 3, …) and with descriptive statistics. In addition, the cumulative duration of exposure will be summarized for subjects exposed for different duration categories (eg., at least one day, ≥ 1 months, ≥ 2 months, …, ≥12 months).

Duration of exposure to IMP will be calculated as:

Date of last administration of IMP – date of first IMP administration + 30 days

Additionally, adjusted duration of exposure is calculated as:

Date of last administration of IMP – date of first IMP administration + 30 days - cumulative gaps in exposure

Calculate cumulative gaps are the number of days from date of previous dose + 30 days to next dose date summed up over the entire period. If subjects had gap of <=30 days between successive doses then gap in exposure will be 0 days for this period.

10.2 Adverse events

Treatment emergent AEs (TEAE) are defined as all AEs started or worsened in severity on or after the date of receiving first dose of IMP and before EOS date except lipid-type AEs starting on the date of first dose of IMP and not worsening (and not deemed IMP related by the investigator). Lipid-type AEs will be defined by the Dyslipidaemia SMQ (see Appendix 13.7). The different handling of lipid-type AEs starting on the date of first dose of IMP is to ensure that pre-existing lipid abnormalities are not reported as TEAEs (lipids are only measured at Day 1 before first IMP and not at Screening).

All subsequently described displays in Section 10.2 will be compiled for the DBPC Period and for the overall study period (treatment start through Month 15). For the displays on the DBPC Period, TEAEs with a start date before or on the End of DBPC period date will be included. For the overall period, TEAEs with a start date before or on the EOS date will be included.

Duration of AEs will not be calculated if there is missing stop date information. If the intensity of an AE is unknown, it is considered as severe. If the relationship to study drug is missing, it is considered as related. Note that if the seriousness of an adverse event is unknown, every attempt should be made to resolve this prior to a snapshot for an interim analysis or database lock; in the exceptional case that the seriousness of an adverse event is still missing then no imputation should be applied for this characteristic.

If a TEAE occurs on the date of switch from the DBPC period to the OL period, the event is attributed to the DBPC treatment. The only exception that TEAEs of injection site reactions (see Appendix 13.5), potentially related to hypersensitivity (Standardized MedDRA® Query [SMQ], narrow scope) will be in OL period.

The number and incidence of TEAEs will be summarized by treatment group, the MedDRA® SOC and PT with the SOC sorted alphabetically and within SOC the PT sorted by descending order of frequencies. The incidence of TEAEs will also be summarized by treatment group (including romosozumab total), intensity and relationship to IMP.

Adverse events will be presented as "number of participants (percentage of participants) [number of events]". In this style of output, "[number of events]" will include all cases of an AE including repeat occurrences in individual participants, while "number of participants" will count each participant only once.

10.2.1 Time at risk of exposure

Time at risk for each subject represents the time a study participant is at risk for having an AE with romosozumab exposure period.

In this study, time at risk (years) during the overall study period is defined as:

(End of last romosozumab – Date of the first dose of romosozumab +1) / 365.25Study participant time at risk represents the time a participant is at risk for having an AE. The definitions for time at risk (in days) are outlined in Section **Error! Reference source not found.**. These definitions will be used for exposure-adjusted AE summaries.

10.2.2 Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

Selected AE summaries will include the EAIR with associated 95% confidence interval and EAER where the EAIR and EAER are expressed per 100 study participant-years of exposure.

The EAIR is defined as the number of participants (n) with a specific AE adjusted for the exposure and will be scaled to 100 study participant-years:$EAIR = 100 \times \frac{n}{\sum_{i=1}^{N}(T_{EXP(i)})}$

where n is the total number of participants with AE of interest, N= number of participants at risk of an AE, and $T_{Exp(i)}$ is the total exposure time for each participant:

- For participantss with the specific AE of interest:time at risk in years to the first occurrence for the AE of interest at the level of coding evaluated
- For participantss without the AE: the total time at risk in years.

Exact Poisson 95% confidence intervals for incidence rates are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990; Fay and Feuer, 1997):

$$LCL = \frac{x^2_{2n,\alpha/2}}{2}$$

$$UCL = \frac{x^2_{2(n+1),1-\alpha/2}}{2}$$

where n is the number of participants with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ2.

The EAER will be the number of AEs including repeat occurrences in individual participants divided by the total time at risk scaled to 100 study participant-years and calculated using:

$$EAER = 100 \times \frac{N_{AE}}{\sum_{i=1}^{N}(T_{Risk(i)})}$$

where is the total number of AEs, n is the total number of participants and $T_{Risk(i)}$ is the time at risk in years for each participant for each exposure period.

No confidence interval will be computed for EAER.

The following summaries will be provided by actual treatment group for the DBPC and the Overall Periods based on the SS. In addition, all summaries of TEAEs based on "100 participant-years" will include EAIR (with 95% confidence interval) and EAER.

10.2.3 Standard AE summaries

- TEAEs overview during DBPC period
- TEAEs overview per 100 patient-years during overall period
- TEAEs by SOC and PT during DBPC period
- TEAEs per 100 patient-years by SOC and PT during overall period
- TEAEs by maximum intensity by SOC and PT during DBPC period
- TEAEs by maximum intensity by SOC and PT during overall period
- TEAEs by maximum relationship to IMP per the Investigator by SOC and PT during DBPC period
- TEAEs by maximum relationship to romosozumab per the Investigator by SOC and PT during overall period
- TEAEs leading to IMP discontinuation by SOC and PT during DBPC period
- TEAEs leading to romosozumab discontinuation by SOC and PT during overall period
- TEAEs leading to study discontinuation by SOC and PT during DBPC period
- TEAEs leading to study discontinuation by SOC and PT during overall period
- TEAEs leading to death by SOC and PT during DBPC period
- TEAEs leading to death by SOC and PT during overall period
- Serious TEAEs by SOC and PT during DBPC period
- Serious TEAEs per 100 patient-years by SOC and PT during overall period
- Serious TEAEs by maximum relationship to study medication per the Investigator by SOC and PT during DBPC period

- Serious TEAEs by maximum relationship to study medication per the Investigator by SOC and PT during overall period
- Fatal TEAEs by maximum relationship to study medication per the Investigator by SOC and PT during DBPC period
- Fatal TEAEs by maximum relationship to study medication per the Investigator by SOC and PT during overall period
- Non-serious TEAEs above reporting frequency threshold of 5% by SOC and PT during DBPC period
- Non-serious TEAEs above reporting frequency threshold of 5% by SOC and PT during overall period
- TEAEs of interest by SOC and PT during DBPC period
- TEAEs of interest by SOC and PT during overall period
- TEAE of special interest (PDILI) by SOC and PT during DBPC period
- TEAEs of special interest (PDILI) by SOC and PT during overall period
- TEAEs of COVID-19 vaccine by SOC and PT during DBPC period

TEAEs of COVID-19 vaccine by SOC and PT during overall period There is no planned statistical testing in the safety analyses.

10.2.4 Adverse events of interest

Subject incidence of adverse events of interest of hypocalcemia, injection site reactions, potentially related to hypersensitivity (Standardized MedDRA® Query [SMQ], narrow scope), malignant or unspecified tumor (SMQ, narrow scope), hyperostosis, osteoarthritis, positively adjudicated adverse events of ONJ, AFF, and positively adjudicated serious CV events will be tabulated by PT and treatment group (see Appendix 13.5). Subcategories are added as appropriate (EG, MI, stroke and other CV events).

10.2.4.1 Osteonecrosis of the jaw adjudication

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

10.2.4.2 Atypical femoral fracture adjudication

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

10.2.4.3 Adjudicated positive cardiovascular events

All deaths and potential cardiovascular-related serious adverse events (SAEs) as predefined search of the MedDRA® terms according to the adjudication manual for cardiovascular event will be submitted to an external independent committee comprised of experienced cardiologists for blinded adjudication. The committee will adjudicate the events and determine whether the event is cardiovascular in nature.

Baseline cardiovascular risk factors will be summarized descriptively as listed in Section 6.2.1.

Only events positively adjudicated by the adjudication committee to meet cardiovascular event definition criteria will be included for analyses. Positively 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, odds ratios and 95% confidence intervals. No statistical tests will be performed.

10.2.5 Adverse events of special interest

An AE of special interest is defined by potential drug-induced liver injury (PDILI) SMQ (see Appendix 13.6).

10.3 Clinical laboratory evaluations

Actual values and changes from baseline of laboratory parameters (hematology and serum chemistry including iPTH and lipids) will be descriptively summarized at each available time point. In addition, last value, minimum value during treatment, and maximum value during treatment will be presented. End of treatment will be defined as last visit of Month 6 during DBPC period or Month 12 during OL period (defined in Section 3.2.4.2 and Section 3.2.4.3) not including the FU visit and during treatment for the minimum and maximum calculation will also exclude the FU visit.

Shift tables from Baseline to each post-Baseline time point will be presented. In addition, shift tables regarding the normal range at end of treatment, minimum and maximum shift at any time will also be produced for each hematology and biochemistry laboratory parameter. The shifts will be categorized using L (low), N (normal), H (high), missing, and total.

Graphs showing central tendency (median) and dispersion (interquartile range) 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
- alkaline phosphatase.

10.3.1 Potential drug-induced liver injury and potential Hy's Law evaluation

The count and percentage of subjects with potential drug-induced liver injury (PDILI) will be tabulated at baseline and on study. For the primary analysis, all on-study visits up to Month 6 will be used, for final analysis all on-study visits with available values will be used. The following endpoints will be applied.

A table will be produced to summarize potential Hy's Law cases. The following two endpoints will be calculated:
Incidence of subjects with

- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥2xULN
- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥2xULN in the absence of ALP ≥2xULN

In order to meet either of the above criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation, if applicable) at the same visit. For example, a subject who experiences a ≥2 x ULN elevation of bilirubin at one visit and a ≥3xULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

The following vital signs variables should be summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C) and pulse rate (beats/min). The observed value and change from Baseline value for each vital sign variable by treatment group and visit will be summarized. A by-subject listing of all vital signs data will be provided. This listing should be presented by treatment group and will include: center, subject identifier, age, sex, race, weight, visit, vital sign variable and result.

10.4.2 Physical examinations

Abnormal results of the physical examination together with details of abnormalities: abnormality clinically significant or not, will be listed by subject and visit.

10.4.3 Height and Weight

Descriptive statistics of actual values and changes from Baseline in body weight, and BMI will be presented by scheduled visit will be summarized using the SS.

10.4.4 Electrocardiograms

ECG data will be analyzed by treatment group and visit for SS.

A summary of the number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECG results at all applicable visits will be provided.

The following ECG variables will be summarized descriptively (absolute values and change from Baseline) by visit: QTcF, RR, PR, QRS and QT.

A by-subject listing of all 12-lead ECG data will be provided.

10.4.5 Immunogenicity Analysis

The incidence and percentage of subjects who develop anti-romosozumab antibodies up to Month 6 (for romosozumab group only) for the DBPC period and up to Month 12 (for both group) for the overall study period will be tabulated. This analysis will be repeated to further include all testing results from samples collected during the 3-month FU period. For subjects

who develop anti-romosozumab antibodies, romosozumab serum concentrations may also be analyzed. Additionally, exploratory analyses may be performed to assess any impact on safety or efficacy.

Further antibody analyses will be provided and details in Appendix 13.8.

11 OTHER ANALYSES

Not applicable.

12 REFERENCES

International Conference on Harmonization. Statistical Principles for Clinical Trials – ICH Harmonised Tripartite Guideline. Guidance for Industry, E9, FDA federal register, 63, 1998

Osteonecrosis of the Jaw Adjudication Manual of Operations for OP0002

Atypical Femoral Fracture Adjudication Manual of Operations for OP0002

Cardiovascular Events Adjudication Manual of Operations for OP0002

Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med. 1997; 16:791–801.

Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. (2008) FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporosis International 19: 385-397.

Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A and the National Osteoporosis Guideline Group (2008) Case finding for the management of osteoporosis with FRAX® - Assessment and intervention thresholds for the UK. Osteoporos Int 19; 1395-1408.

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology 1990;131(2):373-375.

13 APPENDICES

13.1 Alternative osteoporosis therapy (licensed drugs only)

Potential alternative osteoporosis therapies (licensed drugs only) are including but not limited to:

- Strontium (including strontium ranelate and over-the-counter strontium preparations)
- Vitamin K and vitamin K analogs
- iv bisphosphonates
- Oral bisphosphonates
- Denosumab
- TPTD or any PTH analogs
- Systemic oral or transdermal estrogen
- SERMs
- Calcitonin
- Tibolone
- Hormonal ablation therapy
- Active vit D and analogs
- Chinese herbal medicine for treating osteoporosis (including but not limited to TFRD, ICA)

Patients who take any alternative osteoporosis therapy that listed above, will be reviewed and confirmed by UCB medical team within each DEMs. A finalized list will be provided prior to unblinding the study.

13.2 Definitions of adjusted p-values for BMD endpoints

Test ID Endpoint	Endpoint	Raw p-value	Adjusted p-value
1	**Lumbar spine** BMD percent change from Baseline at 6 months	p1	p1
2	**Total hip** BMD percent change from Baseline at 6 months	p2	Max (p1, p2)
3	**Femoral neck** BMD percent change from Baseline at 6 months	p3	Max (p1, p2, p3)

13.3 Fracture Risk Assessment Tool: 10-year Probability of Major Osteoporotic Fracture (FRAX)

FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that provides country/ethnicity-specific models for the assessment of fracture probability in men and women [Kanis et al, 2008a, b]. The approach uses clinical risk factors to estimate 10-year probability of a major osteoporotic fracture (hip, clinical spine, forearm or humerus) or of a hip fracture alone. The estimate of probability can be calculated with clinical risk factors alone, or additionally with baseline femoral neck BMD. The clinical risk factors used for the calculation include sex, age, BMI, a historical fragility fracture, parental history of hip fracture, current tobacco smoking, ever long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and daily alcohol consumption of 3 or more units daily.

13.4 Multiple Imputations for BMD endpoints

First, a repeated measures Gaussian model will be fitted to the data using a Bayesian approach, with non-informative priors for the mean and variance-covariance matrix to provide a joint posterior for the parameters in this model. The repeated measures Gaussian model will include separate mean profiles for each treatment group and the same covariates as those in the primary ANCOVA analysis.

Independent samples will then be drawn from the posterior distributions for the mean and variance-covariance matrix to provide inputs into an imputation model. For each subject with missing data, these sampled values of the parameters for mean vectors and the variance-covariance matrices specify a joint distribution for their observed and unobserved outcome data.

Missing post-baseline BMD will be modelled under missing at random assumption. The ANCOVA model as in primary analysis will include fixed effects for treatment (two levels), Baseline BMD value, machine type at baseline, region, age strata group (stratification factor), and interaction of Baseline BMD value and machine type at baseline as independent variables.

The MI-MAR method will be applied as follows based on raw values:

- Step 1: Any observation after date of ICEs will be set to missing.

- Step 2: Create a dataset, one for each treatment group, of study participants with observed values and those needing estimation by multiple imputation. For the imputation step, missing values will include non-monotone missing values (ie, intermittent missing values between completed assessments) and monotone missing values (ie, where all study participant data is missing after a given time point).
  - **Step 2a**: First, the intermittent missing values in each dataset will be imputed using the MCMC method with multiple chains, monotone missing data imputing pattern, and non-informative priors for all parameters. Unless specified differently, the first 200 iterations will not be used (the 'burn-in' option). A total of 100 sets of imputations will be performed. The seed used for these imputations will be 2022 and all other multiple imputation procedures described in this SAP will use this same seed as well.

The resulting 100 imputed data sets will have a monotone missing data pattern and will be imputed using a method for monotone missingness:

- **Step 2b**: For monotone missing data, monotone regression will be used to impute missing data. A separate regression model is estimated for each variable with missing values (ie, measurement at each time point). Based on the resulting model, a new regression model is then drawn and is used to impute the missing values for the variable. Since the data set has a monotone missing data pattern, the process is repeated sequentially for variables with missing values. The procedure will be based on the 100 imputed datasets generated from the MCMC procedure and will be performed by Imputation.
- **Step 2c**: If an imputed value falls outside of the pre-defined range of values for the given variable, the value will be truncated to be within the predefined range of values for the endpoint of interest.

The SAS® PROC MI procedure will be used for the imputation.

The visits to include in the MCMC and monotone regression steps will be the same, and will correspond to all data available at the time of the analysis, as specified below:

- For dry-runs conducted prior to the Month 6 analysis, all weeks up to Month 6 will be included,
- For the Month 6 analysis, all weeks up to Month 6 will be included,
- For the final analysis, all weeks up to Month 12 will be included.

The stratification factors (age strata group) may be dropped from the imputation model to facilitate model convergence if required (and this holds true for all imputation models). The post-Baseline values will need to be specified in chronological order in the imputation model so that the SAS® PROC MI imputes variables from left to right (ie, the Month 6 value will be first imputed using regression based on Month 3, and then the Month 12 value will be imputed using regression based on Month 3 and Month 6 values, etc.).

The resulting datasets for each treatment arm will be combined into one complete dataset based on each of the 100 imputations (containing 100 times the number of study participants analyzed).

The imputation model based on the MCMC method for intermittent missing values will only allow multivariate normal variables. Therefore, region which has 3 levels will be re-coded as indicator variable:

One indicator variable (region1) will be defined as 0 for regions other than North and 1 for North. Two more indicator variables (region2 and region3) will be defined similarly replacing North with Eastern and South respectively. In the VAR statement of the imputation model, the indicator variables will be ordered as follows: region1 region2 and region3. In the eventuality that two regions required to be pooled due to a low percentage of study participants randomized in one region, the indicator variables defined above will be revised accordingly.

- One indicator variable will be defined for the age stratification variable: will be coded as 1 for <75 years and 0 for ≥75 years.
- One indicator variable will be defined for the machine type at baseline variable: will be coded as 1 for Hologic and 0 for Lunar.

To maintain consistency with the MCMC method for intermittent missing values, these indicator variables will also be used in the monotone regression step for monotone missing values and treated as continuous variables.

- Step 3, the 100 imputed datasets from Step 2 will be combined, and simple means and standard errors will be calculated using Rubin's rules (via SAS® PROC MIANALYZE). For calculation of other descriptive statistics (median, minimum and maximum), Rubin's rules do not apply. Multiple imputation estimates will be computed by calculating arithmetic means of the estimates from the multiple repetitions of the imputation algorithm. Thus, for median, minimum and maximum the following approach will apply:
  - The data will be summarized by treatment, visit and imputation and the summary statistics will be computed.
  - Results will be summarized by taking the mean value of each summary statistic at each visit across all imputations.

- The number of decimal places will remain the same as the original for display purposes (ie, if the mean was presented to 1 decimal place, the mean of the means will also be presented to 1 decimal place).

In Step 3, the analysis will be done on the percentage change from Baseline, and the model will be an ANCOVA model with treatment group and the same covariates as those in the primary ANCOVA analysis.

In Step 5, the results obtained from the 100 ANCOVA analyses in Step 4 (ie, the Least Square Means for the treatment difference and the 95% CI for the contrasts) will be combined with Rubin's rules. Pseudo SAS codes for the sensitivity ANCOVA model of the endpoint as follows:

```
/******** for intermittent missing values *********/
PROC MI data=xxx NIMPUTE = 100 seed=xxx NOPRINT OUT=xxxx min=0 max=1;
 BY trtp;
 VAR type agegp region1 region2 base aval_m3 aval_m6 ;
 MCMC CHAIN=multiple IMPUTE = monotone;
run;
/******** for monotone missing values **********/
proc mi data=xxx seed=xxx nimpute=1 NOPRINT out=xxxx;
var agegp trtp region machinetype base aval_m3 aval_m6;
class agegp trtp region machinetype;
MONOTONE REGRESSION;
BY _imputation_;
run;

PROC MIXED DATA=xxx;
      BY _imputation_;
      CLASS trtp type region agegp;
      MODEL pchg=base trtp type agegp region base*type;
      LSMEANS trtp / om cl stderr pdiff ;
     ods output LSMeans=LMS Diffs=DIFF;
RUN;

*** MIANALYZE;
proc sort data=DIFF; by _imputation_ ; run;
```

```
proc mianalyze data= DIFF;
modeleffects estimate;
stderr stderr;
ods output ParameterEstimates=MIAN_lsdiffs;
run;

proc sort data=lsm; by trtp _imputation_ ; run;

proc mianalyze data=lsm;
by trtp;
modeleffects estimate;
stderr stderr;
ods output ParameterEstimates=MIAN_lsm;
run;
```

13.5 Adverse Event of Interest

MedDRA Version 24.1

- Hypocalcemia (PTs) – Based on agreed Risk Management Plan search strategy

Adjusted calcium decreased
Blood calcium decreased
Calcium deficiency
Calcium ionised decreased
Chvostek's sign
Hypocalcaemia
Hypocalcaemic seizure
Trousseau's sign

- Injection Site reaction (PTs)

Administration site abscess	Administration site pallor	Injection site injury
Administration site abscess sterile	Administration site papule	Injection site irritation
Administration site anaesthesia	Administration site paraesthesia	Injection site ischaemia
Administration site atrophy	Administration site phlebitis	Injection site joint discomfort
Administration site bruise	Administration site photosensitivity reaction	Injection site joint effusion
Administration site calcification	Administration site plaque	Injection site joint erythema
Administration site cellulitis	Administration site pruritus	Injection site joint infection
Administration site coldness	Administration site pustule	Injection site joint inflammation
Administration site cyst	Administration site rash	Injection site joint movement impairment
Administration site dermatitis	Administration site reaction	Injection site joint pain
Administration site discharge	Administration site reaction neonatal	Injection site joint swelling
Administration site discolouration	Administration site recall reaction	Injection site joint warmth
Administration site discomfort	Administration site scab	Injection site laceration
Administration site dryness	Administration site scar	Injection site lymphadenopathy
Administration site dysaesthesia	Administration site streaking	Injection site macule
Administration site eczema	Administration site swelling	Injection site mass
Administration site erosion	Administration site thrombosis	Injection site movement impairment
Administration site erythema	Administration site ulcer	Injection site necrosis

Administration site exfoliation	Administration site urticaria	Injection site nerve damage
Administration site extravasation	Administration site vasculitis	Injection site nodule
Administration site fibrosis	Administration site vesicles	Injection site oedema
Administration site granuloma	Embolia cutis medicamentosa	Injection site pain
Administration site haematoma	Injected limb mobility decreased Injection site abscess	Injection site pallor
Administration site haemorrhage	Injection site abscess sterile	Injection site papule
Administration site hyperaesthesia	Injection site anaesthesia	Injection site paraesthesia
Administration site hypersensitivity	Injection site atrophy	Injection site phlebitis
Administration site hypertrichosis	Injection site bruising	Injection site photosensitivity reaction
Administration site hypertrophy	Injection site calcification	Injection site plaque
Administration site hypoaesthesia	Injection site cellulitis	Injection site pruritus
Administration site indentation	Injection site coldness	Injection site pustule
Administration site induration	Injection site cyst	Injection site rash
Administration site infection	Injection site deformation	Injection site reaction
Administration site inflammation	Injection site dermatitis	Injection site recall reaction
Administration site injury	Injection site discharge	Injection site scab
Administration site irritation	Injection site discolouration	Injection site scar
Administration site ischaemia	Injection site discomfort	Injection site streaking
Administration site joint discomfort	Injection site dryness	Injection site swelling
Administration site joint effusion	Injection site dysaesthesia	Injection site telangiectasia
Administration site joint erythema	Injection site eczema	Injection site thrombosis
Administration site joint infection	Injection site erosion	Injection site ulcer
Administration site joint inflammation	Injection site erythema	Injection site urticaria
Administration site joint movement impairment	Injection site exfoliation	Injection site vasculitis
Administration site joint pain	Injection site extravasation	Injection site vesicles
Administration site joint warmth	Injection site fibrosis	Injection site warmth
Administration site laceration	Injection site haematoma	Malabsorption from injection site

Administration site lymphadenopathy	Injection site haemorrhage	
Administration site macule	Injection site hyperaesthesia	
Administration site mass	Injection site hypersensitivity	
Administration site movement impairment	Injection site hypertrichosis	
Administration site necrosis	Injection site hypertrophy	
Administration site nerve damage	Injection site hypoaesthesia	
Administration site nodule	Injection site indentation	
Administration site odour	Injection site induration	
Administration site oedema	Injection site infection	
Administration site pain	Injection site inflammation	

- Hyperostosis (PTs) -

Acquired foramen magnum stenosis	Foramen magnum stenosis
Acral overgrowth	High turnover osteopathy
Bone formation increased	Intracranial pressure increased
Cervical spinal stenosis	Lumbar spinal stenosis
Diffuse idiopathic skeletal hyperostosis	Macrogenia
Enostosis	Melorheostosis
Exostosis	Periostosis
Exostosis of external ear canal	Vertebral foraminal stenosis
Exostosis of jaw	Vertebral lateral recess stenosis
Extraskeletal ossification	

- Osteoarthritis (PTs) -

Ankle arthroplasty	Nodal osteoarthritis
Arthritis	Osteoarthritis
Arthropathy	Osteoarthropathy
Exostosis	Polyarthritis
Facet joint syndrome	Rapidly progressive osteoarthritis
Hip arthroplasty	Shoulder arthroplasty
Interspinous osteoarthritis	Spinal osteoarthritis
Joint arthroplasty	Vertebral osteophyte
Knee arthroplasty	

13.6 Adverse Event of Special Interest (PDILI)

AESI are defined by the PTs for the PDILI SMQ.

Acquired antithrombin III deficiency
Acquired factor IX deficiency
Acquired factor V deficiency
Acquired factor VIII deficiency
Acquired factor XI deficiency
Acquired hepatocerebral degeneration
Acquired protein S deficiency
Acute graft versus host disease in liver
Acute hepatic failure
Acute on chronic liver failure
Acute yellow liver atrophy
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Allergic hepatitis
Alloimmune hepatitis
Ammonia abnormal
Ammonia increased
Anti factor X activity abnormal
Anti factor X activity decreased
Anti factor X activity increased
Antithrombin III decreased
Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
AST/ALT ratio abnormal
Asterixis
Autoimmune hepatitis
Bacterascites
Bile output abnormal
Bile output decreased
Biliary ascites
Biliary cirrhosis
Biliary fibrosis
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Bilirubin excretion disorder
Bilirubin urine present
Biopsy liver abnormal
Blood bilirubin abnormal

Blood bilirubin increased
Blood bilirubin unconjugated increased
Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased
Blood thromboplastin abnormal
Blood thromboplastin decreased
Bromosulphthalein test abnormal
Cardiohepatic syndrome
Child-Pugh-Turcotte score abnormal
Child-Pugh-Turcotte score increased
Cholaemia
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Chronic graft versus host disease in liver
Chronic hepatic failure
Chronic hepatitis
Coagulation factor decreased
Coagulation factor IX level abnormal
Coagulation factor IX level decreased
Coagulation factor V level abnormal
Coagulation factor V level decreased
Coagulation factor VII level abnormal
Coagulation factor VII level decreased
Coagulation factor X level abnormal
Coagulation factor X level decreased
Coma hepatic
Computerised tomogram liver abnormal
Congestive hepatopathy
Cryptogenic cirrhosis
Diabetic hepatopathy
Drug-induced liver injury
Duodenal varices
Flood syndrome
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gallbladder varices
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Gastric variceal injection

Gastric variceal ligation
Gastric varices
Gastric varices haemorrhage
Gastrooesophageal variceal haemorrhage prophylaxis
Graft versus host disease in liver
Guanase increased
Hepaplastin abnormal
Hepaplastin decreased
Hepatectomy
Hepatic artery flow decreased
Hepatic atrophy
Hepatic calcification
Hepatic cirrhosis
Hepatic cytolysis
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic failure
Hepatic fibrosis
Hepatic function abnormal
Hepatic hydrothorax
Hepatic hypertrophy
Hepatic hypoperfusion
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic mass
Hepatic necrosis
Hepatic pain
Hepatic sequestration
Hepatic steato-fibrosis
Hepatic steatosis
Hepatic vascular resistance increased
Hepatic venous pressure gradient abnormal
Hepatic venous pressure gradient increased
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic

Hepatobiliary disease
Hepatobiliary scan abnormal
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatomegaly
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatosplenomegaly
Hepatotoxicity
Hyperammonaemia
Hyperbilirubinaemia
Hypercholia
Hyperfibrinolysis
Hypertransaminasaemia
Hypocoagulable state
Hypofibrinogenaemia
Hypoprothrombinaemia
Hypothrombinaemia
Hypothromboplastinaemia
Icterus index increased
Immune-mediated cholangitis
Immune-mediated hepatic disorder
Immune-mediated hepatitis
International normalised ratio abnormal
International normalised ratio increased
Intestinal varices
Intestinal varices haemorrhage
Ischaemic hepatitis
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Kayser-Fleischer ring
Liver dialysis
Liver disorder
Liver function test abnormal
Liver function test decreased
Liver function test increased
Liver induration
Liver injury
Liver operation
Liver palpable
Liver scan abnormal

Liver tenderness
Liver transplant
Lupoid hepatic cirrhosis
Lupus hepatitis
Magnetic resonance imaging hepatobiliary abnormal
Magnetic resonance proton density fat fraction measurement
Mitochondrial aspartate aminotransferase increased
Mixed liver injury
Molar ratio of total branched-chain amino acid to tyrosine
Nodular regenerative hyperplasia
Nonalcoholic fatty liver disease
Non-alcoholic steatohepatitis
Non-cirrhotic portal hypertension
Ocular icterus
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Parenteral nutrition associated liver disease
Perihepatic discomfort
Peripancreatic varices
Portal fibrosis
Portal hypertension
Portal hypertensive colopathy
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal vein cavernous transformation
Portal vein dilatation
Portopulmonary hypertension
Primary biliary cholangitis
Protein C decreased
Protein S abnormal
Protein S decreased
Prothrombin level abnormal
Prothrombin level decreased
Prothrombin time abnormal
Prothrombin time prolonged
Prothrombin time ratio abnormal
Prothrombin time ratio increased
Radiation hepatitis
Regenerative siderotic hepatic nodule
Renal and liver transplant
Retrograde portal vein flow
Reye's syndrome
Reynold's syndrome

Splenic varices
Splenic varices haemorrhage
Spontaneous bacterial peritonitis
Steatohepatitis
Subacute hepatic failure
Sugiura procedure
Thrombin time abnormal
Thrombin time prolonged
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
Varices oesophageal
Varicose veins of abdominal wall
White nipple sign
X-ray hepatobiliary abnormal

13.7 Lipid-Type of Adverse Event

Lipid-type AEs are defined by the PTs for the dyslipidaemia SMQ.

Acquired lipoatrophic diabetes
Acquired mixed hyperlipidaemia
Apolipoprotein B/Apolipoprotein A-1 ratio increased
Autoimmune hyperlipidaemia
Blood cholesterol abnormal
Blood cholesterol decreased
Blood cholesterol esterase increased
Blood cholesterol increased
Blood triglycerides abnormal
Blood triglycerides decreased
Blood triglycerides increased
Diabetic dyslipidaemia
Dyslipidaemia
Familial high density lipoprotein deficiency
Familial hypertriglyceridaemia
Fat overload syndrome
High density lipoprotein abnormal
High density lipoprotein decreased
High density lipoprotein increased
Hypercholesterolaemia

Hyperlipidaemia
Hypertriglyceridaemia
Hypo HDL cholesterolaemia
Hypotriglyceridaemia
Intermediate density lipoprotein decreased
Intermediate density lipoprotein increased
LDL/HDL ratio decreased
LDL/HDL ratio increased
Lecithin-cholesterol acyltransferase deficiency
Lipid metabolism disorder
Lipids abnormal
Lipids decreased
Lipids increased
Lipoprotein (a) abnormal
Lipoprotein (a) decreased
Lipoprotein (a) increased
Lipoprotein abnormal
Lipoprotein increased
Lipoprotein metabolism disorder
Low density lipoprotein abnormal
Low density lipoprotein decreased
Low density lipoprotein increased
Metabolic syndrome
Non-high-density lipoprotein cholesterol decreased
Non-high-density lipoprotein cholesterol increased
Primary hypercholesterolaemia
Remnant hyperlipidaemia
Remnant-like lipoprotein particles increased
Total cholesterol/HDL ratio abnormal
Total cholesterol/HDL ratio decreased
Total cholesterol/HDL ratio increased
Type I hyperlipidaemia
Type II hyperlipidaemia
Type IIa hyperlipidaemia
Type IIb hyperlipidaemia
Type III hyperlipidaemia
Type IV hyperlipidaemia
Type V hyperlipidaemia
Very low density lipoprotein abnormal
Very low density lipoprotein decreased
Very low density lipoprotein increased

13.8 Immunogenicity Analysis

ADA analysis: subject classification, incidence, time of onset and time profiles

Anti-romosozumab antibodies (ADA) will be measured using a three-tiered assay approach: screening assay, confirmatory assay and titration assay.

Samples will first be evaluated in the screening assay using a false positivity rate of 5% (reported as 'negative screen' or 'positive screen'), followed by analysis of screened positive samples in the confirmatory assay (which is a drug depletion assay) to confirm the true positivity of the samples (reported as 'negative immunodepletion' or 'positive immunodepletion'). Samples that are confirmed as positive will be evaluated in a titration assay to quantify the ADA level and will be reported as titer (reciprocal dilution factor including minimum required dilution).

Confirmed positive ADA samples will be subjected to an *in vitro* neutralizing antibody (NAb) assay.

Placebo samples will not be analysed for ADA. The summaries and figures will be done for the following analyses:

- Month 1-6 of romosozumab/romosozumab treatment group at 6-month analysis
- Month 1-12 of romosozumab/romosozumab treatment group at final analysis
- Month 1-6 of romosozumab/romosozumab group pooled with month 6-12 of placebo/ romosozumab treatment group at final analysis

The ADA status should be determined for each visit where samples were taken for ADA analysis.

- Sample values that are either 'negative screen' or 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative**
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**

In addition, the anti-drug antibody status will be further classified based on subject levels as outlined below. This classification should be done for entire study duration (i.e. the treatment period including SFU sampling time point).

1. **Pre ADA negative – treatment induced ADA negative**: Includes study participants who are negative at Baseline and antibody negative at all sampling points post treatment. This group also includes study participants who have a missing pre-treatment sample (either missing or insufficient volume) at Baseline with all ADA post-treatment samples negative.
2. **Pre ADA negative – treatment induced ADA positive**: Includes study participants who are negative at Baseline and antibody positive at any sampling point post treatment. This group also includes study participants who have a missing pre-treatment sample (either missing or insufficient volume) at Baseline with one or more ADA positive post-treatment samples.

3. **Pre ADA positive – treatment reduced ADA**: Includes study participants who are positive at Baseline, and antibody negative at all sampling points post treatment
4. **Pre ADA positive – treatment unaffected ADA**: Includes study participants who are positive at Baseline and are positive at any sampling point post treatment with titer values of the same magnitude as Baseline (ie, less than a predefined fold difference increase from the Baseline value, i.e. the minimum significant ratio (MSR) determined during assay validation).
5. **Pre ADA positive – treatment boosted ADA positive**: Includes study participants who are positive at Baseline and are positive at any sampling point post treatment with increased titer values compared to Baseline (greater than a predefined fold difference increase from Baseline value , i.e. the minimum significant ratio (MSR) determined during assay validation).
6. **Inconclusive**: Includes study participants who have a positive or negative pre-treatment sample and some post-treatment samples are missing, while other post-treatment samples are ADA negative.

The fold difference increase (i.e. the minimum significant ratio (MSR) determined during assay validation) from baseline needed to consider a titer value reported post-treatment to be above the assay variation will be noted in the relevant tables, listings and figures.

Based on the overall ADA subject classification above, the following will be determined and presented:

- Total prevalence of pre-Ab : n/N % number of subjects that are preADA positive.
- Total incidence of treatment-emergent ADA positive : n/N % number of subjects in category 2 and category 5

In the case that a sample is collected one or more days following the scheduled visit date in which the drug was administered, the ADA results for that sample will be associated with the scheduled visit and summarized accordingly. Such samples will also be considered when ADA results are summarized over a given study period.

The following summaries, figures and listings will be produced and will be presented using the SS.

- Summary table displaying the number and percentage of study participants with a positive ADA status at the time of each visit by treatment group.
- Summary tables displaying the number and percentage of study participant in each of the ADA subject categories as defined above by treatment group. Total treatment emergent ADA positive and Pre ADA positive will be summarized with numbers and percentage
- Summary tables (per treatment group) of the time point of the first occurrence of treatment emergent ADA positivity. This summary will include the following categories:
  - Category 2: Pre ADA negative – treatment induced ADA positive
  - Category 5: Pre ADA positive – treatment boosted ADA positive (ie. here the MSR need to be taken into account)

The table will summarize the number and percentage of subjects who are either treatment induced ADA positive or treatment boosted ADA positive for the first time at the specified time point and will include the cumulative number and percentage of subjects having an occurrence of treatment emergent ADA positive results at each time point.

- The time to achieving treatment-emergent ADA positivity, separated by treatment group and ADA subject category as defined above, will be analyzed based on Kaplan-Meier methods. Subjects will be considered to have an event at the time point at which treatment-emergent ADA positivity is first achieved. This plot will include the following categories:
  - 4,5 2: Pre ADA negative – treatment induced ADA positive
  - Category 5: Pre ADA positive – treatment boosted ADA positive (this category will be included only in the event that >5% of subjects in either treatment group are classified as Category 5)
- A box-plot of the ADA titer over time will be created per ADA subject category for:

  Category 2: Pre ADA negative – treatment induced ADA positive

  Category 4: pre ADA positive – treatment unaffected ADA positive

  Category 5: pre ADA positive- treatment boosted ADA positive

  The ADA incidence will be indicated on the graph per time point with the numerator: number of ADA positive samples at that sampling time point and denominator: total subjects of SS. The ADA titer results will be presented on the log-scale.
- Spaghetti plots of ADA titer (y-axis) by visit (x-axis),. This plot will include the following ADA subject categories:
  - Category 2: Pre ADA negative – treatment-induced ADA positive
  - Category 5: Pre ADA positive – treatment-boosted ADA positive
  - Category 4: Pre ADA positive – treatment unaffected ADA positive

  All categories will be presented on the same plot (visualized using different colors). Plots will be presented using a semi-logarithmic scale for the ADA titers (ADA negative samples will therefore be excluded from the plot).

NAb analysis

Positive ADA samples will be evaluated in a Nab assay and subjects will be classified as Nab positive or negative.

- NAb negative: no NAb positive samples at baseline or post-baseline
- NAb positive: one or more positive samples at baseline or post-baseline
- Missing: relevant NAb samples are missing, e.g. if subject had samples selected for NAb testing based on their ADA levels, but there was insufficient sample left for NAb testing.

Summary table of the incidence of NAb, defined as (cumulative) proportion of subjects having NAb positive samples at any point up to and including that time point will be summarized Missing samples will not be included in the denominator.

Correlation of ADA and/or NAb with changed PK, PD and/or efficacy

- Individual plots of romosozumab plasma concentration ADA titer and the percent change from baseline in BMD of the lumbar spine. Each time, all three endpoints will be plotted on the Y-axes by visit (x-axis) for the full treatment period with indication of dosing time points (indication if dosing was missed), including SFU. Plots should be labeled and grouped into the pre-defined ADA subject categories as defined above. The individual plots are to be done only for categories 2 and 5.
- A summary of percent change from baseline in BMD of the lumbar spine versus time will be presented graphically including the following ADA categories (2 lines per plot).
  - Total treatment-emergent ADA positive (Category 2 and Category 5)
  - All other categories

  The figure will be repeated per treatment group including placebo.
- Finally, all individual study participant-level ADA results will be listed including the results from the screening assay, confirmatory assay, and titers if applicable both and the NAb results, the ADA status, ADA subject classification and the NAb status.

Evaluation relationship of ADA and NAb with immune related TEAE

- A summary table of all immune related TEAEs by ADA Status. For this summary, subjects will be categorized by the overall ADA subject classification and will be presented for immune related TEAEs occurring prior to becoming treatment emergent ADA positive, TEAEs occurring after becoming TE ADA positive, and TEAEs for subjects who remained TE ADA negative.
- Comparable summary table of all immune related TEAEs by NAb Status

13.9 Region and Site Information

Region	Site Name	Site Identifier
East	Shanghai Sixth People's Hospital	[redacted]
	Huadong Hospital Affiliated to Fudan University	
	The Second Affiliated Hospital of Soochow University	
	Shanghai First People's Hospital	
	Shanghai Ninth People's Hospital	
	Tongji University - Tongji Hospital	
	Nanjing Drum Tower Hospital	
	Zhejiang Rui'an People's Hospital - Gynecology	
	Pingxiang People's Hospital	
	The First Affiliated Hospital of Soochow University	
	Jiangxi Provincial People's Hospital	
North	Beijing Hospital	
	Peking Union Medical College Hospital	
	Tianjin Hospital	
	Beijing Tsinghua Chang Gung Hospital - Endocrinology	
	Beijing Luhe Hospital Capital Medical University	
	Peking University First Hospital	
	Beijing Pinggu District Hospital	
	Beijing Jishuitan Hospital	
	The First Affiliated of Zhengzhou University	
	Tianjin Medical University General Hospital - Endocrinology	
	Peking University Third Hospital	
South	West China Hospital of Sichuan University	
	Guangdong Provincial People's Hospital	
	Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology	
	The First Affiliated Hospital of Jinan University	

	Sichuan Provincial People's Hospital - Endocrinology	[redacted]	
	Yueyang Central Hospital		
	West China Hospital of Sichuan University - Orthopedics		
	Shunde Hospital of Southern Medical Univesity		

13.10 Statistical Analysis Plan Amendment 1

Rationale for the amendment

The major purpose of this amendment was to align with the protocol amendment 2 dated on Jan-14-2020 to be sure the consistency between SAP and protocol.

The following updates have been made in protocol which impact the SAP:

- The serum trough concentrations normalized by body weight is unnecessary and removed from protocol
- Stratification by prevalent vertebral fracture no longer necessary due to the new inclusion criterion #5.
- Subjects has history of myocardial infarction or history of stroke were included as exclusion criteria (#4 and #5).

Modifications and changes

- The serum trough concentrations normalized by body weight was removed
- Stratification by prevalent vertebral fracture was removed.
- Center pooling strategy was added.
- Rescue medication is replaced by prohibited and/or alternative osteoporosis therapy (licensed drugs only)
- EudraCT age and Clinicaltrials.gov age categories were added.
- 10 year probability of major osteoporotic and hip fractures based on WHO risk factor criteria calculated with femoral neck BMD T-score was added.
- Treatment compliance was defined for double-blind and open-label period.
- Classification of collection of cardiovascular risk factors.
- Mixed effects model with repeated measures model (MMRM) was added.
- Multiple imputation methods for BMD endpoints was added.

Specific Changes

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
2.3.2.1	The other PK variables are serum trough concentrations of romosozumab and normalized serum trough concentrations by BW at Day 1 (baseline) and at Months 1, 3, and 6.	The other PK variables are serum trough concentrations of romosozumab at Day 1 (baseline) and at Months 1, 3, and 6.
2.4.2.1	• Serum trough concentrations of romosozumab and normalized serum trough concentrations by BW at Months 7, 9, and 12 in	• Serum trough concentrations of romosozumab at Months 7, 9, and 12 in subjects who are continuing with 6 months of romosozumab treatment

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	subjects who are continuing with 6 months of romosozumab treatment after initially being randomized to 6 months of romosozumab in the DBPC Period (a total of 12 months of romosozumab treatment). • Serum trough concentrations of romosozumab and normalized serum trough concentrations by BW at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months	after initially being randomized to 6 months of romosozumab in the DBPC Period (a total of 12 months of romosozumab treatment). • Serum trough concentrations of romosozumab at Months 7, 9, and 12 (1, 3, and 6 months of romosozumab exposure, respectively) in subjects who are initially randomized to placebo in the DBPC Period and transition to romosozumab treatment for 6 months.
2.5	In the DBPC Period, after screening, approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years) and prevalent vertebral fracture (yes, no), in a 2:1 ratio to receive either 210mg romosozumab subcutaneous (sc) treatment every month (QM) (200 subjects) or matched placebo sc QM (100 subjects) in a blinded manner for 6 months to evaluate if romosozumab treatment for 6 months, compared with placebo, is effective in increasing BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck.	In the DBPC Period, after screening, approximately 300 subjects will be randomized, stratified by age (<75 years, ≥75 years), in a 2:1 ratio to receive either 210mg romosozumab subcutaneous (sc) treatment every month (QM) (200 subjects) or matched placebo sc QM (100 subjects) in a blinded manner for 6 months to evaluate if romosozumab treatment for 6 months, compared with placebo, is effective in increasing BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck.
3.2.3	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 prior to date of first IMP administration will be considered as the Baseline value. For the postbaseline 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	For the Baseline assessment and definition, please refer to section 3.3 for details. For the post-baseline assessment, if more than 1 visit measurement falls within the defined visit window, the result from the visit closest to the target day will be used for analysis and summarization. If 2 evaluations are of the same distance from the target day, the result from the later visit will be used. Scheduled and unscheduled visits/measurements are considered for this purpose.

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	evaluations are of the same distance from the target day, the result from the later visit will be used	
3.2.3	DXA Scans: Window definition (Study Day) for Baseline: Last evaluation prior to or on Study Day 1	DXA Scans: Window definition (Study Day) for Baseline change to Last evaluation prior to first dose of IMP
3.3	For computation of change from Baseline BMD endpoints, Baseline will be identified as the average of all scans obtained on or prior to the first dose date. The randomization date will be used as reference for subjects who did not receive any dose of IMP but who had non-missing observations on study. For computation of other change from Baseline endpoints, Baseline will be identified as the last observation prior to the first dose of IMP (assuming that any observation on the same day as the first dose is prior to dosing).	For computation of change from Baseline BMD of lumbar spine endpoint, Baseline will be identified as the average number of values (averaging is dedicated to the duplicate BMD values taken on the same day) obtained on or prior to the first dose of IMP (assuming that any observation on the same day as the first dose is prior to dosing, unless evidence stated). For computation of change from Baseline BMD of femoral neck and total hip, also other change from Baseline endpoints, the Baseline will be identified as the last observation prior to the first dose of IMP (assuming that any observation on the same day as the first dose is prior to dosing, unless evidence stated).The randomization date will be used as reference for subjects who did not receive any dose of IMP but who had non-missing observations on study.
3.4		Add: Since the PPS will be used for a supportive analysis of the primary endpoint which is assessed at Month 6, the exclusion from PPS is limited to the double-blind period, ie only study participants with IPD prior to Month 6 can be excluded from the PPS. Study participants with IPD after Month 6 will not be excluded from the PPS, but might be excluded from PK-PPS and PD-PPS during OLE Period.
3.7	Center pooling strategy to define regions will be defined once the sites are selected.	Center pooling strategy to define regions will be defined once the sites are selected. Based on the clusters of the sites with considerations of geographical and climate differences, the pooling strategy

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
		is ended up with 3 regions: North, East and South. The majority of the sites are coming from the 3 biggest cities in China – Beijing, Shanghai and Guangzhou. Considering that due to Chinese Conference on Biometric Recognition's (CCBR) involvement in Beijing (north China) and large number of sites in Yangtze Delta sites, these sites will have majority of the subjects. To counterbalance this dominance, the sites in Chengdu with Guangzhou and Hunan will be combined to form South China giving that Chengdu with Guangzhou have similar climate.
4.2	In the data evaluation meetings (DEM), the following blinded overall incidences will be monitored: • Incidence of subjects who discontinued IMP • Incidence of subjects who discontinued IMP due to lack of efficacy as per eCRF • Incidence of subjects who discontinued IMP due to a BMD reduction of 7% from Baseline at the total hip and/or lumbar spine • Incidence of subjects who discontinued IMP due to adverse events • Incidence of subjects who received prohibited medication during ongoing IMP treatment • Incidence of subjects who received prohibited medication after early termination of IMP • Incidence of subjects who died • Incidence of subjects having any of the events of the all above bullets For those sites which show abnormalities in comparison to the average and exceed prespecified margins for the	In the data evaluation meetings (DEM), the following blinded overall incidences will be monitored for safety: • Incidence of subjects who discontinued IMP • Incidence of subjects who discontinued IMP by reasons • Incidence of subjects who discontinued IMP due to safety concern as per eCRF • Incidence of subjects who received prohibited medication during ongoing IMP treatment • Incidence of subjects who received alternative osteoporosis therapy during ongoing IMP treatment • Incidence of subjects who received alternative osteoporosis therapy after early termination of IMP •Incidence of subjects who died For those sites which show strong deviations from the average of all sites during the DEM, appropriate measures such as re-training, following-ups with corrective actions etc. would be considered. Further analyses including time to various discontinuation events (Kaplan-Meier plots), events by Baseline characteristics and events by efficacy endpoints may be conducted to explore the cause and impact of the discontinuations.

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	above assessments during the DEM, appropriate measures such as re-training, following-ups with corrective actions etc. would be considered. Further analyses including time to various discontinuation events (Kaplan-Meier plots), events by Baseline characteristics and events by efficacy endpoints may be conducted to explore the cause and impact of the discontinuations.	All the missing visit or missing data related to COVID-19 will be listed. Additional listings will be provided for the patients' assessments with COVID-19 impact. Additional summary and sensitivity analyses will be provided if deems necessary.
4.6		Add: Baseline Vitamin D (< 20 ng/mL, ≥20 ng/mL and ≤40 ng/mL, > 40 ng/mL) and Baseline use of loading dose of vitamin D (Yes, No)
5.1	The numbers and percentages of subjects that were screened, randomized, completed, prematurely discontinued from IMP and withdraw from study, reason for premature discontinuation from IMP and study, and successfully completing IMP and study will be summarized by the treatment groups and study periods (through Month 6, through Month 12 and through Month 15) for the ES. The number of subjects who completed each visit (as captured in the CRF) will also be summarized. In addition, the number of subjects in each of the following analysis sets: RS, SS, FAS, PPS, PK-PPS, PD-PPS will be summarized as well.	The numbers and percentages of subjects who were screened with screen failure reason for the ES. The number of subjects who did not meet study eligibility criteria will be listed for the ES. The numbers and percentages of subjects that were randomized, completed, prematurely discontinued from IMP, withdraw from study, reason for premature discontinuation from IMP and study, and successfully completing IMP and study will be summarized by the treatment groups and study periods (through Month 6, through Month 12 and through Month 15) for the RS. The number of subjects who completed each visit (as captured in the CRF) will also be summarized. The number of subjects who withdrawal due to AE will be summarized and listed for the RS. In addition, the disposition of subjects into treatments groups and analysis sets (RS, FAS, SS, and PPS) will also be summarized on the RS. Total days on study medication is defined as date of dose received minus date of first dose received + 1.
6.1	The categorical demographic variables:	The categorical demographic variables: • Gender

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	• Gender • Race • Ethnicity • Racial subgroup • Age class (<65, ≥ 65 to <75, and ≥75) • BMI class (<18.5, 18.5 to <23, 23 to <27.5, ≥27.5)	• Race • Ethnicity • Country • EudraCT age categories (18-<65, 65 to <85, and ≥85) • Clinicaltrials.gov age categories (≤18, 19 to <65, and ≥65) • Age class (<65, ≥ 65 to <75, and ≥75) • Age class (<75, ≥75) • Age strata group from IVRS (<75, ≥75) • BMI (kg/m2) (<18.5, 18.5 to <23, 23 to <27.5, ≥27.5)
6.2	• BMD T-score at lumbar spine, total hip and femoral neck • BMD (g/cm2) by machine type (Hologic vs. Lunar) at lumbar spine, total hip and femoral neck • bone turnover markers (sCTX [ng/L], P1NP [ug/L]) • years since menopause (year) • laboratory parameters [calcium corrected by albumin, phosphorus, creatinine, serum 25 hydroxy (OH) vitamin D level, thyroid-stimulating hormone (TSH), and intact parathyroid hormone (iPTH) Total cholesterol, low-density Lipoprotein (LDL), high-density Lipoprotein (HDL), triglycerides] • osteoporosis medication use (Yes, No) • Duration of prior osteoporosis medication (<3 months, 3-6 months, 6-12 months, >12 months) • type of osteoporosis medication use (eg. Oral bisphosphonate, IV bisphosphonate, denosumab, teriparatide (TPTD),	• BMD T-score at lumbar spine, total hip and femoral neck • BMD T-score categories at lumbar spine (≤-3.0, >-3.0 to <-2.5, and ≥ -2.5), total hip (≤-2.5 and > -2.5) and femoral neck (≤-2.5 and > -2.5) • BMD (g/cm2) by machine type (Hologic vs. Lunar) at lumbar spine, total hip and femoral neck • bone turnover markers (sCTX [ng/L], P1NP [ug/L]) • years since menopause (year) • laboratory parameters [calcium corrected by albumin, phosphorus, creatinine, serum 25 hydroxy (OH) vitamin D level, thyroid-stimulating hormone (TSH), and intact parathyroid hormone (iPTH) Total cholesterol, low-density Lipoprotein (LDL), high-density Lipoprotein (HDL), triglycerides] • prior osteoporosis medication use (Yes, No) • type of osteoporosis medication use (eg. Oral bisphosphonate, IV bisphosphonate, denosumab, teriparatide (TPTD), parathyroid hormone (PTH), calcitonin, strontium, fluoride, hormone replacement therapy, traditional herbal medication, activated vitamin D, SERM, vitamin K, other) • Baseline use of vitamin D (Yes, No)

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	parathyroid hormone (PTH), calcitonin, strontium, fluoride, hormone replacement therapy, traditional herbal medication, activated vitamin D, SERM, vitamin K, other) • glucocorticoid use (Yes, No) • 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)	• Baseline use of calcium (Yes, No) • 10 year probability of major osteoporotic and hip fractures based on WHO risk factor criteria (FRAX, see in Appendix 13.3) calculated with femoral neck BMD T-score • 10 year probability of major osteoporotic and hip fractures based on WHO risk factor criteria (FRAX) calculated without femoral neck BMD T-score • parental hip fracture (Yes, No, Unknown) • glucocorticoid use (Yes, No) • secondary osteoporosis (Yes, No) • rheumatoid arthritis (Yes, No) • smoking (Current, Former, Never) • alcohol (Current, Former, Never) • caffeinated beverage use (Current, Former, Never)
6.2.1	Cardiovascular risk factors • Age at study entry (years) • substance use in the past 5 years including tobacco use (never, former, current); alcoholic beverages (none, ≤ 2 per day, ≥ 3 per day); caffeinated beverage use (Yes, No) • history of diabetes (type1, type2, No) • history of hypertension (Yes, No) • history of hypercholesterolemia (Yes, No) • history of cardiovascular disease (Yes, No) • prior myocardial infarction (Yes, No) • prior Stroke (Yes, No) • prior MI or Stroke (Yes, No)	Cardiovascular risk factors • history of diabetes (type1, type2, No) • history of hypertension (Yes, No) • history of hyperlipidemia/hypercholesterolemia (Yes, No) • history of renal impairment (Yes, No) • history of atherosclerosis (Yes, No) • prior heart failure (Yes, No) • prior transient ischaemic attack (Yes, No) • prior angina pectoris (Yes, No) • other prior cardiovascular ischaemic events (Yes, No)

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
6.3		Add: • number of prevalent vertebral fractures (0, 1, 2, ≥3, not readable/missing) Changed incidences of the grade of prevalent vertebral fracture (0, 1, 2) to "incidences of the grade of prevalent vertebral fracture (SQ0, SQ1, SQ2, SQ3)".
7	The IMP will be administered at the study site by staff trained in the injection technique. Date and time of IMP administration will be recorded in the subject's eCRF. Drug accountability must be recorded on the Drug Accountability form. The expected day of administration will be based upon (1) the Baseline date and (2) the previous injection date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be computed based upon the actual and expected days for each of the 2 methods. The ratios of compliance will also be summarized as a continuous variable and categorically (<0.80 and ≥0.80). The general formula for the compliance ratio is given as follows: Compliance Ratio (CR) = {[Study Duration (days)] – [Cumulative Difference (days)]} ÷ {Study Duration (days)} Compliance will be summarized as the number of injections received relative to the number of	The IMP will be administered at the study site by staff trained in the injection technique. Date and time of IMP administration during double-blind period and open-label period will be recorded in the subject's eCRF. Drug accountability must be recorded on the Drug Accountability form. The expected day of administration will be based upon (1) the date of first IMP administration and (2) the previous injection date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be computed based upon the actual and expected days for each of the 2 methods. The ratios of compliance will also be summarized as a continuous variable and categorically (<0.80 and ≥0.80). The general formula for the compliance ratio is given as follows for double-blind period and open-label period: Compliance Ratio (CR) during double-blind period= {[Study Duration (days) during double-blind period] – [Cumulative Difference (days) during double-blind]} ÷ {Study Duration (days) during double-blind period} Compliance Ratio (CR) during open-label period = {[Study Duration (days) during open-label period] – [Cumulative Difference (days) during open-label

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	injections expected. Percent compliance will be calculated as: Percent compliance = 100 x number of injections received ÷ number expected. Treatment compliance will be presented for SS.	period]} ÷ {Study Duration (days) during open-label period} Compliance will be summarized as the number of injections received relative to the number of injections expected. Percent compliance will be calculated as: Percent compliance during double-blind period = 100 x number of injections received during double-blind period ÷ number expected during double-blind period. Percent compliance during open-label period = 100 x number of injections received during open-label period ÷ number expected during open-label period.
8.1.3	In addition, a repeated measurement model will be fit with the percent change from Baseline at Months 3 and 6 in BMD of the lumbar spine as the dependent variable, and Baseline BMD, machine type at baseline, interaction of Baseline BMD and machine type at baseline, visit (categorical), treatment (categorical), interaction of treatment and visit, region and interaction of treatment and region as the independent variables.	In addition, a mixed effects model with repeated measures model (MMRM)will be fit with the percent change from Baseline at Months 3 and 6 in BMD of the lumbar spine as the dependent variable, and Baseline BMD, machine type at baseline, interaction of Baseline BMD and machine type at baseline, visit (categorical), treatment (categorical), interaction of treatment and visit, region and interaction of treatment and region as the independent variables. The MMRM analysis will include subject as a random effect, treatment, age strata group (stratification factor), region, visit, and treatment-by-visit interaction as fixed effects, with adjustment for baseline BMD value. The variance structure will allow for heteroskedasticity of variance. The FAS will be used for the repeated measurement model.
9	Missing PK or PD values (either Baseline or postbaseline values) will not be imputed. Measurement values that are below the lower limit of quantification (LLOQ) will be considered equal to the LLOQ/2 for all analyses.	Missing PK or PD values (either Baseline or postbaseline values) will not be imputed. Measurement values that are below the lower limit of quantification (LLOQ) (BLQ) will be considered equal to the LLOQ/2 for all analyses. If more than 1/3 of the samples are BLQ at a particular visit no summary statistics will

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
		be calculated and only minimum and maximum values will be reported.
9.1	Pharmacokinetic variables will be analyzed for all subjects in the PK-PPS at both Month 6 and final analysis. The serum trough concentrations of romosozumab, actual values and normalized by body weight (BW) will be summarized based on the PK-PPS using descriptive statistics (n, geometric mean, 95% confidence intervals, geometric CV%, mean, standard deviation, median, minimum value, maximum value) for the below analyses: • Month 1-6 of romosozumab/romosozumab treatment group at 6-month analysis • Month 1-12 of romosozumab/romosozumab treatment group at final analysis • Month 1-6 of romosozumab/romosozumab group pooled with month 6-12 of placebo/ romosozumab treatment group at final analysis The serum trough concentrations will be normalized by BW using below formula: BW normalized concentration = concentration x BW(kg) ÷ 70	Pharmacokinetic variables will be analyzed for all subjects in the PK-PPS at both Month 6 and final analysis. The serum trough concentrations of romosozumab, and actual values will be summarized based on the PK-PPS using descriptive statistics (n, geometric mean, 95% confidence intervals, geometric CV%, mean, standard deviation, median, minimum value, maximum value) for the below analyses: • Month 1-6 of romosozumab/romosozumab treatment group at 6-month analysis • Month 1-12 of romosozumab/romosozumab treatment group at final analysis Month 1-6 of romosozumab/romosozumab group pooled with month 6-12 of placebo/ romosozumab treatment group at final analysis
9.1		Added: A population PK analyses will be conducted. Details of the analysis will be described in a separated data analysis plan and results will be reported separately.
10.2		Add: The incidence of patient-year will be also summarized. Add the AE summary for romosozumab total exposure.
10.2.1	The adverse events of interest including injection site reactions,	Subject incidence of adverse events of interest of hypocalcemia, injection site

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	events potentially related to hypersensitivity, hypocalcemia, hyperostosis, osteoarthritis, malignancy, and positively adjudicated osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and CV events will be tabulated by treatment group. Subject incidence of adverse events corresponding to preferred terms of events of interest of hypocalcemia, injection site reactions, potentially related to hypersensitivity (Standardized MedDRA® Query [SMQ], narrow scope), malignant or unspecified tumor (SMQ, narrow scope), hyperostosis, osteoarthritis, adjudicated adverse events of ONJ), and AFF will be provided.	reactions, potentially related to hypersensitivity (Standardized MedDRA® Query [SMQ], narrow scope), malignant or unspecified tumor (SMQ, narrow scope), hyperostosis, osteoarthritis, positively adjudicated adverse events of ONJ, AFF, and positively adjudicated serios CV events will be tabulated by PT and treatment group (see Appendix 13.5). Subcategories are added as appropriate (EG, MI, stroke and other CV events).
10.3	Laboratory parameters (hematology and serum chemistry including iPTH and lipids in changes from Baseline will be descriptively summarized at each available time point.	Actual values and changes from baseline of laboratory parameters (hematology and serum chemistry including iPTH and lipids) will be descriptively summarized at each available time point.
10.4.1		Removed: (with abnormal values flagged as “L” or “H” accordingly)
10.4.2	Descriptive statistics of actual values and changes from Baseline in body weight, and BMI will be presented by scheduled visit will be summarized using the SS.	Abnormal results of the physical examination together with details of abnormalities: abnormality clinically significant or not, will be listed by subject and visit.
10.4.3	Abnormal results of the physical examination together with details of abnormalities: abnormality clinically significant or not, will be listed by subject and visit for SS.	Descriptive statistics of actual values and changes from Baseline in body weight, and BMI will be presented by scheduled visit will be summarized using the SS
10.4.5	The incidence and percentage of subjects who develop anti-romosozumab antibodies (binding, and if positive, neutralizing) up to Month 6 (for	The incidence and percentage of subjects who develop anti-romosozumab antibodies (binding, and if positive, neutralizing) up to Month 6 (for romosozumab group only) for the DBPC

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	romosozumab group only) for the DBPC period and up to Month 12 (for both group) for the overall study period will be tabulated. This analysis will be repeated to further include all testing results from samples collected during the 3-month FU period. For subjects who develop anti-romosozumab antibodies, romosozumab serum concentrations may also be analyzed. Additionally, exploratory analyses may be performed to assess any impact on safety or efficacy. 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. If a subject test positive for antibodies against romosozumab through Month 6 (for the 6-month analysis) and through Month 15 (for the final analysis), the relationship between the presence of antibodies, adverse events, concomitant medications, and bone mineral density could be evaluated.	period and up to Month 12 (for both group) for the overall study period will be tabulated. This analysis will be repeated to further include all testing results from samples collected during the 3-month FU period. For subjects who develop anti-romosozumab antibodies, romosozumab serum concentrations may also be analyzed. Additionally, exploratory analyses may be performed to assess any impact on safety or efficacy. Further antibody analyses will be provided and details in Appendix 13.6.
12		Added reference: Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. (2008) FRAXTM and the assessment of fracture probability in

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
		men and women from the UK. Osteoporosis International 19: 385-397.
Appendix 13.1		Added Appendix 13.1 Alternative osteoporosis therapy (licensed drugs only)
Appendix 13.3		Added Appendix 13.3 Fracture Risk Assessment Tool: 10-year Probability of Major Osteoporotic Fracture (FRAX)
Appendix 13.4		Added Appendix 13.4 Multiple Imputations for BMD endpoints
Appendix 13.5		Added Appendix 13.5 Adverse Event of Interest
Appendix 13.6		Added Appendix 13.6 Immunogenicity Analysis

13.11 Statistical Analysis Plan Amendment 2

Rationale for the amendment

The major purpose of this amendment 2 was to align with the protocol amendment 3 dated on Mar-23-2022 to be sure the consistency between SAP and protocol.

The following updates have been made in protocol which impact the SAP:

- The safety analyses in the 6-month analysis will include all available data collected up to the time of 6-month data snapshot.

Modifications and changes

- The safety analyses in the 6-month analysis will include all available data collected up to the time of 6-month data snapshot.
- Exposure adjusted AEs was added.
- Estimands and sensitivity analyses for primary and key secondary endpoints were added based on ICH E9R1 addendum.
- Visit window for Month 6 was modified.

Specific Changes

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
3.2.1.1	The safety objective of the 6-month analysis will compare the safety of romosozumab treatment with placebo in postmenopausal Chinese women with osteoporosis.	The safety analyses of the 6-month analysis will compare the safety of romosozumab treatment with placebo in postmenopausal Chinese women with osteoporosis. The safety analyses in the 6-month analysis will include all available data collected up to the time of 6-month data snapshot.
3.2.3	DXA Scans Window definition for Month 6: Day 136 – 270 Window definition for Month 12: ≥ Day 271 BTMs Window definition for Month 6: Day 136 – 195 Window definition for Month 2: ≥ Day 316 Vital signs Window definition for Month 6: Day 106 – 195	DXA Scans Window definition for Month 6: Day 136 - End of DBPC period +14 (note: M6 IMP will belong to OL) Window definition for Month 12: ≥ Day End of DBPC period + 15 BTMs Window definition for Month 6: Day 136 – End of DBPC period (note: M6 IMP will belong to OL) Window definition for Month 2: ≥ Day End of DBPC period + 1 - 240 Vital signs Window definition for Month 6:

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	Window definition for Month 7: ≥ Day 286	Day 106 – End of DBPC period (note: M6 IMP will belong to OL) Window definition for Month 7: ≥ Day End of DBPC period + 1 - 285 Added ECG analysis visit window
3.2.4	**3.2.4.1 End of study date** End of study (EOS) date is defined as the date of the last assessment for the Month 15 visit for subjects who completed the study; or the date of the last assessment for the early termination (ET) visit for subjects who discontinued the study. **3.2.4.2 End of DBPC Period date** End of DBPC Period date is defined as the last date of the assessments of the Month 6 visit. For subjects who discontinued from the study before completing Month 6, the EOS date is used for the end of DBPC period date if this date is before Day 180. For those subjects who remained on study but missed the Month 6 visit, the target date for the Month 6 visit (Day 180) will be used as the end of DBPC period date. **3.2.4.3 End of Open-Label Treatment Period date** End of OL Treatment Period date is defined as the date of the last assessment of the Month 12 visit. For subjects who discontinued from the study before completing Month 12, the EOS date is used for the end of 12-month OL Treatment Period date. For those subjects who remained on study but missed the month 12 visit, the target date for the month 12 visit (Day 360) will be used as the end of 12-month treatment period date. **3.2.4.4 End of Follow-Up Period date** End of FU Period date is defined as the date of the last assessment of the FU visit. For subjects who discontinued from the study before completing FU visit, the last contact date is used for the end of FU period date. For those	Update the Timing of analysis cut-off: **3.2.4.1 End of study date** End of study (EOS) date is defined as the date of the last contact; or the date of the last assessment for the early termination (ET) visit for subjects who discontinued the study if no last contact date in EDC CRF form. **3.2.4.2 End of DBPC Period date** End of DBPC Period date is defined as the last date of the assessments of the Month 6 visit or start date of OL visits if Month 6 visit is missed. For subjects who discontinued from the study before completing Month 6, the ET date is used for the end of DBPC period date. **3.2.4.3 Start of Open-Label Period** For subjects entering in the open-label period, the end of double-blind period date is the beginning of the open-label period date. All scheduled assessments occurring on this date are attributed to the double-blind period. The month 6 dose of ROMO is considered as occurring in the open-label period. **3.2.4.4 End of Open-Label Treatment Period date** End of OL Treatment Period date is defined as the date of the last assessment of the Month 12 visit. For subjects who discontinued from the study before completing Month 12, the ET date is used for the end of 12-month OL Treatment Period date. For those subjects who remained on study but

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	subjects who remained on study but missed the FU, the target date for the FU visit (Day 450) will be used as the end of FU period date.	missed the month 12 visit, last OL Treatment + 30 days will be used as the end of 12-month treatment period date. **3.2.4.5 End of Follow-Up Period date** End of FU Period date is defined as the date of the last assessment of the FU visit. For subjects who discontinued from the study before completing FU visit, the last contact date is used for the end of FU period date. For those subjects who remained on study but missed the FU, the final visit + 3 month or final administration of IMP + 4 month will be used as the end of FU period date.
3.7	Center pooling strategy to define regions will be defined once the sites are selected. The appropriateness of including site as a factor in all analyses where specified will be assessed prior to unblinding the study. Based on the clusters of the sites with considerations of geographical and climate differences, the pooling strategy is ended up with 3 regions: North, East and South. The majority of the sites are coming from the 3 biggest cities in China – Beijing, Shanghai and Guangzhou. Considering that due to Chinese Conference on Biometric Recognition's (CCBR) involvement in Beijing (North China) and large number of sites in Yangtze Delta sites (East China), these sites will have majority of the subjects. To counterbalance this dominance, the sites in Chengdu with Guangzhou and Hunan will be combined to form South China giving that Chengdu with Guangzhou have similar climate.	Updated center pooling strategy: Based on the clusters of the sites with considerations of geographical and climate differences, the pooling strategy will consider the following 3 regions: North, East and South. The detail of site and corresponding region is listed in Appendix 13.7.
3.9		Added: Section 13.6 of the protocol amendment 3 describes the primary and secondary analysis to be used in this study. More specifically, the protocol describes

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
		primary analysis using last observation carried forward (LOCF) as the method for handling missing data. This SAP has been modified such that the missing data due to COVID-19 impact will be imputed by multiple imputation. The LOCF method will be also applied in sensitivity analysis. The modification is provided in Section 8.1 in this SAP.
4.6	Subgroup for Baseline Vitamin D was defined as: Baseline Vitamin D (< 20 ng/mL, ≥ 20 ng/mL and ≤ 40 ng/mL, > 40 ng/mL) and Baseline use of loading dose of vitamin D (Yes, No)	Updated to: Baseline Vitamin D (≤ 40 ng/mL, > 40 ng/mL) and loading dose of vitamin D (Yes, No).
5.3		Added Impact Covid-19 section
6.2	• Baseline use of loading dose of vitamin D (Yes, No) • alcohol use (Current, Former, Never) • tobacco (Current, Former, Never) • caffeinated beverage use (Current, Former, Never)	Updated to: • Loading dose of vitamin D (Yes, No) • alcohol use (Yes, No, Unknown) • tobacco (Yes, No, Unknown) • caffeinated beverage use (Yes, No, Unknown)
6.2.1		Add "Unknown" category for risk factors.
7		Updated "exposure during open-lable period to "overall period".
8	The primary efficacy variable is percent changes from Baseline in BMD at the lumbar spine at the end of the DBPC Period (Month 6) as assessed by DXA. Missing baseline BMD by DXA at any anatomical site will not be imputed and evaluated for the BMD analysis. Missing postbaseline BMD will be imputed using the LOCF approach (by carrying forward the last non-missing postbaseline value prior to the missing value from the same anatomical site) in the 6-month analysis. In all visits and including the screening visit, if duplicated DXA assessment were performed on the same visit the mean of the duplicated BMD values will be used for analysis. The corresponding T-score at baseline will	Estimands and sensitivity analyses for primary and key secondary were added based on ICH E9R1 addendum to handle COVID-19 impacted missing data.Section 8.1.1 was update to: Primary analysis of Primary efficacy endpoint Estimands's attributes to be considered for the evaluation of the primary endpoint (1) Target Population: Postmenopausal Chinese women with osteoporosis meet the inclusion and exclusion criteria (2) Treatment: Romosozumab or PBO for 6 months (3) Endpoint: percentage change from baseline in BMD at lumbar spine at end of DBPC period (month 6).

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	be converted using the mean of the duplicated BMD (checking missing DAX assessment during DEMs in section 4.2). 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 and imputation. For anatomical sites that can be measured on different body sides (ie, left and right), only those BMD values that are collected from the same body side as the Baseline BMD will be used for analyses and imputation.	(4) Intercurrent Events (ICEs) and strategies to handle ICEs: (a) ICE #1: treatment discontinuation not due to COVID-19 will be handled by treatment policy strategy (b) ICE #2: alternative osteoporosis therapy will be handled by treatment policy strategy. (c) ICE #3: treatment interruption and impacted BMD data (missing or out of visit window) due to COVID-19 will be handled by hypothetical strategy (5) Population level outcome: difference of least square (LS) means for Romosozumab and PBO ICE #1 Treatment discontinuation not due to COVID-19 and ICE#2 use of alternative osteoporosis therapy is rare (not expected to happen frequently). They will follow treatment policy strategy which align with ITT principle. The treatment policy strategy will include all available data observed at Month 6 regardless of the occurrence of intercurrent events. This means the analysis includes on- and off-treatment values collected after study participants prematurely discontinued study treatment but agreed to remain on the study and continued to attend visits and provide assessments at those visits or data after alternative/prohibited medication administrated. Those observed values will be analyzed according to the study participant's randomized treatment. During COVID-19 pandemic, study procedures (i.e. IMP administration and BMD assessment) are heavily impacted by sites close, participants quarantined or partially lock down. Thus, treatment was interrupted, or BMD assessment could not be performed or performed out of window. Treatment interruption and impacted BMD data (missing or out of visit window) due to COVID-19 will be

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
		considered as ICE #3. Hypothetical strategy, in which the interest is in the treatment effect if the ICE did not occur, is a recommended option for most pandemic-related ICEs (R. Daniel Meyer, et al., 2020). The data after ICE#1 and ICE#2 will be handled by treatment policy strategy and will use the observed data to do analysis. COVID-19 impacted data after ICE#3, then it will be setting to missing and imputed by multiple imputation (MI) under missing at random (MAR) assumption (MI-MAR). Details of this multiple imputation analysis are outlined in Appendix 13.4. This COVID-19 impacted data includes any BMD data after treatment interrupted (exceed 70 days since previous IMP, based on PK modeling which demonstrated that BMD loss begins after 70 days without dosing) and any missing data or out of window (exceed 70 days since previous IMP) data due to Covid-19 (other than actual COVID-19 infection). Missing data other than due to COVID-19 impacted will be imputed by LOCF.
10.1		Added: Additionally, adjusted duration of exposure is defined as the duration of exposure: Date of last administration of IMP – date of first IMP administration + 30 days - cumulative gaps in exposure Calculate cumulative gaps are the number of days from date of previous dose + 30 days to next dose date summed up over the entire period. If subjects had gap of <=30 days between successive doses then gap in exposure will be 0 days for this period.
10.2	Treatment emergent AEs (TEAE) are defined as all AEs started or worsened in severity on or after the date of receiving first dose of IMP and before	Updated to: Treatment emergent AEs (TEAE) are defined as all AEs started or worsened in severity on or after the date of receiving

SAP Section(s) impacted	Previous SAP text	Key components of revised SAP text
	end-of-study. AEs reported during the OL Treatment Period with no IMP administered during the same period will not be considered treatment emergent. No summaries of these events will be produced although they will be included in listings.	first dose of IMP and before EOS date except lipid-type AEs starting on the date of first dose of IMP and not worsening (and not deemed IMP related by the investigator). Lipid-type AEs will be defined by the Dyslipidaemia SMQ (see Appendix 13.7). The different handling of lipid-type AEs starting on the date of first dose of IMP is to ensure that pre-existing lipid abnormalities are not reported as TEAEs (lipids are only measured at Day 1 before first IMP and not at Screening).
10.2		Added: TEAEs of injection site reactions, potentially related to hypersensitivity (Standardized MedDRA® Query [SMQ], narrow scope) will be in OL and others in DB period.
10.2.1		Added section to define time at risk of exposure.
10.2.2		Added section to define for exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)
10.2.3		Added TEAE for COVID-19 vaccine related TEAE.
10.2.5		Added the AE of special interest for PDILI.
Appendix 13.4		Updated multiple imputation for BMD endpoints.
Appendix 13.6		Added SMQ terms for PDILD.
Appendix 13.7		Added SMQ terms for dyslipidaemia.
Appendix 13.9		Added: Region and site information.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Lead Clinical Development Representative

[redacted]

Date/Signature

Clinical Trial Statistician

[redacted]

Date/Signature

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