SAMSUNG BIOEPIS

Clinical Study Protocol

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

Product	SB16 (proposed denosumab biosimilar)	
EudraCT Number	2020-001479-34	
US IND Number (if applicable)	N/A	
Protocol Number	SB16-3001	
Study Phase	Phase III	
Version and Effective Date	Version 2.0	May 03, 2021
	Version 1.0	Apr 06, 2020
Sponsor	Samsung Bioepis Co., Ltd. 76, Songdogyoyuk-ro, Yeonsu-gu, Incheon, 21987 Republic of Korea	

SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB16 (proposed denosumab biosimilar)
Name of Active Ingredient:	Denosumab
Title of Study: 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 No: SB16-3001	**Phase:** III
Investigator Sites:	Approximately 44 investigator sites globally
Planned Study Period:	• Screening period: 28 days after signing the informed consent form (ICF) - Additional 28 days will be allowed to subjects who are not eligible only due to vitamin D deficiency, for vitamin D repletion and repeat of serum vitamin D test. • Main period: Approximately 12 months after Randomisation • Transition period: Approximately 6 months after Month 12
Objectives: <u>Primary objective</u> 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 subjects with postmenopausal osteoporosis (PMO). <u>Secondary objectives</u> 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®	

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- To evaluate the pharmacokinetic (PK) profile of SB16 compared to Prolia®
- To evaluate the pharmacodynamic (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

Study Design:

For the Main period

This is a Phase III, randomised, double-blind, parallel group, multicentre, equivalence study to evaluate the efficacy, safety, PK, PD, and immunogenicity of SB16 compared to Prolia® in PMO. Subjects will be randomised in a 1:1 ratio to receive either SB16 or Prolia® subcutaneously at Months 0 and 6. Study visits will occur at Months 0, 0.5, 1, 3, 6, 9, and 12.

BMD assessment will be done at Months 6 and 12. Blood sampling for safety, PK, PD, and immunogenicity will be done at Months 0, 0.5, 1, 3, 6, 9, and 12.

For the Transition period

This is a Phase III, randomised, double-blind, multicentre, transition study to investigate the safety, tolerability, immunogenicity, PK, PD, and efficacy of SB16 in subjects with PMO who transitioned from the Prolia® arm, compared with subjects who maintained Prolia® treatment after Month 12 from the Main period of the SB16-3001 study.

The Transition period is up to 6 months after Month 12 of the Main period of the SB16-3001 study. Subjects will receive either SB16 or Prolia® subcutaneously at Month 12.

At Month 12, subjects receiving Prolia® from the Main period of the SB16-3001 study will be randomised again in a 1:1 ratio to either continue on Prolia® (Prolia®/Prolia®) or be transitioned to SB16 (Prolia®/SB16) up to Month 18. Subjects receiving SB16 from the Main period of the SB16-3001 study will continue to receive extended treatment of SB16 up to Month 18 but they will also follow the randomisation procedure to maintain blinding.

BMD assessment and blood sampling for safety, PK, PD, and immunogenicity will be done at Month 18.

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Number of Subjects:

Approximately 432 subjects will be randomised in the study.

Target Population:

Postmenopausal women with osteoporosis

Main Eligibility Criteria:

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Postmenopausal women (defined as lack of menstrual period for at least 12 months prior to Screening, for which there is no other pathological or physiological cause) who are 55 to 80 years of age at Screening
   - Serum follicle stimulating hormone (FSH) test can be done at Screening in case of uncertainty.
2. Ambulatory and visually unimpaired to participate in the study at Screening, in the opinion of the Investigator
3. Absolute BMD consistent with T-score at the total hip or lumbar spine of ≥ -4 and ≤ -2.5, determined by central imaging centre at Screening
4. At least three evaluable vertebrae within L1 to L4, one evaluable femoral neck, and one evaluable hip joint for BMD measurement, determined by central imaging centre at Screening
5. Biologic (defined as any therapeutic monoclonal antibody or fusion receptor protein, including denosumab, denosumab biosimilars, or romosozumab) naïve at Screening
6. Body weight of ≥ 50 kg and ≤ 90 kg at Screening
7. Has provided informed consent voluntarily and must be able to, in the opinion of the Investigator, understand the implications of taking part in the study, be willing to follow the study requirements, and complete the study

Subjects must meet the following criteria to be enrolled in the Transition period:

1. Have been enrolled and completed the scheduled Month 12 of the Main period of the SB16-3001 study

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Exclusion criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. One severe or more than two moderate vertebral fractures on spinal X-ray according to Genant classification, determined by central imaging centre at Screening
2. History of hip fracture or bilateral hip replacement at Screening
3. Uncorrected vitamin D deficiency (defined as serum 25-hydroxyvitamin D level < 20 ng/mL [50 nmol/L]) at Screening
4. Hypercalcemia or hypocalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcemia > 2.62 mmol/L [10.5 mg/dL]) at Screening
5. Inadequate haematological function at Screening defined as the following:
   a. White blood cell count < 3.5×10^3 cells/μL (< 3.5×10^9 cells/L)
   b. Haemoglobin < 9 g/dL
   c. Platelet count < 100,000/mm^3 (< 100×10^9/L)
6. Inadequate renal or hepatic function at Screening defined as the following:
   a. Estimated glomerular filtration rate (eGFR) < 45 mL/min by the Modification of Diet in Renal Disease (MDRD) formula or under dialysis
   b. Serum alanine transaminase and aspartate transaminase ≥ 2 × upper limit of reference range
7. Known allergic reactions, hypersensitivity, or intolerance to denosumab or to any ingredients of the investigational product (IP), including latex allergy or hereditary problems of fructose intolerance at Screening
8. May not tolerate long-term calcium or vitamin D supplementation or subject with malabsorption of calcium or vitamin D supplements, in the opinion of the Investigator, at Screening
9. Use of any of the below medications that can affect BMD:
   a. Oral bisphosphonate at any dose for osteoporosis treatment:
      - Used for > 3 years cumulatively at Screening
      - Used for ≤ 3 years cumulatively and passed < 1 year since the last dose at Screening

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b. Intravenous bisphosphonate at any dose within 5 years prior to Screening

c. Parathyroid hormone (PTH) or PTH analogues at any dose within 2 years prior to Screening

d. Systemic hormone replacement therapy (oral or transdermal oestrogen), selective oestrogen receptor modulators (SERMs), tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening

- Exceptionally, non-systemic vaginal oestrogen treatment is permitted.

e. Calcitonin or its derivatives, calcimimetics (such as cinacalcet or etelcalcetide), or calcitriol at any dose within 3 months prior to Screening

f. Systemic glucocorticoids (≥ 5 mg prednisone equivalent per day or cumulative dose ≥ 50 mg) for more than 10 days within 3 months prior to Screening

g. Fluoride or strontium intended for osteoporosis treatment at any dose at any time at Screening

h. Any non-biologic IP for osteoporosis treatment that mechanism of action is not within excluded medications in exclusion criteria number 9-a to 9-g at any dose within 5 years prior to Screening

i. Other bone active drugs at any dose within 3 months prior to Screening

10. Use of any non-biologic IP that is not indicated for osteoporosis from another study at any dose within five half-lives of that product prior to Randomisation or use of an investigational device at Screening

11. Non-osteoporosis medical conditions that can affect BMD at Screening:

a. History of hyperparathyroidism or hypoparathyroidism, or current hyperparathyroidism or hypoparathyroidism

b. Current uncontrolled hyperthyroidism or hypothyroidism

c. History of bone disease such as osteomalacia, osteogenesis imperfecta, osteopetrosis, achondroplasia, or Paget's disease of the bone

d. History of chronic inflammatory diseases, obvious sclerosis, osteophytosis, severe scoliosis, or other degenerative changes due to other co-morbidities that may interfere with the interpretation of dual-energy X-ray absorptiometry (DXA) imaging results

e. History of metabolic or other endocrinologic diseases such as malabsorption syndrome

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(including celiac disease), Cushing disease, acromegaly, or hyperprolactinemia

12. History of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fracture at Screening or related-risk based on the physical examination including oral at Screening
13. History of active periodontal disease or invasive dental procedure within 6 months prior to Screening or plan to do invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) during the study period
14. Fracture (except atypical femoral fracture and hip fracture) which has been in active healing within 12 months prior to Screening at the discretion of the Investigator
15. History of clinically significant active infection within 2 weeks prior to Randomisation, and for cellulitis, erysipelas, or infections that requires hospitalisation or intravenous antibiotics, within 8 weeks prior to Randomisation
16. Known history for hepatitis B or hepatitis C or human immunodeficiency virus infection, or positive testing for hepatitis B (hepatitis B virus surface antigen [HBsAg]) or hepatitis C (hepatitis C virus antibody [HCV Ab]) virology at Screening
17. History of acute or chronic pancreatitis at Screening
18. History of acute myocardial infarction or New York Heart Association (NYHA) III/IV congestive heart failure within 1 year prior to Randomisation
19. History of cardiac arrythmia or long QT syndrome or electrocardiogram (ECG) abnormalities (e.g., that required hospitalisation, emergency cardioversion, or defibrillation) indicating safety risk at Screening
20. Malignancy not cured within 5 years prior to Randomisation
    - Exceptionally, completely excised and cured basal cell carcinoma or cervical carcinoma in situ can be permitted.
21. History of organ transplantation at Screening
22. History of alcohol or substance-abuse within 12 months prior to Screening
23. Any clinically significant disease or disorder or laboratory abnormality which, in the opinion of the Investigator, would prevent the subject from completing the study or the interpretation of the study results at Screening and Randomisation

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Subjects meeting the following criteria must not be enrolled in the Transition period:

1. Found to be of increased risk to continue enrolment, in the opinion of the Investigator

Investigational Products:

- Name: SB16 (proposed denosumab biosimilar) or European Union (EU) sourced Prolia®
- Formulation: Pre-filled syringe (PFS) of 1 mL contains 60 mg of denosumab (60 mg/mL)
- Route of administration: Subcutaneous injection
- Dose regimen: 60 mg every 6 months

Non-investigational Products:

- Elemental calcium (at least 1 g per day)
- Vitamin D (at least 800 IU per day)

Above dose of daily calcium and vitamin D will be given from Randomisation to end of study (EOS)/early termination (ET). During the screening period, subjects will receive calcium and vitamin D at the discretion of the Investigator.

Main Criteria for Evaluation:

Primary endpoint

- Percent change from baseline in lumbar spine BMD at Month 12

Secondary endpoints for the Main period

Efficacy endpoints

- Percent change from baseline in lumbar spine BMD at Month 6
- Percent change from baseline in total hip BMD at Months 6 and 12
- Percent change from baseline in femoral neck BMD at Months 6 and 12

Safety endpoints

- Incidence of adverse events (AEs)
- Incidence of serious AEs (SAEs)

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PK endpoint

- Serum drug concentration at Months 0, 0.5, 1, 3, 6, 9, and 12

PD endpoints

- Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12
- Area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX
- Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12

Immunogenicity endpoint

- Incidence of anti-drug antibodies (ADAs) at Months 0, 0.5, 1, 3, 6, 9, and 12
- Incidence of neutralising antibodies (NAbs) at Months 0, 0.5, 1, 3, 6, 9, and 12

<u>Secondary endpoints for the Transition period</u>

Safety endpoints

- Incidence of AEs
- Incidence of SAEs

Immunogenicity endpoint

- Incidence of ADAs at Month 18
- Incidence of NAbs at Month 18

Efficacy endpoints

- Percent change from baseline in lumbar spine BMD at Month 18
- Percent change from baseline in total hip BMD at Month 18
- Percent change from baseline in femoral neck BMD at Month 18

PK endpoint

- Serum drug concentration at Month 18

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PD endpoints

- Serum CTX concentration at Month 18
- Serum P1NP concentration at Month 18

Statistical Methods:

Analysis sets for efficacy analyses

Full Analysis Set (FAS) consists of all randomised subjects. Following the intent-to-treat principle, subjects will be analysed according to the treatment group they are 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 FAS.

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.

Efficacy analyses

For the European Medicines Agency (EMA), Korea Ministry of Food and Drug Safety (MFDS), and other regulatory submissions, the primary efficacy analysis will be performed for the PPS using an analysis of covariance 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% confidence interval (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%]. To conduct the sensitivity analysis 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 missing at random. Available case analysis will also be performed for the FAS.

For the United States of America (US) Food and Drug Administration (FDA) submission, the primary efficacy analysis will be performed for the FAS using an analysis of covariance with the baseline value of lumbar spine

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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 pre-defined 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. For sensitivity analysis, available case analysis will be performed for the FAS and the same analysis will be repeated for the PPS.

As the secondary efficacy endpoints, percent change from baseline in BMD (lumbar spine, total hip, and femoral neck) will be analysed similarly to the primary endpoint.

Safety analyses

Safety analyses will be performed for the Safety Set (SAF1) and Safety Set for the Transition period (SAF2).

All reported terms for AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®).

All AE data will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term, and treatment group. SAEs leading to IP discontinuation and treatment emergent AEs (TEAEs) by causality and severity will be summarised similarly.

Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment group and visit. Other safety variables will be summarised unless otherwise specified.

PK and PD analyses

PK analyses will be performed for the PK Analysis Set (PKS). Serum drug concentration will be summarised descriptively by treatment group and visit.

PD analyses will be performed for the PD Analysis Set (PDS). Serum CTX and P1NP concentrations will be summarised descriptively by treatment group and visit. In addition, the $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX will be analysed using an analysis of variance model.

Immunogenicity analyses

Immunogenicity analyses will be performed for the SAF1 and SAF2. ADA and NAb results will be summarised with frequency and percentage by treatment group and visit. The incidence of overall ADA will be summarised by treatment group.

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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% CI of [4.83%, 5.87%]. For the 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 US 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 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 standard deviation 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.

GRAPHICAL STUDY DESIGN AND SCHEDULE OF ACTIVITIES

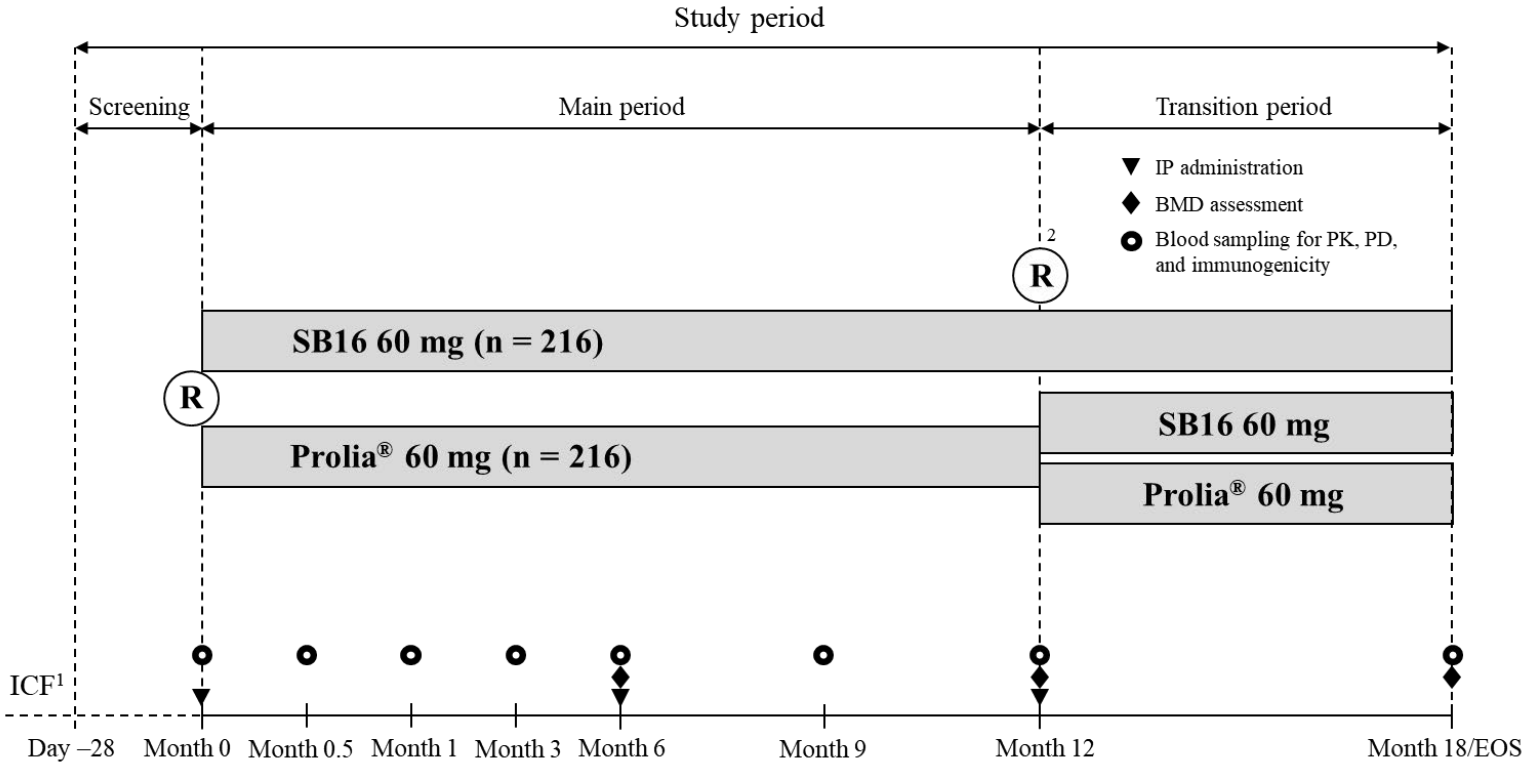

Figure 1. Graphical Study Design

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.

Table 1. Schedule of Activities

Assessment	Study Period									
		Main Period						Transition Period		
Study Visit	Screening[1]	1	2	3	4	5	6	7	EOS	ET[28]
Timepoint		Month[2] 0	Month 0.5[3]	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	
Days from Month 0	–28 to –1	0	15	30	91	182	273	364	546	
Visit Window (Day)	0	0	±3	±3	±7	±7	±7	±7	±7	±7
Informed consent[4]	✓									
Demographic information[5]	✓									
Medical and surgical history[6]	✓									
ECG[7]	✓									
Serum FSH, PTH, TSH and virology markers[8]	✓									
Lateral spine X-ray (lumbar and thoracic)[9]	✓									
Vital signs[10]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination[11]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height and weight[12]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Haematology, biochemistry tests, and urinalysis (dipstick)[13]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BMD (lumbar spine, total hip, and femoral neck)[14]	✓					✓		✓	✓	✓
Serum vitamin D[15]	✓					✓		✓		
Inclusion/exclusion criteria	✓	✓						✓		
Randomisation[16]		✓						✓[17]		
PK assessment[18]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Immunogenicity assessment[19]		✓	✓	✓	✓	✓	✓	✓	✓	✓
PD assessment (bone turnover markers [serum CTX/P1NP])[20, 21]		✓[22]	✓	✓	✓	✓	✓	✓	✓	✓
IP administration[23]		✓				✓		✓		
Injection site reaction[24]		✓				✓		✓		

Assessment	Study Period									
		Main Period						Transition Period		
Study Visit	Screening[1]	1	2	3	4	5	6	7	EOS	ET[28]
Timepoint		Month[2] 0	Month 0.5[3]	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	
Days from Month 0	–28 to –1	0	15	30	91	182	273	364	546	
Visit Window (Day)	0	0	±3	±3	±7	±7	±7	±7	±7	±7
Non-IP administration[25]		Continuously								
Previous and concomitant medications[26]	Continuously									
Adverse events[27]	Continuously									

EOS = end of study; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; PTH = parathyroid hormone; TSH = thyroid stimulating hormone; BMD = bone mineral density; PK = pharmacokinetic; PD = pharmacodynamic; CTX = C-telopeptide of type I collagen; P1NP = procollagen type I N-terminal propeptide; IP = investigational product

1. In subjects who are not eligible only due to vitamin D deficiency, serum vitamin D (25-hydroxyvitamin D) can be re-tested only once after vitamin D repletion and re-test result will be used for eligibility review. Additional 28 days will be allowed to those subjects. Vitamin D repletion method will be determined by the Investigator considering subject's serum vitamin D level.
   * To avoid repetition of unnecessary procedures, screening procedures previously performed other than vitamin D re-test will not be repeated in this case.
2. Visit date will be calculated based on Month 0.
3. Month 0.5 is 15 days after Month 0.
4. Informed consent should be obtained prior to any study related procedures.
5. Demographic information includes the year of birth, gender, race, ethnicity, current smoking status, daily alcohol consumption amount, and parent fractured hip history.
6. Medical and surgical history of 5 years prior to Screening will be included. Also, previous fracture history in a lifetime will be collected.
7. Standard 12-lead ECGs will be recorded at Screening.
8. Blood sample for serum FSH (optional), PTH, TSH and virology markers (hepatitis B and C virology [HBsAg and HCV Ab]) will be collected at Screening.
9. Lateral spine X-ray (lumbar and thoracic) will be done at Screening.
10. Vital signs include body temperature measurement, blood pressure, and heart rate. Vital signs will be assessed at Screening, prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
11. Physical examination will be done at Screening, prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET. The result for physical examinations must be confirmed by the Investigator.
12. Body weight will be measured and recorded at Screening and prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET. Whereas height will be measured and recorded only at Screening.
13. Samples for haematology, biochemistry tests, and urinalysis (dipstick) will be collected at Screening, prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, EOS/ET, and additionally for subject's safety purpose during the study period at the Investigator's discretion.
    • Haematology: Haemoglobin, haematocrit, platelet count, red blood cell count, and white blood cell count (total and differential)
    • Chemistry: Sodium, potassium, chloride, creatinine, blood urea nitrogen, eGFR using MDRD equation, glucose, calcium, albumin corrected serum calcium, phosphorus, total bilirubin, albumin, total cholesterol, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase
    • Urinalysis (dipstick): Protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, and urobilinogen
14. Lumbar spine, total hip, and femoral neck BMD will be measured at Screening, prior to dosing at Months 6 and 12, and EOS/ET.
15. Blood sample for serum vitamin D (25-hydroxyvitamin D) will be collected at Screening and prior to dosing at Months 6 and 12.

16. Randomisation must proceed after all screening procedures including eligibility confirmation.
17. At Month 12, subjects receiving Prolia® will be re-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.
18. Blood sample for PK assessment will be collected prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
19. Blood sample for immunogenicity assessment will be collected prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
20. Blood sample for PD assessment will be collected prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
21. Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
22. On the day of baseline PD assessment (Month 0), calcium should not be given before the PD blood sampling.
23. SB16 and Prolia® will be subcutaneously administered 60 mg every 6 months.
24. Monitoring for injection site reaction will be done after IP administration at Months 0, 6, and 12.
25. Daily elemental calcium (≥ 1 g) and vitamin D (≥ 800 IU) will be given to the subjects from Randomisation to EOS/ET. Instruction for non-IP supplementation will be done at Months 0, 0.5, 1, 3, 6, 9, and 12.
26. Previous and concomitant medication within 5 years prior to Screening and concomitant medication thereafter. Also, previous oral bisphosphonate history in a lifetime will be collected.
27. AEs will be collected from the time of signing the ICF until the EOS/ET. SAEs will be collected until 6 months after the last IP dose or EOS/ET, whichever longer. If the subject would withdraw before receiving the first dose of IP, AEs and SAEs should be collected up until the time the subject withdraws.
28. Subjects who withdraw from the study before EOS will be asked to return to the investigational site for the ET procedures to be performed at 6 months from the last IP dose.

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
$AUEC_{0\text{-}M6}$	Area under the effect curve from time zero to Month 6
BMD	Bone mineral density
CHO	Chinese Hamster Ovary
CI	Confidence interval
CRO	Contract Research Organisation
CSR	Clinical study report
CTX	C-telopeptide of type I collagen
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study
ET	Early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GIOP	Glucocorticoid-induced osteoporosis
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibody
ICF	Informed consent form
ICH	International Council of Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MDRD	Modification of Diet in Renal Disease

MedDRA®	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
NAb	Neutralising antibody
NYHA	New York Heart Association
OPG	Osteoprotegerin
P1NP	Procollagen type I N-terminal propeptide
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic Analysis Set
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PMO	Postmenopausal osteoporosis
PPS	Per-Protocol Set
PTH	Parathyroid hormone
RAN	Randomised Set
RANK	Receptor activator of nuclear factor kappa B
RANKL	Receptor activator of nuclear factor kappa-B ligand
SAE	Serious adverse event
SAF1	Safety Set
SAF2	Safety Set for the Transition period
SAP	Statistical analysis plan
SERM	Selective oestrogen receptor modulator
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TSH	Thyroid stimulating hormone
US	United States of America
WHO	World Health Organisation

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1. Introduction

1.1. Background

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. [4] Fractures resulting from osteoporosis become increasingly common in women after age 55 years and men after age 65 years, resulting in substantial bone-associated morbidities, and increased mortality and health-care costs. [5] An estimated 2.7 million hip fractures occurred in 2010 worldwide, of which 1,364,717 (51%) were calculated to be potentially preventable (264,162 in men, and 1,100,555 in women), if osteoporosis (defined as a femoral neck T-score of –2.5 standard deviation or less) could be avoided. [6]

Several chemical entities with original modes of action have been approved for the treatment of postmenopausal osteoporosis (PMO) after demonstration of an anti-fracture efficacy at the level of the axial skeleton (spine) or appendicular skeleton (all non-vertebral, major non-vertebral, or hip). [7] These products include bisphosphonates with daily or intermittent dosing formulations, selective oestrogen receptor modulators (SERMs), calcitonin, active vitamin D metabolites, teriparatide, and strontium ranelate. Some of them have also been approved for the treatment of osteoporosis in men.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappa B ligand (RANKL) that blocks its binding to receptor activator of nuclear factor kappa B (RANK), inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Denosumab showed effectiveness in the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and treatment to increase bone mass in men with osteoporosis at high risk for fracture and is approved as Prolia®. [8; 9] Also it showed effectiveness in the treatment of giant cell tumour and prevention of skeletal-related events in patients with bone metastases, and is approved as Xgeva®. [10; 11] The recommended dose of Prolia® is 60 mg every 6 months as a subcutaneous injection and that of Xgeva® is 120 mg every 4 weeks as a subcutaneous injection.

A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine') and is expected to increase accessibility of biologics to a wider patient population.

1.2. Overview of SB16

SB16 has been developed as a similar biological medicinal product to Prolia® and Xgeva® having denosumab as the active substance. Prolia® is currently indicated for osteoporosis in postmenopausal women and in men, glucocorticoid-induced osteoporosis (GIOP), and bone loss associated with hormone ablation therapy in prostate cancer patients by both European Medicines Agency (EMA) and the United States of America (US) Food and Drug Administration (FDA). In addition, US FDA approved Prolia® for the treatment of bone loss associated with adjuvant aromatase inhibitor therapy for breast cancer. [8; 9] Xgeva® is currently indicated for the prevention of skeletal-related events in patients with advanced malignancies involving bone and the treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity by both EMA and US FDA. In addition, US FDA approved Xgeva® for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. [10; 11]

SB16 is manufactured with Chinese Hamster Ovary (CHO) mammalian cell expression system in suspension culture by recombinant deoxyribonucleic acid (DNA) technology and purified by various affinity and ion exchange chromatography.

According to the guideline International Council of Harmonisation (ICH) Q6B, characterisation of a

biological therapeutic must involve its physicochemical properties, biological activities, purity, impurities, and quantity. The characterisation study will employ the 'state-of-the-art' analytical methods in order to investigate the primary, secondary, higher-order structures, and the post-translational modifications associated the structural heterogeneity, the charge variants, the purity, and the biological activities.

1.2.1. Non-clinical Studies of SB16

As outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues", [12] a risk-based approach was taken to the non-clinical evaluation of SB16. A series of *in vitro* biologic activity studies is to be performed in order to demonstrate non-clinical similarity between SB16, Prolia®, and Xgeva®. In line with the guideline, if similarity is to be demonstrated in quality and *in vitro* comparisons to provide non-clinical evidence of similarity between SB16, Prolia®, and Xgeva®, *in vivo* studies will not be performed. Moreover, *in vitro* studies are considered to be the more sensitive measurement than with *in vivo* studies. Also, non-clinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies were not performed, as they are not required for non-clinical testing of biosimilars as outlined in the guideline. [12]

1.3. Comparator Investigational Product: Prolia®

1.3.1. Non-clinical Data of Reference Product

In ovariectomised monkeys, once-monthly treatment with Prolia® suppressed bone turnover and increased BMD and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg). Bone tissue was normal with no evidence of mineralisation defects, accumulation of osteoid, or woven bone.

Because the biological activity of Prolia® in animals is specific to nonhuman primates, evaluation of genetically engineered ('knockout') mice or use of other biological inhibitors of the RANK/RANKL pathway, namely osteoprotegerin (OPG)-Fc, provided additional information on the pharmacodynamic (PD) properties of Prolia®. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued.

The carcinogenic potential of Prolia® has not been evaluated in long-term animal studies.

The genotoxic potential of Prolia® has not been evaluated.

Prolia® had no effect on female fertility or male reproductive organs in monkeys at doses that were 13- to 50-fold higher than the recommended human dose of 60 mg subcutaneously administered once every 6 months, based on body weight (mg/kg). [8; 9]

1.3.2. Clinical Data of Reference Product in Postmenopausal Osteoporosis

The efficacy and safety of Prolia® in the treatment of PMO was demonstrated in a 3-year, randomised, double-blind, placebo-controlled trial. Enrolled women had a baseline BMD T-score between –2.5 and –4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis,

osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7,808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was –2.8, and 23% of women had a vertebral fracture at baseline. Women were randomised to receive subcutaneous injections of either placebo (n = 3,906) or Prolia® 60 mg (n = 3,902) once every 6 months. All women received at least 1 g calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4 to L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

Prolia® significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$). The incidence of new vertebral fractures at 3 years was 7.2% in the placebo-treated women compared to 2.3% for the Prolia®-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at 3 years.

Prolia® was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for Prolia®-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years ($p = 0.004$).

Treatment with Prolia® significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index, baseline BMD, and level of bone turnover.

After Prolia® discontinuation, BMD returned to approximately baseline levels within 12 months. [2; 8; 9]

1.4. Study Rationale

A biosimilar is a biological medicinal product that is highly similar to an already authorised original biological medicinal product (reference medicinal product) in terms of quality, tolerability, and efficacy based on a comprehensive comparability exercise. [12; 13] EMA and US FDA have developed specific guidelines for a biologic drug to be approved as a biosimilar. [13; 14] These guidelines recommend a stepwise approach in developing a biosimilar starting with extensive physicochemical and biological characterisation before initiating clinical studies for the comparison of the efficacy, tolerability, pharmacokinetic (PK) properties, and immunogenicity of the biosimilar. The purpose of this study is to demonstrate the equivalence in efficacy of SB16 compared to Prolia® and to evaluate the safety and immunogenicity in subjects with PMO. In addition, systemic exposure and the PD profiles of SB16 to Prolia® will also be evaluated.

1.5. Risk and Benefit Assessment

1.5.1. Known Potential Risks

According to Prolia® Prescribing Information and Summary of Product Characteristics, there are potential risks such as hypersensitivity, hypocalcaemia, disturbances of mineral metabolism, osteonecrosis of the jaw, atypical subtrochanteric, diaphyseal femoral fractures, serious infection,

dermatologic adverse reactions, and musculoskeletal pain. Also, as this is a therapeutic protein, there is a potential for immunogenicity with investigational products (IPs; SB16 or Prolia®). [8; 9]

In order to ensure the safety of subjects who participate in the study, safety will be monitored during the whole study period based on the vital signs, laboratory safety assessments, physical examination including the evaluation of injection site, and reported AEs.

Subject should be instructed to report any symptoms, especially symptoms related to AE of special interests (AESIs) in Section 8.3 without delay and should be managed appropriately. Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. Thus, next treatment will be discussed at early termination (ET)/end of study (EOS) to prevent loss of bone mass and/or fractures.

Participation in clinical study requires frequent visits than usual medical practice, thus, additional risk under the Coronavirus Disease 2019 should be considered. The Sponsor will consider whether to start, continue, temporarily halt, or close the study at some or all study sites based on the risk assessment based on relevant parties' input on an ongoing basis.

This study will take place at multicentre with accessible medical facilities which will allow immediate treatment of medical emergencies. All study related procedures will be conducted by medical staffs with appropriate level of training and expertise and an understanding of the IPs, its target, and mechanism of action. An independent Data and Safety Monitoring Board (DSMB) will convene at pre-specified intervals to conduct interim monitoring of accumulating safety data. Following each data review, the DSMB will make recommendations regarding the conduct of the study, including continuation of the study without modifications, modification of the protocol, pausing of subject enrolment until the resolution of an issue, or termination of the study for safety reasons.

1.5.2. Known Potential Benefits

Prolia® binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Prolia® prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Prolia® reduces fracture risk and increases BMD in PMO. A meta-analysis that compared denosumab with placebo showed a 68% reduction in the risk of vertebral fractures (hazard ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.40), a 39% reduction in the risk of hip fractures (hazard ratio, 0.61; 95% CI, 0.37 to 0.98), and a 19% reduction in the risk of nonvertebral fractures (hazard ratio, 0.81; 95% CI, 0.69 to 0.95). [8; 9]

Although clinical data is currently unavailable for SB16, SB16 is expected to have similar clinical outcome to Prolia® based on the physicochemical and biological similarity.

1.5.3. Assessment of Potential Risks and Benefits

If left untreated, osteoporosis can progress painlessly until bone break. These broken bones, also known as fractures, occur typically in the hip, spine, and wrist; hip and spinal fractures in particular can have serious consequences. Thus, benefit of Prolia® treatment including reducing fracture risk and increase in BMD outweigh the potential risks.

The available data demonstrate a high degree of physicochemical and biological similarity of SB16 with the reference medicinal product (Prolia®). The suitability of the methodology employed to evaluate the similarity of SB16 and Prolia® in a pharmaceutical setting were confirmed by EMA and the US

FDA. The known and potential risks of receiving SB16 are expected to be similar to those seen with Prolia®. In conclusion, sufficient evidence supports the administration of SB16, as a similar biological medicinal product of Prolia®, to subjects with PMO.

Risk assessment for the Coronavirus Disease 2019 will be documented on an ongoing basis in relevant documents. The risk assessment and associated mitigation measures based on inputs from relevant stakeholders will be prioritised to consider the rights, safety, and wellbeing of the study subjects.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. 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 BMD at Month 12 in PMO.

2.1.2. 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

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Percent change from baseline in lumbar spine BMD at Month 12

2.2.2. Secondary Endpoints for the Main Period

Efficacy endpoints

- Percent change from baseline in lumbar spine BMD at Month 6
- Percent change from baseline in total hip BMD at Months 6 and 12
- Percent change from baseline in femoral neck BMD at Months 6 and 12

Safety endpoints

- Incidence of AEs
- Incidence of serious AEs (SAEs)

PK endpoint

- Serum drug concentration at Months 0, 0.5, 1, 3, 6, 9, and 12

PD endpoints

- Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12
- Area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX
- Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12

Immunogenicity endpoint

- Incidence of anti-drug antibodies (ADAs) at Months 0, 0.5, 1, 3, 6, 9, and 12
- Incidence of neutralising antibodies (NAbs) at Months 0, 0.5, 1, 3, 6, 9, and 12

2.2.3. Secondary Endpoints for the Transition Period

Safety endpoints

- Incidence of AEs
- Incidence of SAEs

Immunogenicity endpoint

- Incidence of ADAs at Month 18
- Incidence of NAbs at Month 18

Efficacy endpoints

- Percent change from baseline in lumbar spine BMD at Month 18
- Percent change from baseline in total hip BMD at Month 18
- Percent change from baseline in femoral neck BMD at Month 18

PK endpoint

- Serum drug concentration at Month 18

PD endpoints

- Serum CTX concentration at Month 18
- Serum P1NP concentration at Month 18

3. Study Design

3.1. Overview of Study Design

For the Main period

This is a Phase III, randomised, double-blind, parallel group, multicentre, equivalence study to evaluate the efficacy, safety, PK, PD, and immunogenicity of SB16 compared to Prolia® in PMO. Subjects will be randomised in a 1:1 ratio to receive either SB16 or Prolia® subcutaneously at Months 0 and 6. Study visits will occur at Months 0, 0.5, 1, 3, 6, 9, and 12.

For the Transition period

This is a Phase III, randomised, double-blind, multicentre, transition study to investigate the safety, tolerability, immunogenicity, PK, PD, and efficacy of SB16 in subjects with PMO who transitioned from the Prolia® arm, compared with subjects who maintained Prolia® treatment after Month 12 from the Main period of the SB16-3001 study.

Subjects will be enrolled in the Transition period for up to 6 months after Month 12 of the Main period of the SB16-3001 study. Subjects will receive either SB16 or Prolia® subcutaneously at Month 12.

At Month 12, subjects receiving Prolia® from the Main period of the SB16-3001 study will be randomised again in a 1:1 ratio to either continue on Prolia® (Prolia®/Prolia®) or be transitioned to SB16 (Prolia®/SB16) up to Month 18. Subjects receiving SB16 from the Main period of the SB16-3001 study will continue to receive extended treatment of SB16 up to Month 18 but they will also follow the randomisation procedure to maintain blinding.

3.2. Rationale for Study Design

3.2.1. Scientific Rationale for Study Design

The purpose of this study is to demonstrate the equivalence in clinical efficacy of SB16 and European Union (EU) sourced Prolia® in subjects with PMO.

According to EMA and US FDA guideline, the endpoints and study populations should be clinically relevant and sensitive in detecting clinically meaningful differences in safety and effectiveness between the proposed biosimilar product and reference product. [15; 13] Among the approved indications by both EMA and US FDA, PMO population is considered the most appropriate population to assess clinical similarity between SB16 and Prolia®.

As the most sensitive clinical endpoint in PMO, percent change of BMD at Month 12 will be compared between SB16 and Prolia® to demonstrate the clinical similarity. BMD is a validated biomarker for the evaluation of the treatment effect and risk of fracture, and BMD change after denosumab treatment was shown in the several studies. [1; 2; 3]

This study is a randomised, double-blind, multicentre study for 18 months. And transition will be performed at Month 12 to investigate the clinical impact (safety and immunogenicity) of switching.

3.2.2. Rationale for Pharmacokinetic Assessments

A randomised, three-arm, parallel, single-dose comparative PK study will be conducted in healthy male subjects to demonstrate similarity in PK profiles of SB16 and EU sourced Prolia® and US sourced Prolia®. However, since target-mediated clearance of denosumab can be more accurately investigated in PMO patients, additional PK assessments will be performed in this comparative efficacy study to provide supportive evidence to PK similarity.

3.2.3. Rationale for Pharmacodynamic Assessments

In pivotal trials of Prolia®, denosumab treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum CTX (85% reduction) by 3 days, with reductions maintained over the dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to approximately ≥ 45% (range 45-80%), reflecting the reversibility of denosumab's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment. [8; 9]

Thus, together with BMD which is a primary endpoint of SB16 Phase III study as a strong predictor of fracture in denosumab, PD markers such as serum P1NP and CTX will be measured and compared. CTX was also selected for the Phase I trial because this proximal PD marker is more sensitive than other bone turnover markers.

Instead of true clinical outcomes such as fracture, SB16 will compare the change of BMD to Prolia® for demonstration of biosimilarity. Also, PD markers such as serum P1NP and CTX will be measured and compared.

3.2.4. Rationale for Immunogenicity Assessments

Biological/biotechnology-derived proteins can induce an unwanted immune response that is triggered by more than a single factor and the consequence of immunogenicity may vary considerably, ranging from irrelevant to therapy to serious and life-threatening. Immune responses may affect both safety and effectiveness such as altering PK, inducing anaphylaxis, or promoting development of NAbs that neutralise the product as well as its endogenous protein counterpart.

In clinical studies of Prolia®, NAbs have not been observed for denosumab. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 5 years tested positive for non-NAbs with no evidence of altered pharmacokinetics, toxicity, or clinical response. [8; 9]

For subjects' safety and for demonstrating biosimilarity, immunogenicity will be assessed in this study according to the recommended guideline.

3.3. Duration of Study Participation

The duration of study participation will be 28 days of screening period, 12 months of Main period, and 6 months of Transition period.

In subjects who are not eligible only due to vitamin D deficiency, additional 28 days of screening period (a total of 56 days) will be allowed for vitamin D repletion and re-test.

3.4. Number of Subjects

Approximately 432 subjects are planned to be randomised from approximately 44 sites for study duration.

3.5. End of Study Definition

A subject is considered to have completed the study if she has completed the last scheduled visit or the last scheduled procedure shown in the Schedule of Activities (Table 1). EOS is defined as completion of the last scheduled visit (Month 18) shown in the Table 1. The end of this clinical study is defined as completion of the last subject's EOS/ET.

4. Study Population

4.1. Overview

The study population for this study is subjects with PMO. Eligibility for participation in this study will be based on the inclusion/exclusion criteria.

4.2. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Postmenopausal women (defined as lack of menstrual period for at least 12 months prior to Screening, for which there is no other pathological or physiological cause) who are 55 to 80 years of age at Screening
    - Serum follicle stimulating hormone (FSH) test can be done at Screening in case of uncertainty.
2. Ambulatory and visually unimpaired to participate in the study at Screening, in the opinion of the Investigator
3. Absolute BMD consistent with T-score at the total hip or lumbar spine of ≥ –4 and ≤ –2.5, determined by central imaging centre at Screening
4. At least three evaluable vertebrae within L1 to L4, one evaluable femoral neck, and one evaluable hip joint for BMD measurement, determined by central imaging centre at Screening
5. Biologic (defined as any therapeutic monoclonal antibody or fusion receptor protein, including denosumab, denosumab biosimilars, or romosozumab) naïve at Screening
6. Body weight of ≥ 50 kg and ≤ 90 kg at Screening
7. Has provided informed consent voluntarily and must be able to, in the opinion of the Investigator, understand the implications of taking part in the study, be willing to follow the study requirements, and complete the study

Subjects must meet the following criteria to be enrolled in the Transition period:

1. Have been enrolled and completed the scheduled Month 12 of the Main period of the SB16-3001 study

4.3. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. One severe or more than two moderate vertebral fractures on spinal X-ray according to Genant classification, determined by central imaging centre at Screening
2. History of hip fracture or bilateral hip replacement at Screening
3. Uncorrected vitamin D deficiency (defined as serum 25-hydroxyvitamin D level < 20 ng/mL [50 nmol/L]) at Screening
4. Hypercalcemia or hypocalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcemia > 2.62 mmol/L [10.5 mg/dL]) at Screening

5. Inadequate haematological function at Screening defined as the following:
   a. White blood cell count < 3.5×10^3 cells/μL (< 3.5×10^9 cells/L)
   b. Haemoglobin < 9 g/dL
   c. Platelet count < 100,000/mm^3 (< 100×10^9/L)
6. Inadequate renal or hepatic function at Screening defined as the following:
   a. Estimated glomerular filtration rate (eGFR) < 45 mL/min by the Modification of Diet in Renal Disease (MDRD) formula or under dialysis
   b. Serum alanine transaminase and aspartate transaminase ≥ 2 × upper limit of reference range
7. Known allergic reactions, hypersensitivity, or intolerance to denosumab or to any ingredients of the IP, including latex allergy or hereditary problems of fructose intolerance at Screening
8. May not tolerate long-term calcium or vitamin D supplementation or subject with malabsorption of calcium or vitamin D supplements, in the opinion of the Investigator, at Screening
9. Use of any of the below medications that can affect BMD:
   a. Oral bisphosphonate at any dose for osteoporosis treatment:
      - Used for > 3 years cumulatively at Screening
      - Used for ≤ 3 years cumulatively and passed < 1 year since the last dose at Screening
   b. Intravenous bisphosphonate at any dose within 5 years prior to Screening
   c. Parathyroid hormone (PTH) or PTH analogues at any dose within 2 years prior to Screening
   d. Systemic hormone replacement therapy (oral or transdermal oestrogen), SERMs, tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening
      • Exceptionally, non-systemic vaginal oestrogen treatment is permitted.
   e. Calcitonin or its derivatives, calcimimetics (such as cinacalcet or etelcalcetide), or calcitriol at any dose within 3 months prior to Screening
   f. Systemic glucocorticoids (≥ 5 mg prednisone equivalent per day or cumulative dose ≥ 50 mg) for more than 10 days within 3 months prior to Screening
   g. Fluoride or strontium intended for osteoporosis treatment at any dose at any time at Screening
   h. Any non-biologic IP for osteoporosis treatment that mechanism of action is not within excluded medications in exclusion criteria number 9-a to 9-g at any dose within 5 years prior to Screening
   i. Other bone active drugs at any dose within 3 months prior to Screening
10. Use of any non-biologic IP that is not indicated for osteoporosis from another study at any dose within five half-lives of that product prior to Randomisation or use of an investigational

device at Screening

11. Non-osteoporosis medical conditions that can affect BMD at Screening:
    a. History of hyperparathyroidism or hypoparathyroidism, or current hyperparathyroidism or hypoparathyroidism
    b. Current uncontrolled hyperthyroidism or hypothyroidism
    c. History of bone disease such as osteomalacia, osteogenesis imperfecta, osteopetrosis, achondroplasia, or Paget's disease of the bone
    d. History of chronic inflammatory diseases, obvious sclerosis, osteophytosis, severe scoliosis, or other degenerative changes due to other co-morbidities that may interfere with the interpretation of dual-energy X-ray absorptiometry (DXA) imaging results
    e. History of metabolic or other endocrinologic diseases such as malabsorption syndrome (including celiac disease), Cushing disease, acromegaly, or hyperprolactinemia
12. History of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fracture at Screening or related-risk based on the physical examination including oral at Screening
13. History of active periodontal disease or invasive dental procedure within 6 months prior to Screening or plan to do invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) during the study period
14. Fracture (except atypical femoral fracture and hip fracture) which has been in active healing within 12 months prior to Screening at the discretion of the Investigator
15. History of clinically significant active infection within 2 weeks prior to Randomisation, and for cellulitis, erysipelas, or infections that requires hospitalisation or intravenous antibiotics, within 8 weeks prior to Randomisation
16. Known history for hepatitis B or hepatitis C or human immunodeficiency virus infection, or positive testing for hepatitis B (hepatitis B virus surface antigen [HBsAg]) or hepatitis C (hepatitis C virus antibody [HCV Ab]) virology at Screening
17. History of acute or chronic pancreatitis at Screening
18. History of acute myocardial infarction or New York Heart Association (NYHA) III/IV congestive heart failure within 1 year prior to Randomisation
19. History of cardiac arrythmia or long QT syndrome or electrocardiogram (ECG) abnormalities (e.g., that required hospitalisation, emergency cardioversion, or defibrillation) indicating safety risk at Screening
20. Malignancy not cured within 5 years prior to Randomisation
    - Exceptionally, completely excised and cured basal cell carcinoma or cervical carcinoma in situ can be permitted.
21. History of organ transplantation at Screening
22. History of alcohol or substance-abuse within 12 months prior to Screening
23. Any clinically significant disease or disorder or laboratory abnormality which, in the opinion

of the Investigator, would prevent the subject from completing the study or the interpretation of the study results at Screening and Randomisation

Subjects meeting the following criteria must not be enrolled in the Transition period:

1. Found to be of increased risk to continue enrolment, in the opinion of the Investigator

4.4. Lifestyle Considerations

Before the day of PD assessment (bone turnover markers [serum CTX and P1NP]), subjects should fast at least 8 hours before blood sampling. PD blood sampling should be performed in the morning hours. On the day of baseline PD assessment (Month 0), calcium should not be given before the PD blood sampling.

All subjects should be encouraged to maintain good oral hygiene and receive routine dental check-ups (see Section 8.3).

4.5. Screen Failure, Re-test, and Re-screening

4.5.1. Screen Failure

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet one or more criteria required for participation in the trial during the screening procedures.

If the subject is not randomised within 28 days after signing the informed consent form (ICF), the subject must be screen failed.

Exceptionally, if the subject is not eligible **only due to vitamin D deficiency**, additional 28 days of screening period is allowed. In this case if the subject is not randomised within 56 days after signing the ICF, the subject must be screen failed.

4.5.2. Re-test

Clinical laboratory test for eligibility review will not be allowed for re-test unless any technical error (e.g., missing value due to sample mishandling) was found.

Exceptionally, in subjects who are not eligible **only due to vitamin D deficiency**, serum vitamin D can be re-tested only once after vitamin D repletion and re-test result will be used for eligibility review. Additional 28 days of screening period will be allowed to those subjects. Vitamin D repletion method will be determined by the Investigator considering subject's serum vitamin D level. To avoid repetition of unnecessary procedures, screening procedures previously performed other than vitamin D re-test will not be repeated in this case.

Re-scanning of DXA or lateral spine X-ray during the study period is not allowed except for cases where it has been confirmed that the image is not evaluable by the central imaging centre due to quality issue.

4.5.3. Re-screening

Re-screening is allowed for administrative reason only, i.e. not medical issues. Subjects who did not meet eligibility criteria at Screening cannot be re-screened. Each case of re-screening must be discussed and agreed with the Sponsor on a case-by-case basis. Subject can be re-screened only once; new subject number will be assigned for the re-screened subject and all the screening procedures will be done after signing ICF.

5. Treatment and Investigational Product

5.1. Treatment of the Subjects

5.1.1. Dosing and Treatment Schedule

Subjects will be administered SB16 or Prolia® 60 mg pre-filled syringe (PFS) as a single subcutaneous injection at Months 0 and 6 in the Main period and Month 12 in the Transition period.

All subjects should receive at least of elemental calcium 1 g daily and at least 800 IU vitamin D daily.

Dosing visits will involve a window period of ± 7 days from the scheduled dosing date except Month 0. No visit windows are allowed for the Month 0 and first IP administration is performed during this visit.

Dose modifications of IP are not allowed.

5.1.2. Assignment of Subjects to Treatment Group

A unique subject number will be assigned to the subject by the Interactive Web Response System (IWRS) at Screening.

Subjects who meet all criteria for enrolment will be randomised in a ratio of 1:1 to receive either SB16 or Prolia® at Month 0.

A unique randomisation number will be assigned to the subject number by the IWRS at Randomisation to ensure that treatment group assignment is unbiased and concealed from subjects, Investigators, and other study personnel. The randomisation number is linked to the treatment group assignment, which in turn is linked to IP kit number.

The assigned subject number(s) and randomisation number(s) will not be re-used.

For the Transition period, the same subject number used in the randomised, double-blind period will be conveyed to register the subject using the IWRS. At Month 12, subjects receiving Prolia® from the Main period of the SB16-3001 study will be randomised again in a 1:1 ratio to either continue on (Prolia®/Prolia®) or be transitioned to SB16 (Prolia®/SB16) up to Month 18. Subjects receiving SB16 from the Main period of the SB16-3001 study will continue to receive extended treatment of SB16 up to Month 18 but they will also follow the randomisation procedure to maintain blinding.

5.1.3. Blinding

This study is double-blinded in order to eliminate observer or performance bias. Subjects, Investigators, and other study personnel will be unaware of the treatment group assignments throughout the study period. Unblinding is referred to Section 8.4.

To ensure the blinding of the treatment group assignment, blinding cap will be applied to IP PFS (SB16 or Prolia®).

The IP (SB16 and Prolia®) PFS will be packaged and labelled identically, to ensure the blinding of the treatment group assignment.

5.2. Investigational Product

5.2.1. Identity of Investigational Product

- Name: SB16 (proposed denosumab biosimilar) or EU sourced Prolia®

- Formulation: PFS of 1 mL contains 60 mg of denosumab (60 mg/mL)
- Route of administration: Subcutaneous injection
- Dose regimen: 60 mg every 6 months

5.2.2. Formulation, Packaging, and Labelling

These IP PFSs will be packed and labelled in a double-blinded manner for clinical use. The labels for carton and PFS will contain the protocol number, unique identifier, Sponsor company name, expiry or re-test date, storage condition, and other details according to the Good Manufacturing Practice (GMP) and other relevant local laws and/or regulations.

The temperature will be monitored properly during the study period. The IP should be stored in a secure area and clearly labelled and stored away from other IP or medication to prevent confusion (e.g., in a clearly marked box on a separate shelf of the refrigerator).

A detailed guideline for IP preparation, administration, storage, and destruction will be provided in the pharmacy manual.

5.2.3. Product Storage and Stability

IPs should be stored at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. The temperature will be monitored properly during the study period. If continuous monitoring is not available then manual temperature logs should be generated and recorded to ensure proper storage conditions. If a temperature deviation occurred, responsible person should contact the Sponsor to determine if the IP is still appropriate for use.

Do not freeze IPs. The IPs must not be used beyond the expiration date. Once removed from the refrigerator, IPs must not be exposed to temperatures above 25°C/77°F and must be used within 14 days. If not used within the 14 days, IPs should be discarded. Protect IPs from direct light and heat. Avoid vigorous shaking of IPs.

5.2.4. Preparation and Administration of Investigational Products

IPs should be inspected visually prior to administration. IPs are clear, colourless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. If particulates, cloudiness, or discoloration are visible, the IPs must not be used.

Prior to administration, IPs may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Refrain from warming IPs in any other way.

IPs will be administered as a single subcutaneous injection in the upper arm, the upper thigh, or the abdomen. Only the Investigator or trained designee with an appropriate qualification (per local regulation) can perform and monitor the administration of IPs. In this study, IPs must be administered only on an on-site basis.

5.2.5. Treatment Compliance and Investigational Product Accountability

All IP injections will be given by the Investigator or designee to ensure compliance. The exact date and time of IP injection must be recorded in the source documentation and the electronic case report form (eCRF).

The Investigator and/or designee should maintain the documents of IP accountability and record the IP

kit number administered to subjects. IP accountability and dispensing records must be kept current and contain the following information:

- The identification of the subjects to whom the drug was dispensed
- The date(s) and quantity of the drug dispensed to the subject
- The dispensing and inventory logs must be available for inspection by the study monitor

The Investigator and/or designee is responsible for accounting all unused IP and all used IP containers. The Investigator uses this information to maintain an accurate and complete dispensing and inventory record.

IP supplies are shipped to the investigational site as needed. The monitor will review drug accounting during routine monitoring visits with the documents containing relevant information. At the completion or termination of the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their resolution must be documented.

The used IP should be disposed and/or destructed after use according to the local regulation. In case that the IP is disposed after use, the Investigator is responsible for accounting other materials of used IP such as IP container. The Investigator uses this information to maintain an accurate and complete dispensing and inventory record provided by the Sponsor.

All unused IPs should be returned to the Sponsor or designated vendor unless local destruction is approved by the Sponsor. If destruction is authorised at the investigational site, the Investigator must ensure that the materials are destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IPs must be adequately documented.

5.3. Non-investigational Product

- Elemental calcium (at least 1 g per day)
- Vitamin D (at least 800 IU per day)

Above dose of daily calcium and vitamin D will be given from Randomisation to EOS/ET. During the screening period, subject may receive the calcium and vitamin D at the discretion of the Investigator.

If hypocalcaemia or hypercalcemia occurs, the Investigator can modify dietary intake of calcium and adjust the calcium and/or vitamin D dosage if needed. In such cases, the change should be reported in the eCRF and hypocalcaemia or hypercalcemia reported as an AE if clinically significant.

Intolerance to the non-IP can occur, especially for calcium. Calcium intolerance can manifest as bloating or constipation. The formulation and/or dose frequency (e.g., dose divided two times a day) can be changed to reduce intolerance and increase compliance by the Investigator's discretion.

If intolerance continues after lowering the dose, temporarily discontinuation can be considered. Permanent discontinuation of calcium and/or vitamin D should be discussed with the Sponsor. Investigator should document in source data.

On the day of baseline PD measurement (Month 0), calcium intake is not allowed before the PD blood sampling.

Vitamin D and calcium supplements will be made available at the investigational sites. The Sponsor will not provide these supplementations, but they will be reimbursed if required.

5.4. Permitted and Prohibited Concomitant Medication or Treatment

5.4.1. Permitted Concomitant Medications or Treatment

Any other procedures or medications except for prohibited concomitant medications or treatments that are considered necessary for the subject's welfare, and that are not expected to interfere with the evaluation of the IP may be given at the Investigator's discretion.

5.4.2. Prohibited Concomitant Medications, Procedures or Treatments

The following medications will be prohibited during the study period.

- Xgeva®
- Drugs used for osteoporosis: Including but not limited to romosozumab, bisphosphonates, SERM, hormone replacement therapy, tibolone, PTH and its analogues, calcitonin, fluoride, and strontium
  - During the study period, non-systemic vaginal oestrogen treatment is permitted at the Investigator's discretion if clinically needed for the treatment.
- Drugs that affect bone metabolism: Including but not limited to androgens, aromatase inhibitors, calcitriol, adrenocorticotropic hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone, corticosteroids, calcimimetics (cinacalcet and etelcalcetide), aluminium, lithium, heparin (including unfractionated heparin and low molecular weight heparins), warfarin, phenytoin, primidone, carbamazepine, phenobarbital, valproate, oxcarbazepine, topiramate, barbiturate, protease inhibitors, methotrexate, chemotherapeutic agents, cyclosporine, tacrolimus, and prescribed vitamin K
  - During the study period, inhaled or topical glucocorticoid is permitted at the Investigator's discretion if clinically needed for the treatment.
- Any kind of monoclonal antibodies or fusion receptor protein

Planned invasive dental procedures (e.g., dental implants or oral surgery) and major surgeries or bone surgeries (unless required for AE/SAE management) are prohibited during the study period.

6. Study Assessment

6.1. Efficacy Assessment

6.1.1. Bone Mineral Density

BMD of lumbar spine (L1 to L4), total hip, and femoral neck will be measured at Screening, prior to dosing at Months 6, 12, and EOS/ET. BMD will be measured only by either GE Lunar or Hologic machines.

Site staffs who will perform BMD measurement in this study must read and understand the image acquisition guideline before performing study procedure. Only DXA devices certified by the central reading centre are allowed to be used in this study. If one or more DXA devices are certified in an investigational site, a subject is strongly recommended to be scanned on the same DXA machine at all follow up timepoints and not switch between scanners. If a scanner switch (e.g., due to breakdown) or repair (hardware or software) should occur due to unforeseen reasons the imaging vendor needs to be immediately notified prior to the change or as soon as possible. The replacement machine should be from the same manufacturer consistently from Screening to EOS/ET. Scanning of subjects on DXA

machines from different manufacturers at follow up timepoints is not allowed.

All original DXA images will be kept in the investigational sites and copies will be sent to the central reading centre for analysis and archiving.

A detailed instruction for BMD measurement will be provided in the image acquisition guideline.

According to the World Health Organisation (WHO) criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of –2.5 or less). (Table 2) The reference standard from which the T-score is calculated will be based on Caucasian values for all races except African Americans.

Table 2. World Health Organisation Categories of Bone Density

Normal	T-score –1.0 and above
Osteopenia	T-score between –1.0 and –2.5
Osteoporosis	T-score at or below –2.5
Severe Osteoporosis	T-score at or below –2.5 with one or more fractures

6.2. Safety Assessment

6.2.1. Adverse Events

AEs will be assessed throughout the whole study period in accordance as described in Section 8.

6.2.2. Clinical Laboratory Evaluations

For the assessments of clinical laboratory parameters, blood and urine samples will be collected by the study site at the time points indicated in the Schedule of Activities (Table 1). Detail instructions of collecting, processing, storing, and shipping for blood and urine samples are described in the laboratory manual.

The parameters for clinical laboratory tests are listed in Table 3. Reference ranges will be provided to the Investigator.

Table 3. Parameters for Clinical Laboratory Tests

Haematology	• Haemoglobin • Haematocrit • Platelet count • Red blood cell count • White blood cell count (total and differential)
Biochemistry	• Sodium • Potassium • Chloride • Creatinine • Blood urea nitrogen • eGFR using MDRD equation • Glucose • Calcium • Albumin corrected serum calcium • Phosphorus

	• Total bilirubin • Albumin • Total cholesterol • Alanine aminotransferase • Aspartate aminotransferase • Alkaline phosphatase
Hormone	• FSH (optional) • Thyroid-stimulating hormone (TSH) • PTH • Vitamin D (25-hydroxyvitamin D)
Virology	• HBsAg • HCV-Ab
Urinalysis (Dipstick)	• Protein • Blood • Leucocytes • Nitrite • Glucose • Ketone • pH • Specific gravity • Bilirubin • Urobilinogen

The Investigator will check any laboratory values which have potential significance in subject's safety during the study period. The Investigator will also evaluate any change in laboratory values. Each out of range result should be assessed as not clinically significant or clinically significant by Investigator. Any clinically significant abnormality must be recorded on the eCRF as either medical history or AE as appropriate (see Section 8).

Clinical laboratory tests can be performed at the unscheduled visit due to subject missing the visit, repeatedly due to technical issues (e.g., sampling error, handling error, tube breakage), or additionally for subject's safety purpose during the study period at the Investigator's discretion.

6.2.3. Physical Examination

Physical examinations must be performed by trained medical personnel at Screening and prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET. The physical examination should include an assessment of the subject's general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory systems, and the subject's abdomen.

The Investigator should assess all physical examinations and any clinically significant abnormality must be recorded on the eCRF as either medical history or AE as appropriate (see Section 8).

Body weight will be measured and recorded at Screening and prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET. Whereas height will be measured and recorded only at Screening.

6.2.4. 12-lead Electrocardiogram

12-lead ECG measurements will be performed at Screening, and can be performed by Investigator's discretion if needed. QT interval and corrected QT interval (QTc) will be collected.

The Investigator should assess all 12-ECG and any clinically significant abnormality must be recorded on the eCRF as either medical history or AE as appropriate (see Section 8).

6.2.5. Vital Signs

Vital signs include blood pressure, heart rate, and body temperature. Vital signs will be assessed at Screening, and prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.

The Investigator should assess all vital signs and any clinically significant abnormalities must be recorded on the eCRF as either medical history or AE as appropriate (see Section 8).

6.3. Pharmacodynamic Assessment

Blood sample for PD assessment will be taken at prior to dosing at Months 0, 6, and 12. Also, blood samples will be taken at Months 0.5, 1, 3, and 9, and EOS/ET.

Blood sample for CTX and P1NP assessment should be collected after fasting for at least 8 hours and during the morning hours.

In all cases, the exact date and time of the PD sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for PD samples are described in the laboratory manual.

The Sponsor or its designated representative will store PD samples after the end of the clinical study for the maximum 10 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis). Subjects' samples may be used for method validation and/or investigation, only for this study.

6.4. Other Assessments

6.4.1. Pharmacokinetic Assessment

Blood sample for PK assessment will be taken in all randomised subjects at prior to dosing at Months 0, 6, and 12. Also, blood samples will be taken at Months 0.5, 1, 3, and 9, and EOS/ET.

In all cases, the exact date and time of the PK sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for PK samples are described in the laboratory manual.

The Sponsor or its designated representative will store PK samples after the end of the clinical study for the maximum 10 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis). Subjects' samples may be used for method validation and/or investigation, only for this study.

6.4.2. Immunogenicity Assessment

Blood sample for immunogenicity assessment will be taken in all randomised subjects at prior to dosing at Months 0, 6, and 12. Also, blood samples will be taken at Months 0.5, 1, 3, and 9, and EOS/ET.

In all cases, the exact date and time of the immunogenicity sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for immunogenicity samples are described in the laboratory manual.

The Sponsor or its designated representative will store immunogenicity samples after the end of the clinical study for the maximum 10 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis). Subjects'

samples may be used for method validation and/or investigation, only for this study.

6.4.3. Spine X-ray

Lateral thoracic and lumbar spine X-rays assessment will be done at Screening to determine any potential exclusions due to vertebral fractures as determined by Genant scoring. A detailed instruction for spine X-ray assessment will be provided in the image acquisition guideline.

7. Study Procedures

7.1. Study Flow and Visit Schedule

During this study, all procedures and assessments will be performed at time points specified in the Schedule of Activities (Table 1). Detail instructions of collecting, processing, storing, and shipping for blood and urine samples are described in the laboratory manual. All results should be recorded in the source documents along with the date and time the procedures were performed.

7.1.1. Screening (Day –28 to Day –1)

Screening shall be performed within 28 days before Randomisation (i.e. excluding the day of Randomisation).

All subjects must provide written informed consent prior to any study related procedures being performed.

- Written informed consent

The following procedures should be performed:

- Demographic information
- Medical and surgical history
- 12-lead ECG
  - 12-lead ECG should be measured prior to both the vital sign assessment and the blood sampling
- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Height and weight
- Serum FSH (optional), PTH, TSH, and virology markers (Hepatitis B and C virology [HBsAg and HCV Ab])
- Haematology, biochemistry tests, and urinalysis (dipstick)
- Lateral spine X-ray (lumbar and thoracic)
- BMD (lumbar, total hip, and femoral neck)
- Serum vitamin D (25-hydroxyvitamin D)
- Previous and concomitant medications

- AEs
- Eligibility assessment

If the subject is not randomised within 28 days after signing the ICF, the subject must be screen failed.

Clinical laboratory test for eligibility review will not be allowed for re-test unless any technical error (e.g., missing value due to sample mishandling) was found.

Exceptionally, in subjects who are not eligible **only due to vitamin D deficiency**, serum vitamin D can be re-tested only once after vitamin D repletion and re-test result will be used for eligibility review. Additional 28 days will be allowed to those subjects. In this case if the subject is not randomised within 56 days after signing the ICF, the subject must be screen failed. To avoid repetition of unnecessary procedures, screening procedures previously performed other than vitamin D re-test will not be repeated in this case.

During the screening period, subject may receive the calcium and vitamin D at the discretion of the Investigator.

Re-scanning of DXA or lateral spine X-ray during the study period is not allowed except for cases where it has been confirmed that the image is not evaluable by the central imaging centre due to quality issue.

Once the subject is confirmed eligible for the study, the subject will be reminded in particular of the study restrictions such as prohibited medications and other study requirements. The Investigator shall pay attention to each subject's particular needs in order to provide the necessary training and advice and foster protocol compliance.

7.1.2. Treatment Period

7.1.2.1. Visit 1 (Month 0)

The following procedures should be performed:

✓ Eligibility assessment

✓ Randomisation

- Randomisation must proceed after all screening procedures and eligibility confirmation.

✓ Prior to dosing

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.

- On the day of baseline PD measurement (Month 0), calcium should not be given before the PD blood sampling.

✓ IP administration

- SB16 and Prolia® will be subcutaneously administered

✓ Post dosing

- Monitoring for injection site reaction

✓ Any time regardless of IP dosing

- Concomitant medications
- AEs
- Instruction for non-IP supplementation

7.1.2.2. Visit 2 (Month 0.5 ± 3 Days)

Month 0.5 is 15 days after Month 0.

The following procedures should be performed:

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Concomitant medications
- AEs
- Instruction for non-IP supplementation

7.1.2.3. Visit 3 (Month 1 ± 3 Days)

Month 1 is 30 days after Month 0.

The following procedures should be performed:

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination

- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Concomitant medications
- AEs
- Instruction for non-IP supplementation

7.1.2.4. Visit 4 (Month 3 ± 7 Days)

Month 3 is 91 days after Month 0.

The following procedures should be performed:

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Concomitant medications
- AEs
- Instruction for non-IP supplementation

7.1.2.5. Visit 5 (Month 6 ± 7 Days)

Month 6 is 182 days after Month 0.

The following procedures should be performed:

✓ Prior to dosing

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.

- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- BMD (lumbar, total hip, and femoral neck)
- Serum vitamin D (25-hydroxyvitamin D)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.

✓ IP administration

- SB16 and Prolia® will be subcutaneously administered

✓ Post dosing

- Monitoring for injection site reaction

✓ Any time regardless of IP dosing

- Concomitant medications
- AEs
- Instruction for non-IP supplementation

7.1.2.6. Visit 6 (Month 9 ± 7 Days)

Month 9 is 273 days after Month 0.

The following procedures should be performed:

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Concomitant medications

- AEs
- Instruction for non-IP supplementation

7.1.2.7. Visit 7 (Month 12 ± 7 Days)

Month 12 is 364 days after Month 0.

The following procedures should be performed:

✓ Prior to dosing

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- BMD (lumbar, total hip, and femoral neck)
- Serum vitamin D (25-hydroxyvitamin D)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Eligibility assessment

✓ Randomisation

- Subjects receiving Prolia® will be re-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.

✓ IP administration

- SB16 and Prolia® will be subcutaneously administered

✓ Post dosing

- Monitoring for injection site reaction

✓ Any time regardless of IP dosing

- Concomitant medications
- AEs
- Instruction for non-IP supplementation

7.1.3. End of Study Visit (Month 18 ± 7 Days)

EOS (Month 18) is 546 days after Month 0.

Following discontinuation of IP administration, increased fracture risk can be expected, including the risk of multiple vertebral fractures. This risk should be informed to the subject and next treatment will be decided at EOS at the Investigator discretion to prevent loss of bone mass and/or risk of fractures.

The following procedures should be performed:

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- BMD (lumbar, total hip, and femoral neck)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment
- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Concomitant medications
- AEs

7.1.4. Early Termination Visit (6 Months from the Last Investigational Product Dosing ± 7 Days)

Subjects who withdraw from the study before EOS will be asked to return to the investigational site for the ET procedures to be performed at 6 months from the last IP dose. Following discontinuation of IP administration, increased fracture risk can be expected, including the risk of multiple vertebral fractures. This risk should be informed to the subject and next treatment will be decided at ET at the Investigator discretion to prevent loss of bone mass and/or risk of fractures.

The following procedures should be performed:

- Vital signs
  - Vital sign should be measured prior to the blood sampling being performed.
- Physical examination
- Weight
- Haematology, biochemistry tests, and urinalysis (dipstick)
- BMD (lumbar, total hip, and femoral neck)
- Blood sampling for PK assessment
- Blood sampling for immunogenicity assessment

- Blood sampling for PD assessment
  - Blood sample for CTX and P1NP should be collected in the morning hours after fasting for at least 8 hours.
- Concomitant medications
- AEs

7.1.5. Unscheduled Visit

Unscheduled visit is allowed during study period at the discretion of the Investigator, if deemed clinically necessary for the subject's safety. Any tests, procedures, or assessments performed at the unscheduled visits must be recorded in the source documents and be entered in the eCRF if entry is available. If a subject is discontinued from the study during unscheduled visit and subject refused ET visit, it should be recorded in the eCRF.

7.2. Discontinuation

7.2.1. Discontinuation of Subjects

Subject must be discontinued from the study permanently in the event of any of the following:

- Consent withdrawal by subject
  - If a subject withdraws her consent, the Investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (e.g., AE); however, the subject could refuse to provide such reason
  - If the main reason for consent withdrawal is considered related to the study, the Investigator may select appropriate reason among the reasons listed below other than consent withdrawal
- Death
- Unacceptable toxicity that makes subject study participation impossible, agreed by the Investigator (e.g., osteonecrosis of jaw or serious hypersensitivity reactions to denosumab)
- Protocol deviations that may affect the subject's safety seriously and/or integrity of data (including ineligibility) agreed by the Investigator (e.g., IP dosing out of visit window or using prohibited medication during the study period)
- Lack of efficacy or disease progression (e.g., decrease of BMD or osteoporotic fracture) that requires change of osteoporosis drug, agreed by the Investigator
- Lost to follow-up
- Unblinding of treatment arm to subject or investigator
- The Investigator's discretion for any other reason

If a subject is prematurely discontinued from IP after the first IP dose, the subject will complete the ET procedures.

If the subject refused ET visit, it should be recorded in the eCRF. In all cases, the reason for IP discontinuation must be recorded in the eCRF and in the subject's medical record.

7.2.2. Discontinuation of Study Sites

Study site participation may be discontinued if Sponsor, the Investigator, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the study site judges it necessary for any reason. Health authorities and IRB/IEC will be informed about the discontinuation of the study in accordance with applicable regulations.

7.2.3. Discontinuation of the Study

The Sponsor may terminate this study prematurely, for reasonable cause provided that written notice is submitted in advance of the intended termination:

- Poor enrolment of subjects making completion of the study within acceptable time frame
- Discontinuation of development of the study drug
- The decision by the Sponsor to terminate the study based on medical/ethical, business decision, or study conduct-related reasons

If the study is terminated or discontinued prematurely, the Sponsor will promptly notify to the Investigator. Investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the subject's interests.

Health authorities and IRB/IEC will be informed about the discontinuation of the study in accordance with applicable regulations.

8. Safety Monitoring and Reporting

8.1. Adverse Events

8.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered the medicinal (investigational) product or other protocol-imposed intervention and which does not necessarily have to have a causal relationship with this treatment or intervention. An AE can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any dose of a medicinal (investigational) product or other protocol-imposed intervention regardless of attribution.

All AEs during the period of observation (as specified in Section 8.1.2) including the events that occurred prior to administration of an IP should be reported as an AE in the AE section of the eCRF.

Pre-existing conditions which worsen (i.e., increase in severity) that meet the definition of an AE during the study are to be reported as AEs.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

The AEs that emerge during treatment with an IP (i.e. treatment-emergent AE [TEAE]) will be analysed for the purposes of safety analyses.

8.1.1.1. Clinically Significant Abnormality

If there are any abnormalities discovered during the laboratory test, physical examination, vital signs, and/or other safety assessments and the abnormality is assessed clinically significant by the Investigator, it should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening or if the abnormality is consistent with a current diagnosis (underlying disease or other AEs). If it is not specified or defined elsewhere in the protocol, clinically significant abnormality may include the events that led to an intervention, including withdrawal of the IP treatment, dose reduction, significant additional concomitant medication, and others evaluated as clinically significant by the Investigator.

If a clinically significant clinical laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be reported as an AE in the eCRF. If the abnormality can be characterised by a precise clinical term, the clinical term should be reported as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be reported as 'hyperkalaemia'.

Observations of the same clinically significant abnormality from visit to visit should not be repeatedly reported as AEs in the eCRF, unless their severity, seriousness, or aetiology changes.

8.1.2. Period of Observation for Adverse Events

AEs will be collected from the time of signing the written informed consent until the EOS/ET. SAEs will be collected until 6 months after the last IP dose or EOS/ET, whichever longer.

If the subject would withdraw before receiving the first dose of IP, AEs and SAEs should be collected up until the time the subject withdraws.

Unresolved AEs should be followed until AE resolution or stabilisation, or until the EOS/ET, whichever comes first.

If the subject has an unresolved SAE or AESI at the EOS/ET, these cases will be followed until event resolution or stabilisation (see Section 8.2.2).

8.1.3. Reporting Adverse Events

AEs are to be reported in the eCRF and reviewed by the Investigator. When reporting an AE, a diagnosis (when possible and appropriate) rather than each individual sign and symptom should be reported.

Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 8.2.1 for SAE definition). If an AE is classified as an SAE, it must be reported to Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2. For an SAE, a diagnosis with a description of signs and symptoms as well as other supporting information that led to the diagnosis should be described in the SAE form provided to the Sponsor, or its designated representative (see Section 8.2.2.).

8.1.4. Severity Assessment

The Investigator is responsible for assessing and reporting the severity of AEs.

Following classifications should be used to classify AEs:

- Mild events are usually transient and do not interfere with the subject's daily activities,
- Moderate events introduce a low level of inconvenience or concern to the subject and may

interfere with daily activities,

- Severe events interrupt the subject's usual daily activities.

8.1.5. Causality Assessment

The Investigator is responsible for assigning a causal relationship to each AE. The causal relationship between the IP and/or non-IP and the AE should be defined as not related (no) or related (yes).

Events should be classified as 'related' if there is a reasonable possibility that the IP and/or non-IP caused the AE. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Events should be classified as 'not related' if there is no reasonable possibility that the IP and/or non-IP caused the AE.

8.1.6. Expectedness Assessment

Expectedness of AEs will be assessed by referring to the safety information in the Investigator's brochure of the relevant safety section, if deemed necessary. More detailed information on expectedness assessment will be explained in the Investigator's brochure.

8.1.7. Withdrawal due to Adverse Events

Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons and recorded on the appropriate eCRF section. Subjects withdrawn due to an AE should be followed up until the time point specified in the Section 8.1.2. When a subject withdraws from the study due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.

Subjects who discontinue the administration of IPs because of serious or significant safety issues should be followed closely until the events are fully and permanently resolved or stabilised.

8.2. Serious Adverse Events

8.2.1. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence at any dose that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly/birth defects,
- Is medically important.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias

or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

8.2.1.1. Life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2.1.2. Hospitalisation

AEs reported from clinical studies associated with inpatient hospitalisation or prolongations of hospitalisation are considered serious. Staying at an observation unit in the emergency room for more than 24 hours qualifies for hospitalisation. Any events leading to subsequent emergency room visit for less than 24 hours should be in the discretion of Investigator to assess serious as medically important.

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition (prior to ICF signed) not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality),
- Social admission for convenience (e.g., admission of a subject who does not have a carer),
- Administrative admission (e.g., for a yearly physical exam),
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol),
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery).

Pre-planned treatments or surgical procedures should be noted in the screening documentation for the individual subject.

8.2.2. Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. A paper SAE form can be used as backup in every case when the eCRF would not be available.

In particular, if the SAE is fatal or life-threatening, Sponsor must be notified immediately, irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. Sponsor will then follow expedited reporting procedures according to local and international regulations as appropriate.

The Investigator is obligated to pursue and provide information to Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information

may be more detailed than that captured on eCRF. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

All unresolved SAEs will be followed until event resolution or stabilisation (for chronic events), if possible, even when a subject is withdrawn from treatment. For chronic events that do not fully resolve until years later, the outcome should be reported as 'resolved with sequelae' as soon as the event has stabilised or returned to baseline. Follow-up information for the SAE should be actively sought and submitted as the information becomes available.

8.3. Adverse Events of Special Interest

The following AEs will be classified as AESIs in this study:

- Hypocalcaemia
- Hypersensitivity to IP
- Osteonecrosis of the jaw
- Atypical femoral fractures
- Skin infections

8.3.1. Hypocalcaemia

It is important to identify subjects at risk for hypocalcaemia. Clinical monitoring of calcium levels will be done at each pre-defined visit. If any subject presents with suspected symptoms of hypocalcaemia during the study, calcium levels should be measured. Subjects should be encouraged to report symptoms indicative of hypocalcaemia.

8.3.2. Hypersensitivity

Hypersensitivity reactions to denosumab including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported. If a hypersensitivity reaction to denosumab occurs, appropriate treatment should be given. If serious hypersensitivity reactions such as anaphylaxis occur, the IP should be permanently discontinued.

8.3.3. Osteonecrosis of the Jaw

Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection with delayed healing and has been reported with denosumab use. All subjects will be enrolled after assessing subjects' oral health by the Investigator and should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, prolonged pain involving jaw or gingival swelling or non-healing ulcers or discharge during treatment with denosumab. Discontinuation of IP should be considered.

8.3.4. Atypical Femoral Fractures

Atypical femoral fractures have been reported in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also

been reported in patients with certain co-morbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, and hypophosphatasia) and with use of certain pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, and proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture.

Discontinuation of the IP in subjects suspected to have an atypical femur fracture should be considered depending evaluation of the subject based on an individual benefit-risk assessment. During denosumab treatment, subjects should be advised to report new or unusual thigh, hip, or groin pain. Subjects presenting with such symptoms should be evaluated for an incomplete femoral fracture.

8.3.5. Skin infections

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. Skin infections leading to hospitalisation will be separately reported as well. Subjects should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

8.4. Unblinding of Assigned Treatment

Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's safety by their Investigator or a regulatory body. Emergency unblinding should be decided based on the medical decision by Investigator considering subjects' safety. In general, unblinding of subjects during the conduct of the clinical study should only be performed where there are compelling medical or safety reasons to do so. The responsibility to break the treatment code in emergency situations resides solely with the Investigator. The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual.

The Sponsor must be notified immediately after a subject and/or the investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information. In case failure of unblinding through IWRS system, the Investigator will follow the manual unblinding process described in IWRS manual.

8.5. Independent Data and Safety Monitoring Board

An independent DSMB will be assigned for this study. The DSMB will consist of external experts and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the DSMB Charter and in the DSMB statistical analysis plan (SAP).

In addition, an ongoing blinded review of AEs, including clinical laboratory data will be continuously undertaken by the Sponsor medical monitor and project safety monitor.

9. Statistical Methods and Data Analysis

Further information on the statistical methods for this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the final clinical study report (CSR).

Statistical analysis and reporting will be performed as follows:

- Interim safety analysis for independent DSMB meeting
  - A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP.
  - The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an independent unblind statistician.
- Final CSR
  - The final analysis will take place after the last subject completes the procedures at Month 18 or the corresponding visit. All study data will be analysed and reported for the final CSR.

9.1. Statistical Hypotheses

This is a study to demonstrate equivalence, in terms of percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia®. 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.

9.2. Analysis Sets

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

- Randomised Set (RAN) consists of all subjects who have received a randomisation number.
- Full Analysis Set (FAS) consists of all RAN subjects. Following the intent-to-treat principle, subjects will be analysed according to the treatment group they are 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.
- Safety Set (SAF1) consists of all subjects who receive at least one IP. Subjects will be analysed according to the treatment received.
- Safety Set for the Transition period (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.
- PK Analysis Set (PKS) consists of all subjects in the SAF1 who have at least one PK sample analysed.
- PD Analysis Set (PDS) consists of all subjects in the SAF1 who have at least one CTX or P1NP sample analysed.

9.3. Subject Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarised by treatment group for the RAN. Continuous variables (e.g., age, weight, height) will be summarised with descriptive statistics (n, mean, standard deviation, median, minimum, maximum) and categorical variables (e.g., gender, race, and ethnicity) will be summarised with frequency and percentage.

Comparison between treatment groups in demographics and baseline characteristics will be performed using the chi-square test or *F*-test as appropriate. 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.

Relevant medical history, and continuing medical conditions will be summarised by treatment group for the RAN.

9.4. Analysis of the Primary Objective

The primary efficacy analysis will aim to demonstrate equivalence in terms of percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia®.

For the EMA, Korea Ministry of Food and Drug Safety (MFDS), and other regulatory submissions, the primary efficacy analysis will be performed for the PPS using an analysis of covariance with the baseline value of lumbar spine BMD as a covariate and treatment group as 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%]. To conduct the sensitivity analysis 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 missing at random. Available case analysis will also be performed for the FAS.

For the US FDA submission, the primary efficacy analysis will be performed for the FAS using an analysis of covariance with the baseline value of lumbar spine BMD as a covariate and treatment group as 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 pre-defined 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. For sensitivity analysis, available case analysis will be performed for the FAS and the same analysis will be repeated for the PPS.

No formal adjustment of Type I error rates will be performed.

9.5. Analysis of the Secondary Objectives

9.5.1. Efficacy Analyses

As the secondary efficacy endpoint, percent change from baseline in BMD (lumbar spine, total hip, and femoral neck) will be analysed similarly to the primary endpoint.

9.5.2. Safety Analyses

Safety analyses will be performed for Main period, Transition period, and overall study period unless specified otherwise. Analyses for Main and Transition period will be performed in the SAF1 and SAF2 respectively and analyses for the overall study period will be performed in the SAF1.

All reported terms for AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). For all AE and SAE tables, subjects will be counted once for each preferred term and each system organ class.

A TEAE will be defined as any AE with an onset date on or after the date of the initiation of study drug. AEs which are already present before the initiation of study drug and increase in severity after the initiation of study drug will be considered as TEAEs. Pre-existing AEs before the initiation of study during with no increase in severity after the initiation of study drug will not be considered as TEAEs.

All TEAEs and SAEs will be summarised by the frequency and percentage of subjects experiencing events by system organ class, preferred term, and treatment group. SAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the initiation of study drug will be listed by subject.

Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment group and visit. Other safety variables will be summarised unless otherwise specified, and all safety variables will be listed.

Duration of exposure to IP and number of subcutaneous injections will be summarised descriptively by treatment group for the SAF1. Prior and concomitant medications will be summarised by treatment group with frequency and percentage.

9.5.3. Pharmacokinetic and Pharmacodynamic Analyses

PK analyses will be performed for the PKS. Serum drug concentration will be summarised descriptively by treatment group and visit.

PD analyses will be performed for the PDS. Serum CTX and P1NP concentrations will be summarised descriptively by treatment group and visit.

In addition, the $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX will be analysed using an analysis of variance model.

9.5.4. Immunogenicity Analyses

Immunogenicity analyses will be performed for the SAF1 and SAF2. ADA and NAb results will be summarised with frequency and percentage by treatment group and visit. In addition, incidence of overall ADA will be summarised by treatment group.

9.6. Sample Size Calculations

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% CI of [4.83%, 5.87%]. For the 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 US 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 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 standard deviation 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.

10. Data Collection and Management

10.1. Data Confidentiality

Study information will be labelled with a code number, and will not include the subject's name, hospital number or other information that could identify them. A list linking the code and the subject's name will be kept in the site files as required by ICH E6 (R2) Good Clinical Practice (GCP).

The coded information will be sent to the Sponsor (or designee) who will analyse it and report the study results both to regulatory and ethical authorities. The Sponsor may also place data on public websites or publish journal articles based upon these results. Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research. Such data sharing practices will be covered by confidentiality agreements. No-one outside the investigator site will have access to subject-identifiable information.

10.2. Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. The monitors will work in accordance with the CRO standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organisation. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will verify adherence to the protocol at the Investigator site. All protocol deviations will be reported to the Sponsor. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted at regular intervals according to ICH E6 (R2) GCP. The monitor will provide written reports to the Sponsor on each occasion they contact the Investigator regardless of whether it is by phone or in person.

Further details on the monitoring processes and the level of source data verification to be performed will be outlined in the monitoring plan.

10.3. Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP, or whichever longer according to the relevant local

laws and/or regulation. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for the same period of time. These documents may be transferred to another responsible party, deemed acceptable by the Sponsor, and who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records and obtain written permission to do so.

10.4. Future Use of Stored Specimens and Data

The Sponsor or designated representative can store PK, PD, and/or immunogenicity samples for the maximum 10 years after the end of the clinical study. The Sponsor or designated representative should operate under the same regulations related to and take the same responsibility to save personal data. The sample may be used for additional assay to be performed if considered scientific relevant or requested by regulatory authorities in order to have the possibility to perform the assay.

10.5. Database Management and Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy.

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the medical records.

Data must be entered into eCRFs in English by the designated investigator site personnel in a timely manner. Forms should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the eCRF must be carried out by the Investigator or a designated member of staff. These changes may be made either on the initiative of the site staff or in response to monitoring or data queries. Any changes to written data must be made using ICH E6 (R2) GCP corrections and any change to electronic data should be made in a system which can provide an audit trail. Monitors and clinical data managers will review the eCRF for accuracy and can generate queries to the investigational staff for resolution. Corrections will be recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. The Investigator must sign and date the eCRF pages as indicated.

Medical/surgical history and underlying diseases and AEs will be coded using the MedDRA®. Concomitant medications will be coded using the WHO-Drug Dictionary. The versions of coding dictionaries used will be stated in the CSR.

10.6. Quality Control and Quality Assurance

During the conduct of the study, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH E6 (R2) GCP are being followed. The monitors may review source documents to confirm that the data recorded are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities and the authorised representative of the Sponsor including monitors and auditors' direct or remote access to source documents to perform this verification without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. The investigational site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that

the Investigators and their relevant personnel are available during the monitoring visits and possible audits and/or regulatory inspections and that sufficient time is devoted to the process.

10.7. Protocol Deviation

Protocol deviations will be pre-defined prior to subject enrolment and documented separately named as 'Protocol Deviation Definition List' which includes category (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, and non-compliance with treatment), deviation description, severity (major or minor), time point for each protocol deviation. Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

Protocol deviations 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.

11. Ethics Considerations and Administrative procedures

11.1. Institutional Review Boards and Independent Ethics Committees

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the IRB/IEC.

The Investigator must provide the Sponsor with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the Investigator site. The Investigator will supply documentation to the Sponsor relating to the annual renewal of the protocol from the IRB/IEC and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC on a regular basis and in accordance with the timelines required locally. Upon completion of the study, the Investigator will provide the ethics committee with a report on the outcome of the study if required by local regulations.

11.2. Ethical Conduct of the Study

This study will be conducted and informed consent will be obtained from each subject according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for ICH E6 (R2) GCP and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

11.3. Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject enters into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP. The Investigator will provide each subject with a copy of the signed and dated ICF and this will be documented in the subject's source notes.

11.4. Investigator Information

11.4.1. Investigator Obligations

This study will be conducted in accordance with the ICH E6 (R2) GCP (2016), the ethical principles that have their origin in the Declaration of Helsinki (2013) and local laws and regulations.

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. The Investigator must obtain the informed consent of each subject to whom IP is administered.

11.4.2. Training of Investigator Site Personnel

Before the first subject is enrolled into the study, a Sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and will also train them in any study-specific procedures.

The Investigator will ensure that appropriate training relevant to the study is given to all investigational site staff and that any new information relevant to the performance of this study is forwarded to the investigational staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other investigational staff).

11.4.3. Protocol Signatures

The Investigator must sign the Investigator Signature Page of this protocol prior to starting recruitment for the study. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH E6 (R2) GCP and applicable regulatory requirements

11.4.4. Coordinating Investigator

The Sponsor will designate the Coordinating Investigator who will have the responsibility for the coordination of the Investigators in a multicentre clinical study.

11.4.5. Financing and Insurance

Samsung Bioepis Co., Ltd. is the Sponsor of this study and will support the financial aspects for the study conduct at the investigational site. Details of financial agreements are provided in the Clinical Study Agreements with the Investigator sites and in contracts with other companies involved in study operations.

The Sponsor has obtained suitable insurance for this study. A copy of the insurance details will be provided to each Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.

12. Publication Policy

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human subjects. The Sponsor will register and maintain the information of clinical studies on a public registry program. The Sponsor is committed to the public disclosure of the results from clinical studies through posting on public clinical study data banks. The Sponsor will comply with the guidelines of regulatory authorities with regards to public registration and disclosure of clinical study

data.

The clinical study data collected during the study are confidential and proprietary to the Sponsor. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed abstract or presentation.

Any publications from this study should be approved by the Sponsor prior to publication or presentation. The rights of the Investigator with regard to publication of this study are described in the Clinical Study Agreement.

13. References

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Protocol Signature Pages

SIGNATURE PAGE

Declaration of Sponsor Representative

Protocol Title: 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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Representative

Name: [redacted]

Institution: Samsung Bioepis Co., Ltd.

Signature: [redacted] Date: May 03, 2021
(MMM DD, YYYY)

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: 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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Principal Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____
(MMM DD, YYYY)

CHANGE HISTORY OF PROTOCOL AMENDMENT

Version 2.0, May 03, 2021

Section Affected	Original Content	Amended/New Content	Rationale
Title of Study	**Sponsor** Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea	**Sponsor** Samsung Bioepis Co., Ltd. ~~**107, Cheomdan-daero,** 76~~, **Songdogyoyuk-ro,** Yeonsu-gu, Incheon, 21987 Republic of Korea	Change in Sponsor company address
SYNOPSIS Objectives	Secondary objectives The secondary objectives are: • To evaluate the efficacy of SB16 compared to Prolia® by - Percentage change from baseline in total hip BMD - Percentage change from baseline in femoral neck BMD	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 add secondary objective considering percentage change from baseline in lumbar spine BMD at Month 6
SYNOPSIS Main Eligibility Criteria	Exclusion criteria (…) 9. Use of any of the below medications that can affect BMD: (…) d. Systemic hormone replacement therapy (oral or transdermal oestrogen), selective oestrogen receptor	Exclusion criteria (…) 9. Use of any of the below medications that can affect BMD: (…) d. Systemic hormone replacement therapy (oral or transdermal oestrogen), selective oestrogen receptor	To modify considering vaginal tablet

Section Affected	Original Content	Amended/New Content	Rationale
	modulators (SERMs), tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening • Exceptionally, vaginal oestrogen creams can be permitted.	modulators (SERMs), tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening • Exceptionally, ~~**vaginal oestrogen creams can be**~~ **non-systemic vaginal treatment is** permitted.	
	Exclusion criteria (…) 14. Any active healing fracture (besides atypical femoral fracture), determined by the Investigator within 12 months prior to Screening	Exclusion criteria (…) 14. ~~**Any active healing fracture (besides atypical femoral fracture), determined by the Investigator within 12 months prior to Screening**~~ **Fracture (except atypical femoral fracture and hip fracture) which has been in active healing within 12 months prior to Screening at the discretion of the Investigator**	To add hip fracture considering exclusion criterion 2, and modify the description for clarity
SYNOPSIS Main Criteria for Evaluation	Secondary endpoints for the Main period (…) PD endpoints • Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12 • Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12	Secondary endpoints for the Main period (…) PD endpoints • Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12 • **Area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX** • Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12	To add $AUEC_{0\text{-}M6}$ of serum CTX as a secondary endpoint

Section Affected	Original Content	Amended/New Content	Rationale
	Secondary endpoints for the Main period (…) Immunogenicity endpoint • Incidence of anti-drug antibodies (ADAs) and neutralising antibodies (NAbs) at Months 0, 0.5, 1, 3, 6, 9, and 12	Secondary endpoints for the Main period (…) Immunogenicity endpoint • Incidence of anti-drug antibodies (ADAs) ~~**and neutralising antibodies (NAbs)**~~ at Months 0, 0.5, 1, 3, 6, 9, and 12 • **Incidence of neutralising antibodies (NAbs) at Months 0, 0.5, 1, 3, 6, 9, and 12**	To separate immunogenicity endpoint of ADA and NAb
	Secondary endpoints for the Transition period (…) Immunogenicity endpoint • Incidence of ADAs and NAbs at Month 18	Secondary endpoints for the Transition period (…) Immunogenicity endpoint • Incidence of ADAs ~~**and NAbs**~~ at Month 18 • **Incidence of NAbs at Month 18**	To separate immunogenicity endpoint of ADA and NAb

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Statistical Methods	Analysis sets for efficacy analyses (…) 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 that will lead to exclusion from this set will be pre-defined prior to unblinding the treatment group assignment for analyses.	Analysis sets for efficacy analyses (…) 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.	To add the additional information for major protocol deviations
	Efficacy analyses For the European Medicines Agency (EMA) submission,	Efficacy analyses For the European Medicines Agency (EMA**), Korea Ministry of Food and Drug Safety (MFDS), and other regulatory** submissions,	To add the analysis method of primary objective for Korea MFDS and other regulatory agencies except EMA and FDA
	Efficacy analyses (…) the primary efficacy analysis will be performed for the PPS using a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate.	Efficacy analyses (…) the primary efficacy analysis will be performed for the PPS using ~~**a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate**~~ **an analysis of covariance**	Difference caused by DXA model will be removed since lumbar spine BMD value will be corrected by

Section Affected	Original Content	Amended/New Content	Rationale
		with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor.	cross-calibration. Additionally, the number of patients within some centres is expected to be small, so 'sites (or pooled centres)' is excluded and analysis method is also modified. The effect 'site (or pooled centres)' will be analysed through sensitivity analysis.
	Efficacy analyses (…) To conduct the sensitivity analysis 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.	Efficacy analyses (…) To conduct the sensitivity analysis 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 missing at random**.	To add the additional information for missing data imputation
	Efficacy analyses (…) For the United States of America (US) Food and Drug Administration (FDA) submission, the primary efficacy	Efficacy analyses (…) For the United States of America (US) Food and Drug Administration (FDA) submission, the primary efficacy	Difference caused by DXA model will be removed since

Section Affected	Original Content	Amended/New Content	Rationale
	analysis will be performed for the FAS using a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate.	analysis will be performed for the FAS using ~~**a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate**~~ **an analysis of covariance with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor**.	lumbar spine BMD value will be corrected by cross-calibration. Additionally, the number of patients within some centres is expected to be small, so 'sites (or pooled centres)' is excluded and analysis method is also modified. The effect 'site (or pooled centres)' will be analysed through sensitivity analysis.
	PK and PD analyses (…) PD analyses will be performed for the PD Analysis Set (PDS). Serum CTX and P1NP concentrations will be summarised descriptively by treatment group and visit.	PK and PD analyses (…) PD analyses will be performed for the PD Analysis Set (PDS). Serum CTX and P1NP concentrations will be summarised descriptively by treatment group and visit. **In addition, the $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX will be analysed using an analysis of variance model.**	To add analysis method for $AUEC_{0\text{-}M6}$ of serum CTX

Original Content

Table 1. Schedule of Activities

Assessment	Study Period				
	Screening[1]	Main Period			
Study Visit		1	2	3	4
Timepoint	Day –28 to Day –1	Month[2] 0	Month 0.5[3]	Month 1	Month 3
Visit Window (Day)	0	0	±3	±3	±7

Assessment	Study Period				
	Main Period		Transition Period		ET[28]
Study Visit	5	6	7	EOS	
Timepoint	Month 6	Month 9	Month 12	Month 18	
Visit Window (Day)	±7	±7	±7	±7	±7

Assessment
Study Visit
Timepoint
Visit Window (Day)
(…)
Non-IP administration[25] administration[25]

1. In subjects who are not eligible only due to vitamin D deficiency, serum vitamin D (25-hydroxyvitamin D) can be re-tested only once after vitamin D repletion and re-test result will be used for eligibility review. Additional 28 days will be allowed to those subjects. Vitamin D repletion method will be determined by the Investigator considering subject's serum vitamin D level.

Amended/New Content

Assessment	Study Period				
		Main Period			
Study Visit	**Screening[1]**	1	2	3	4
Timepoint		Month[2] 0	Month 0.5[3]	Month 1	Month 3
Days from Month 0	**–28 to –1**	**0**	**15**	**30**	**91**
Visit Window (Day)	0	0	±3	±3	±7

Assessment	Study Period				
	Main Period		Transition Period		ET[28]
Study Visit	5	6	7	EOS	
Timepoint	Month 6	Month 9	Month 12	Month 18	
Days from Month 0	**182**	**273**	**364**	**546**	
Visit Window (Day)	±7	±7	±7	±7	±7

Assessment
Study Visit
Timepoint
Days from Month 0
Visit Window (Day)
(…)
Non-IP administration[25] ~~**administration[25]**~~

1. In subjects who are not eligible only due to vitamin D deficiency, serum vitamin D (25-hydroxyvitamin D) can be re-tested only once after vitamin D repletion and re-test result will be used for eligibility review. Additional 28 days will be allowed to those subjects. Vitamin D repletion method will be determined by the Investigator considering subject's serum vitamin D level.

Rationale

To add days from Month 0 used in IWRS setting

To add days from Month 0 used in IWRS setting

Editorial change

Modified for clarity

Section Affected	Original Content	Amended/New Content	Rationale
	* Other screening procedures previously performed will not be repeated in this case.	* **To avoid repetition of unnecessary procedures, ~~Other~~** screening procedures previously performed **other than vitamin D re-test** will not be repeated in this case.	
	2. 'Month' means calendar month. Visit date will be calculated based on Month 0. 3. Month 0.5 is on the 15th day from Month 0.	2. **~~'Month' means calendar month.~~** Visit date will be calculated based on Month 0. 3. Month 0.5 is **~~on the 15th day from~~** 15 days after Month 0.	To add days from Month 0 used in IWRS setting
	5. Demographic information includes the year of birth, gender, race, ethnicity, current smoking status, daily alcohol assumption amount, and parent fractured hip history.	5. Demographic information includes the year of birth, gender, race, ethnicity, current smoking status, daily alcohol **consumption ~~assumption~~** amount, and parent fractured hip history.	Modified for clarity
	8. Blood sample for serum FSH, PTH, TSH and virology markers (hepatitis B and C virology [HBsAg and HCV Ab]) will be collected at Screening.	8. Blood sample for serum FSH **(optional)**, PTH, TSH and virology markers (hepatitis B and C virology [HBsAg and HCV Ab]) will be collected at Screening.	To add 'optional' since FSH test will be done if required
	25. Daily calcium (≥ 1 g) and vitamin D (≥ 800 IU) will be given to the subjects from Randomisation to EOS/ET. Instruction for non-IP supplementation will be done at Months 0, 0.5, 1, 3, 6, 9, and 12.	25. Daily **elemental** calcium (≥ 1 g) and vitamin D (≥ 800 IU) will be given to the subjects from Randomisation to EOS/ET. Instruction for non-IP supplementation will be done at Months 0, 0.5, 1, 3, 6, 9, and 12.	Modified for clarity
	26. Previous and concomitant medication within 5 years prior to Screening and concomitant medication thereafter.	26. Previous and concomitant medication within 5 years prior to Screening and concomitant medication thereafter. **Also, previous oral bisphosphonate history in a lifetime will be collected.**	To confirm exclusion criterion 9a
LIST OF ABBREVIATION	N/A	**$AUEC_{0\text{-}M6}$ Area under the effect curve from time zero to Month 6**	To add abbreviation

Section Affected	Original Content	Amended/New Content	Rationale
S		**MFDS** **Ministry of Food and Drug Safety**	
LIST OF STUDY STAFF	**SPONSOR:** **Samsung Bioepis Co., Ltd.** 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea [redacted] Clinical Project Manager [redacted] Clinical Development Lead [redacted] Clinical Research Scientist [redacted] Statistician [redacted] Safety Physician [redacted] Project Safety Lead [redacted]	**SPONSOR:** **Samsung Bioepis Co., Ltd.** ~~**107, Cheomdan-daero,**~~ **76, Songdogyoyuk-ro,** Yeonsu-gu, Incheon, 21987 Republic of Korea [redacted] Clinical Project Manager [redacted] Clinical Development Lead [redacted] Clinical Research Scientist [redacted] Statistician [redacted] Safety Physician [redacted]	Changes in company address and staff

Section Affected	Original Content	Amended/New Content	Rationale
		Project Safety Lead [redacted]	
2.1.2. Secondary Objectives	The secondary objectives are: • To evaluate the efficacy of SB16 compared to Prolia® by - Percentage change from baseline in total hip BMD - Percentage change from baseline in femoral neck BMD	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 add secondary objective considering percentage change from baseline in lumbar spine BMD at Month 6
2.2.2. Secondary Endpoints for the Main Period	<u>PD endpoints</u> • Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12 • Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12	<u>PD endpoints</u> • Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12 • **Area under the effect curve from time zero to Month 6 ($AUEC_{0-M6}$) of percent change from baseline in serum CTX** • Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12	To add $AUEC_{0-M6}$ of serum CTX as a secondary endpoint
2.2.3. Secondary Endpoints for the Transition Period	<u>Immunogenicity endpoint</u> Incidence of ADAs and NAbs at Month 18	<u>Immunogenicity endpoint</u> • Incidence of ADAs ~~**and NAbs**~~ at Month 18 • **Incidence of NAbs at Month 18**	To separate immunogenicity endpoint of ADA and NAb

Section Affected	Original Content	Amended/New Content	Rationale
4.3. Exclusion Criteria	9. Use of any of the below medications that can affect BMD: (…) d. Systemic hormone replacement therapy (oral or transdermal oestrogen), selective oestrogen receptor modulators (SERMs), tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening • Exceptionally, vaginal oestrogen creams can be permitted.	9. Use of any of the below medications that can affect BMD: (…) 1. Systemic hormone replacement therapy (oral or transdermal oestrogen), selective oestrogen receptor modulators (SERMs), tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening • Exceptionally, ~~**vaginal oestrogen creams can be**~~ **non-systemic vaginal treatment is** permitted.	To modify considering vaginal tablet
	14. Any active healing fracture (besides atypical femoral fracture), determined by the Investigator within 12 months prior to Screening	14. ~~**Any active healing fracture (besides atypical femoral fracture), determined by the Investigator within 12 months prior to Screening**~~ **Fracture (except atypical femoral fracture and hip fracture) which has been in active healing within 12 months prior to Screening at the discretion of the Investigator**	To add hip fracture considering exclusion criterion 2, and modify the description for clarity
4.5.2. Re-test	(…) Other screening procedures previously performed will not be repeated in this case. Re-scanning of DXA or lateral spine X-ray is not allowed except for cases where it has been confirmed that the image is not evaluable by the central imaging centre due to quality issue.	(…) **To avoid repetition of unnecessary procedures,** ~~**Other**~~ screening procedures previously performed **other than vitamin D re-test** will not be repeated in this case. Re-scanning of DXA or lateral spine X-ray **during the study period** is not allowed except for cases where it has been confirmed that the image is not evaluable by the central imaging centre due to quality issue.	Modified for clarity

Section Affected	Original Content	Amended/New Content	Rationale
5.1.1. Dosing and Treatment Schedule	(…) All subjects should receive at least of calcium 1 g daily and at least 800 IU vitamin D daily.	(…) All subjects should receive at least of **elemental** calcium 1 g daily and at least 800 IU vitamin D daily.	Modified for clarity
5.3. Non-investigational Product	• Calcium (at least 1 g per day) • Vitamin D (at least 800 IU per day)	• **Elemental c~~C~~**alcium (at least 1 g per day) • Vitamin D (at least 800 IU per day)	Modified for clarity
5.4.2. Prohibited Concomitant Medications, Procedures or Treatments	(…) • Drugs used for osteoporosis: Including but not limited to romosozumab, bisphosphonates, SERM, hormone replacement therapy, tibolone, PTH and its analogues, calcitonin, fluoride, and strontium	(…) • Drugs used for osteoporosis: Including but not limited to romosozumab, bisphosphonates, SERM, hormone replacement therapy, tibolone, PTH and its analogues, calcitonin, fluoride, and strontium - **During the study period, non-systemic vaginal oestrogen treatment is permitted at the Investigator's discretion if clinically needed for the treatment.**	To align with exclusion criterion 9d
	(…) • Drugs that affect bone metabolism: Including but not limited to androgens, aromatase inhibitors, calcitriol, adrenocorticotropic hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone, corticosteroids, calcimimetics (cinacalcet and etelcalcetide), aluminium, lithium, heparin, anticonvulsant (except benzodiazepine), barbiturate, protease inhibitors, methotrexate, chemotherapeutic agents, cyclosporine, tacrolimus, and vitamin K	(…) • Drugs that affect bone metabolism: Including but not limited to androgens, aromatase inhibitors, calcitriol, adrenocorticotropic hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone, corticosteroids, calcimimetics (cinacalcet and etelcalcetide), aluminium, lithium, heparin **(including unfractionated heparin and low molecular weight heparins)**, **~~anticonvulsant (except benzodiazepine),~~ warfarin, phenytoin, primidone, carbamazepine, phenobarbital, valproate, oxcarbazepine, topiramate,** barbiturate, protease inhibitors, methotrexate,	To make the drugs listed more specific

Section Affected	Original Content	Amended/New Content	Rationale
		chemotherapeutic agents, cyclosporine, tacrolimus, and **prescribed** vitamin K	
Table 3. Parameters for Clinical Laboratory Tests	**(…)** / (…) **Bone Turnover Marker (PD Marker)** / • Serum CTX • Serum P1NP	**(…)** / (…) ~~**Bone Turnover Marker (PD Marker)**~~ / ~~• Serum CTX~~ ~~• Serum P1NP~~	To delete PD markers because it overlaps with section 6.3
	(…) / (…) **Hormone** / • FSH • Thyroid-stimulating hormone (TSH) • PTH • Vitamin D (25-hydroxyvitamin D)	**(…)** / (…) **Hormone** / • FSH **(optional)** • Thyroid-stimulating hormone (TSH) • PTH • Vitamin D (25-hydroxyvitamin D)	To add 'optional' since FSH test will be done if required
7.1.1. Screening (Day –28 to Day –1)	(…) • Serum FSH, PTH, TSH, and virology markers (Hepatitis B and C virology [HBsAg and HCV Ab])	(…) • Serum FSH **(optional)**, PTH, TSH, and virology markers (Hepatitis B and C virology [HBsAg and HCV Ab])	To add 'optional' since FSH test will be done if required
	(…) Other screening procedures previously performed will not be repeated in this case. Re-scanning of DXA or lateral spine X-ray is not allowed except for cases where it has been confirmed that the image is not evaluable by the central imaging centre due to quality issue.	(…) **To avoid repetition of unnecessary procedures, ~~Other~~** screening procedures previously performed **other than vitamin D re-test** will not be repeated in this case. Re-scanning of DXA or lateral spine X-ray **during the study period** is not allowed except for cases where it has been confirmed that the image is not evaluable by the central imaging centre due to quality issue.	Modified for clarity

Section Affected	Original Content	Amended/New Content	Rationale
7.1.2.2. Visit 2 (Month 0.5 ± 3 Days)	Month 0.5 is on the 15th day from Month 0.	Month 0.5 is ~~on the 15th day from~~ **15 days after** Month 0.	To add days from Month 0 used in IWRS setting
7.1.2.3. Visit 3 (Month 1 ± 3 Days)	Month 1 is after one calendar month from Month 0.	Month 1 is ~~after one calendar month from~~ **30 days after** Month 0.	To add days from Month 0 used in IWRS setting
7.1.2.4. Visit 4 (Month 3 ± 7 Days)	Month 3 is after 3 calendar months from Month 0.	Month 3 is ~~after 3 calendar months from~~ **91 days after** Month 0.	To add days from Month 0 used in IWRS setting
7.1.2.5. Visit 5 (Month 6 ± 7 Days)	Month 6 is after 6 calendar months from Month 0.	Month 6 is ~~after 6 calendar months from~~ **182 days after** Month 0.	To add days from Month 0 used in IWRS setting
7.1.2.6. Visit 6 (Month 9 ± 7 Days)	Month 9 is after 9 calendar months from Month 0.	Month 9 is ~~after 9 calendar months from~~ **273 days after** Month 0.	To add days from Month 0 used in IWRS setting
7.1.2.7. Visit 7 (Month 12 ± 7 Days)	Month 12 is after 12 calendar months from Month 0.	Month 12 is ~~after 12 calendar months from~~ **364 days after** Month 0.	To add days from Month 0 used in IWRS setting
7.1.3. End of Study Visit (Month 18 ± 7 Days)	EOS (Month 18) is after 18 calendar months from Month 0.	EOS (Month 18) is ~~after 18 calendar months from~~ **546 days after** Month 0.	To add days from Month 0 used in IWRS setting
	(...)	(...)	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
	Following discontinuation of IP administration, increased fracture risk expected, including the risk of multiple vertebral fractures.	Following discontinuation of IP administration, increased fracture risk **can be** expected, including the risk of multiple vertebral fractures.	
7.1.4. Early Termination Visit (6 Months from the Last Investigational Product Dosing ± 7 Days)	(...) Following discontinuation of IP administration, increased fracture risk expected, including the risk of multiple vertebral fractures.	(...) Following discontinuation of IP administration, increased fracture risk **can be** expected, including the risk of multiple vertebral fractures.	Editorial change
8.3. Adverse Events of Special Interest	(...) 8.3.4 Skin infections	(...) ~~**8.3.4**~~ **8.3.5.** Skin infections	Editorial change
9. Statistical Methods and Data Analysis	Further information on the statistical methods for this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the main clinical study report (CSR). Statistical analysis and reporting will be performed as follows: • Interim safety analysis for independent DSMB meeting - A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP. - The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an	Further information on the statistical methods for this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the ~~**main**~~ **final** clinical study report (CSR). Statistical analysis and reporting will be performed as follows: • Interim safety analysis for independent DSMB meeting - A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP. - The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an	To reflect Sponsor's decision not to perform interim database lock and main CSR

Section Affected	Original Content	Amended/New Content	Rationale
	independent unblind statistician. • Main CSR - The main analysis will take place after the last subject completes the procedures at Month 12 or the corresponding visit. Available efficacy and safety data, PK, PD, and immunogenicity data will be analysed and reported. - At the time of this reporting, a limited number of identified individuals of the Sponsor or Contract Research Organisation (CRO) will be unblinded for reporting purpose. However, subjects, the Investigators, and other study personnel will remain blinded throughout the entire study period.	independent unblind statistician. ~~• Main CSR~~ ~~- The main analysis will take place after the last subject completes the procedures at Month 12 or the corresponding visit. Available efficacy and safety data, PK, PD, and immunogenicity data will be analysed and reported.~~ ~~- At the time of this reporting, a limited number of identified individuals of the Sponsor or Contract Research Organisation (CRO) will be unblinded for reporting purpose. However, subjects, the Investigators, and other study personnel will remain blinded throughout the entire study period.~~	
9.2. Analysis Sets	• 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 that will lead to exclusion from this set will be pre-defined prior to unblinding the treatment group assignment for analyses.	• 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.	To add the additional information for major protocol deviations
9.4. Analysis of the Primary	For the EMA submission,	For the EMA**, Korea Ministry of Food and Drug Safety (MFDS), and other regulatory** submissions,	To add the analysis method of primary

Section Affected	Original Content	Amended/New Content	Rationale
Objective			objective for Korea MFDS and other regulatory agencies except EMA and FDA
	(…) the primary efficacy analysis will be performed for the PPS using a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate.	(…) the primary efficacy analysis will be performed for the PPS using ~~**a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate**~~ **an analysis of covariance with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor**.	Difference caused by DXA model will be removed since lumbar spine BMD value will be corrected by cross-calibration. Additionally, the number of patients within some centres is expected to be small, so 'sites (or pooled centres)' is excluded and analysis method is also modified. The effect 'site (or pooled centres)' will be analysed through sensitivity

Section Affected	Original Content	Amended/New Content	Rationale
			analysis.
	(…) To conduct the sensitivity analysis 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.	(…) To conduct the sensitivity analysis 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 missing at random**.	To add the additional information for missing data imputation
	(…) For the US FDA submission, the primary efficacy analysis will be performed for the FAS using a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate.	(…) For the US FDA submission, the primary efficacy analysis will be performed for the FAS using ~~**a linear mixed model with treatment as a fixed effect, and the baseline value of lumbar spine BMD and site (or pooled centres) as a covariate**~~ **an analysis of covariance with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor**.	Difference caused by DXA model will be removed since lumbar spine BMD value will be corrected by cross-calibration. Additionally, the number of patients within some centres is expected to be small, so 'sites (or pooled centres)' is excluded and analysis method is also modified. The effect 'site (or pooled

Section Affected	Original Content	Amended/New Content	Rationale
			centres)' will be analysed through sensitivity analysis.
9.5.3. Pharmacokinetic and Pharmacodynamic Analyses	(…) PD analyses will be performed for the PDS. Serum CTX and P1NP concentrations will be summarised descriptively by treatment group and visit.	(…) PD analyses will be performed for the PDS. Serum CTX and P1NP concentrations will be summarised descriptively by treatment group and visit. **In addition, the $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX will be analysed using an analysis of variance model.**	To add analysis method for $AUEC_{0\text{-}M6}$ of serum CTX
10.5. Database Management and Coding	(…) Concomitant medications will be coded using the WHO-Drug Dictionary Enhanced.	(…) Concomitant medications will be coded using the WHO-Drug Dictionary ~~**Enhanced**~~.	WHO-Drug Dictionary Enhanced is no longer available because WHO-Drug Dictionary Global is the only released type since Mar 2021
10.6. Quality Control and Quality Assurance	(…) The Investigator and institution will allow the domestic and foreign regulatory authorities, the Sponsor's monitors and auditors' direct access to source documents to perform this verification.	(…) The Investigator and institution will allow the domestic and foreign regulatory authorities~~,~~ **and the authorised representative of** the Sponsor~~'s~~ **including** monitors and auditors' direct **or remote** access to source documents to perform this verification **without violating the**	To describe remote access to source documents considering Coronavirus Disease 2019 pandemic

Section Affected	Original Content	Amended/New Content	Rationale
		confidentiality of the subject, to the extent permitted by the applicable laws and regulations.	situation
13. References	(…) 8. Prescribing Information of Prolia®. FDA. (Feb 10, 2020). Retrieved Mar 31, 2020 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125320s202lbl.pdf 9. Summary of Product Characteristics of Prolia®. EMA. (Feb 11, 2020) Retrieved Mar 31, 2020 from https://www.ema.europa.eu/en/documents/product-information/prolia-epar-product-information_en.pdf 10. Prescribing Information of Xgeva®. FDA. (Oct 01, 2019). Retrieved Mar 31, 2020 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s201lbl.pdf 11. Summary of Product Characteristics of Xgeva®. EMA. (Mar 24, 2020) Retrieved Mar 31, 2020 from https://www.ema.europa.eu/en/documents/product-information/xgeva-epar-product-information_en.pdf	(…) 8. Prescribing Information of Prolia®. FDA. (~~**Feb 10**~~ **Apr 23**, 2020). Retrieved ~~**Mar 31, 2020**~~ **Apr 15, 2021** from ~~**https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125320s202lbl.pdf**~~ **https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s205lbl.pdf** 9. Summary of Product Characteristics of Prolia®. EMA. (~~**Feb 11**~~ **Dec 04**, 2020) Retrieved ~~**Mar 31, 2020**~~ **Apr 15, 2021** from https://www.ema.europa.eu/en/documents/product-information/prolia-epar-product-information_en.pdf 10. Prescribing Information of Xgeva®. FDA. (~~**Oct 01, 2019**~~ **Jun 09, 2020**). Retrieved ~~**Mar 31, 2020**~~ **Apr 15, 2021** from ~~**https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s201lbl.pdf**~~ **https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s203lbl.pdf** 11. Summary of Product Characteristics of Xgeva®. EMA. (~~**Mar 24**~~ **Aug 07**, 2020) Retrieved ~~**Mar 31, 2020**~~ **Apr 15, 2021** from https://www.ema.europa.eu/en/documents/product-information/xgeva-epar-product-information_en.pdf	To reflect the latest version