SAMSUNG BIOEPIS

Clinical Study Report (CSR)

Statistical Analysis Plan

A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Compare the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity between SB16 (proposed denosumab biosimilar) and Prolia in Postmenopausal Women with Osteoporosis

Protocol Number	SB16-3001
Study Phase	Phase III
Type of analysis	Clinical Study Report
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1.0	Jan 31, 2023	[redacted]	First version

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LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUEC	Area Under the Effect Curve
$AUEC_{0\text{-}M6}$	Area Under the Effect Curve from time zero to Month 6
BLQ	Below the Limit of Quantification
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-telopeptide of Type I Collagen
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GE	General Electric
HBsAG	Hepatitis B Virus Surface Antigen
HCV-Ab	Hepatitis C Virus Antibody
HLT	High Level Term
ICF	Informed Consent Form
IE	Intercurrent Event
IP	Investigational Product
IQC	Instrument Quality Control
IWRS	Interactive Web Response Systems

LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MNAR	Missing Not at Random
NAb	Neutralising Antibody
P1NP	Procollagen Type I N-terminal Propeptide
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic Analysis Set
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PMO	Postmenopausal Osteoporosis
PPS	Per-Protocol Set
PT	Preferred Term
PTH	Parathyroid Hormone
QTc	corrected QT interval
RAN	Randomised Set
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI units	International System of Units
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
US	United States of America
WHO	World Health Organisation
Xcal	Cross-calibration

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analyses of efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity data for Protocol SB16-3001. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed. This Statistical Analysis Plan (SAP) is based on the Protocol version 2.0, dated May 03, 2021.

The CSR SAP will be used for the final analysis after database lock. All efficacy, safety, PK, PD, and immunogenicity data will be analysed and reported for the final CSR.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to demonstrate the equivalence of SB16 to Prolia, in terms of percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12 in postmenopausal osteoporosis (PMO).

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of SB16 compared to Prolia by
  - Percentage change from baseline in lumbar spine BMD
  - Percentage change from baseline in total hip BMD
  - Percentage change from baseline in femoral neck BMD
- To evaluate the safety and tolerability of SB16 compared to Prolia
- To evaluate the PK profile of SB16 compared to Prolia
- To evaluate the PD profile of SB16 compared to Prolia
- To evaluate the immunogenicity of SB16 compared to Prolia
- To evaluate the safety, tolerability, immunogenicity, PK, PD, and efficacy in subjects with PMO who transitioned to SB16 from Prolia compared to subjects who maintained Prolia from the main period

2.3. Sample Size Calculation

The equivalence margin for the mean difference of percent change from baseline in lumbar spine BMD at Month 12 is derived from 3 historical studies with Prolia. In denosumab Phase II study, mean (standard error) percent change from baseline in lumbar spine BMD at Month 12 is 4.55% (0.47) and

0.81% (0.48) for denosumab and placebo arms, respectively.[1] FREEDOM study reported the mean percent change from baseline as 5.5% and 0.0%,[2] and in Bone study, mean percent change from baseline is 4.4% and –0.5% for denosumab and placebo arms, respectively.[3]

A meta-analysis estimates 5.35% of mean percent change from baseline in lumbar spine BMD at Month 12 with 95% confidence interval (CI) of [4.83%, 5.87%]. For the European Medicines Agency (EMA) submission, 40% of lower limit of 95% CI was 2.0%, which implies that approximately 60% treatment effect is obtained to preserve the treatment effect over placebo, and this margin is corresponds to the EMA's recommendation. For the United States of America (US) Food and Drug Administration (FDA) submission, 1.45% which is 30% of lower limit of 95% CI was chosen to preserve approximately 70% of the treatment effect over placebo per the US FDA's recommendation.

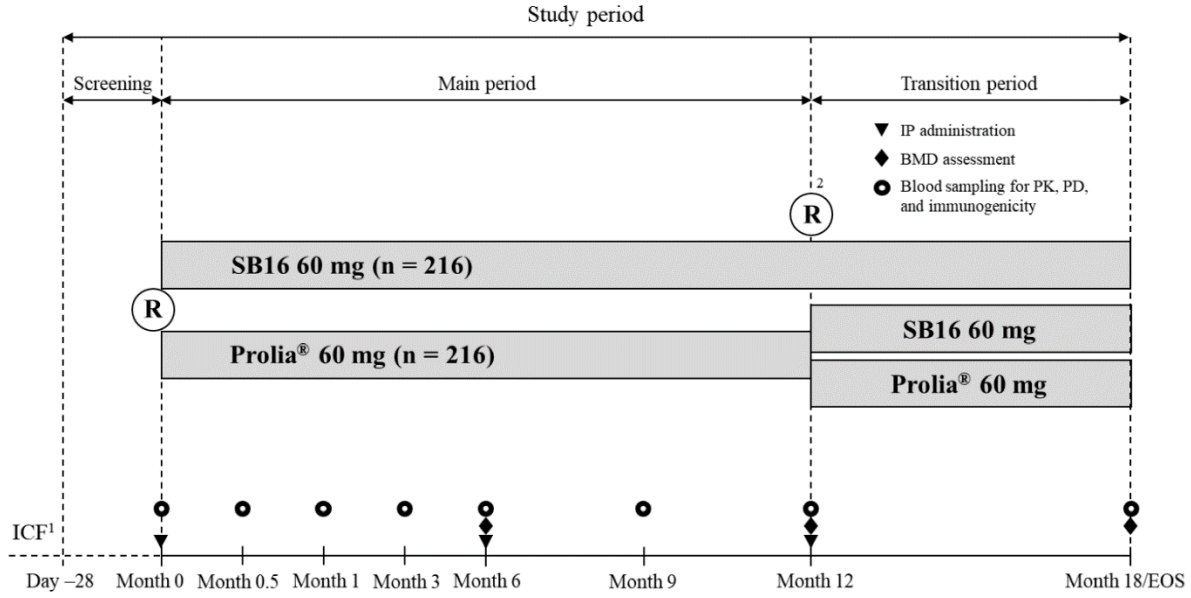
With the given equivalence margin of [–2.0%, 2.0%] for the EMA submission, 140 subjects per treatment group was calculated with the assumptions of no mean difference, common standard deviation (SD) of 5.13 at the overall 5% significance level. Assuming a 15% loss from randomised subjects after 12 months, a sample size of 165 subjects per treatment group (overall sample size of 330) will give 140 completers per treatment group after 12 months, which is estimated to give 80% power to detect the equivalence within the margin of [–2.0%, 2.0%].

With the given equivalence margin of [–1.45%, 1.45%] for the US FDA submission, 216 subjects per treatment group was calculated with the assumptions of no mean difference, common SD of 5.13 at the overall 10% significance level. Overall sample size of 432 is estimated to give 80% power to detect the equivalence within the margin of [–1.45%, 1.45%].

Therefore, the sample size of 432 allows enough power to detect the equivalence in both situations.

3. GENERAL CONSIDERATIONS

Figure 1 Graphical Study Design



ICF = informed consent form; ® = Randomisation; n = number of subjects; IP = investigational product; BMD = bone mineral density; PK = pharmacokinetic; PD = pharmacodynamic; EOS = end of study
[1] Informed consent should be obtained prior to any study related procedures.
[2] At Month 12, subjects receiving Prolia will be randomised in a 1:1 ratio to either continue to receive Prolia or be transitioned to SB16. Subjects receiving SB16 will continue to receive SB16 up to Month 18 but they will also follow the randomisation procedure to maintain blinding.

All summaries by period defined in the SAP refers to the analysis period. The analysis period consists of the main, transition and overall study periods; each period is defined as below:

Main period starts from the first administration of Investigational Product (IP) at Month 0 (including IP administration time), or starts from the randomisation for subject who do not receive IP at Month 0, ends prior to the administration of IP at Month 12 post re-randomisation (excluding IP administration time) for subjects treated post re-randomisation, ends at re-randomisation date for discontinued subject without receiving IP at Month 12, or ends at Early Termination (ET) visit (study discontinuation decision date, when ET visit is not conducted) for subjects discontinued prior to re-randomisation.

Transition period starts from the administration of IP at Month 12 post re-randomisation (including IP administration time), or starts from the post re-randomisation for subject who do not receive IP at Month 12, ends at End of Study (EOS)/ET visit (study discontinuation decision date, when ET visit is not conducted).

Overall study period starts from the first administration of IP at Month 0 (including IP administration time), or starts from the randomisation for subject who do not received IP at Month 0, ends at

EOS/ET visit (study discontinuation decision date, when ET visit is not conducted).

For the summaries of the **main period**, the treatment group refers to the treatment assigned at Month 0 or received during the main period, labelled as follows:

- SB16
- Prolia

For the summaries of the **transition period**, the treatment group refers to the treatment assigned at Month 12 or received during the transition period, labelled as follows:

- SB16+SB16
- Prolia Overall (Prolia+SB16 / Prolia+Prolia)
- Prolia+SB16
- Prolia+Prolia

For the **overall study period**, summary will be provided for the following overall treatment groups.

- SB16 (SB16* / SB16+SB16)
- Prolia Overall (Prolia* / Prolia+SB16 / Prolia+Prolia)
- Prolia+SB16
- Prolia+Prolia

For analysis using planned treatment group (e.g Full Analysis Set, Per-Protocol set), SB16* or Prolia* means subjects initially randomised to SB16 or Prolia and early terminated before re-randomisation at Month 12.

For analysis using actual treatment group (e.g Safety Set 1), SB16* or Prolia* means subjects initially received to SB16 or Prolia and early terminated before receiving IP at Month 12, including subjects who were re-randomised and not treated at Month 12.

Treatment groups for the listing will be presented as below:

- SB16
- SB16+SB16
- Prolia
- Prolia+SB16
- Prolia+Prolia

3.1. Analysis Sets

The following sets will be used for the analyses performed in the study:

- Enrolled Set (ENR) consists of all subjects who provide informed consent for this study.

- Randomised Set (RAN) consists of all subjects who have received a randomisation number.
- Full Analysis Set (FAS) consists of all RAN subjects. Subjects will be analysed according to the treatment assigned at randomisation. However, subjects who do not have any lumbar spine BMD assessment result after randomisation by accident and do not receive any IP during the study period will be excluded from this analysis set.
- Per-Protocol Set (PPS) consists of all FAS subjects who have lumbar spine BMD assessment results at baseline and Month 12 without any major protocol deviations that have impact on the lumbar spine BMD assessment results. Major protocol deviations may include deviations from inclusion/exclusion criteria, withdrawal criteria, IP compliance, concomitant medication, and study procedure. Major protocol deviations that will lead to exclusion from this set will be pre-defined using the final version of merged protocol deviation list prior to unblinding the treatment group assignment for analyses. Subjects meeting of following criteria will be excluded from PPS as well even if it's not captured as a protocol deviation:

  a. Lumbar spine BMD assessment (+/- 14 days) at Month 12 (including ET visit mapping to Month 12, when subject discontinued before Month 12) is out of visit window

- Safety Set 1 (SAF1) consists of all subjects who receive at least one IP. Subjects will be analysed according to the treatment received.
- Safety Set 2 (SAF2) consists of all subjects in the SAF1 who receive IP after re-randomisation at Month 12. Subjects will be analysed according to the treatment received.
- Pharmacokinetic Analysis Set (PKS) consists of all subjects in the SAF1 who have at least one PK sample analysed.
- Pharmacodynamic Analysis Set (PDS) consists of all subjects in the SAF1 who have at least one C-telopeptide of Type I Collagen (CTX) or Procollagen type I N-terminal Propeptide (P1NP) sample analysed without any major protocol deviations that have an impact on the pharmacodynamic results. Definition of PDS is revised from the definition specified in the protocol since some major protocol deviations impact the serum CTX and P1NP results. These subjects will not be included in PDS.

The number of subjects in the analysis sets will be summarised by overall treatment group for the RAN. A by-subject listing of analysis population details will be provided for the RAN by treatment group and will include country, centre, subject identifier, inclusion/exclusion flag for each analysis set and reason for exclusion from PPS and PDS.

A by-subject listing of allocation to treatment consisting of randomisation number, treatment allocation and randomised date for main and transition periods respectively will be provided for the RAN. A listing of allocation to treatment will be also provided by centre for the RAN. A listing of allocation to treatment in transition period will be provided by centre for the RAN.

A listing of allocated IPs information consisting Interactive Web Response Systems (IWRS) dispensed medication ID, treatment and lot number, actual medication ID, treatment and lot number

will be provided for the RAN.

3.2. Protocol Deviations

Protocol deviations will be pre-defined prior to subject enrolment and documented separately named as Protocol Deviation Definition List which includes classification (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, non-compliance with study procedure), deviation description, severity (major or minor), and time point for each protocol deviation. Major protocol deviations are defined as those deviations from the study protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. Protocol deviations that are a result of Coronavirus Disease 2019 (COVID-19) will be identified in the DV (protocol deviation) domain through protocol deviation categories of COVID-19. This will allow the reporting of the protocol deviations related to COVID-19 in the Study Data Tabulation Model (SDTM) datasets.

Protocol deviations and analysis sets will be reviewed and confirmed prior to database lock to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock.

A summary of the number and percentage of subjects with protocol deviation by protocol deviation severity (major and minor), and protocol deviation classification will be presented by main treatment group for the RAN. The summary of protocol deviation will be also provided by centre and main treatment group. The summary of COVID-19 related protocol deviation will be presented by main treatment group.

A by-subject listing of protocol deviations will be provided by treatment group including subject identifier, visit, protocol deviation classification, protocol deviation description, protocol deviation severity, exclusion from analyses set (Yes/No) for the RAN. Additionally, a by-subject listing of COVID-19 related protocol deviations will be provided by treatment group.

3.3. Disposition and Withdrawals

Subject Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from enrolment to study completion. The subject disposition summaries by overall treatment group include the following:

- A summary of the number of enrolled subjects, the number and percentage of screen failures and major reasons for screening failures, using the ENR. Subjects with multiple screening records will be counted once as a unique subject based on the latest screening result. For re-screened subjects who subsequently deemed ineligible, the latest screening failure reason will be counted.
- A summary of the number of subjects randomised at Month 0, received treatment (at least one

dose of IP), completed, discontinued from main period of study, with the primary reason for study discontinuation before Month 12 and relationship to COVID-19, using the RAN.

Completion of the main period is defined as completion of required assessment prior to re-randomisation at Month 12 visit.

- If a subject is re-randomised at Month 12, the subject is considered as having completed the main period.
- If a subject is discontinued without re-randomisation at Month 12, neither completing Month 12 assessment, the subject is considered as having discontinued during the main period.
- If a subject is discontinued without re-randomisation at Month 12, but completed Month 12 BMD assessment, either at scheduled or ET visit, the subject is considered as having completed the main period.

- A summary of the number of subjects re-randomised at Month 12, received treatment, completed, discontinued from transition period, with the primary reason for study discontinuation and relationship to COVID-19, using the RAN. The completion of transition period is defined as completion of Month 18 visit.

The summary of subject disposition above will be also provided by country and overall treatment group.

- A by-subject listing of subject disposition will be generated using the ENR, including the primary reasons of study discontinuation or screening failure, and the first/last date of IP administration, and relationship with COVID-19 for study discontinuation.

Visit not performed/ window deviation (including relatedness to COVID-19)

- Subjects with planned visit not done, primary reason for visit not done including relatedness to COVID-19 will be summarised using the RAN by visit and the overall treatment group.
- Subjects with planned visit window deviation and primary reason for visit window deviation will be summarised using the RAN by visit and the overall treatment group.
- A by-subject listing of planned visits not done, visit window deviation will be generated using the RAN, including primary reasons not done, primary reasons for visit window deviation, and relatedness to COVID-19 for not done.

3.4. Study Day

Study day will be calculated from the first IP dosing date. Study day of the first IP dosing date will be Day 1.

- If the date of interest is on or after the first IP dosing date, then:

Study Day = (date of interest – first IP dosing date) + 1

- If the date of interest is prior to the first IP dosing date, then:

Study Day = (date of interest – first IP dosing date)

When the date of interest is partial or missing, study day will be calculated after proper imputation as described in APPENDIX 1 and the date of interest will appear as partial date along with the calculated study day in the listing.

3.5. Baseline

Baseline value will be defined as the last available measurement value recorded prior to first IP administration. Per protocol, on the first IP dosing date, the prior to dosing assessment is the last planned measurement prior to IP administration. Serum vitamin D (25-hydroxyvitamin D) has no planned measurement on the first IP dosing date (Month 0), therefore unscheduled serum vitamin D assessment on the first IP dosing date is considered as prior dosing assessment. For subjects who have been randomised but not treated with any IP, the randomisation date will be used as the reference date for baseline value calculation.

3.6. Retests, Unscheduled Visits and Early Termination Data and Analysis Visit Mapping

In general, the measurements collected at the scheduled visit will be presented in the by-visit summaries.

Measurements collected at ET visit will be mapped to the scheduled visit according to the analysis visit window for different measurement. Measurement of Haematology, Biochemistry, Urinalysis, vital signs, weight, and immunogenicity follows Table 1. BMD measurement follows Table 3. PD and PK measurement follow Table 4. If ET measurement allocates to a visit without a scheduled measurement, ET measurement will be considered for analysis by visit. If ET measurement allocates to a visit with existing scheduled measurement, ET measurement will not be considered for analysis by visit. By-subject listings will display the ET visit without mapping.

Table 1: Analysis Visit Window for Haematology, Biochemistry, Urinalysis, Vital Signs, Weight, Anti-drug Antibody (ADA), and Neutralising Antibody (NAb)

Study Analysis Visit	Target Study Day	Time Interval (Study Day)	
		Start	End
Month 0	Day 1	1	1
Month 0.5	Day 16	2	23
Month 1	Day 31	24	61
Month 3	Day 92	62	137
Month 6	Day 183	138	IP administration at Month 6 (if available)*

Study Analysis Visit	Target Study Day	Time Interval (Study Day)	
		Start	End
Month 9	Day 274	IP administration at Month 6 (if available)*	319
Month 12	Day 365	320	The earlier of day 456 or IP administration at Month 12 (if available)**
Month 18	Day 547	IP administration at Month 12 (if available)**	

* On the date of IP administration at Month 6, the procedures performed prior to IP administration should be included in Month 6 (Refer protocol Section 7.1.2.5). The procedures performed post dosing should be included in Month 9.
** On the date of IP administration at Month 12, the procedures performed prior to IP administration should be included in Month 12 (Refer protocol Section 7.1.2.7). The procedures performed post IP dosing should be included in Month 18.

Table 2: Analysis Visit Window for Vitamin D

Study Analysis Visit	Target Study Day	Time Interval (Study Day)	
		Start	End
Screening	Day -28 to Day -1	− 28	1
Month 6	Day 183	2	IP administration at Month 6 (if available)*
Month 12	Day 365	IP administration at Month 6 (if available)*	The earlier of day 456 or IP administration at Month 12 (if available)**

* On the date of IP administration at Month 6, the procedures performed prior to IP administration should be included in Month 6 (Refer protocol Section 7.1.2.5). The procedures performed post dosing should be included in Month 12.
** On the date of IP administration at Month 12, the procedures performed prior to IP administration should be included in Month 12 (Refer protocol Section 7.1.2.7).

Table 3: Analysis Visit Window for BMD

Study Analysis Visit	Target Study Day	Time Interval (Study Day)
		Start/End
Month 6	Day 183	−/+ 30 Day
Month 12	Day 365	−/+ 30 Day
Month 18	Day 547	−/+ 30 Day

Table 4: Analysis Visit Window for PD and PK

Study Analysis Visit	Target Study Day	Time Interval (Study Day) Start/End
Month 0	Day 1	NA
Month 0.5	Day 16	−/+ 3 Day
Month 1	Day 31	−/+ 3 Day
Month 3	Day 92	−/+ 7 Day
Month 6[1]	Day 183	−/+ 14 Day
Month 9	Day 274	−/+ 14 Day
Month 12[2]	Day 365	−/+ 14 Day
Month 18	Day 547	−/+ 14 Day

[1] The procedures performed after IP administration at Month 6 should be excluded from Month 6.
[2] The procedures performed after IP administration at Month 12 should be excluded from Month 12.

The unscheduled/retested measurements will not be included in the by-visit summaries. Unless stated otherwise, unscheduled/retested measurements (except for baseline) will contribute to the post-baseline worst-case value for shift tables and incidence of post-baseline significant abnormality tables. If the unscheduled/retested measurement recorded on the same day as first IP administration, the unscheduled/retested measurement will be assumed to be post-dose, unless there is clear evidence to suggest the measurement is conducted prior to IP administration by comparing measurement time. Unscheduled/retested measurements will be mapped to scheduled visit according to the visit window for different measurements. Unscheduled/retested measurements of Haematology, Biochemistry, Urinalysis follow Table 1. Vitamin D measurement follows Table 2. PD measurement follows Table 4.

Listings will include scheduled, unscheduled, retested, and ET visit. And visit label of Month X (R0X) is to indicate if the measurement is retested or unscheduled.

3.7. Common Calculations

For the purpose of converting days to years or months, 1 year will be equal to 365.25 days and 1 month will be equal to 30.44 days. One week will be equal to 7 days.

For continuous measurements, change from baseline and percent change from baseline at Visit X will be calculated respectively as follows:

- Change from baseline at Visit X = Test Value at Visit X – Baseline Value
- Percent change from baseline at Visit X

  = [(Test Value at Visit X – Baseline Value) / Baseline Value] × 100

3.8. Software Version

All report outputs will be conducted using SAS version 9.3 or higher.

4. STATISTICAL CONSIDERATIONS

4.1. Multicentre Studies

This study will be conducted by multiple investigators at multiple centres internationally. Centre is included as a stratification factor in the randomisation scheme, for the primary efficacy analysis, no formal adjustments for the central effect will be conducted. Multicentre will be pooled by country, and treatment effect by country will be explored by a forest plot showing two-sided 90% CI and 95% CI of the mean difference in primary efficacy endpoint between main treatment group within each country.

Summaries of subject disposition, demographics, and other baseline characteristics by country and overall treatment group will be provided.

4.2. Missing Data

Imputation of missing efficacy endpoint BMD will be handled as described in Section 7.1.2. Missing safety endpoint will not be imputed, unless otherwise specified in the relevant section.

Imputation of partial dates for date of last menstruation, diagnosed date of PMO, medications, procedures, non-Investigation product (non-IP), and adverse events (AEs) is described in APPENDIX 1.

4.3. Multiple Comparisons/Multiplicity

One primary endpoint has been defined for this study, with one critical treatment contrast (SB16 vs Prolia) and one time point of primary interest (Month 12). The secondary endpoints defined are intended to provide supportive evidence relating to the primary objective. No interim analyses are planned for the primary analysis. Hence no formal adjustments for multiplicity will be performed.

4.4. Active-Control Studies Intended to Show Equivalence

This is an active-control study intended to demonstrate equivalence between SB16 and Prolia in terms of percent change from baseline in lumbar spine BMD at Month 12. The null hypothesis tested for the primary efficacy analysis is that either (1) SB16 is inferior to Prolia or (2) SB16 is superior to Prolia based on a pre-specified equivalence margin.

For EMA, Korea Ministry of Food and Drug Safety (MFDS), and other regulatory submissions, equivalence will be declared if the two-sided 95% CI of the mean difference in percent change from

baseline in lumbar spine BMD at Month 12 between SB16 and Prolia lies within the pre-defined equivalence margin of [−2.0%, 2.0%].

For the US FDA submission, equivalence will be declared if the two-sided 90% CI of the mean difference in percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia lies within the pre-defined equivalence margin of [−1.45%, 1.45%].

4.5. Examination of Subgroups

The uniformity of the treatment effect for the primary efficacy analysis will be examined for the following subgroups:

- Age (< 65 years vs. ≥ 65 years)
- BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2)
- Prevalent vertebral fracture (Yes, No, Not assessable)
- Country (Czech Republic, Denmark, South Korea, Lithuania, Poland)
- Overall ADA result up to Month 12 (Positive, Negative, Inconclusive)

Summaries of the primary efficacy variable by main treatment group and subgroup will be produced. Primary efficacy analysis will be repeated within each subgroup. A forest plot showing the least squares mean difference and 90% and 95% CI within each subgroup and overall will be provided. No formal statistical analysis will be performed within subgroup.

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Subject demographics and other baseline characteristics will be summarised by overall treatment group for the RAN, PKS, and PDS.

Continuous variables (e.g., age, weight, height, and body mass index [BMI]) will be summarised with descriptive statistics (n, mean, SD, median, minimum, and maximum). Categorical variables (e.g., sex, race, and ethnicity) will be summarised with frequency and percentages. The summaries provided include the following:

- A summary of demographic characteristics variables by overall treatment group.
- A summary of demographic characteristics variables by overall treatment group and country.
- A summary of other baseline characteristics variables by overall treatment group.
- A summary of other baseline characteristics variables by overall treatment group and country for the RAN.

By-subject listings will be provided for the following:

- By-subject listings of demographic and other baseline characteristics will be provided by treatment group for the RAN.
- By-subject listing of X-ray assessment will be provided by treatment group for the RAN.

Demographics Characteristics

- Age (years) – calculated as Year of Informed Consent – Year of birth
- Age group (< 65 years, ≥ 65 years)
- Sex – Female
- Race – American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- Ethnicity – Hispanic or Latino, Indian (Indian subcontinent), Chinese, Japanese, Mixed ethnicity, Other
- Country - Czech Republic, Denmark, South Korea, Lithuania, Poland
- Height (cm) at screening and Weight (kg) at baseline
- BMI (kg/m^2) – derived as weight (kg) / $[height\ (m)]^2$
- BMI level (< 25 kg/m^2 , ≥ 25 kg/m^2)

Other Baseline Characteristics

- Years since diagnosis of PMO, calculated as (Randomisation date – Diagnosed date of PMO + 1) / 365.25
- Years since menopause, calculated as (Randomisation date – Date of last menstruation + 1) / 365.25
- Previous fracture history (Yes, No)
- Hip fracture history of the parents (Yes, No)
- Prevalent vertebral fracture (Yes, No, Not assessable), number of vertebral fracture (0, 1, 2, >2, Not assessable), and grade of most severe vertebral fracture (Normal, Mild, Moderate, Severe, Not assessable)
    - Prevalent vertebral fractures were diagnosed based on lateral thoracic and spine radiographs (T4 to L4) using a Genant scoring method. There are two primary radiograph reviewers (double read) and an adjudicator in the independent radiograph review. The result of the adjudication will be considered the final assessment if adjudication is available. If adjudication is not available, the result of the first reviewer will be considered the final assessment.

- The grade of most severe vertebral fracture will be determined as follows:
  1) 'Normal' if all vertebrae among T4 to L4 is evaluable and there is no fracture
  2) 'Mild', 'Moderate', 'Severe' if there is any fracture among T4 to L4, the worst-case will be reported
  3) 'Not assessable' if there is unknown fracture status at no less than one vertebra and there is no fracture at remaining evaluable vertebrae

- The fracture number will be calculated based on the actual number of vertebral fractures.

- Active healing fracture (Yes, No) – only included in listing
- Serum 25 (OH) vitamin D level (nmol/L)
- Oral bisphosphonate history (Yes, No), total cumulated period of oral bisphosphonate administration prior to screening (months)
- Duration of oral bisphosphonate administration (year ≤ 1, $1 <$ years ≤ 2, $2 <$ years ≤ 3)
- BMD (g/cm^2) of lumbar spine, total hip, and femoral neck – the lumbar spine BMD measurement in data set up to Month 12 which specified in Section 7 will be used.
- T-score at lumbar spine, total hip, and femoral neck – Original BMD T-score used for eligibility confirmation
- Serum CTX (ng/mL) and Serum P1NP (ng/mL) – the major protocol deviation or active healing fracture which specified in Section 7.5 may affect the data.
- Current smoking status (Yes, No)
- Current alcohol consumption status (Yes, No) and consumption amount (< 3 units/day, ≥ 3 units/day)

Statistical Tests for Demographic and Other Baseline Characteristics

Comparison between main treatment group in demographics and other baseline characteristics will be performed for the RAN using the chi-square test for categorical variables or analysis of variance (ANOVA) for continuous variables. The results of these tests will be provided including the *p*-value only for descriptive purposes and will not be used as a formal basis to determine the factors to be included in primary or secondary efficacy analysis models. If baseline imbalances are detected for any of the factors, additional analyses may be performed to adjust for these baseline differences.

6. MEDICAL AND SURGICAL HISTORY

Medical and surgical histories will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary version 23.0 or higher.

Medical and surgical histories will be summarised by MedDRA primary System Organ Class (SOC) and Preferred Term (PT) for overall treatment group using number and percentage of subjects for the RAN. Primary SOC will be presented alphabetically; PT will be sorted within each primary SOC in descending order of subject frequency based on the treatment SB16 group, then alphabetically if tied. If a subject had multiple conditions with the same PT and primary SOC, the subject will be counted only once under the same PT and primary SOC.

By-subject listing of medical and surgical histories will be provided by treatment group for the RAN.

7. EFFICACY, PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

BMD will be measured by either General Electric (GE) Lunar or Hologic machines. There are three type of measurements for the BMD result, original BMD measurement, Instrument Quality Control (IQC) corrected BMD measurement, and IQC and Cross-calibration (Xcal) corrected BMD measurement. IQC and Xcal corrected BMD measurement will be summarised and analysed by treatment group in CSR analysis. Original BMD measurement and IQC corrected BMD measurement will be included in listings only.

Lumbar spine BMD is assessed at four locations, L1 to L4 vertebrae. If during the study, more than one vertebra becomes un-evaluable (within L1-4) due to artifacts, deformity or sequelae of prior orthopedic surgery or trauma, central imaging will process the remaining spine scans for evaluable vertebrae (within L1-4) as long as there are at least 2 evaluable vertebrae to analyse. This will be done for all post-screening timepoints per subject whenever at least one timepoint has un-evaluable vertebrae. For consistency in lumbar spine BMD measurement across visits, if a vertebra is excluded at one timepoint, the same vertebra will be excluded at all other timepoints. For example, an L1 exclusion made at Month 12 will also be applied to Screening and Month 6 and will be applied to subsequent visits as well. In this example the total lumbar spine BMD for all visits would only include L2, L3, and L4. Therefore, lumber spine BMD will be reported as two sets of data, assessment up to Month 12, and assessment up to Month 18.

Lumber spine BMD up to Month 12 is calculated based on Screening assessment, scheduled and unscheduled assessment up to Month 12, and ET assessment within Month 12 window (refers to Table 3). Primary efficacy analysis will use IQC and Xcal corrected lumber spine BMD measurement in data set up to Month 12. Missing value will be imputed as specified in Section 7.1. And the secondary endpoint analysis for lumbar spine BMD at Month 6 will use this data.

Lumbar spine BMD up to Month 18 is calculated based on Screening assessment, all scheduled and unscheduled assessment, and ET assessment. Exclusion of vertebrae assessment after Month 12 may result in additional exclusion prior to or at Month 12. Lumber spine BMD at Screening, Month 6, and Month 12 among the data set up to Month 18 will be difference from the lumbar spine BMD value in data set up to Month 12. The secondary endpoint for lumbar spine BMD at Month 18 will be analysed using IQC and Xcal corrected lumbar spine BMD measurement in data set up to Month 18.

7.1. Primary Efficacy Analysis

7.1.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is percent change from baseline in lumbar spine BMD at Month 12, calculated as [(lumbar spine BMD at Month 12 – lumbar spine BMD at baseline) / lumbar spine BMD at baseline] × 100%.

For the EMA, MFDS, and other regulatory submissions, the primary efficacy analysis will be performed for the PPS using an analysis of covariance (ANCOVA) with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor. The equivalence will be declared if the two-sided 95% CI of the mean difference in percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia lies within the pre-defined equivalence margin of [−2.0%, 2.0%].

For the US FDA submission, the primary efficacy analysis will be performed for the FAS using an ANCOVA with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor. The equivalence will be declared if the two-sided 90% CI of the mean difference in percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia lies within the predefined equivalence margin of [−1.45%, 1.45%]. Missing data will be imputed using multiple imputation method for subjects who drop out for the study prior to the primary analysis time point under the assumption of missing at random (MAR).

Primary Estimand

The primary estimand including supplementary estimand is as follows:

	EMA, MFDS, and other regulatory submissions	**US FDA submission**
Population	Subjects who met the inclusion/exclusion criteria and adhere to protocol as defined in the Section 3.1 (PPS)	Subjects who met the inclusion/exclusion criteria as defined in the Section 3.1 (FAS)
Treatment condition	SB16 vs. Prolia	SB16 vs. Prolia
Endpoint	Percent change from baseline in lumbar spine BMD at Month 12	Percent change from baseline in lumbar spine BMD at Month 12
Population-level summary	Mean difference in percent change from baseline in lumbar spine BMD at Month 12	Mean difference in percent change from baseline in lumbar spine BMD at Month 12
Intercurrent Events (IEs) and strategies	*Restrict the inclusion of subjects with IEs that impact the assessment of treatment effect; hence the main estimator will be based on the PPS as defined in Section 3.1.*	IE1: Early discontinuation from study prior the Month 6 *Hypothetical strategy: primary endpoint will not be collected; treatment effect will be estimated as if patients remain on treatment.* IE2: Early discontinuation from study after the Month 6 and prior to Month 12

	EMA, MFDS, and other regulatory submissions	**US FDA submission**
		Treatment policy strategy: primary endpoint will be collected; treatment effect will be estimated regardless of IE2 IE3: subjects who do not have any lumbar spine BMD assessment result after randomisation by accident and do not receive any IP *Restrict the inclusion of subjects with IE3, hence the main estimator will be based on the FAS as defined in Section 3.1.*
Main Estimator	A two-sided 95% CI of the mean difference in percent change from baseline in lumbar spine BMD at Month 12 will be obtained using an ANCOVA with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor.	A two-sided 90% CI of the mean difference in percent change from baseline in lumbar spine BMD at Month 12 will be obtained using an ANCOVA with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor. Missing data will be imputed using multiple imputation method for subjects who drop out for the study prior to the primary analysis time point under the assumption of MAR.
Sensitivity Estimator		Tipping point
Supportive Estimand 1	Primary efficacy analysis (ANCOVA) will be repeated using FAS, missing data will be imputed using multiple imputation method for subjects who drop out for the study prior to the primary analysis time point under the assumption of MAR.	Primary efficacy analysis (ANCOVA) will be repeated using PPS.
Supportive Estimand 1 Sensitivity Estimator	Tipping point	
Supportive Estimand 2	Available case analysis will also be performed using the FAS.	Available case analysis will also be performed for the FAS.

7.1.2. Missing Data Imputation Methods of Primary Efficacy Endpoint

A summary of the number and percentage of subjects missing BMD assessment and reason of missing will be provided for the FAS. Reason of missing BMD assessment may be the same as the reason of visit not done and will be excluded from this summary, when the visit is skipped.

When analysing primary efficacy endpoint using FAS, missing data will be imputed using multiple imputation method for subjects who drop out for the study prior to the primary analysis time point

under the assumption of MAR. Intermittent missing prior to drop out/study completion will be imputed using the same approach.

Multiple imputation methods replace each missing primary efficacy endpoint value with a set of (m=25) plausible values based on a prediction model. The prediction model will be a regression model with the following covariates: treatment group, baseline lumbar spine BMD, percent change from baseline in lumbar spine BMD at Month 6 and Month 12.

Algorithm for the Multiple Imputation of Missing Values

If non-monotone missing pattern (intermittent missing) is observed, the Markov Chain Monte Carlo (MCMC) monotone-data imputation method will first be used to generate a monotone missing data pattern. A set (m=25) of imputed dataset with monotone missing pattern will be generated from the above method.

For data with monotone missing pattern, the monotone regression imputation method will be used to generate a set (m=25) of imputed complete dataset. If MCMC monotone-data imputation is performed prior to using monotone regression method, monotone regression imputation will create single imputed dataset based on each of 25 imputed datasets from MCMC monotone-data imputation. The pseudo SAS code and seed (899745) can be found in APPENDIX 8.

Analysing Multiply Imputed Datasets

ANCOVA model as defined in Section 7.1.1 will be performed in each of the imputed complete datasets (m=25). The analysis results (least square mean difference and associated standard errors) will be combined for making statistical inference. The pseudo SAS code can be found in APPENDIX 8.

7.1.3. Sensitive Analysis of Primary Efficacy Endpoint

Under the Estimand framework, tipping point analysis will be conducted to evaluate the robustness of multiple imputation under the assumption of MAR. A two-dimensional tipping point analysis will be applied to ANCOVA model as defined in Section 7.1.1 using the FAS, to assess the robustness of the conclusions based on the assumption of MAR. A succession of delta adjustments via multiple imputation methods will be used to impute the missing primary endpoint point in two treatment groups independently, exploring various missing not at random (MNAR) assumption. The tipping point is denoted as the delta adjustment that would have to be imputed to overturn a statistically significant result. Clinical judgement will be applied to the plausibility of the tipping point (delta adjustment). The pseudo SAS code can be found in APPENDIX 8.

7.1.4. Supportive Analysis of Primary Efficacy Endpoint

When primary estimand uses PPS, ANCOVA model as defined in Section 7.1.1 will be repeated for the FAS, missing data will be imputed using multiple imputation method for subjects who drop out for the study prior to the primary analysis time point under the assumption of MAR. To stress-test the supportive analysis result for robustness to MAR assumption, tipping point analysis will be conducted, using same method as described in section 7.1.3. Available case analysis will also be performed for the FAS.

When primary estimand uses FAS, available case analysis will be performed for the FAS and the same analysis will be repeated for the PPS.

7.2. Secondary Efficacy Analysis

Percent Change from Baseline in Lumbar Spine BMD

The percent change from baseline in lumbar spine at Month 6 and 18 will be analysed using the same model for primary analysis as described in Section 7.1 for the FAS based on available case and multiple imputation assuming MAR respectively; and the PPS. The treatment comparison of interest for time points prior to re-randomisation (Month 12 included) include the comparison between main treatment group SB16 and Prolia; treatment comparison of interest for time points after re-randomisation include the comparison between transition treatment group SB16+SB16 and Prolia Overall; SB16+SB16 and Prolia+Prolia; Prolia+SB16 and Prolia+Prolia.

A descriptive summary of lumbar spine BMD value and percent change from baseline by treatment group and visit will be provided for the FAS and PPS. The percent change from baseline in lumbar spine BMD will be plotted by treatment group and visit for the FAS and PPS with mean and standard error based on available case.

By-subject listings of lumbar spine BMD will be provided by treatment group for the FAS.

Percent Change from Baseline in Total Hip and Femoral Neck BMD

A descriptive summary of total hip and femoral neck BMD value and percent change from baseline by treatment group and visit will be provided for the FAS and PPS. The percent change from baseline in total hip and femoral neck BMD will be plotted by treatment group and visit for the FAS and PPS with mean and standard error based on available case.

A listing of total hip and femoral neck BMD will be provided by treatment group for the FAS.

7.3. Exploratory Efficacy Analysis

Exploratory efficacy analysis is not needed for CSR analysis.

7.4. Pharmacokinetic Analysis

The PK analysis will be performed using the PKS.

Blood sample collection compliance will be confirmed during protocol deviation review. In the case of a major protocol deviation, PK data collected during the affected treatment period will be excluded from summary statistics, but will be included in listing and individual serum concentration figure. If the serum concentration results at ET visit are not mapped to the analysis visit, they will be listed in listing only. The major protocol deviations that may affect the PK data defined as follows.

- A blood sample collected after dosing at Month 0, 6, and 12 will be excluded from the PK analysis.
- If IP administration is not performed at any one of visit, the sample from the next visit will be excluded from the PK analysis.
- If treatment group is switched, the sample from the next visit will be excluded from the PK analysis.
- If IP which underwent a temperature excursion is administered and it is deemed unacceptable use, the sample from the next visit will be excluded from the PK analysis.

A blood sample excluded from the PK analysis will still be reported in the listing.

Serum pharmacokinetic concentrations will be summarised descriptively by overall treatment group and scheduled visit. The following descriptive statistics will be presented for serum concentrations: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric SD, geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum and maximum values. Below the limit of quantification (BLQ) values will be treated as zero for the computation of descriptive statistics, and the generation of individual serum concentration-time profile, except for geometric mean, geometric SD, and geometric CV%, for which they will be excluded. BLQ will be presented as BLQ in the listings.

The following figure of serum concentrations will be generated. SB16 and Prolia will be shown in same figure with different legend. Figures will be displayed in black and white.

- Arithmetic Mean (±SD) serum drug concentration over time by overall treatment group − linear scale.
- Individual serum drug concentration over time by overall treatment group − linear scale.

By-subject listing of serum pharmacokinetic concentrations will be provided for the SAF1 who have at least one PK sample available for analysis.

7.5. Pharmacodynamic Analysis

The PD analysis will be performed for the PDS. All PD assessment data will be reported and analysed with the same precision as the source regardless of how many significant figures or decimals the data carry. Values of serum CTX and P1NP concentration outside the quantification range will be imputed as for the descriptive statistics: values with '<xxx' will be set to 'xxx', where xxx is lower limit of quantification (LLOQ). However, for the listing, the original values of '<xxx' will be presented as it is recorded. The LLOQ of serum CTX and P1NP concentration is 0.043 ng/mL and 9.92 ng/mL, respectively.

Blood sample collection compliance will be confirmed during protocol deviation review. In the case of a major protocol deviation, PD assessment data collected during the affected treatment period will be excluded from summary statistics, but will be included in listing and individual serum CTX and P1NP concentrations figure. If the serum CTX and/or P1NP concentration results at ET visit are not mapped to the analysis visit, they will be listed in listing only. The major protocol deviations that may affect the PD assessment data defined as follows.

- If a blood sample is not collected prior to dosing at Month 0, 6, and 12, the sample at the visit will be excluded from the PD analysis.
- If a blood sample is not collected after fasting for at least 8 hours, the sample at the visit will be excluded from the PD analysis.
- If a blood sample is not collected in the morning (prior to 12:00 PM), the sample at the visit will be excluded from the PD analysis.
- If a blood sample for CTX at Month 0 is collected after taking calcium, the sample at the visit will be excluded from the PD analysis.
- If IP administration is not performed at any one of visit, the sample from the next visit will be excluded from the PD analysis.
- If treatment group is switched, the sample from the next visit will be excluded from the PD analysis.
- If IP which underwent a temperature excursion is administered and it is deemed unacceptable use, the sample from the next visit will be excluded from the PD analysis.
- If prohibited medication is used, the sample after taking the prohibited medication for the first time will be excluded from the PD analysis.

In addition, if an active healing fracture containing 'Fracture' but not "Tooth fracture" in AE preferred term occurs in the middle of the study, the serum CTX or P1NP concentrations after having fracture will be excluded from the PD analysis.

A blood sample excluded from the PD analysis will still be reported in the listing.

7.5.1. CTX and P1NP Concentration

The following summaries will be provided for serum CTX and P1NP concentrations using the PDS:

- A summary of percent change from baseline in serum CTX concentration by overall treatment group and visit.
- A summary of percent change from baseline in serum P1NP concentration by overall treatment group and visit.
- By-subject listing of PD assessment will be provided by treatment group for the SAF1 who have at least one serum CTX or P1NP sample available for analysis.

The following figure of serum CTX and P1NP concentrations will be generated. The treatment group will be shown in same figure with different legend. Figures will be displayed in black and white.

- Median (±interquartile range) percent change from baseline in serum CTX concentration over time by overall treatment group using the PDS − linear scale.
- Median (±interquartile range) percent change from baseline in serum P1NP concentration over time by overall treatment group using the PDS − linear scale.
- Individual serum CTX concentration over time by overall treatment group using the SAF1 − linear scale.
- Individual serum P1NP concentration over time by overall treatment group using the SAF1 − linear scale.

7.5.2. Pharmacodynamic Parameters

The geometric mean of area under the effect curve (AUEC) from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX concentration will be analysed by main treatment group using ANOVA on the log-transformed $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX concentration with the main treatment group as a fixed effect. The ratio of least-squares geometric mean (SB16 vs. Prolia) will also be presented with corresponding 90% CI.

The $AUEC_{0\text{-}M6}$ will be calculated using the trapezoidal rule, including serum CTX concentration at Month 0, 0.5, 1, 3, and 6. Actual study day of serum CTX sample collection should be used. Subjects who have serum CTX concentration available for analysis at Month 0, 0.5, 1, 3, and 6 will be included in the calculation of AUEC. AUEC will be calculated as:

$$\sum_{i=a}^{b-1}\{0.5 \times (Y_i + Y_{i+1}) \times (t_{i+1} - t_i)\}$$

where Y_i is the percent change from baseline in serum CTX concentration at visit i, t is the time at the specified visit i (the actual date and time of serum CTX sample collection for post-baseline visit;

the actual date and time of first IP administration at Month 0 for baseline visit), a is the baseline assessment, and b is the last assessment up to Month 6. If AUEC yield a negative value, the absolute value of AUEC will be used in summary and further analysis.

Serum CTX concentration is expected to decrease after IP administration. After reaching maximum reduction, the reduction effect of serum CTX will gradually diminish, may become zero, or even increase from baseline. If change from baseline in serum CTX concentration at Month 6 is positive value, the $AUEC_{0\text{-}M6}$ will be calculated from baseline up to the time where percent change from baseline equals zero. Upon the first measurement of CTX value increase from baseline, Y_i' and t_i' at the time when percent change equals zero can be calculated based on linear equation, $t_i' = \frac{Y_i t_{i-1} - Y_{i-1} t_i}{Y_i - Y_{i-1}}$, $Y_i' = 0$. $AUEC_{0\text{-}M6}$ equals $AUEC_{0\text{-}ti'}$. Considering this rebound effect, the net $AUEC_{0\text{-}M6}$ will be provided for listing. If the rebound is seen, the net $AUEC_{0\text{-}M6}$ equals $AUEC_{0\text{-}ti'}$ minus $AUEC_{ti'\text{-}M6}$. Otherwise, net $AUEC_{0\text{-}M6}$ equals $AUEC_{0\text{-}M6}$

8. SAFETY ANALYSIS

Safety analyses will be performed for the main, transition, and overall study periods unless specified otherwise. Analyses for the main and transition periods will be performed in the SAF1 and SAF2 respectively and analyses for the overall study period will be performed in the SAF1. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

8.1. Study Medication Exposure

IP refers to SB16 (proposed denosumab biosimilar) or Prolia. Non-IP refers to Calcium and/or Vitamin D. Exposure to study medication in main period (up to Month 12) and overall study period (up to Month 18) will be provided respectively for IP, using the SAF1.

Prior non-IP is defined as non-IP with stop date prior to the first administration date of IP. Concomitant non-IP is defined as any non-IP ongoing at the first administration date of IP or with a start date on or after the first administration date of IP. Algorithm of concomitant non-IP is detailed in APPENDIX 1.

The duration of exposure for IP will be calculated as follows.

Duration of exposure (days) in main period = minimum of [maximum of (study discontinuation decision date, ET visit date), IP administration date at Month 12, (last IP administration date before Month 12 + 182)] – first IP administration date + 1

Duration of exposure (days) in overall study period = minimum of [maximum of (study discontinuation decision date, ET visit date), EOS visit date, (last IP administration date + 182)] – first IP administration date + 1

Maximum (study discontinuation decision date, ET visit date) will be included above calculation if subjects discontinued from study. The IP exposure summaries includes the following:

- A summary of statistics for total number of subcutaneous injections (1 injection, 2 injections, 3 injections), duration of exposure to IP in main period and overall study period by treatment group.

By-subject listings of IP administration (including the evaluation of injection site reaction) and non-IP administration will be provided by treatment group for the SAF1, respectively.

8.2. Prior/Concomitant Medications and Procedures

Prior and concomitant medications will be coded using the World Health Organisation (WHO) Drug dictionary version dated Mar 2020 or above.

See APPENDIX 1 for handling of partial date for medications and procedures, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case: i.e., concomitant.

Prior medication or procedure is defined as medication or procedure with stop date prior to the first administration date of IP. Concomitant medication or procedure will be presented for main, transition, and overall study periods separately. Concomitant medication or procedure during the overall study period is defined as any medication or procedure ongoing at the first administration date of IP or with a start date on or after the first administration date of IP. Algorithm of concomitant medications and procedures is detailed in APPENDIX 1.

Any concomitant medication or procedure which started prior to, on or after the date of the first administration of IP, and stopped before the date of IP administration post re-randomisation (the EOS/ET visit if a subject discontinued prior to the IP administration post re-randomisation or study discontinuation decision date, when ET visit is not conducted) or are ongoing at the date of IP administration post re-randomisation (the EOS/ET visit if a subject discontinued prior to the IP administration post re-randomisation or study discontinuation decision date, when ET visit is not conducted) will be included in main period.

Any concomitant medication or procedure which started prior to, on or after the date of IP administration post re-randomisation will be included in transition period.

A summary of the number and percentage of subjects with prior, and concomitant medication will be provided by Anatomical Therapeutic Chemical (ATC) Drug Class and preferred term for treatment group. If a subject takes multiple medication with the same ATC Drug Class and preferred term, the subject will be counted only once under the same ATC Drug Class and preferred term. ATC Drug Class will be presented in alphabetical order. Preferred term will be sorted within each ATC Drug Class in descending order based on the treatment SB16 group, then alphabetically if tied.

- Summary of prior medications will be provided by overall treatment group using SAF1.

- Summary of concomitant medications will be performed for each analysis period.

A by-subject listing of prior and concomitant medications will be provided by treatment group for the SAF1.

A by-subject listing of COVID-19 related concomitant medications will be provided by treatment group for the SAF1. COVID-19 related concomitant medication is defined as concomitant medication with reason of Treatment-Emergent Adverse Event (TEAE) for COVID-19 or TEAE related to COVID-19.

Concomitant procedures (including surgery) will be coded using the MedDRA central coding dictionary version 23.0 or higher and taken from informed consent form (ICF) until the EOS visit or ET visit. A by-subject listing of concomitant procedures will be provided by treatment group using the SAF1.

8.3. Prohibited Medications and Procedures

Prohibited medications with ATC Drug Class/preferred term or prohibited procedures are defined in APPENDIX 6 and will be confirmed by medical reviewer during protocol deviation review. Final confirmed prohibited medications/procedures will be reported as protocol deviations.

Summaries of the number and percentage of subjects with prohibited medication will be provided by ATC Drug Class and preferred term for each study analysis period , in the similar manner as concomitant medications analysis.

A by-subject listing of prohibited medications will be provided by treatment group for the SAF1.

A by-subject listing of COVID-19 related prohibited medications will be provided by treatment group for the SAF1. COVID-19 related prohibited medication is defined as prohibited medication with reason of TEAE for COVID-19 or TEAE related to COVID-19.

8.4. Laboratory Evaluations

Laboratory test (Table 4) results from the central laboratory (and the vitamin D test at screening from local lab in Korea) will be reported in International System of Units (SI units) and summarised by overall treatment group using the SAF1.

Table 5: Parameters for Clinical Laboratory Tests

Parameter	Clinical Laboratory Tests
Haematology	• Haemoglobin • Haematocrit • Platelet count • Red blood cell count

Parameter	Clinical Laboratory Tests
	• White blood cell count (total and differential) Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Biochemistry	• Sodium • Potassium • Chloride • Creatinine • Blood urea nitrogen • Estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) equation • Glucose • Calcium • Albumin corrected serum calcium • Albumin • Phosphorus • Total bilirubin • Total cholesterol • Alanine aminotransferase • Aspartate aminotransferase • Alkaline phosphatase
Hormone	• Follicle stimulating hormone (FSH) (optional) • Thyroid-stimulating hormone (TSH) • Parathyroid hormone (PTH) • Vitamin D (25-hydroxyvitamin D)
Virology	• Hepatitis B virus surface antigen (HBsAg) • Hepatitis C virus antibody (HCV-Ab)
Urinalysis (Dipstick)	• Protein • Blood • Leucocytes • Nitrite • Glucose • Ketone • pH • Specific gravity

Parameter	Clinical Laboratory Tests
	• Bilirubin • Urobilinogen

Values of laboratory parameters outside the quantification range will be imputed as for the descriptive statistics: values with '<xxx' and '>yyy' will be set to 'xxx' and 'yyy' respectively, where xxx and yyy are lower limit of quantification and upper limit of quantification. However, for the listing, the original values of '<xxx' or '>yyy' will be presented as it is recorded.

The following summaries will be provided for laboratory tests for the SAF1:

- A summary of each Haematology, Biochemistry parameter actual value, and change from baseline by overall treatment group and scheduled visit.
- A summary of Urinalysis parameter by overall treatment group and scheduled visit.
- A summary of Hormone (except serum vitamin D) and Virology parameter by overall treatment group at baseline.
- A summary of serum Vitamin D value and change from baseline by overall treatment group and scheduled visit (Screening, Month 6, and Month 12).
- A summary of each Haematology, Biochemistry parameter based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 by overall treatment group and scheduled visit. The CTCAE v5.0 grading of laboratory values is detailed in APPENDIX 5.
- A summary of the number and percentage of subjects experiencing low, normal or high values at baseline and at post-baseline scheduled visit, by Haematology, Biochemistry, Vitamin D parameter and overall treatment group (shift table, by main treatment group for Vitamin D summary). The worst case of laboratory values is detailed in APPENDIX 4.
- A summary of the number and percentage of subjects experiencing clinically significant laboratory abnormalities, by Haematology, Biochemistry, Vitamin D parameter, and overall treatment group at each scheduled visit. Clinically significant is assessed by investigator and recorded in electronic case report form (eCRF). Clinically significant will be reported as "Normal", "Abnormal, not clinically significant", or "Abnormal, clinically significant". The overall incidence of abnormality up to Month 6, Month 12, and Month 18 will be also summarised. When summarising overall incidence, a subject will be counted only once in the worst category of abnormality among post-baseline assessments. The order of severity is "Abnormal, clinically significant" > "Abnormal, not clinically significant" > "Normal".

By-subject listings of Haematology, Biochemistry, Urinalysis, Hormone, Vitamin D, and Virology will be provided by treatment group respectively. Laboratory reference range of Haematology, Biochemistry and Hormone parameters, and Vitamin D (including local lab in Korea) will be listed

with corresponding low and high range in SI unit.

By-subject listings of subjects with clinically significant abnormal Haematology, Biochemistry and Vitamin D result will be provided by treatment group respectively.

8.5. Vital Signs and Weight

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate and body temperature) and weight will be summarised by overall treatment group, using the SAF1. Unscheduled/retested measurements will not be included in the by-visit summaries. Vital signs summaries include:

- A summary of each vital sign parameter and weight actual value and change from baseline by overall treatment group and scheduled visit.
- A summary of the number and percentage of subjects experiencing clinically significant vital sign abnormalities by vital sign parameter and overall treatment group at each scheduled visit. The unscheduled/retested measurements will not be considered in this summary.

By-subject listings of vital sign parameters and weight will be provided separately. Clinically significant abnormal for vital sign parameters will be listed separately.

Clinically Significant Abnormal Criteria

Clinically significant abnormal continuous vital signs measurements will be identified in accordance with the following predefined clinically significant abnormal criteria:

Table 6: Clinically Significant Abnormal Criteria of Vital Signs

Variable	Unit	Criterion[a]	
		Low	High
Systolic blood pressure	mmHg	≤ 80 mmHg AND decreased ≥ 30 mmHg from baseline value	≥ 180 mmHg AND increased ≥ 30 mmHg from baseline value
Diastolic blood pressure	mmHg	≤ 50 mmHg AND decreased ≥ 20 mmHg from baseline value	≥ 105 mmHg AND increased ≥ 20 mmHg from baseline value
Heart rate	Bpm	≤ 40 bpm AND decreased ≥ 15 bpm from baseline value	≥ 120 bpm AND increased ≥ 15 bpm from baseline value
Body temperature	˚C	< 35.5˚C	> 37.9˚C

[a] For the baseline time point, only the criterion on absolute values is applicable.

8.6. Immunogenicity Analysis

The number and percentage of subjects with ADA results (i.e., Positive, Negative) and NAb results (i.e., Positive, Negative) will be presented by overall treatment group and visit using the SAF1.

In addition, the number and percentage of subjects with ADA positive will be summarised by titre and overall treatment group in each visit using the SAF1.

The incidence of overall ADA results (i.e., Positive, Negative, Inconclusive) up to Month 6, Month 12 and Month 18 will be presented by overall treatment group using the SAF1.

Overall ADA result up to Month 6, Month 12 and Month 18 will be summarised for subjects with baseline ADA and have at least one ADA result after first IP administration up to above visit. Overall ADA result is defined as below:

- "Positive" for a subject with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least one positive result after first IP administration at Month 0 for subjects with negative ADA at baseline, and treatment-boosted ADA indicates at least one positive result with higher titre level compared to baseline after first IP administration at Month 0 for subjects with positive ADA at baseline.
- "Negative" for a subject with negative ADA at baseline and without positive ADA post-baseline.
- "Inconclusive" for a subject with positive ADA at baseline and without positive result with higher titre level observed post-baseline.

In addition, the incidence of overall ADA results (i.e., Positive, Negative, Inconclusive) for the transition period (from Month 12 to Month 18) will be presented by transition treatment group using the SAF2.

Overall ADA results for the transition period will be summarised for subjects with at least ADA result up to Month 12 and have at least one ADA result after transition up to Month 18. Overall ADA result for the transition period is defined as below:

- "Positive" for a subject with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least one positive result after IP administration at Month 12 for subjects with overall negative ADA up to Month 12, and treatment-boosted ADA indicates at least one positive result with higher titre level after IP administration at Month 12 compared to maximum positive ADA up to Month 12 for subjects with at least one positive ADA results up to Month 12.
- "Negative" for a subject with overall negative ADA up to Month 12 and without positive ADA after IP administration at Month 12 until Month 18.
- "Inconclusive" for a subject with at least one positive ADA up to Month 12 and without positive result with higher titre level observed after IP administration at Month 12 up to Month 18, compared to the maximum positive ADA up to Month 12.

A by-subject listing for immunogenicity assessment will be provided.

8.7. Other Observations Related to Safety

12-lead Electrocardiogram (ECG)

ECG are collected at screening only. ECG summary includes:

- A summary of QT interval, corrected QT interval (QTc), and the number and percentage of subjects experiencing clinically significant result by overall treatment group using the SAF1.

A by-subject listing of ECG results will be provided.

9. ADVERSE EVENTS

AE analyses will be performed for the main, transition, and overall study periods unless specified otherwise. All summaries of main and overall study periods will be based on the SAF1. Summary of transition period will be based on the SAF2. All reported AEs will be coded using MedDRA central coding dictionary version 23.0 or higher.

- Pre-treatment AE is defined as any AE with an onset date before the date of first administration of IP.
- TEAE will be defined as any AE with an onset date on or after the date of the first administration of IP until 6 months after last IP dose, or EOS/ET (study discontinuation decision date, when ET visit is not conducted), whichever occur later. AEs which are already present before the initiation of IP and increase in severity after the initiation of IP will be considered as TEAEs. Pre-existing AEs before the initiation of IP with no increase in severity after the initiation of IP will not be considered as TEAEs. See APPENDIX 1 for handling of partial dates for AEs.
- AE of Special Interest (AESI) includes hypocalcaemia, hypersensitivity to IP, osteonecrosis of the jaw, atypical femoral fractures, and skin infections. AESI will be evaluated by investigator and recorded in eCRF.
- Serious Adverse Event (SAE) will be evaluated by investigator and recorded in eCRF.

In general, AE summaries will provide the number and percentages of subjects reporting at least one AE and the total number of events reported by SOC, PT for each analysis period and treatment group. Subject will be counted once under each PT and each SOC. SOC will be presented in descending order of subject frequency based on the treatment SB16 (main and overall study periods) or SB16+SB16 (transition period), then alphabetically if tied. PT will be sorted within each SOC in descending order of subject frequency based on the treatment SB16 (main and overall study periods) or SB16+SB16 (transition period), then alphabetically if tied.

Any TEAE with an onset date on or after the date of the first administration of IP and before IP dose post re-randomisation will be included in the main period analysis. AEs that start in the main period and continue into the transition period will be included in the main period only.

Any TEAE with an onset date on or after the date of IP administration at Month 12 will be included in the transition period.

Summary of all Adverse Events

A summary of all AEs will be provided, including number and percentage of subjects and number of events under each category. The following categories will be presented for each analysis period as specified at Section 3 (main, transition, and overall study periods). SAEs will be collected until 6 months after last IP administration or EOS/ET, whichever occur later. Six months after the last IP administration date or EOS/ET will be considered in the definition of end date for each analysis period for AE.

- AEs (only included in the overall study period summary)
- Pre-treatment Adverse Events (Pre-AEs) (only included in the overall study period summary)
- TEAEs
- TEAEs by severity and causality
- TEAEs of special interest by category
- TEAEs leading to IP permanent discontinuation (only included in the overall study period summary)
- TEAEs leading to IP permanent discontinuation related to IP/non-IP (only included in the overall study period summary)
- Injection site reactions
- Serious TEAEs
- Serious TEAEs by severity and causality
- Serious TEAEs leading to IP permanent discontinuation (only included in the overall study period summary)
- Serious TEAEs leading to IP permanent discontinuation related to IP/non-IP (only included in the overall study period summary)
- TEAEs leading to death

A by-subject listing of all AEs will be provided by treatment group.

Adverse Events for COVID-19

Summaries of TEAEs for COVID-19 will be provided for each analysis period as specified at Section 3 (main, transition, and overall study periods), where the verbatim term contains key text

"COVID", including number and percentage of subjects and number of events under each category. However, if the AE is related to COVID-19 vaccination, it will be excluded from COVID-19 summary statistics and listing. The following categories will be presented.

- TEAEs for COVID-19: includes TEAEs, where the PT contains key text "COVID-19".
- TEAEs related to COVID-19: includes TEAEs other than COVID-19 which have a relationship with COVID-19 infection/disease.
- TEAEs post COVID-19 infection: includes TEAEs post first occurrence of COVID-19 infection (except COVID-19) in subjects infected with COVID-19. TEAEs post COVID -19 infection is defined as any TEAE with an onset date on or after the start date of the first of TEAEs for COVID-19.
- Serious TEAEs for COVID-19
- Serious TEAEs related to COVID-19
- Serious TEAEs among COVID-19 infected subjects

A by-subject listing of AEs for COVID-19 will be provided by treatment group.

Pre-treatment AEs (Pre-AEs)

- A summary of pre-treatment AEs using SAF1 by overall treatment group, SOC and PT, using number and percentage of subjects and number of events.

Treatment-Emergent Adverse Events (TEAEs)

The following TEAEs will be summarised by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods).

- Summaries of TEAEs by treatment group, SOC and PT, using number and percentage of subjects and number of events.
- Summaries of TEAEs > 2% in either treatment group by SOC and PT, using number and percentage of subjects and number of events.
- Summaries of TEAEs > 5% in either treatment group by SOC and PT, using number and percentage of subjects and number of events.

Other AEs

The following other AEs will be summarised by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods).

- Summaries of other AEs (TEAEs excluding SAEs) > 5% in either treatment group by SOC and PT, using number and percentage of subjects and number of events.

TEAEs by Severity

- Summaries of TEAEs by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods), SOC, PT, and severity using number and percentage of subjects and number of events.

Severity will be reported as mild, moderate, or severe. TEAEs with a missing severity will not be taken into account when calculating worst-case severity. If a subject reported TEAEs in the same SOC (or PT) more than once with different severity in each analysis period, the subject will be counted once in the worst-case severity.

TEAEs by Relationship (Causality)

The following TEAEs by causality will be summarised by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods).

- Summaries of TEAEs by treatment group, SOC, PT, and IP causality using number and percentage of subjects and number of events.
- Summaries of TEAEs by treatment group, SOC, PT, and non-IP causality using number and percentage of subjects and number of events.

Relationship with IP/non-IP will be reported as “Related”, and “Not related”. Missing relationship will not be taken into account when calculating worst-case relationship. If a subject reported TEAEs in the same SOC (or PT) more than once within difference causality in each analysis period, the subject will be counted once in the worst-case relationship.

Injection Site Reactions

Clinically significant injection site reaction will be reported in AE form. Injection site reaction will be identified by coded High Level Term (HLT), where HLT is “Injection site reactions”.

- Summaries of injection site reactions by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods), SOC, and PT using number and percentage of subjects and number of events.

A by-subject listing of injection site reactions will be provided by treatment group.

TEAEs Leading to IP Permanent Discontinuation

- Summaries of TEAEs leading to IP permanent discontinuation for overall study period by overall treatment group, SOC, and PT using number and percentage of subjects and number of events.

A by-subject listing of TEAEs leading to permanent discontinuation of IP will be provided by treatment group.

TEAEs Leading to Death

- Summaries of TEAEs leading to death by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods), SOC, and PT using number and percentage of subjects and number of events.

A by-subject listing of TEAEs leading to death will be provided by treatment group.

Serious Adverse Events (SAEs)

The following serious TEAEs will be summarised by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods).

- Summaries of serious TEAEs by treatment group, SOC, and PT using number and percentage of subjects and number of events.
- Summaries of serious TEAEs leading to IP permanent discontinuation for overall study period by overall treatment group, SOC, and PT using number and percentage of subjects and number of events.
- Summaries of serious TEAEs by treatment group, SOC, PT, and severity using number and percentage of subjects and number of events.
- Summaries of serious TEAEs by treatment group, SOC, PT, and IP causality using number and percentage of subjects and number of events.
- Summaries of serious TEAEs by treatment group, SOC, PT, and non-IP causality using number and percentage of subjects and number of events.

A by-subject listing of SAEs will be provided by treatment group.

AEs of Special Interest

- Summaries of treatment-emergent AESIs by treatment group for each analysis period as specified at Section 3 (main, transition, and overall study periods), SOC, and PT using number and percentage of subjects and number of events.

A by-subject listing of AESIs will be provided by treatment group.

Deaths

A by-subject listing of deaths will be provided by treatment group, including primary cause of death.

TEAEs by overall ADA result

As specified in Section 8.6, all TEAEs based on categories of overall ADA result (Positive, Negative, and Inconclusive) will be summarised by treatment group, SOC, and PT using number and percentage of subjects and number of events.

- Summaries of TEAEs by overall ADA result up to Month 12, main treatment group, SOC, and PT for SAF1 and main period
- Summaries of TEAEs by overall ADA result after transition up to Month 18, transition treatment group, SOC, and PT for SAF2 and transition period
- Summaries of TEAEs by overall ADA result up to Month 18, overall treatment group, SOC, and PT for SAF1 and overall period

10. REFERENCES

1. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med.* 2006; Feb 23;354(8):821-31.
2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009; Aug 20;361(8):756-65.
3. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008; Jun;93(6):2149-57.

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. However, in general, when calculating relative days, partial dates with missing day only will be assumed to be 15th of the month, and partial dates with both missing day and month will be assumed to be June 30. Otherwise, the following rules in the given table will be applied for each case.

Algorithm for Adverse Events, Medications, and Procedures

For the end date imputation, the last visit date is defined as the last available visit date, i.e., including unscheduled visit date after the EOS visit.

When the start date is missing,

	Case	Imputed Value
Missing Day	year and month = year and month of first IP taken date	first IP taken date
	year and month <> year and month of first IP taken date	1st of the month
Missing Day and Month	year = year of first IP taken date	first IP taken date
	year <> year of first IP taken date	1st of January
Completely Missing	N/A	

If complete (imputed) end date is available and the imputed start date is greater than the (imputed) end date, then imputed start date should be set to the (imputed) end date.

When the end date is missing,

	Case	Imputed Value
Missing Day	year and month <> year and month of last visit date	last day of the month
	year and month = year and month of last visit date	last visit date
Missing Day and Month	year < year of last visit date	31st of December

	Case	Imputed Value
	year = year of last visit date	last visit date
Completely Missing	N/A	

If the imputed end date is less than the existing start date, then use start date as end date.

Algorithm for Treatment-Emergent

After imputation for partial dates is implemented, whether AE is TEAE will be decided.

When start date is present,

- If known/imputed start date ≥ the date of first dose of IP and ≤ 6 months after last IP dose or EOS/ET (study discontinuation decision date, when ET visit is not conducted), whichever occur later, then AE is considered as TEAE

When start date is completely missing but end date is present,

- If known/imputed end date ≥ the date of first dose of IP and ≤ 6 months after last IP dose or EOS/ET (study discontinuation decision date, when ET visit is not conducted), whichever occur later, then AE is considered as TEAE

When both start date and end date are completely missing,

- AE is considered as TEAE

Algorithm for Concomitant Medications, Procedures, and non-IP

After imputation for partial dates is implemented, whether medication, procedure, or non-IP is concomitant will be decided.

When both start date and end date are present,

- If known/imputed end date ≥ the date of first dose of IP and known/imputed start date ≤ the date of EOS/ET visit (study discontinuation decision date, when ET visit is not conducted), then medication/procedure/non-IP is considered as concomitant

When start date is present and end date is completely missing,

- If known/imputed start date ≤ the date of EOS/ET visit (study discontinuation decision date, when ET visit is not conducted), then medication/procedure/non-IP is considered as concomitant

When start date is completely missing but end date is present,

- If known/imputed end date ≥ the date of first dose of IP, then medication/procedure/non-IP is considered as concomitant

When both start date and end date are completely missing,

- Medication/procedure/non-IP is considered as concomitant

Algorithm for Partial Diagnosed Date of PMO

	Case	Imputed Value
Missing Day	year and month = year and month of randomisation date	Randomisation date
	year and month < year and month of randomisation date	the 15th of the month
Missing Day and Month	year = year of randomisation date	Randomisation date
	year <> year of randomisation date	30th of June
Completely Missing	N/A	

APPENDIX 2. LABORATORY TEST PARAMETERS

Analytic	Sex	Age	Normal Range		SI Unit
			Low	High	
Haematology					
Haemoglobin	F	15-999	120	160	g/L
Haematocrit	F	15-999	0.36	0.46	L/L
Platelet count	F	15-999	150	350	x10E9/L
Red blood cell count	F	15-999	4.1	5.2	x10E12/L
White blood cell count (total)	F	5-999	4.0	10.7	x10E9/L
Neutrophils (%)	F	7-999	43	74	%
Total Lymphs (%)	F	13-999	20	44	%
Monocytes (%)	F	7-999	3	10	%
Eosinophils (%)	F	13-999	0	7	%
Basophils (%)	F	31-999	0	2	%
Neutrophils (Abs)	F	7-999	1.6	7.4	x10E9/L
Total Lymphs (Abs)	F	13-999	1.0	4.0	x10E9/L
Monocytes (Abs)	F	7-999	0.1	0.9	x10E9/L
Eosinophils (Abs)	F	13-999	0.0	0.7	x10E9/L
Basophils (Abs)	F	31-999	0.0	0.2	x10E9/L
Biochemistry					
Sodium	F	0-999	135	148	mmol/L
Potassium	F	0-999	3.5	5.3	mmol/L
Chloride	F	0-999	98	110	mmol/L
Creatinine	F	19-999	44	80	umol/L
Blood urea nitrogen	F	19-999	2.1	8.9	mmol/L
eGFR using MDRD equation	F	19-999	60	125	mL/min/SA[#]
Glucose	F	0-999	3.9	7.8	mmol/L
Calcium	F	0-999	2.14	2.62	mmol/L
Albumin corrected serum calcium	F	0-999	2.14	2.62	mmol/L
Albumin	F	0-999	32	55	g/L
Phosphorus	F	13-59	0.87	1.55	mmol/L
Phosphorus	F	60-999	0.68	1.61	mmol/L

Analytic	Sex	Age	Normal Range		SI Unit
			Low	High	
Total bilirubin	F	8-999	0	21	umol/L
Total cholesterol	F	0-999	0.00	5.17	mmol/L
Alanine aminotransferase	F	19-999	0	45	U/L
Aspartate aminotransferase	F	7-999	0	41	U/L
Alkaline phosphatase	F	18-999	35	104	U/L
Hormone					
FSH*	F	0-999	23.0	116.3	IU/L
TSH	F	21-999	0.55	4.78	mIU/L
PTH	F	0-999	1.6	6.9	pmol/L
Vitamin D (25-hydroxyvitamin D)	F	0-999	75	250	nmol/L

* The normal range for postmenopausal women.
# SA: 1.73m^2.

APPENDIX 3. NOMRAL RANGE FOR VITAMIN D IN KOREAN SITES

Site	Sex	Age	Normal Range		Conventional Unit*
			Low	High	
0101	F	-	30	100	ng/mL
0102	F	-	30	100	ng/mL
0103	F	21-999	30	100	ng/mL
0104	F	0-999	30	100	ng/mL
0105	F	0-99	30	100	ng/mL
0106	F	-	>= 30	-	ng/mL
0107	F	-	>30	-	ng/mL
0108	F	-	>30	100	ng/mL
0109	F	-	>32	-	ng/mL

* The conversion factor between ng/mL and nmol/L is 2.5, 1 ng/mL = 2.5 nmol/L.

APPENDIX 4. WORST CASE OF LABORATORY PARAMETERS

Category	Parameter	SI Unit	Worst Value Direction
Hematology	Hemoglobin	g/L	Low
Hematology	Platelet count	x10E9/L	Low
Hematology	White blood cell count (total)	x10E9/L	Low
Hematology	Neutrophils (Abs)	x10E9/L	Low
Hematology	Total Lymphs (Abs)	x10E9/L	Low
Chemistry	Sodium	mmol/L	Low
Chemistry	Potassium	mmol/L	High
Chemistry	Creatinine	umol/L	High
Chemistry	eGFR using MDRD equation	mL/min/SA[#]	Low
Chemistry	Glucose	mmol/L	High
Chemistry	Calcium	mmol/L	Low
Chemistry	Albumin corrected serum calcium	mmol/L	Low
Chemistry	Albumin	g/L	Low
Chemistry	Total bilirubin	umol/L	High
Chemistry	Total cholesterol	mmol/L	High
Chemistry	Alanine aminotransferase	U/L	High
Chemistry	Aspartate aminotransferase	U/L	High
Chemistry	Alkaline phosphatase	U/L	High
Hormone	Vitamin D (25-hydroxyvitamin D)	nmol/L	Low

[#] SA: 1.73m^2.

APPENDIX 5. CTCAE V5.0 GRADING FOR LABORATORY VALUES

Grade is classified based on the numeric lab result criteria in CTCAE v5.0 grading. The clinical criteria or condition will not be used.

Analytic	CTCAE SOC	CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haematology						
Haemoglobin	Blood and lymphatic system disorders	Anemia	< Lower Limit of Normal (LLN) - 10.0 g/dL; < LLN – 6.2 mmol/L; < LLN - 100 g/L	< 10.0 - 8.0 g/dL; < 6.2 - 4.9 mmol/L; < 100 - 80 g/L	< 8.0 g/dL; < 4.9 mmol/L; < 80 g/L	
Platelet count	Investigations	Platelet count decreased	< LLN - 75,000/mm3; < LLN - 75.0 x 10^9 /L	< 75,000 - 50,000/mm3; < 75.0 - 50.0 x 10^9 /L	< 50,000 - 25,000/mm^3; < 50.0 - 25.0 x 10^9 /L	< 25,000/mm^3; < 25.0 x 10^9 /L
White blood cell count (total)	Investigations	White blood cell decreased	< LLN - 3000/mm3; < LLN - 3.0 x 10^9 /L	< 3000 - 2000/mm3; < 3.0 - 2.0 x 10^9 /L	< 2000 - 1000/mm^3; < 2.0 - 1.0 x 10^9 /L	< 1000/mm^3; < 1.0 x 10^9 /L
White blood cell count (total)	Blood and lymphatic system disorders	Leukocytosis	-	-	> 100,000/mm^3; > 100.0 x 10^9 /L	
Neutrophils (Abs)	Investigations	Neutrophil count decreased	< LLN - 1500/mm3; < LLN - 1.5 x 10^9 /L	< 1500 - 1000/mm3; < 1.5 - 1.0 x 10^9 /L	< 1000 - 500/mm^3; < 1.0 - 0.5 x 10^9 /L	< 500/mm^3; < 0.5 x 10^9 /L
Total Lymphs (Abs)	Investigations	Lymphocyte count decreased	< LLN - 800/mm3; < LLN - 0.8 x 10^9 /L	< 800 - 500/mm3; < 0.8 - 0.5 x 10^9 /L	< 500 - 200/mm^3; < 0.5 - 0.2 x 10^9 /L	< 200/mm^3; < 0.2 x 10^9 /L
Total Lymphs (Abs)	Investigations	Lymphocyte count increased	-	> 4,000 - 20,000/mm3; > 4.0 - 20.0 x 10^9 /L	> 20,000/mm^3; > 20.0 x 10^9 /L	
Biochemistry						
Sodium	Metabolism	Hypernatremia	> Upper Limit of	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L

Analytic	CTCAE SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
	and nutrition disorders		Normal (ULN) - 150 mmol/L			
Sodium	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	125 -129 mmol/L	120-124 mmol/L	< 120 mmol/L
Potassium	Metabolism and nutrition disorders	Hyperkalemia	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium	Metabolism and nutrition disorders	Hypokalemia	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Creatinine	Investigations	Creatinine increased	> ULN – 1.5 x ULN	> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN	> 3.0 x baseline; > 3.0 - 6.0 x ULN	> 6.0 x ULN
Glucose	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	< 40 - 30 mg/dL; < 2.2 - 1.7 mmol/L	< 30 mg/dL; < 1.7 mmol/L
Albumin corrected serum calcium	Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L	Corrected serum calcium of > 12.5 - 13.5 mg/dL; > 3.1 - 3.4 mmol/L	Corrected serum calcium of > 13.5 mg/dL; > 3.4 mmol/L
Albumin corrected serum calcium	Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L	Corrected serum calcium of < 7.0 - 6.0 mg/dL; < 1.75 - 1.5 mmol/L	Corrected serum calcium of < 6.0 mg/dL; < 1.5 mmol/L
Albumin	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	< 2 g/dL; < 20 g/L	
Total bilirubin	Investigations	Blood bilirubin	>ULN - 1.5 x ULN if	>1.5 - 3.0 x ULN if	> 3.0 - 10.0 x ULN if	> 10.0 x ULN if

Analytic	CTCAE SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
		increased	baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	baseline was normal; > 3.0 - 10.0 x baseline if baseline was abnormal	baseline was normal; > 10.0 x baseline if baseline was abnormal
Total cholesterol	Investigations	Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	> 400 - 500 mg/dL; > 10.34 - 12.92 mmol/L	> 500 mg/dL; > 12.92 mmol/L
Alanine aminotransferase	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal
Aspartate aminotransferase	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal
Alkaline phosphatase	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal

APPENDIX 6. PROHIBITED MEDICATIONS AND PROCEDURES

Note: List of prohibited medications and procedures will be finally confirmed by medical reviewer.

Medications or Procedures	Time to be prohibited	Category	**ATC drug class/Preferred terms or MedDRA terms**	**Remark**
Prohibited Medications				
Contraceptives which affect the amonorrhea	Prior to randomisation	ATC3	G03A	Related protocol deviation ID: I02 ※ Lack of menstrual period < Duration of administration of contraceptives which affect the amonorrhea
Therapeutic monoclonal antibody or fusion receptor protein (including denosumab, denosumab biosimilars, or romosozumab)	Prior to randomisation	ATC4, Preferred term	ATC4 code: L01XC Preferred terms: Denosumab; Romosozumab	Related protocol deviation ID: I06 ※ Medical reviewer will check the prohibited medications that are not defined on ' ATC Codes/Preferred Drug Name '.
Oral bisphosphonate	Prior to randomisation	ATC4	M05BA, M05BB	Related protocol deviation ID: E10
Intravenous bisphosphonate	Within 5 years prior to Screening or prior to randomisation	ATC4	M05BA	Related protocol deviation ID: E11
PTH or PTH analogues	Within 2 years prior to Screening or prior to randomisation	ATC4	H05AA	Related protocol deviation ID: E12
Systemic hormone replacement therapy (oral	Within 1 year prior to Screening	ATC2, ATC3, ATC4	ATC2 code: L02	Related protocol deviation ID: E13 ※ Medical reviewer will check the prohibited

Medications or Procedures	Time to be prohibited	Category	**ATC drug class/Preferred terms or MedDRA terms**	**Remark**
or transdermal oestrogen), selective oestrogen receptor modulators (SERMs), tibolone, aromatase inhibitors, or androgens (Exceptionally, non-systemic vaginal oestrogen treatment is permitted)	or prior to randomisation		ATC3 codes: A14A, G03A, G03B, G03C, G03E, G03F ATC4 codes: D11AE, G03XC	medications that are not defined on ' ATC Codes/Preferred Drug Name '.
Calcitonin or its derivatives, calcimimetics (such as cinacalcet or etelcalcetide), or calcitriol	Within 3 months prior to Screening or prior to randomisation	ATC4, Preferred term	ATC4 codes: H05BA, H05BX Preferred term: Calcitriol	Related protocol deviation ID: E14
Systemic glucocorticoids (prednisone equivalent)	Within 3 months prior to Screening or prior to randomisation	ATC4	H02AB, H02BX	Related protocol deviation ID: E15
Fluoride or strontium intended for osteoporosis treatment	Prior to randomisation	ATC4, Preferred term	ATC4 code: A12CD Preferred term: Strontium ranelate	Related protocol deviation ID: E16
Non-biologic IP for osteoporosis treatment	Within 5 years prior to Screening or prior to randomisation	ATC4	M05BX	Related protocol deviation ID: E17 ※ Medical reviewer will check the prohibited medications that are not defined on ' ATC Codes/Preferred Drug Name '.
Bone active drugs	Within 3 months prior to Screening	ATC2, ATC3, ATC4,	ATC2 code: H02	Related protocol deviation ID: E18

Medications or Procedures	Time to be prohibited	Category	**ATC drug class/Preferred terms or MedDRA terms**	**Remark**
	or prior to randomisation	Preferred term	ATC3 codes: G03G, H01A, L01A, L01B ATC4 codes: A02AB, A02AD, B01AB, B02BA, H01CA, J05AE, L01CA, L01CD, L01DB, L01DC, L01XX, L02AE, L04AD, N01AF, N01AG, N03AA, N05AN, N05CA, N05CB, V04CD Preferred terms: Aluminium chlorohydrate; Carbamazepine; Methotrexate; Methylphenobarbital; Oxcarbazepine; Phenobarbital; Primidone; Topiramate; Valproic acid; Valpromide; Warfarin; Any product that contains "phenytoin"	
Non-biologic IP that is not indicated for osteoporosis from another study within five half-lives of that product or an investigational device	Prior to randomisation			Related protocol deviation ID: E19 ※ Medical reviewer will check the prohibited medications.

Medications or Procedures	Time to be prohibited	Category	**ATC drug class/Preferred terms or MedDRA terms**	**Remark**
Xgeva (Denosumab) or drugs used for osteoporosis or drugs that affect bone metabolism, or any kind of monoclonal antibodies or fusion receptor protein	Whole study period after randomisation	ATC2, ATC3, ATC4, Preferred drug name	ATC2 Codes: L02, H02 ATC3 Codes: A14A, G03A, G03B, G03C, G03E, G03F, G03G, H01A, L01A, L01B ATC4 Codes: A02AB, A02AD, A12CD, B01AB, B02BA, D11AE, G03XC, H01CA, H05AA, H05BA, H05BX, J05AE, L01CA, L01CD, L01DB, L01DC, L01XC, L01XX, L04AD, M05BA, M05BB, M05BX, N01AF, N01AG, N03AA, N05AN, N05CA, N05CB, V04CD Preferred drug names: Aluminium chlorohydrate; Calcitriol; Carbamazepine; Denosumab; Methotrexate; Methylphenobarbital;	Related protocol deviation ID: M01

Medications or Procedures	Time to be prohibited	Category	**ATC drug class/Preferred terms or MedDRA terms**	**Remark**
			Oxcarbazepine; Phenobarbital; Primidone; Romosozumab; Strontium ranelate; Topiramate; Valproic acid; Valpromide; Warfarin; Any product that contains "phenytoin"	
Oral barium, radioisotope injection, oral contrast for CT	Screening, Months 6, 12, and 18 (EOS)/ET, Unscheduled visits ※ Prohibited within 7 days before BMD assessment	ATC2, ATC3	ATC2 code: V09 ATC3 codes: V08A, V08B	Related protocol deviation ID: M03
Prohibited Procedures				
Invasive dental procedures (e.g., dental implants or oral surgery), major surgeries, or bone surgeries (unless required for AE/SAE management)	Whole study period after randomisation	SOC, HLT	SOC term: Surgical and medical procedures HLT term: Dental and gingival therapeutic procedures	Related protocol deviation ID: M02

APPENDIX 7. VISIT NAME

Study Period	Visit Long Name
Screening	Screening
Main Treatment Period	Month 0
	Month 0.5
	Month 1
	Month 3
	Month 6
	Month 9
	Month 12
Transition Period	Month 18 (EOS)*
* For table, ET visit will be mapped to scheduled visit as described in section 3.6. EOS visit will be presented as 'Month 18 (EOS)'. For listing, EOS and ET visit will be presented as 'Month 18 (EOS)/ET'.	

APPENDIX 8. SAMPLE CODES FOR PRIMARY ANALYSIS

```
/* Non-Monotone missing data to be imputed to monotone missing */
proc mi data=indat seed=899745 nimpute=25 out=out_mono;
      by trt_group;
      var trt_group BMD_BL BMD_pchg_M6 BMD_pchg_M12;
      mcmc  chain=multiple impute=monotone;
run;
/* Monotone missing data to be imputed by regression predictive
model */
proc mi data=out_momo seed=899745 nimpute=1 out=out_complete;
      by _Imputation_ ;
      class trt_group;
      monotone reg;
      var trt_group BMD_BL BMD_pchg_M6 BMD_pchg_M12;
run;

/* Analysis of covariance (ANCOVA) */
ods output lsmeans=lsm diffs=LSmean_diff;
proc mixed data = out_complete;
      by _ Imputation_;
      class trt_group;
      model BMD_pchg_M12 = trt_group BMD_BL/ solution;
      lsmeans trt_group /stderr diff cl alpha=0.05 (alpha=0.1 for US
      FDA);
run;

/* Estimation and inference for multiply imputed datasets*/
ods output ParameterEstimates=milsm;
proc mianalyze data= lsm alpha=0.05 (alpha=0.1 for US FDA) ;
      by trt_group;
      modeleffects estimate;
      stderr stderr;
run;

ods output ParameterEstimates=midiff;
proc mianalyze data=LSmean_diff alpha=0.05 (alpha=0.1 for US FDA);
      modeleffects estimate;
      stderr stderr;
run;
```

```
/* Tipping point analysis*/
```

Monotone missing data will be imputed for a tipping point analysis with incremental or decre mental shifts (k) of delta value for the SB16 and Prolia treatment groups independently. This is illustrated by the example PROC MI code shown below:

```
/* need to define the maximum plausible BMD_pchg shift value. For
example, 0.5 departure from group mean with ten equal space, coded
as i= -0.5 to 0.5 by 0.1 */

%do k = - max_BMD_shift %to max_BMD_shift %by &delta;
%do j = - max_BMD_shift %to max_BMD_shift %by &delta;

      proc mi data= out_momo seed=899745 nimpute=1 out=out_complete;
            class trt_group;
            monotone reg;
            var trt_group BMD_BL BMD_pchg_M6 BMD_pchg_M12;
            mnar   adjust(BMD_pchg_M12/ shift=&k
       adjustobs=(trt='SB16'))
                  adjust(BMD_pchg_M12/ shift=&j
             adjustobs=(trt='Prolia'));

      run;

/* repeat the primary analysis ANCOVA and combined inference for
multiply imputed datasets as above */

%end;
%end;
```

Note: Please add BMD_pchg_M18 to code for imputation if the analysis includes Month 18 visit.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGES

SIGNATURE PAGE

Declaration of the authors

Protocol Title Applicable to this CSR Statistical Analysis Plan:
A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Compare the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity between SB16 (proposed denosumab biosimilar) and Prolia in Postmenopausal Women with Osteoporosis

Protocol Number: SB16-3001

Protocol Version and Effective Date: Amendment 1 (Version 2.0) May 03, 2021

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(Mmm dd, yyyy)

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Institution: Samsung Bioepies Co., Ltd.

Signature: _____ Date: _____
(Mmm dd, yyyy)