Protocol Number: FKS518-002 (LUMIADE-3)

Official Title: A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)

NCT Number: NCT04934072

Document Date: 17 January 2023

CLINICAL STUDY PROTOCOL

Title:	A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)
Protocol number:	FKS518-002
Study phase:	Phase III
Test product:	FKS518 - Proposed biosimilar to denosumab
EudraCT number:	2020-004422-31
Sponsor:	Fresenius Kabi SwissBioSim GmbH Terre Bonne Business Park Route de Crassier 23 – Bâtiment A3 CH – 1262 Eysins Switzerland
Contract Research Organization:	[redacted]
Coordinating investigator:	[redacted]
Protocol version and date:	[redacted] Final 6.0, 17 Jan 2023, incorporating Protocol Amendment 5

This study will be performed in compliance with the principles of Good Clinical Practice.

PROTOCOL SIGNATURE PAGE – SPONSOR

A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

[redacted]

[redacted]

[redacted]

PROTOCOL SIGNATURE PAGE – CONTRACT RESEARCH ORGANIZATION

A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

[redacted]

PROTOCOL SIGNATURE PAGE – COORDINATING INVESTIGATOR

A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

Coordinating investigator:

[redacted]

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)

The information contained in this protocol and all other information relevant to FKS518 are the confidential and proprietary information of Fresenius Kabi SwissBioSim GmbH, and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Fresenius Kabi SwissBioSim GmbH.

I have read the protocol (Version 6.0 dated 17 Jan 2023, incorporating Protocol Amendment 5), including all appendices and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practice and International Council for Harmonisation guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Fresenius Kabi SwissBioSim GmbH or specified designees. I will discuss the material with them to ensure that they are fully informed about FKS518 and the study.

My site has implemented risk minimization and the mitigation plan for COVID-19 in line with local regulations and best practices, including precautions such as use of personal protective equipment for subjects, site staff, and other visitors, site staff health-check, and the disinfection of site premises.

Investigator: *Print Name; Title*

Institution

Signature Date

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of a serious adverse event (SAE), the Investigator will send a Safety Report Form immediately and no later than 24 hours after becoming aware of the SAE to:

[redacted]

In Europe, Asia-Pacific, and Africa (EAPA):

[redacted]

In the Americas:

[redacted]

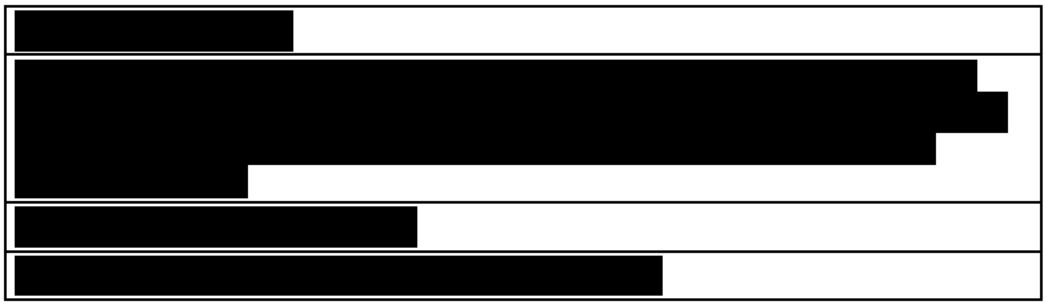
SUMMARY OF CHANGES

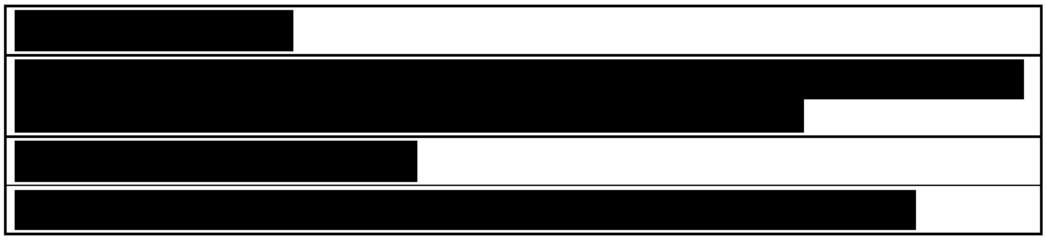
Version 6.0, 17 Jan 2023
Protocol Amendment 5 (Substantial)
Rationale: Firstly, a Coordinating Investigator has been appointed for this study: [redacted] Secondly, one of the changes included in the previous protocol amendment, clarifying that when 2 blood samples are required for the bone biomarker assessment the second sample does not need to be taken in a fasting state, had not been correctly implemented for the Week 52 samples, as only the pre-dose sample (fasting) is required at that visit. This has been corrected in the current protocol amendment. Similarly, one of the changes included in the previous protocol amendment, allowing the DXA to be performed within ±7 days of the Week 52 and Week 78 study visits, was not stated in all relevant sections of the protocol. This has now been corrected. Finally, the names of the Sponsor Signatories have been updated.
The following changes are incorporated into Version 6.0 of the protocol:

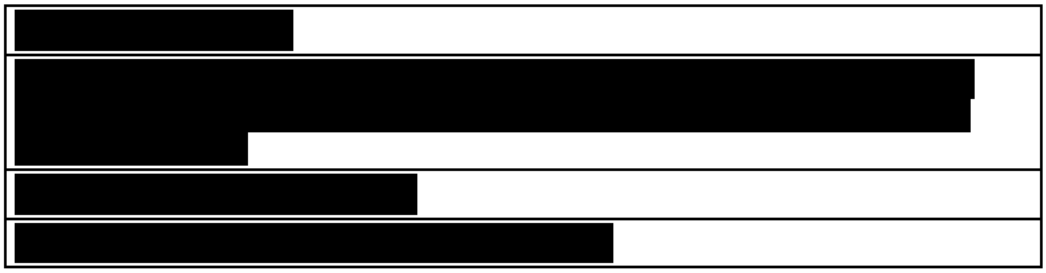
Description of change:
A Coordinating Investigator, [redacted] has been included in the protocol.
Sections of the protocol affected:
New Coordinating Investigator Signature Page; Synopsis; Section 14; Section 18.1, Appendix 1.

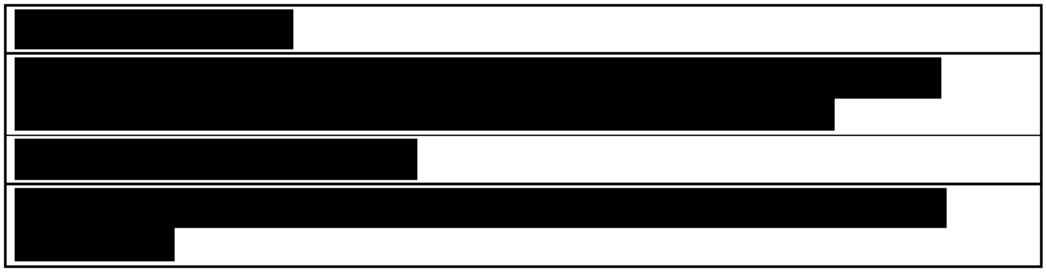
Description of change:
Correction of wording regarding Week 52 bone biomarkers sampling.
Sections of the protocol affected:
Schedule of assessments Table 1, footnote n; Section 6.4.

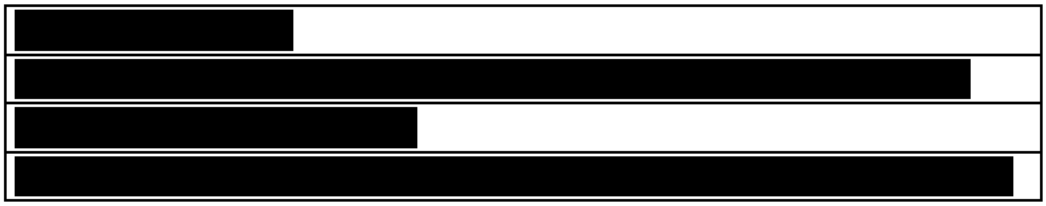
Description of change:
Clarification that the DXA can be performed within ±7 days of the Week 52 and Week 78 study visits.
Sections of the protocol affected:
Synopsis; Section 4.1; Section 6.2.1.

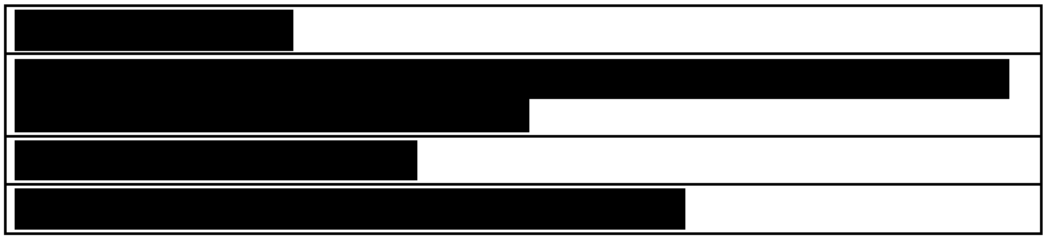


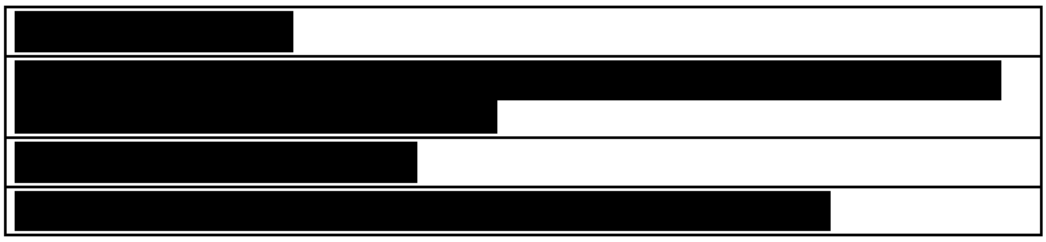


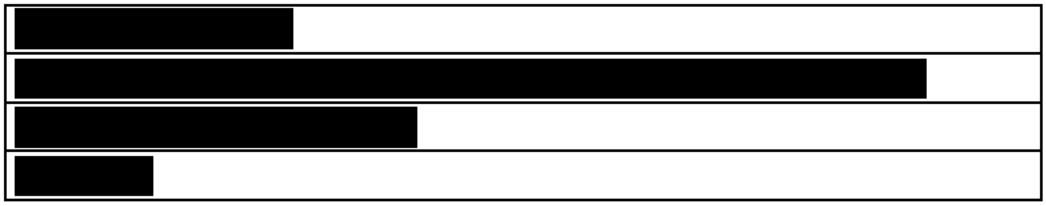


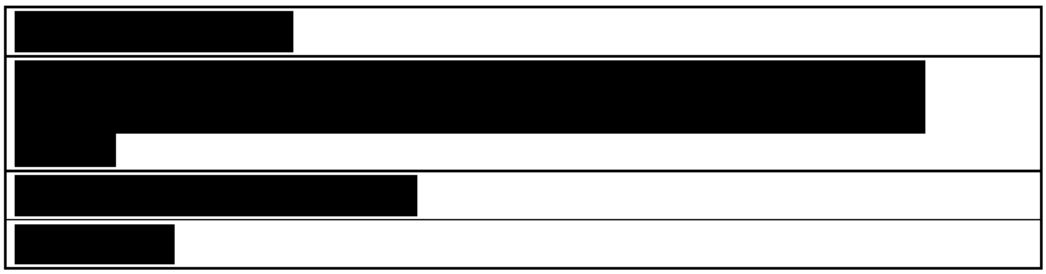


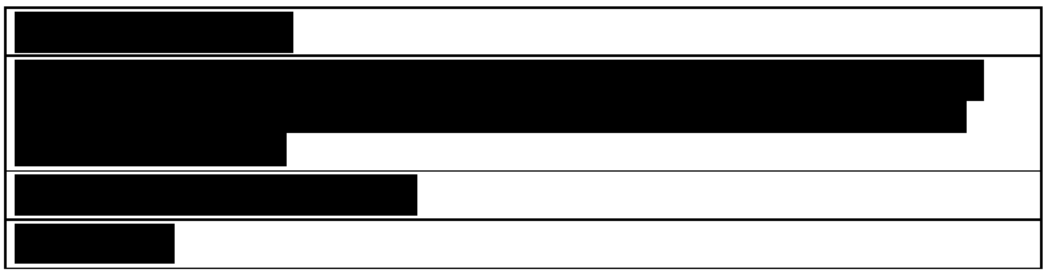


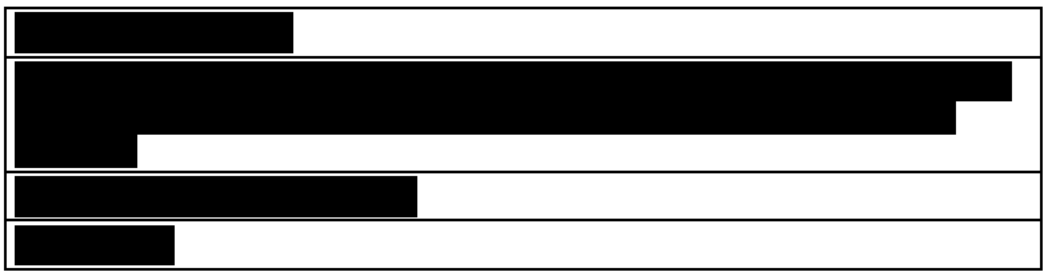












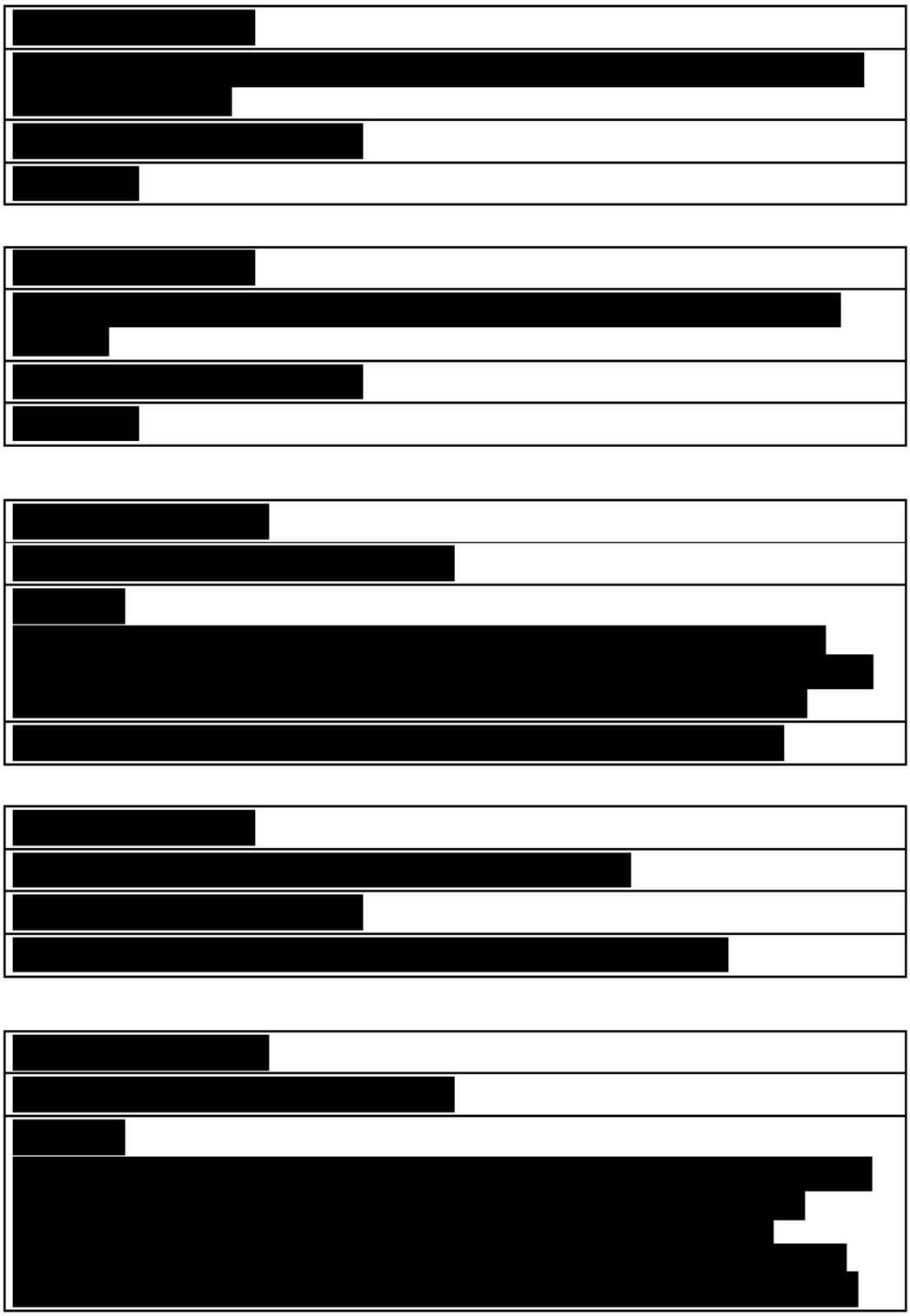
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



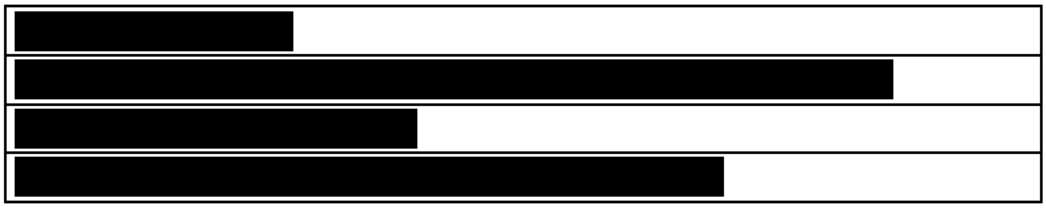
[redacted]

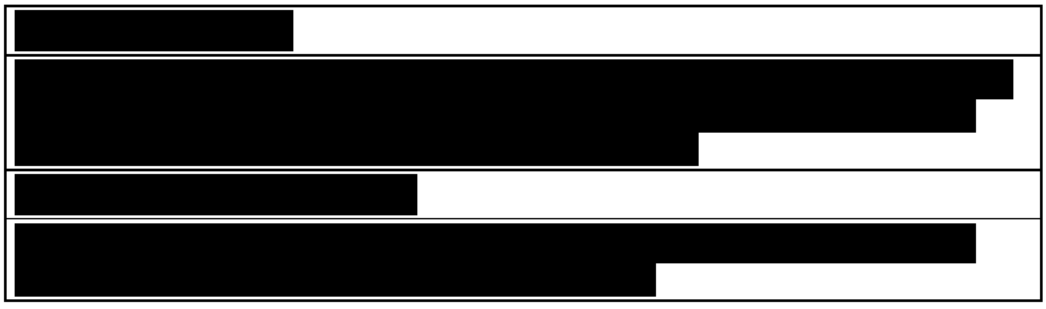
[redacted]

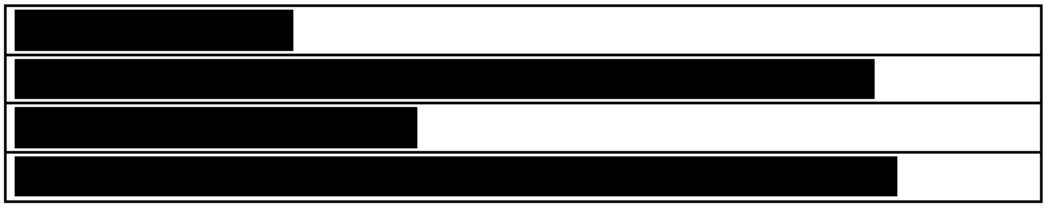
[redacted]

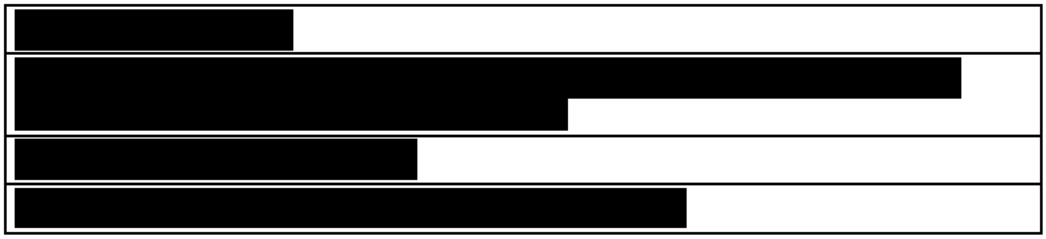
[redacted]

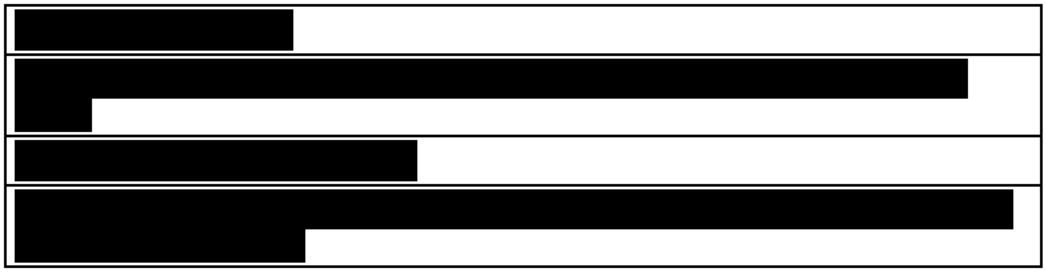
[redacted]

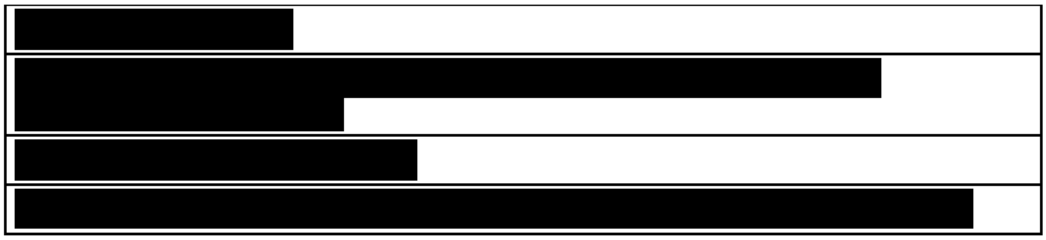


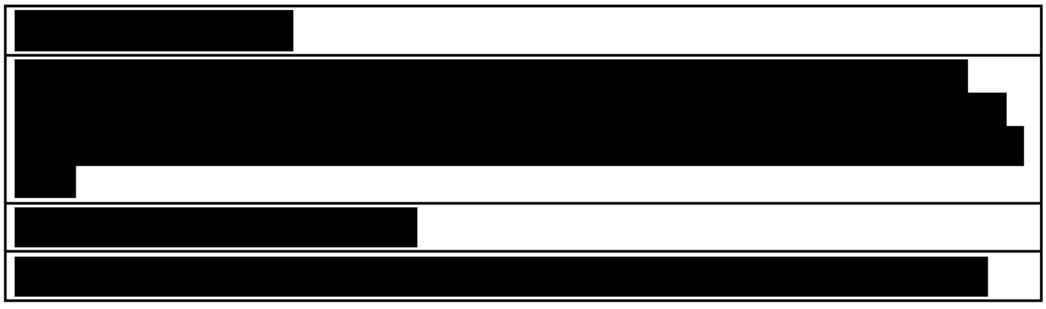


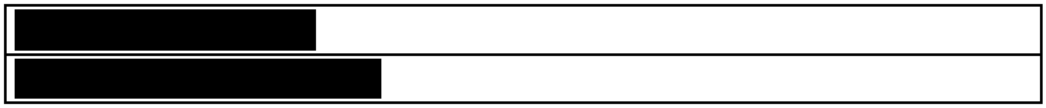












PROTOCOL SUMMARY

Protocol number: FKS518-002

Protocol title: A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and, Immunogenicity of FKS518 - Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 study)

Sponsor: Fresenius Kabi SwissBioSim GmbH

Coordinating investigator: [redacted]

Study phase: Phase III

Study sites: It is planned to recruit approximately 75 sites globally.

Objectives:

Primary:

To demonstrate equivalent efficacy of the proposed biosimilar denosumab FKS518 to United States (US)-licensed Prolia (US-Prolia) in women with postmenopausal osteoporosis (PMO).

For Marketing Authorization Application (MAA) in the European Union (EU) and European Economic Area (EEA) only: To demonstrate equivalent efficacy and pharmacodynamics (PD) of the proposed biosimilar denosumab FKS518 to US-licensed Prolia (US-Prolia) in women with PMO.

Secondary:

To compare the safety, tolerability, PD, and immunogenicity of FKS518 to US-Prolia in women with PMO.

[redacted]

Study design:

This is a double-blind, randomized, multicenter, 2-arm, multiple-dose, parallel-group study with a transition period, to compare the efficacy, safety, tolerability, and immunogenicity of the proposed biosimilar denosumab FKS518 with US-Prolia in ambulatory women with PMO. Bone biomarkers (PD) and PK will also be assessed. The study design is outlined in Figure 1.

This study will enroll female subjects aged 55 to 85 years with confirmed postmenopausal status and lumbar spine bone mineral density (LS-BMD) T-score ≤-2.5 and ≥-4.0, as measured by dual energy x-ray absorptiometry (DXA). Subjects will be instructed to take 1000 mg calcium and at least 400 IU vitamin D supplementation daily.

The Investigator will obtain signed informed consent form (ICF) from the subject before any study procedures are performed. Subjects whose eligibility is confirmed at baseline will be randomized in a 1:1 ratio by an Interactive Response Technology (IRT) system to receive either FKS518 or US-Prolia at a dose of 60 mg delivered by subcutaneous injection starting at Day 1, and then every 26 weeks (6 months) for a total of 3 administrations within 78 weeks. Randomization will be stratified by age (<65 years; ≥65 years) and prior bisphosphonates therapy (Yes; No). Subjects in this study will not be dosed until the first 10 subjects in the comparative Phase I PK/PD study (FKS518-001) have been exposed to a single dose of either FKS518 or US-Prolia and followed for 48 hours and, after being evaluated by the Sponsor, no unexpected safety profile indicative of a materially altered benefit-risk that would prohibit further recruitment of subjects is detected.

The efficacy endpoints will be evaluated during the Core Treatment Period up to Week 52 (26 weeks after the second study drug administration), along with other endpoints, within ±7 days of the third investigational product (IP) injection. At Week 52, after efficacy, PD, and safety assessments have been performed, subjects will enter the Transition Period. Subjects who were originally randomized to receive US-Prolia will be re-randomized in a 1:1 ratio to receive a third administration of US-Prolia or to switch to FKS518 at Week 52. Subjects who discontinue the study before Week 52 will not be re-randomized. Subjects who were originally randomized to FKS518 will continue to receive this treatment at Week 52. Re-randomization will not impact the double-blind nature of the study as blinding will be kept. During the Transition Period, safety, immunogenicity, and efficacy data will be analyzed up to Week 78.

In order to minimize missing data in the evaluation of the treatment effect under the treatment policy strategy, subjects who discontinue treatment early will be encouraged to remain in the study and attend all study visits of the period in which they were discontinued (Core Treatment or Transition Periods), even if it is decided that the next dose will not be administered.

The clinical sites shall implement risk minimization and the mitigation plan for coronavirus disease 2019 (COVID-19), including precautions such as use of personal protective equipment for subjects, site staff, and other visitors, site staff health-check, and the disinfection of site premises.

Efficacy (including bone mineral density [BMD] and PD bone biomarkers, ie, C-terminal cross-linking telopeptide of type 1 collagen [CTX] and procollagen type 1 N-terminal propeptide [P1NP]), safety, immunogenicity, and PK assessments are detailed in the Schedule of Assessments (Table 1 and Table 2).

Study duration: The study will include a Screening Period of maximum 4 weeks (28 days) prior to first drug administration, a double-blind Core Treatment Period up to Week 52, and a double-blind single Transition Period from Week 52 up to Week 78, with administration of the study drug on Day 1, Week 26 (Month 6), and Week 52 (Month 12). An End of Study Visit will be performed 26 weeks (6 months) after the last administration of study drug (at Week 78). Total study duration will be up to 82 weeks (including up to 4 weeks of screening).

The start of the study will be the date on which the first subject provides informed consent, and the end of the study will be the last subject's last assessment.

Planned number of subjects: It is planned to enroll 526 randomized subjects (263 subjects per arm) to obtain 446 completed subjects in the Per Protocol (PP) Analysis Set in the Core Period (up to Week 52), assuming a 15% drop-out rate (including clinically important protocol deviations).

Target population: Female subjects aged ≥55 to ≤85 years with PMO.

Inclusion criteria:

1. Female ≥55 to ≤85 years of age, inclusive, at screening.
2. Have a body mass index (BMI) ≥18 to ≤32 kg/m^2.
3. Subject should have confirmed postmenopausal status, defined as age-related or early/premature amenorrhea ≥12 consecutive months and increased follicle-stimulating hormone (FSH) >40 mIU/mL at screening; or surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to screening.
4. Absolute BMD consistent with T-score ≤-2.5 and ≥-4.0 at the lumbar spine as measured by DXA as per central assessment.
5. At least 2 vertebrae in the L1-L4 region and at least 1 hip joint are evaluable by DXA.
6. Clinically acceptable physical examinations and laboratory tests (hematology, clinical chemistry, coagulation panel, and urinalysis) and no history or evidence of any clinically significant concomitant medical disorder that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with study evaluations or procedures.
7. Subjects must voluntarily give written informed consent before any study-related activities are performed. Subjects must read and fully understand the ICF and the requirements of the trial and must be willing to comply with all trial visits and assessments. A separate Information Sheet (containing important information about COVID-19, clinical research study participation,

and subject consent) will be provided to and signed by each subject to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the subject.

Exclusion criteria:

Disease-related

1. History and/or presence of 1 severe or >2 moderate vertebral fractures or hip fracture confirmed by x-ray.
2. Presence of active healing fracture at screening.
3. History and/or presence of bone-related disorders, such as but not limited to Paget's disease, osteomalacia, hyperparathyroidism (or parathyroid disorders), or renal osteodystrophy.
4. Osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (eg, tooth extraction, dental implants, or oral surgery in the past 6 months), poor oral hygiene, periodontal, and/or pre-existing dental disease as assessed by the Investigator.
5. Evidence of hypocalcemia (albumin-adjusted serum calcium <2.13 mmol/L or <8.5 mg/dL) or hypercalcemia (albumin-adjusted serum calcium >2.6 mmol/L or >10.5 mg/dL) as assessed by the central laboratory at screening.
6. Vitamin D deficiency (25-hydroxy vitamin D levels <12 ng/mL) as assessed by central laboratory at screening (retest is allowed once).
7. Known intolerance to calcium or vitamin D supplements.

Other medical conditions

8. History of known or suspected clinically relevant drug hypersensitivity to any components of the study drug formulations, comparable drugs, or to latex.
9. History of an episode of life-threatening or severe hypersensitivity in response to a medicinal product and/or environmental exposure.
10. Renal impairment: creatinine clearance <30 mL/min at screening or receiving dialysis.
11. Medical evidence of current or history of primary or secondary immunodeficiency as per Investigator's judgment.
12. Infection-related exclusions:
    a. Severe herpes zoster (disseminated, multidermatomal, herpes encephalitis, or ophthalmic herpes) or recurrent herpes zoster (defined as 2 episodes within 2 years), or any opportunistic invasive infection (eg, histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infestations) within 6 months before screening.
    b. Frequent (more than 3 of the same type of infection per year requiring treatment) chronic or recurrent infections (eg, urinary tract or upper respiratory tract infections).
    c. A positive test for HIV subtype 1 or 2, or hepatitis C virus (HCV), or evidence of acute or chronic hepatitis B infection, evaluated by testing for hepatitis B (hepatitis B surface antigen [HBsAg] and/or core antibody) at screening. Polymerase chain reaction (PCR) for HCV RNA and hepatitis B virus (HBV) DNA is allowed to confirm active disease if HCV or HBV antibodies are present without a positive result for HBsAg.
    d. A serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks before randomization.
    e. Required treatment with oral antibiotics and/or antifungal drugs within 14 days prior to screening.
    f. Confirmed or, based on the signs and symptoms observed at the time of assessment, suspected active COVID-19 infection at the time of screening and/or randomization.
13. Major surgical procedure within 8 weeks prior to the screening or the subject is scheduled to have a surgical procedure during the study.
14. Current or history of any malignancy, or myeloproliferative or lymphoproliferative disease within 5 years before screening. Exception: subjects with resected [redacted] basal cell or

squamous cell carcinoma, or carcinoma of cervix in situ that has been treated with no evidence of recurrence can be included.

15. History of clinically significant drug or alcohol abuse within the last year prior to randomization.
16. The subject should not participate in the study if they have any ongoing or recent (ie, at the time of screening) medical condition that may interfere with the study conduct, interpretation of study data, and/or otherwise put the subject at an unacceptable risk or could lead to noncompliance with requirements of the study; eg, subjects with rheumatoid arthritis or other autoimmune conditions are not eligible. The Investigator should specifically evaluate the subject's eligibility taking into consideration COVID-19 risk factors and situation.

Prior or concomitant therapy

17. Prior denosumab (Prolia, Xgeva, or proposed denosumab biosimilar) exposure.
18. Prior use of fluoride within the 5 years before inclusion in the study.
19. Any current or prior use of strontium ranelate.
20. Any current or prior use of intravenous bisphosphonates. Prior use of oral bisphosphonates is excluded if:
    a. More than 3 years cumulative use prior to screening, unless last dose received is >5 years prior to screening, OR
    b. Any dose within 12 months before screening, except if subject received less than 1 month of cumulative use between 6 and 12 months prior to screening.
21. Current or prior use of teriparatide and other parathormone (PTH) analogs within 12 months before screening.
22. Current or prior use of systemic oral or transdermal estrogen or selective estrogen receptor modulators or tibolone within 6 months before screening.
23. Current or prior use of calcitonin or cinacalcet within 3 months before screening.
24. Current or prior use of any cathepsin K inhibitor (eg, odanacatib) within 18 months before screening.
25. Current or prior use of romosozumab or antisclerostin antibody.
26. Current or prior use of other osteoporotic agents used for the prevention or treatment of osteoporosis will be excluded according to the Investigator's judgment after consultation with the Medical Monitor.
27. Current use within 3 months before screening of any medication with known influence on the skeletal system (eg, systemic corticosteroids, heparin, lithium, etc). Subjects with a stable dose of systemic prednisone <5 mg or equivalent systemic corticosteroid for more than 4 weeks before screening are eligible. However, use of systemic glucocorticosteroids ≥5 mg prednisone or equivalent per day for more than 14 days within 3 months before randomization is not permitted.
28. Concomitant treatment with another biologic drug.
29. Prior use of other biologic investigational drugs for the treatment of PMO.
30. Prior use of any investigational drugs within 5 drug half-lives prior to screening or planned intake of an investigational drug during the course of this study.
31. Have received a COVID-19 vaccine within 4 weeks before randomization or COVID-19 vaccination is ongoing at the time of screening. COVID-19 vaccination is considered ongoing if a multidose regimen has been started but has not been completed.

Test product:

Name: FKS518 (proposed denosumab biosimilar)

Dose: 60 mg every 26 weeks (6 months)

Route of administration: subcutaneous injection.

Control product:

Name: US-licensed Prolia (denosumab)

Dose: 60 mg every 26 weeks (6 months)

Route of administration: subcutaneous injection.

Endpoints:

Primary endpoint:

- Percent change from baseline in LS-BMD by DXA at Week 52.
- Area under the effect curve (AUEC) of serum CTX up to Week 26 *(for MAA in the EU and EEA only)*.

Secondary endpoints:

Efficacy:

- Percent change from baseline in BMD at femoral neck and total hip by DXA at Week 52.

Pharmacodynamic:

- Percent change from baseline in serum P1NP at Week 52.
- Percent change from baseline in serum CTX at Week 52.

Safety and tolerability:

- Occurrence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) during Core Treatment Period, Transition Period, and overall.
- Occurrence of treatment-emergent adverse events of special interest (AESIs): drug-related hypersensitivity/allergic reactions (Common Terminology criteria for Adverse Events [CTCAE] Grade ≥3 or reported as SAEs), and adverse events leading to IP discontinuation or study withdrawal during Core Treatment Period, Transition Period, and overall.
- Occurrence of injection site reactions (local tolerability) during Core Treatment Period, Transition Period, and overall.

Immunogenicity:

- Antidrug antibody (ADA) incidence during Core Treatment Period, Transition Period, and overall.
- ADA titer during the Core Treatment Period, Transition Period.
- Neutralizing antibody (NAb) incidence during the Core Treatment Period, Transition Period, and overall.

[redacted]

[redacted]

Statistical methods:

Sample size

A sample size of 526 randomized subjects (263 subjects per arm) is chosen to provide approximately 446 subjects (223 subjects per arm) in the PP Analysis Set at Week 52, assuming a 15% drop-out rate (including clinically important protocol deviations leading to exclusion from the PP Analysis Set).

A total of 446 subjects will provide 90% power to demonstrate equivalence between treatments for the primary endpoint LS-BMD, with equivalence margins of [-1.45%, 1.45%] and a Type I error of 2.5%, assuming a 0.2% difference between the 2 treatment groups and a common standard deviation (SD) of 4%. A total of 446 subjects will provide 93.7% power assuming no difference between the 2 treatment groups.

The drop-out rate/protocol deviation rate will be monitored on blinded data through the first 52 weeks. The number of randomized subjects may be adjusted based on the observed drop-out rate. If larger than anticipated, an investigation on the reasons for dropping out will be conducted.

(For MAA in the EU and EEA only): For the co-primary endpoint AUEC(0-W26) of serum CTX, based on simulated population PK/PD data with equivalence margins of [0.89, 1.12], assuming that the reference population and test population are identical, an analysis of covariance (ANCOVA) of the natural logarithm (log) transformed AUEC (derived in WinNonlin from simulated PD data) controlling for the natural log of the baseline serum CTX, demonstrated that a sample size of n=223 per arm is considered adequate to guarantee >99% power to show equivalence between FKS518 and US-Prolia.

A total of 446 subjects will provide >89% power to demonstrate equivalence between treatments for both the primary endpoint LS-BMD and co-primary endpoint AUEC(0-W26) of serum CTX with a conservative assumption of independence between endpoints.

Primary efficacy analysis: Percent change from baseline at Week 52 in LS-BMD will be analyzed on the Intention-to-Treat (ITT) Analysis Set using an ANCOVA with treatment, age strata (<65 years; ≥65 years), and prior bisphosphonates therapy strata (Yes; No) as fixed effects, and baseline LS-BMD as a covariate. The difference between treatments will be estimated by the least squares (LS) mean difference between FKS518 and US-Prolia, with its 95% confidence interval (CI) and compared to the pre-defined equivalence margins. The primary analysis will be repeated on the PP Analysis Set. FKS518 will be considered equivalent to US-Prolia if the 95% CI for the difference in mean percent change from baseline to Week 52 in LS-BMD lies entirely within the equivalence interval of [-1.45%, 1.45%].

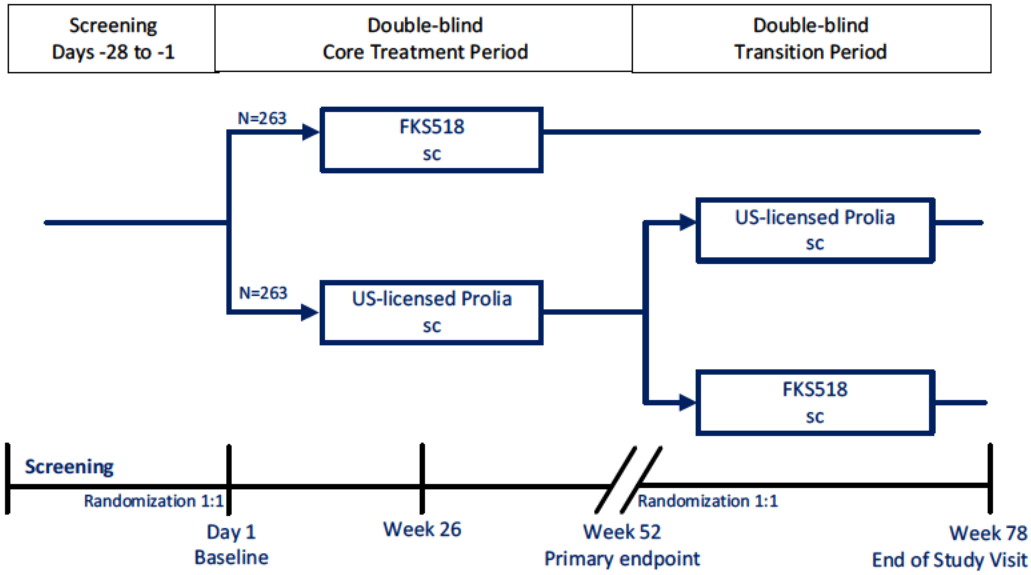
Co-primary efficacy analysis (for MAA in EU and EEA only): The natural log transformed AUEC(0-W26) of serum CTX will be analyzed on the PD Analysis Set using an ANCOVA with treatment, age strata, and prior bisphosphonates therapy as fixed effects, and the natural log of baseline serum CTX concentration as a covariate. The difference between treatments will be estimated by the LS mean difference between FKS518 and US--Prolia, with its 95% CI. The point estimate and the limits of the 95% CI will be back transformed on the original scale. FKS518 will be considered equivalent to US-Prolia on CTX if the 95% CI for the ratio of means of AUEC(0-W26) lies entirely within the equivalence interval of [0.89, 1.12].

A similar model to the primary analysis will be used for the secondary efficacy endpoint, percent change from baseline at Week 52 in BMD at femoral neck and total hip.

All efficacy endpoints will be analyzed on the ITT and PP Analysis Sets. Descriptive summary statistics will be provided throughout. Safety and immunogenicity data will be listed and summarized using appropriate descriptive statistics on the Safety Analysis Set. [redacted]
Protocol version and date: Final 6.0, 17 Jan 2023 (incorporating Protocol Amendment 5)

STUDY SCHEMATIC

Figure 1 Study Schematic



sc=subcutaneous
Note: Following screening, subjects will be randomized in a 1:1 allocation ratio into 2 arms: US-Prolia or FKS518. At Week 52 the subjects in the US-Prolia arm will be 1:1 randomized into 2 separate arms to either continue with US-Prolia or transition to FKS518.

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments: Screening to Week 52

	Screening		Core Treatment Period (1:1 FKS518 vs US-Prolia)															End of Core Treatment Period/ Start of Transition Period
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Week	**-4 to -1**	**Baseline**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W26**	**W28**	**W30**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Day (window)	**-28 to -1**	**1**	**15 (±2)**	**29 (±2)**	**57 (±2)**	**85 (±2)**	**113 (±2)**	**141 (±2)**	**169 (±2)**	**183 (±2)**	**197 (±2)**	**211 (±2)**	**225 (±2)**	**253 (±2)**	**281 (±2)**	**309 (±2)**	**337 (±2)**	**365 (±2)**
Informed consent [a]	X																	
Medical history including osteoporosis risk factors [b]	X																	
Demographics	X																	
Previous and concomitant medications and procedures	X [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height (with BMI calculation) [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [g]	X									X								X
Chest x-ray [h]	X																	
Thoracic and lumbar x-ray [i]	X																	(X)

Table 1 Schedule of Assessments: Screening to Week 52

	Screening		Core Treatment Period (1:1 FKS518 vs US-Prolia)															End of Core Treatment Period/ Start of Transition Period
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Week	**-4 to -1**	**Baseline**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W26**	**W28**	**W30**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Day (window)	**-28 to -1**	**1**	**15 (±2)**	**29 (±2)**	**57 (±2)**	**85 (±2)**	**113 (±2)**	**141 (±2)**	**169 (±2)**	**183 (±2)**	**197 (±2)**	**211 (±2)**	**225 (±2)**	**253 (±2)**	**281 (±2)**	**309 (±2)**	**337 (±2)**	**365 (±2)**
LS-BMD by DXA [j]	X																	X [u]
Femoral neck and total hip BMD by DXA [k]	X																	X [u]
FSH (subjects ≤60 years)	X																	
Viral serology [l]	X																	
Clinical laboratory [m]	X	X	X	X		X				X	X	X		X				X
PD (bone biomarkers) sampling [n]	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X
PK sampling [o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sampling [p]	X	X	X	X	X	X				X			X		X			X
Eligibility check	X [q]	X																
Randomization [r]		X																X
IP administration [s]		X								X								X
Injection site reactions [t]		X	X							X	X							X

Table 1 Schedule of Assessments: Screening to Week 52

	Screening		Core Treatment Period (1:1 FKS518 vs US-Prolia)															End of Core Treatment Period/ Start of Transition Period
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Week	**-4 to -1**	**Baseline**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W26**	**W28**	**W30**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Day (window)	**-28 to -1**	**1**	**15 (±2)**	**29 (±2)**	**57 (±2)**	**85 (±2)**	**113 (±2)**	**141 (±2)**	**169 (±2)**	**183 (±2)**	**197 (±2)**	**211 (±2)**	**225 (±2)**	**253 (±2)**	**281 (±2)**	**309 (±2)**	**337 (±2)**	**365 (±2)**
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA=antidrug antibodies; AE=adverse event; BMD=bone mineral density; BMI=body mass index; COVID-19=coronavirus disease 2019; CTX=C-terminal cross-linking telopeptide of type 1 collagen; DXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; FSH=follicle--stimulating hormone; HBcAb=hepatitis B core antibody; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IP=investigational product; LS-BMD=lumbar spine bone mineral density; NAb=neutralizing antibodies; P1NP=procollagen type 1 N-terminal- propeptide; PCR=polymerase chain reaction; PD=pharmacodynamic; PK=pharmacokinetic; V=Visit; W=Week

[a] Informed consent must be obtained from each subject prior to performing any screening assessments. Note: A separate Information Sheet (containing important information about COVID-19, clinical research study participation, and subject consent) will be provided to and signed by each subject to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the subject.

[b] Risk factors for osteoporosis include history of fractures, family history of hip fracture, low BMI, age ≥70 years, smoking status (former/current smoker), and alcohol consumption.

[c] Subjects will be instructed to take 1000 mg calcium and at least 400 IU vitamin D supplementation daily. At screening, use of all prior and concomitant medication from 4 weeks before the Screening Visit and all previous osteoporosis treatments should be recorded.

[d] A complete physical examination will be performed at Screening, Baseline, Week 26, and Week 52; a brief physical examination will be performed at all other study visits.

[e] Height (by stadiometer) only at Screening, Week 26, and Week 52. Height should always be measured in the same stadiometer and following the same procedure (eg, without shoes). BMI will be calculated at screening only.

[f] Vital signs (including body temperature, respiratory rate, pulse rate, and blood pressure) will be measured after 5 minutes rest in the supine position. During the study, measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Body temperature measurement should be performed first at each study visit and should precede every other assessment of each visit. In the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.

[g] Subjects are required to rest in a supine position for at least 5 minutes prior to recording of 12-lead ECG. ECGs will be assessed locally.

[h] If a chest x-ray or radiograph was taken within 2 months prior to screening and shows no clinically significant abnormality, and there are no signs and symptoms suggestive of pulmonary disease that would exclude the subject from the study, then a chest x-ray or radiograph does not need to be repeated at screening.

[i] Previous x-rays taken within 6 months prior to screening will be acceptable. Images will be evaluated centrally and should be submitted to the central imaging vendor. Additional spine x-rays will be performed if there is a suspicion of a fracture (eg, new onset of persistent or pronounced back pain or material worsening of back pain); these will be assessed locally.

[j] The same DXA system (ie, Lunar or Hologic) must be used for all study procedures for a particular subject for the duration of the study. All DXA scan data will be submitted electronically to the central imaging vendor for analysis. DXA scans of the lumbar spine will be performed in duplicate, ie, subjects will be removed from the table in between scans. Lumbar spine scans must include L1 through L4.

[k] The same DXA system (ie, Lunar or Hologic) must be used for all study procedures for a particular subject for the duration of the study. All DXA scan data will be submitted electronically to the central imaging vendor for analysis. For proximal femur DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fractures the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location.

[l] Includes tests for HIV-1 and HIV-2, HBsAg, HBcAb, and HCV antibody. Note: Reflex testing by PCR for HCV RNA and HBV DNA is allowed if HCV or HBV antibodies are present without a positive result for HBV surface antigen.

[m] Clinical laboratory tests will include hematology, clinical chemistry, coagulation panel (screening only), and urinalysis (dipstick).

[n] Bone biomarkers: serum CTX and P1NP. Blood sampling must be collected in the morning (between 8:00 and 10:00 am) after an overnight fast. On the first 2 dosing days (Day 1 and Week 26), 2 samples will be obtained for bone biomarkers: pre-dose (between 8:00 and 10:00 am and fasting) and 5±1 hours post-dose (not fasting). On the third dosing day (Week 52), only the pre-dose sample (between 8:00 and 10:00 am and fasting) will be obtained.

[o] PK samples must be collected prior to the immunogenicity sampling. On dosing days (Day 1, Week 26, and Week 52), 2 PK samples will be obtained: pre-dose and 5 ±1 hours post-dose.

[p] Blood sampling for immunogenicity (ADA and NAb). Blood samples must be drawn prior to the IP when applicable, and the PK samples must be collected prior to the immunogenicity sampling. Separate samples will be collected for ADA and NAb assessments. The screening sample will be used for assay validation purposes, it will not be reported in the results.

[q] Eligibility check to include COVID-19 eligibility, to be performed by the Investigator and the Medical Monitor.

[r] On Day 1, subjects will be randomized in a 1:1 allocation ratio into 2 arms: US-Prolia or FKS518. At Week 52, the subjects in the US-Prolia arm will be 1:1 randomized into 2 separate arms to either continue with US-Prolia or to transition to FKS518.

[s] Proposed biosimilar FKS518 and reference product will be injected as a single subcutaneous dose of 60 mg every 26 weeks; 3 drug administrations within 78 weeks.

[t] Late onset injection site reactions to be documented as recommended in the electronic case report form completion guide.

[u] DXA can be performed within ±7 days of Day 365.

Table 2 Schedule of Assessments: Week 52 to Week 78 – End of Study

	Transition Period						End of Study/ Early Termination [a]
Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**
Week	**W52**	**W56**	**W60**	**W64**	**W68**	**W72**	**W78**
Day (window)	**365 (±2)**	**393 (±2)**	**421 (±2)**	**449 (±2)**	**477 (±2)**	**505 (±2)**	**547 (±7)**
Concomitant medication and procedures	X	X	X	X	X	X	X
Physical examination [b]	X	X	X	X	X	X	X
Body weight and height (with BMI calculation) [c]	X	X	X	X	X	X	X
Vital signs [d]	X	X	X	X	X	X	X
12-lead ECG [e]	X						X
Thoracic and lumbar x-ray [f]	(X)						(X)
LS-BMD by DXA [g]	X [n]						X [n]
Femoral neck and total hip BMD by DXA [h]	X [n]						X [n]
Clinical laboratory [i]	X	X			X		X
PD (biomarkers sampling) [j]	X						
PK sampling [k]	X	X	X	X	X	X	X
Immunogenicity sampling [l]	X			X			X
Injection site reaction [m]	X	X					
AE monitoring	X	X	X	X	X	X	X

ADA=antidrug antibodies; AE=adverse event; BMD=bone mineral density; BMI=body mass index; CTX=C-terminal cross-linking telopeptide of type 1 collagen; DXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; IP=investigational product; LS-BMD=lumbar spine bone mineral density; NAb=neutralizing antibodies; P1NP=procollagen type 1 N-terminal propeptide; PD=pharmacodynamic; PK=pharmacokinetic; V=Visit; W=Week

[a] The Week 78 Visit procedures will be performed for the End of Study Visit and the Early Termination Visit. In case of premature discontinuation from the study, the Investigator should make every effort to ensure the subject completes the Early Termination visit as soon as possible, but not earlier than 4 weeks after last injection (for immunogenicity assessment).
If a subject discontinues IP prior to Week 52, the subject will remain in the study up to the completion of the Week 52 assessments. If a subject discontinues IP during the Transition Period, the subject will remain in the study up to the completion of the End of the Study Visit.

[b] A complete physical examination will be performed at Week 52 and at the End of Study/Early Termination Visit; a brief physical examination will be performed at the remaining study visits.

[c] Height (by stadiometer) only at Week 52 and Week 78/End of Study. Height should always be measured in the same stadiometer and following the same procedure (eg, without shoes). BMI will be calculated at screening only.

[d] Vital signs (including body temperature, respiratory rate, pulse rate, and blood pressure) will be measured after 5 minutes rest in the supine position. During the study, measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Body temperature measurement should be performed first at each study visit and should precede every other assessment of each visit. In the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.

[e] Subjects are required to rest in a supine position for at least 5 minutes prior to recording of 12-lead ECG. ECGs will be assessed locally.

[f] Spine x-rays will be performed if there is a suspicion of a fracture (eg, new onset of persistent or pronounced back pain or material worsening of back pain); these will be assessed locally.

[g] The same DXA system (ie, Lunar or Hologic) must be used for all study procedures for a particular subject for the duration of the study. All DXA scan data will be submitted electronically to the central imaging vendor for analysis. DXA scans of the lumbar spine will be performed in duplicate, ie, subjects will be removed from the table in between scans. Lumbar spine scans must include L1 through L4.

[h] The same DXA system (ie, Lunar or Hologic) must be used for all study procedures for a particular subject for the duration of the study. All DXA scan data will be submitted electronically to the central imaging vendor for analysis. For proximal femur DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fractures the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location.

[i] Clinical laboratory tests will include hematology, clinical chemistry, and urinalysis (dipstick).

[j] Bone biomarkers: serum CTX and P1NP. Blood sampling must be collected in the morning (between 8:00 and 10:00 am) after an overnight fast.

[k] PK samples must be collected prior to the immunogenicity sampling.

[l] Blood sampling for immunogenicity (ADA and NAb). Blood samples must be drawn prior to the IP when applicable, and the PK samples must be collected prior to the immunogenicity sampling. Separate samples will be collected for ADA and NAb assessments.

[m] Late onset injection site reactions to be documented as recommended in the electronic case report form completion guide.

[n] DXA can be performed within ±7 days of the Day 365 and Day 547.

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUEC	area under the effect curve
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	Contract Research Organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal cross-linking telopeptide of type 1 collagen
DXA	dual energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FKSBS	Fresenius Kabi SwissBioSim GmbH (the Sponsor)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus

HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
ITT	Intention-to-Treat
log	logarithm
LS	least squares
LS-BMD	lumbar spine bone mineral density
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibodies
NCI	National Cancer Institute
ONJ	osteonecrosis of the jaw
P1NP	procollagen type 1 N-terminal propeptide
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PFS	prefilled syringe
[redacted]	[redacted]
PMO	postmenopausal osteoporosis
PP	Per Protocol
PTH	parathormone
RMP	reference medicinal product
RP	reference product
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	standardized Medical Dictionary for Regulatory Activities queries
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

ULN	upper limit of normal
US	United States (of America)
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Background

Denosumab is a fully human monoclonal antibody of immunoglobulin G2 subtype, inhibiting receptor activator of nuclear factor kappa-B ligand, which is an essential factor for the formation, activation, and survival of osteoclasts. Its production is increased when estrogen is decreased, as it is after menopause and in conditions of hormone ablation, leading to an increased bone resorption.

Denosumab is marketed in the European Union (EU) and United States (US) as Prolia® and Xgeva®. Prolia is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. It is also approved as treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and in adult patients with long-term systemic glucocorticoid therapy at increased risk of fracture. Indications for Xgeva include treatment of giant cell tumor of bone and prevention of skeletal-related events in patients with cancer.

Prolia (60 mg) and Xgeva (120 mg) contain the same active substance (denosumab) and qualitatively the same excipients, but differ in strength and presentation. The mechanism of action of denosumab is the same across all indications currently approved for the reference products (RPs)/reference medicinal products (RMPs) Prolia and Xgeva (Prolia European Public Assessment Report [EPAR] Product Information, Xgeva EPAR Product Information, Food and Drug Administration [FDA] Prolia Prescribing Information, FDA Xgeva Prescribing Information).

FKS518, containing the active substance denosumab, is being developed by Fresenius Kabi SwissBioSim GmbH (FKSBS, the Sponsor) as a proposed biosimilar to Prolia and Xgeva.

1.1.2 Nonclinical Studies

A panel of state-of-the-art and fit-for-purpose methods measuring physicochemical and biological properties has been used to evaluate the analytical comparability, indicating similar results between FKS518 and the EU-approved RMP and the US-licensed RP Prolia and Xgeva. Based on the results of extensive structural and biological characterization to date, it is considered that the safety profile of the proposed biosimilar will be similar to that of the RP. Therefore, no animal studies are currently planned in the development program for FKS518, which is consistent with the European Medicines Agency (EMA) regulatory requirements for biosimilar development (EMA/CHMP/BMWP/403543/2010).

Refer to the Investigator's Brochure for further details on the nonclinical development.

1.1.3 Clinical Studies

The pharmacokinetic (PK) features of denosumab were evaluated in clinical studies of Prolia and Xgeva. The FKS518 clinical development plan is based on the available PK, efficacy, and safety data accumulated for the RP/RMP. In accordance with EMA Guideline (2012) and FDA Guidance (2016), the clinical comparability program of FKS518 consists of the following 2 clinical studies:

- A Phase I PK, pharmacodynamic (PD), safety, and immunogenicity study comparing the proposed denosumab biosimilar FKS518 with US-Prolia in healthy subjects (Study FKS518-001).

- The current Phase III efficacy, PD, safety, and immunogenicity study comparing the proposed denosumab biosimilar FKS518 with US-Prolia in women with postmenopausal osteoporosis (PMO).

Subjects in the Phase III study will not be dosed until the first 10 subjects in the comparative Phase I PK/PD study have been exposed to a single dose of either FKS518 or US-Prolia and followed for 48 hours and, after being evaluated by the Sponsor, no unexpected safety profile indicative of a materially altered benefit risk that would prohibit further recruitment of subjects is detected.

1.2 Study Rationale

The purpose of this clinical study is to evaluate the efficacy, PD, safety, and immunogenicity of FKS518, a proposed biosimilar to denosumab compared to the US-licensed Prolia (US-Prolia), in women with PMO. Limits to prior osteoporosis treatment that could add risk for cumulative effect or affect the interpretation of results have been established as exclusion criteria.

Data from this study, combined with the Phase I PK/PD equivalence study FKS518-001 in healthy volunteers, will provide evidence to support similarity between FKS518 and denosumab in terms of PK, PD, efficacy, safety, tolerability, and immunogenicity.

1.3 Benefit/Risk Assessment

FKS518 shows structural and functional similarity with the RP, US-Prolia, pointing toward a commonality of benefits and risks between FKS518 and the RP.

The safety profile of denosumab is considered well-established through extensive experience in clinical studies and post-marketing surveillance, providing a robust reference point for safety assessment of the proposed biosimilar product. In general, biologic agents are highly specific in their pharmacologic actions. The predominant manifestations of their toxicity are the consequences of on-target effects, so called exaggerated pharmacology. Accordingly, most of the adverse effects causally related to denosumab appear to derive from its PD effects (ie, suppression of bone turnover). These

exaggerated pharmacology-related adverse events (AEs) include common events such as hypocalcemia, hypophosphatemia, and musculoskeletal pain, as well as relatively rare or uncommon events such as osteonecrosis/avascular necrosis (including osteonecrosis of the jaw [ONJ]) and atypical fractures.

As high analytical similarity between FKS518 and the RP has been demonstrated, the AEs related to exaggerated PD effects can be expected at similar frequencies and, thus, the probability of detecting unexpected adverse effects is very low. The clinical benefits of FKS518 are based on the same PD effects.

Minor variations in the safety profile between FKS518 and the RP cannot be excluded. If these are to become clinically noticeable, they are most likely to manifest in the form of hypersensitivity as a consequence of the discriminatory ability of the immune system. Occurrence of Grade ≥3 or serious hypersensitivity has been classified as an adverse event of special interest (AESI) and will be closely monitored during all clinical investigations with FKS518.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of FKS518 can be found in the Investigator's Brochure.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with FKS518 are justified by the anticipated benefits that may be afforded to subjects with PMO.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate equivalent efficacy of the proposed biosimilar denosumab FKS518 to US-Prolia in women with PMO.

For Marketing Authorization Application (MAA) in the EU and European Economic Area (EEA) only: The primary objective is to demonstrate equivalent efficacy and PD of the proposed biosimilar denosumab FKS518 to US-Prolia in women with PMO.

2.2 Secondary Objectives

The secondary objective is to compare the safety, tolerability, PD, and immunogenicity of FKS518 with US-Prolia in women with PMO.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is the percent change from baseline in lumbar spine bone mineral density (LS-BMD) by dual energy x-ray absorptiometry (DXA) at Week 52.

For MAA in the EU and EEA only: The co-primary endpoint is the area under the effect curve (AUEC) of serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) up to Week 26.

Information about the corresponding estimands is provided in Section 9.4.1.

3.2 Secondary Endpoints

Efficacy:

- Percent change from baseline in bone mineral density (BMD) at femoral neck and total hip by DXA at Week 52.

Pharmacodynamic:

- Percent change from baseline in serum procollagen type 1 N-terminal propeptide (P1NP) at Week 52.
- Percent change from baseline in serum CTX at Week 52.

Safety and tolerability:

- Occurrence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) during the Core Treatment Period, Transition Period, and overall.
- Occurrence of treatment-emergent AESIs: drug-related hypersensitivity/allergic reactions (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3 or reported as SAEs) and AEs leading to investigational product (IP) discontinuation or study withdrawal during the Core Treatment Period, Transition Period, and overall.
- Occurrence of injection site reactions (ISRs) (local tolerability) during the Core Treatment Period, Transition Period, and overall.

Immunogenicity:

- Antidrug antibody (ADA) incidence during the Core Treatment Period, Transition Period, and overall.
- ADA titer during the Core Treatment Period and Transition Period.

- Neutralizing antibody (NAb) incidence during the Core Treatment Period, Transition Period, and overall.

[redacted]

4 STUDY PLAN

4.1 Overall Study Design and Plan

This is a double-blind, randomized, multicenter, 2-arm, multiple-dose, parallel-group study with a transition period, to compare efficacy, safety, tolerability, and immunogenicity of the proposed biosimilar to denosumab FKS518 with US-Prolia in ambulatory women with PMO. Bone biomarkers (PD) and PK will also be assessed. The study design is outlined in Figure 1.

This study will enroll female subjects aged 55 to 85 years with confirmed postmenopausal status and LS-BMD T-score ≤-2.5 and ≥-4.0, as measured by DXA. Subjects will be instructed to take 1000 mg calcium and at least 400 IU vitamin D supplementation daily.

The Investigator will obtain signed informed consent form (ICF) from the subject before any study procedures are performed. Subjects whose eligibility is confirmed at baseline will be randomized in a 1:1 ratio by an Interactive Response Technology (IRT) system to receive either FKS518 or US-Prolia at a dose of 60 mg delivered by subcutaneous injection starting at Day 1, and then every 26 weeks (6 months) for a total of 3 administrations within 78 weeks. Randomization will be stratified by age (<65 years; ≥65 years), and prior bisphosphonates therapy (Yes; No). Subjects in this study will not be dosed until the first 10 subjects in the comparative Phase I PK/PD study (FKS518-001) have been exposed to a single dose of either FKS518 or US-Prolia and followed for 48 hours and, after being evaluated by the Sponsor, no unexpected safety profile indicative of a materially altered benefit-risk that would prohibit further recruitment of subjects is detected.

The efficacy endpoints will be evaluated during the Core Treatment Period up to Week 52 (26 weeks after the second study drug administration), along with other endpoints, within ±7 days of the third IP injection. At Week 52, after efficacy and safety assessments have been performed, subjects will enter the Transition Period. Subjects who were originally randomized to receive US-Prolia will be re-randomized in a 1:1 ratio to receive a third administration of US-Prolia or to switch to FKS518 at Week 52. Subjects who discontinue the study before Week 52 will not be re-randomized. Subjects who were originally randomized to FKS518 will continue to receive this treatment at Week 52. During the Transition Period, safety, immunogenicity, and efficacy data will be analyzed up to Week 78.

The study will have a duration of up to 82 weeks, including a Screening Period of maximum 4 weeks (28 days) prior to first drug administration, a double-blind Core Treatment Period up to Week 52, and a double-blind single Transition Period from Week 52 up to Week 78, with administration of the study drug on Day 1, Week 26 (Month 6), and Week 52 (Month 12). An End of Study Visit will be performed 26 weeks (6 months) after the last administration of study drug (at Week 78).

In order to minimize missing data in the evaluation of the treatment effect under the treatment policy strategy, subjects who discontinue treatment early will be encouraged to remain in the study and attend all study visits of the period in which they were discontinued (Core Treatment or Transition Periods), even if it is decided that the next dose will not be administered.

The clinical sites shall implement risk minimization and the mitigation plan for coronavirus disease 2019 (COVID-19), including precautions such as use of personal protective equipment for subjects, site staff, and other visitors, site staff health-check, and the disinfection of site premises.

Efficacy (including BMD and PD bone biomarkers [ie, CTX and P1NP]), safety, immunogenicity, and PK assessments are detailed in the Schedule of Assessments (Table 1 and Table 2).

4.2 Discussion of Study Design

The proposed clinical study is a double-blind, randomized, multicenter, 2-arm, multiple subcutaneous dose, parallel-group study with a single transition period, in women with PMO. The proposed study design allows a comparison of the efficacy, safety, and immunogenicity between FSK518 and US-licensed Prolia to be made. Additionally, further to FDA request, the comparative clinical study will assess the safety of a single transition from US-Prolia to FKS518 (compared to continuation of US-Prolia). The single transition will allow to evaluate general safety, hypersensitivity, and immunogenicity after switching from the RP to the biosimilar.

The indication selected for the study is PMO women. This indication is considered to be the most sensitive and most likely to show any clinical differences between FKS518 and Prolia. Contraindications and special warnings for Prolia are taken into account as exclusion criteria in this study. Since age and previous treatment with bisphosphonates are known factors affecting efficacy, subjects will be stratified by age (<65 years; ≥65 years) and previous treatment with bisphosphonates (Yes; No). The stratification is based on correlation of primary efficacy endpoint with age and extent of bone loss. Previous treatment with bisphosphonates is related to the efficacy and baseline CTX values.

The selected primary endpoint LS-BMD is the most widely used PD measure correlated with fracture risk. BMD has a very low dynamic range and very high inter-subject variability making it a less sensitive marker. The limits of the acceptance range for the primary endpoint, percent change from baseline in LS-BMD at Week 52, are based on the meta-analysis of the following 3 FDA-reviewed studies which determined the treatment effect of denosumab compared to placebo as 5.35% (95% confidence interval [CI]: 4.83% to 5.87%): Bone, 2008; Cummings, 2009; and McClung, 2006.

The resorption marker serum CTX is a less universally validated endpoint for fracture risk than BMD, but it is a sensitive PD parameter to detect potential differences between

biosimilar denosumab and the RP (Vasikaran, 2011). Suppression of serum CTX levels occurs early in contrast to slow BMD increases after administration of denosumab. Serum CTX is selected as a secondary endpoint (change from baseline to Week 52), and as a co-primary endpoint (AUEC[0-W26]) for MAA in the EU and EEA only. To assess that the change in bone formation is similar between the biosimilar and the RP, the bone formation marker P1NP is also selected as secondary endpoint.

A duration of 12 months (ie, 2 cycles of treatment) is considered appropriate for evaluation of efficacy, as it represents a time point when the BMD increase is measurable but has not reached a plateau.

In agreement with EMA and FDA, the selected dose is the approved dose of Prolia: 60 mg denosumab every 6 months by subcutaneous administration.

4.3 End of Study

For each subject, participation in the study ends with the completion of the End of Study Visit. The study overall ends when the last subject has completed the last study visit.

5 STUDY POPULATION

It is planned to enroll 526 randomized subjects (263 subjects per arm) in approximately 75 sites globally.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Female ≥55 to ≤85 years of age, inclusive, at screening.

2. Have a body mass index (BMI) ≥18 to ≤32 kg/m^2.

3. Subject should have confirmed postmenopausal status, defined as age-related or early/premature amenorrhea ≥12 consecutive months and increased follicle-stimulating hormone (FSH) >40 mIU/mL at screening; or surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to screening (see Section 6.1.2 for details on required FSH testing).

4. Absolute BMD consistent with T-score ≤-2.5 and ≥-4.0 at the lumbar spine as measured by DXA as per central assessment.

5. At least 2 vertebrae in the L1-L4 region and at least 1 hip joint are evaluable by DXA.

6. Clinically acceptable physical examinations and laboratory tests (hematology, clinical chemistry, coagulation panel, and urinalysis) and no history or evidence of any clinically significant concomitant medical disorder that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with study evaluations or procedures.

7. Subjects must voluntarily give written informed consent before any study-related activities are performed. Subjects must read and fully understand the ICF and the requirements of the trial and must be willing to comply with all trial visits and assessments. A separate Information Sheet (containing important information about COVID-19, clinical research study participation and subject consent) will be provided to and signed by each subject to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the subject.

5.2 Exclusion Criteria

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

Disease-related

1. History and/or presence of 1 severe or >2 moderate vertebral fractures or hip fracture confirmed by x-ray (see Section 6.3.9 for definition of severe and moderate fracture).

2. Presence of active healing fracture at screening.

3. History and/or presence of bone-related disorders, such as but not limited to Paget's disease, osteomalacia, hyperparathyroidism (or parathyroid disorders), or renal osteodystrophy.

4. Osteonecrosis of the jaw or risk factors for ONJ such as invasive dental procedures (eg, tooth extraction, dental implants, or oral surgery in the past 6 months), poor oral hygiene, periodontal, and/or pre-existing dental disease as assessed by the Investigator.

5. Evidence of hypocalcemia (albumin-adjusted serum calcium <2.13 mmol/L or <8.5 mg/dL) or hypercalcemia (albumin-adjusted serum calcium >2.6 mmol/L or >10.5 mg/dL) as assessed by the central laboratory at screening.

6. Vitamin D deficiency (25-hydroxy vitamin D levels <12 ng/mL) as assessed by central laboratory at screening (retest is allowed once).

7. Known intolerance to calcium or vitamin D supplements.

Other Medical Conditions

8. History of known or suspected clinically relevant drug hypersensitivity to any components of the study drug formulations, comparable drugs, or to latex.

9. History of an episode of life-threatening or severe hypersensitivity in response to a medicinal product and/or environmental exposure.

10. Renal impairment: creatinine clearance <30 mL/min at screening or receiving dialysis.

11. Medical evidence of current or history of primary or secondary immunodeficiency as per Investigator's judgment.

12. Infection-related exclusions:

    a. Severe herpes zoster (disseminated, multidermatomal, herpes encephalitis, or ophthalmic herpes) or recurrent herpes zoster (defined as 2 episodes within 2 years), or any opportunistic invasive infection (eg, histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infestations) within 6 months before screening.

    b. Frequent (more than 3 of the same type of infection per year requiring treatment) chronic or recurrent infections (eg, urinary tract or upper respiratory tract infections).

    c. A positive test for HIV subtype 1 or 2, or hepatitis C virus (HCV), or evidence of acute or chronic hepatitis B infection, evaluated by testing for hepatitis B (hepatitis B surface antigen [HBsAg] and/or core antibody) at screening. Polymerase chain reaction (PCR) for HCV RNA and hepatitis B virus (HBV) DNA is allowed to confirm active disease if HCV or HBV antibodies are present without a positive result for HBsAg.

    d. A serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks before randomization.

    e. Required treatment with oral antibiotics and/or antifungal drugs within 14 days prior to screening.

    f. Confirmed or, based on the signs and symptoms observed at the time of assessment, suspected active COVID-19 infection at the time of screening and/or randomization.

13. Major surgical procedure within 8 weeks prior to the screening or the subject is scheduled to have a surgical procedure during the study.

14. Current or history of any malignancy, or myeloproliferative, or lymphoproliferative disease within 5 years before screening. Exception: subjects with resected cutaneous basal cell or squamous cell carcinoma, or carcinoma of cervix in situ that has been treated with no evidence of recurrence can be included.

15. History of clinically significant drug or alcohol abuse within the last year prior to randomization.

16. The subject should not participate in the study if they have any ongoing or recent (ie, at the time of screening) medical condition that may interfere with the study conduct, interpretation of study data, and/or otherwise put the subject at an unacceptable risk or could lead to noncompliance with requirements of the study; eg, subjects with rheumatoid arthritis or other autoimmune conditions are not eligible. The Investigator

should specifically evaluate the subject's eligibility taking into consideration COVID-19 risk factors and situation.

Prior or Concomitant Therapy

17. Prior denosumab (Prolia, Xgeva, or proposed denosumab biosimilar) exposure.

18. Prior use of fluoride within the 5 years before inclusion in the study.

19. Any current or prior use of strontium ranelate.

20. Any current or prior use of intravenous bisphosphonates. Prior use of oral bisphosphonates is excluded if:

    a. More than 3 years cumulative use prior to screening, unless last dose received is >5 years prior to screening, OR

    b. Any dose within 12 months before screening, except if subject received less than 1 month of cumulative use between 6 and 12 months prior to screening.

21. Current or prior use of teriparatide and other parathormone (PTH) analogs within 12 months before screening.

22. Current or prior use of systemic oral or transdermal estrogen or selective estrogen receptor modulators or tibolone within 6 months before screening.

23. Current or prior use of calcitonin or cinacalcet within 3 months before screening.

24. Current or prior use of any cathepsin K inhibitor (eg, odanacatib) within 18 months before screening.

25. Current or prior use of romosozumab or antisclerostin antibody.

26. Current or prior use of other osteoporotic agents used for the prevention or treatment of osteoporosis will be excluded according to the Investigator's judgment after consultation with the Medical Monitor.

27. Current use within 3 months before screening of any medication with known influence on the skeletal system (eg, systemic corticosteroids, heparin, lithium, etc). Subjects with a stable dose of systemic prednisone <5 mg or equivalent systemic corticosteroid for more than 4 weeks before screening are eligible. However, use of systemic glucocorticosteroids ≥5 mg prednisone or equivalent per day for more than 14 days within 3 months before randomization is not permitted.

28. Concomitant treatment with another biologic drug.

29. Prior use of other biologic investigational drugs for the treatment of PMO.

30. Prior use of any investigational drugs within 5 drug half-lives prior to screening or planned intake of an investigational drug during the course of this study.

31. Have received a COVID-19 vaccine within 4 weeks before randomization or COVID-19 vaccination is ongoing at the time of screening. COVID-19 vaccination is considered ongoing if a multidose regimen has been started but has not been completed.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who fail to meet the eligibility criteria and should not be randomized or receive the IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, reasons for failure, and any SAE. For screen failures, non-serious AEs during the screening will be collected only in the source documents (subject's records).

For laboratory parameters that initially do not meet eligibility requirements, a single retest within the 28-day screening period is permitted if the results are due to a documented laboratory error. Retesting is also allowed once for low 25-hydroxy vitamin D levels after consultation with, and agreement by, the Medical Monitor. Consultation with the Medical Monitor is required to identify whether repeat testing of any particular parameter would be clinically relevant (see Section 6.3.10). If inclusion/exclusion criteria are not met based on the results of the repeated tests, the subject should be considered a screen failure and not be enrolled in the study.

Re-screening of a screen failure subject is not allowed.

5.4 Premature Discontinuation

5.4.1 Premature Discontinuation of Investigational Product

All subjects that receive at least 1 dose of IP and who are permanently discontinued from the IP should be encouraged to remain in the study and attend all study visits of the period in which they were discontinued (Core Treatment or Transition Periods), with the aim to collect as much safety and efficacy data as possible. If a subject discontinues IP prior to Week 52, the subject will remain in the study up to the completion of the Week 52 assessments. If the IP has been administered at Week 52 (last planned study dose), the subject should be encouraged to remain in the study up to the completion of the End of Study Visit.

If premature withdrawal from IP occurs, the Investigator must make every effort to determine the primary reason for IP discontinuation. The date and primary reason for stopping study drug should be recorded in the electronic case report form (eCRF). In

addition, the Investigator must contact the IRT system to register the subject's early permanent treatment discontinuation.

The IP MUST be discontinued under the following circumstances:

- Adverse events.
    - AEs that in the judgment of the Investigator, taking into account the subject's overall status, advise against the subject continuing treatment.
    - Due to the language in the label of the comparator in this study (denosumab/US-Prolia), the IP should be discontinued if a subject develops: severe dermatologic reactions; severe bone, joint, or muscle pain; or anaphylactic or other clinically significant allergic reaction.
    - Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the subject's overall status, advise against the subject continuing treatment.
    - Potential Hy's Law events (elevations in liver biochemistry of alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥3x upper limit of normal [ULN] together with total bilirubin ≥2x ULN confirmed in a second test).
    - Anaphylactic or other serious allergic reactions.
    - If study drug cannot be resumed due to a toxicity and/or in case of toxicity that unacceptably endangers the safety of the subject (see Section 7.4.1).
- Lost to follow-up.
- Protocol noncompliance (protocol deviations). Any important protocol deviation that results in a significant risk to the subject's safety if the treatment is continued.
    - Use of prohibited medications following discussion with the Medical Monitor.
- Lack of efficacy.
- Withdrawal of consent from treatment.
- Investigator's decision.
    - The Investigator should withhold further dosing if the benefit risk of further exposure is no longer considered favorable for the subject.

The IP may also be discontinued if there is a delay >2 weeks from the scheduled IP injection date (see Section 7.4.1).

Subjects who discontinue IP for any of the reasons listed above will continue to be followed for efficacy and safety assessments. They are NOT considered withdrawn from the study.

In case of discontinuation for potential Hy's Law events, subjects will be followed up until liver test elevations return to normal or to the baseline state.

The IP can be re-introduced if the cause of IP interruption is solved and the re-start of treatment is medically justified and not otherwise prohibited (eg, treatment with prohibited medication), nevertheless it requires the approval of Medical Monitor.

5.4.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason, without any reprisal.

The Investigator has the right to terminate participation of a subject for any of the following reasons:

- Adverse event.
- Lost to follow-up.
- Death.
- Withdrawal of consent from the study.
- Other.

If a subject is withdrawn from the study, the Sponsor or designee will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

If the subject withdraws consent for disclosure of further information, the Sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Although a subject is not obliged to give her reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

At the time of premature withdrawal from the study, the Investigator should make every effort to ensure the subject completes the Early Termination visit as soon as possible, but not earlier than 4 weeks after last IP administration, for immunogenicity assessments (see Table 2).

Subjects who prematurely withdraw from the study cannot subsequently rejoin the study. Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled subjects.

For details on the discontinuation of study sites or the study as a whole, see Section 15.

5.4.3 Lost to Follow-up

A subject will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator (or designee) must make every effort to regain contact with the subject (there will be at least 2 attempts to contact the subject via telephone and 2 written communications). These contact attempts should be documented in the subject's records.
- Should the subject continue to be unreachable, she will be considered to have withdrawn from the study.

5.4.4 Medical Care of Subjects After End of Study

After subjects leave the study, medical care will be at the discretion of the Investigator following institutional standard of care and the Sponsor will not provide any additional IP to subjects.

6 DESCRIPTION OF STUDY ASSESSMENTS

A detailed schedule of study procedures/assessments is provided in Table 1 and Table 2.

Unless indicated otherwise, all laboratory samples will be processed and shipped to the central laboratory, as described in the central laboratory manual. The central laboratory will analyze the samples or send them to reference laboratory(ies) for analysis, as indicated in the manual. Refer to the central laboratory manual for the maximum total volume of blood to be collected per subject throughout the study.

6.1 Demographics and Other Screening Assessments

The screening procedures will be performed and completed within 28 to 1 days prior to randomization.

Safety assessments that are also part of the screening assessments are described in Section 6.3.

6.1.1 Informed Consent

Each subject must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the subject's standard care (see Section 10.3).

A separate Information Sheet (containing important information about COVID-19, clinical research study participation, and subject consent) will be provided to and signed by each subject to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the subject.

6.1.2 Medical History, Disease-related History, and Prior and Concomitant Medications and Procedures

Relevant information related to the subject's PMO will be collected and entered in the eCRF.

Postmenopausal status is defined as age-related amenorrhea ≥12 consecutive months and increased FSH >40 mIU/mL. Women aged >60 years, or with surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to screening; or early/premature postmenopausal (confirmed previous postmenopausal status) will not need to undergo FSH testing (see Section 6.3.10).

Assessment of BMD by DXA is described in Section 6.2.1.

Risk factors for osteoporosis, including age of menopause and menarche, nulliparity, low dietary calcium intake, sedentary lifestyle, history of fractures, family history of hip

fracture (first degree relatives), low BMI, age ≥70 years, smoking status (former/current smoker), and alcohol consumption will be recorded in the eCRF at the Screening Visit.

Other relevant medical history and current medical conditions (excluding PMO), history of tuberculosis or any treatment for active/latent tuberculosis, and previous surgeries before screening will be recorded in the eCRF for randomized subjects only. Note: If a therapy was administered for a previous medical history it will be collected in the Prior and Concomitant Medication or Procedures page of the eCRF.

At the Baseline Visit, medical history will be reviewed and updated to ensure that the subject remains qualified for the study. Significant findings that are observed with an onset date after the subject has signed the ICF and that meet the definition of an AE must also be recorded in the Adverse Event eCRF page (see Section 8.3).

Use of all prior and concomitant medication from 4 weeks before the Screening Visit until the Week 78/End of Study visit and all previous osteoporosis treatments should be recorded. Refer to Section 7.6 for further information about prior and concomitant medications and procedures.

6.1.3 Demographics

The age at screening, and race and ethnicity (if permitted by local regulation) of the subject are to be recorded in the eCRF.

6.2 Efficacy Assessments

6.2.1 Dual Energy X-ray Absorptiometry

Assessment of BMD by DXA will be performed at screening, Week 52, and Week 78/End of Study, as indicated in the Schedule of Assessments (Table 1 and Table 2). Efficacy assessments can be performed within ±7 days of study Day 365 and study Day 547.

The same DXA system (ie, Lunar or Hologic) must be used for all study procedures for a particular subject for the duration of the study. The central facility will monitor DXA machines quality control throughout the study.

Bone density will be measured at the lumbar spine and the proximal femur. Lumbar spine scans must include L1 through L4.

DXA scans of the lumbar spine will be performed in duplicate, ie, subjects will be removed from the table in between scans.

For proximal femur DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fractures the

hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location.

All DXA scan data will be submitted electronically to the central imaging vendor for analysis. A separate procedure manual provided by the central imaging vendor will give specific instructions for acquisition of scans as well as performance of Instrument Quality Control. Sites unable to submit data electronically can submit on CD or other media as specified in the DXA Procedural Manual, but electronic submission is preferred.

After analysis by the central imaging vendor, the study site may be asked to re-acquire a duplicate scan due to malpositioning or other technical reasons. The investigative sites should comply with the requests from the central imaging vendor and encourage the subject to return to the site for re-scan. Repeat scans should be performed as soon as possible after the request is received.

Assessment of bone biomarkers is described in Section 6.4.

6.3 Safety and Tolerability Assessments

6.3.1 General Considerations

The safety profile of the IP will be assessed through the recording, reporting, and analysis of AEs, physical examination findings, vital signs, a 12-lead ECG tracing, laboratory tests (clinical chemistry, hematology, and urinalysis), and local tolerability. Baseline medical conditions and concomitant medication will be recorded and accounted for during the evaluation of safety.

Comprehensive assessment of any apparent toxicity experienced by any subject will be performed from the time of giving the informed consent until completion of the study or withdrawal from the study. The Investigator or delegate will report all AEs, whether observed by the Investigator or site staff, or reported by the participating subject. The reporting period for AEs is described in Section 8.3.

Dedicated assessments of common and/or clinically important known or potential adverse reactions for the originator product will be performed and reported, as appropriate.

Signs and symptoms suggestive of hypersensitivity as judged by the Investigator will be captured and reported. The corresponding standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) will be used to aggregate these reports.

Local tolerability at the administration site will be assessed and reported.

6.3.2 Monitoring of Subjects with Adverse Events

AEs are periodically assessed and documented during the study. The final outcomes of all AEs must be evaluated and recorded at the final study visit unless already done. All SAEs

that are not resolved at the time of the final study visit must be monitored and followed up by the Investigator until stabilized (or judged to be permanent) or until the outcome is known or otherwise explained, unless the subject is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented. All information on AEs unresolved at study completion must be noted in the source documents. In addition, the Investigator should ensure that suitable ancillary care in accordance with local practices is provided to subjects with unresolved AEs, unless the subject is documented as "lost to follow-up."

Any SAE considered directly related to the IP with an onset after a subject has completed the final study visit must be recorded in the source documents and reported promptly to the study Sponsor.

AEs will be followed, recorded, and reported in line with the procedures described in Section 8.

6.3.3 Local Tolerability

Local tolerability in terms of ISRs will be assessed by inspection of the skin and appendages in proximity to the site of administration. This local tolerability assessment will be performed by the Investigator or designee to determine the presence of eg, erythema, rash, tenderness, swelling, itching, bruising, pain, extravasation, phlebitis, or other types of reaction. The Investigator is also requested to ask subjects during assessment about any such reactions that may have occurred since last assessment. All such findings including the time of onset and resolution as well as the need for ancillary care will be recorded in source data and transferred into the corresponding eCRF page. Non-serious ISRs are only to be reported in the dedicated eCRF page. ISR that qualify as SAEs (eg, ulceration that leads to or prolongs hospitalization) or meets definition of an AESI must be recorded as an SAE/AESI on the corresponding page of the eCRF. The severity of all ISRs is to be graded according to the current version of the National Cancer Institute (NCI)-CTCAE. Late onset ISRs will be documented as recommended in the eCRF completion guide.

6.3.4 Physical Examination

Comprehensive and brief physical examinations will be performed at the times specified in the Schedule of Assessments (Table 1 and Table 2).

The comprehensive physical examination will include assessments of the standard physical examination items, including general appearance, skin, head/neck, pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, musculoskeletal system, extremities, eyes (inspection and vision control), nose, throat, and neurologic status. The brief physical examination will target on symptoms or findings previously reported and will include, at a minimum, general appearance, pulmonary, cardiovascular, and throat examination.

The results of physical examination should be recorded in source document and eCRF as normal or abnormal. Any abnormality should be specified as clinically significant or not clinically significant in the eCRF. All clinically significant abnormalities noted during a physical examination before signing of the first informed consent until the first IP administration are to be recorded in the medical history section of the eCRF; all clinically significant abnormalities occurring or worsening thereafter should be recorded as AEs in the AE section of the eCRF.

6.3.5 Body Weight and Height

Body weight will be recorded at screening and at subsequent visits as specified in the Schedule of Assessments and documented in the eCRF.

Height will be measured at screening, Week 26, Weeks 52, and Week 78/End of Study. Height should always be measured in the same stadiometer and following the same procedure (eg, without shoes).

Body mass index will be calculated at screening only.

6.3.6 Vital Signs

Vital signs (including body temperature, respiratory rate, pulse rate, and blood pressure) will be measured after 5 minutes rest in the supine position at the time points noted in the Schedule of Assessments (Table 1 and Table 2). During the study, measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons.

Body temperature measurement will be performed first and will precede every other assessment of each visit. In the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.

Blood pressure measurements (systolic and diastolic) and pulse rate should be obtained with the subject's arm unconstrained by clothing or other material. The measurements will be obtained from the arm not used for blood sampling, where possible, using an appropriate cuff size and with the arm supported at the level of the heart.

When vital signs are scheduled to be assessed at the same time as blood is being collected, the vital signs should be measured prior to the blood collection is performed.

If the Investigator determines that there are any clinically significant abnormalities noted in the vital signs measurements, these should be recorded as AEs.

6.3.7 Electrocardiograms

Standard 12-lead ECGs will be performed at the times specified in the Schedule of Assessments (Table 1 and Table 2). ECGs will be assessed locally by the Investigator.

Subjects should rest in the supine position for 5 minutes before the tracings start. Only the overall evaluation (normal/abnormal) will be recorded in the eCRF. If abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator. Clinically significant ECG abnormalities should be recorded in the AE section of the eCRF.

6.3.8 Chest X-ray

Posterior-anterior and lateral chest x-ray (or chest radiographs) should be obtained at screening and reviewed by the Investigator. If chest x-rays or radiographs were taken within 2 months prior to screening and show no clinically significant abnormality, and there are no signs and symptoms suggestive of pulmonary disease that would exclude the subject from the study, then a chest x-ray or radiograph does not need to be repeated at screening. The previous x-ray imaging should be available for the Investigator to review; otherwise, a report by a Radiologist is required.

The chest x-ray finding should be recorded as normal or abnormal. Any abnormality should be specified. All clinically significant abnormalities noted in chest x-ray before signing of the informed consent until the first IP administration have to be recorded in the medical history section of the eCRF; all clinically significant abnormalities occurring or worsening thereafter should be recorded as AEs in the AE section of the eCRF.

6.3.9 Thoracolumbar Spine X-ray

Fractures at screening will be assessed by thoracic and lumbar spine x-ray. Severe fracture is defined as vertebral height loss >50%, and moderate fracture is defined as height loss from 25% to 50%.

Thoracic and lumbar spine x-ray should be obtained at screening and reviewed by the Investigator and sent for central reading. Previous x-rays taken within 6 months prior to screening will be acceptable.

Additional spine x-rays will be performed if there is a suspicion of a fracture (eg, new onset of persistent or pronounced back pain or material worsening of back pain); these will be assessed locally.

6.3.10 Clinical Laboratory Assessments

Blood samples will be collected for the laboratory tests outlined below in accordance with the timing noted in the Schedule of Assessments (Table 1 and Table 2), and sent to the central laboratory for analysis. All samples should be clearly identified. In the case that usage of the central laboratory is limited due to unforeseen changes in the COVID-19 situation, certain safety assessments may be performed at a local laboratory with the pre-approval of the Sponsor.

Table 3 Clinical Laboratory Assessments

Hematology	Red blood cell count, hemoglobin, hematocrit, total and differential white blood cell count (percentage and absolute values), and platelet count.
Clinical Chemistry	Glucose, total protein, albumin, sodium, potassium, calcium, phosphorus, magnesium, chloride, total cholesterol, triglycerides, creatinine, blood urea nitrogen, uric acid, bilirubin (total, direct), AST, ALT, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase (CPK), creatine kinase–myocardial band isoenzyme (CK-MB), 25-hydroxy vitamin D, C-reactive protein, and estimated glomerular filtration rate. FSH, TSH, and PTH (screening only).
Coagulation Panel	Activated partial thromboplastin time and prothrombin time (screening only).
Urinalysis	Dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen. Full urinalysis (dipstick plus microscopic evaluation) at the Investigator's discretion only if warranted by an abnormal dipstick finding.
Viral Serology	HBsAg, HBV core antibody, HCV antibody, HIV-1, and HIV-2 (screening only).

[redacted]

[redacted]

6.4 Pharmacodynamics: Bone Biomarkers

Serum samples will be collected for analysis of CTX and P1NP at the time points specified in the Schedule of Assessments (Table 1 and Table 2) to evaluate bone resorption (CTX) and bone formation (P1NP) in response to treatment with FKS518 (see Section 4.2).

Blood sampling must be collected in the morning (between 8:00 and 10:00 am) after an overnight fast. On the first 2 dosing days (Day 1 and Week 26), 2 samples will be obtained for bone biomarkers: pre-dose (between 8:00 and 10:00 am and fasting) and

5±1 hours post-dose (not fasting). On the third dosing day (Week 52), only the pre-dose sample (between 8:00 and 10:00 am and fasting) will be obtained.

Concentrations of the bone biomarkers will be measured by immunoassay at a qualified laboratory under the monitoring of the Sponsor.

[redacted]

The screening sample for bone biomarkers will be used to measure CTX and P1NP concentrations within each subject at the Screening Visit. The screening results will not be used as inclusion criteria or for baseline estimates for calculation of percent change from baseline (the samples taken pre-dose on Day 1 will be used for this purpose). The screening biomarker results will be reported with the other study results at the end of study and may be used to evaluate baseline variability of bone biomarkers within each subject by comparing screening and baseline values, which would provide context for the natural variability of biomarkers relative to observations from denosumab treatment with a single dose of 60 mg.

The PD (CTX and P1NP) determination will be performed for all subjects in the study using validated methods by a qualified laboratory under the responsibility of the Sponsor.

After completion of the study, PD (CTX and P1NP) samples will be stored for a maximum of 10 years as from the last subject's last visit in this study at the designated storage facility meeting the below requirements:

- Utilize Good Clinical Practice (GCP)-compliant sample management system.
- Perform GCP-compliant receipt and storage of biosamples.
- Perform GCP-compliant outbound shipment of biosamples.
- Perform GCP-compliant destruction of biosamples (if requested).

Refer to the central laboratory manual for details regarding the processing and shipment of samples.

[redacted]

[redacted]

6.6 Immunogenicity

Serum immunogenicity samples will be collected at the time points specified in the Schedule of Assessments (Table 1 and Table 2) to determine the incidence of ADA, ADA titers, and NAb incidence. A sample will be obtained at screening for assay validation purposes, but it will not be reported in the results. Blood samples for immunogenicity assessments must be drawn prior to the administration of the IP when applicable. Separate samples will be collected for ADA and NAb assessments.

The assay strategy is based on a multi-tiered approach. In the first tier, all samples will be assessed using a screening assay. In the second tier, samples testing putatively positive in the screening assay will then be analyzed in a confirmatory assay. Samples that are positive in the confirmatory assay will then be further characterized to determine the ADA titers. Finally, in the third tier, all confirmed positive samples will be tested in a NAb assay to determine if ADAs against the drug are neutralizing the biological activity.

ADA assays will be performed by a bioanalytical laboratory under the responsibility of the Sponsor using methods validated according to regulatory guidelines. Immunogenicity assessments will be described in the bioanalytical plans, which will be finalized before the beginning of sample analysis. Bioanalytical reports will also be generated, one for each ADA and NAb analysis, by the bioanalytical laboratory and will be included in the CSR appendix.

After completion of the study, immunogenicity samples will be stored for a maximum of 10 years as from the last subject's last visit in this study at the designated storage facility meeting the below requirements:

- Utilize GCP-compliant sample management system.
- Perform GCP-compliant receipt and storage of biosamples.
- Perform GCP-compliant outbound shipment of biosamples.
- Perform GCP-compliant destruction of biosamples (if requested).

The immunogenicity samples will be processed, shipped, and stored as described in the laboratory manual.

7 TREATMENTS

7.1 Investigational Products

7.1.1 Description of Investigational Products

The study drugs to be administered in this study are the proposed denosumab biosimilar FKS518 and US-Prolia.

Test Product

IP/non-IP:	IP
Name:	FKS518 (proposed denosumab biosimilar)
Dose:	60 mg every 26 weeks (6 months)
Route of administration:	Subcutaneous injection
Manufacturer:	[redacted]

Active Comparator

IP/non-IP:	IP
Name:	US-licensed Prolia (denosumab)
Dose(s):	60 mg every 26 weeks (6 months)
Route of administration:	Subcutaneous injection
Manufacturer:	Amgen Inc, US

7.1.2 Preparation, Handling, and Storage

FKS518 and US-Prolia will be supplied as single-use prefilled syringes (PFSs) for subcutaneous administration. Each PFS contains 60 mg of denosumab in 1 mL (60 mg/mL) solution for injection.

The list of excipients is available in the Investigator's Brochure.

[redacted]

Refer to the Pharmacy Manual for full details regarding the preparation of the IP.

7.1.3 Packaging, Labeling, and Shipment

All IPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

[redacted]

Refer to the Pharmacy Manual for full details for packaging, labeling, and shipment of the IP.

7.2 Blinding

To ensure that the blind of the study drug is maintained, each IP (FKS518 and US-Prolia) PFS will be blinded. The PFSs will be identical in appearance prior to delivery to clinical site.

The study will be double-blinded with the subjects, the Investigators, and the Sponsor being blinded to the IP administered until the end of the study. Randomization data will be kept strictly confidential, accessible only to authorized staff, until the time of unblinding.

Breaking of the blinding is only allowed in the case of an emergency, when knowledge of the IP is essential for the clinical management of the subject. Subjects whose treatment assignments are unblinded will not receive any further IP.

Emergency unblinding will be organized through IRT system. The Investigator must record the date of unblinding and the reason. All breaks of the study blind must be adequately documented.

If a suspected unexpected serious adverse reaction (SUSAR) is reported, the Contract Research Organization (CRO) Global Patient Safety Department may unblind the treatment assignment for the individual subject through the IRT system. If an expedited regulatory report is required, this report will usually identify the subject's treatment assignment according to regulations. When applicable, an expedited report will be sent to all Investigators in accordance with regulations. Code breaks performed at a place other than the study site will also be documented carefully, as per the CRO policies.

7.3 Method of Assigning Treatment

Each subject will have a unique subject screening number obtained from the IRT system. This will be assigned at the Screening Visit. The Investigator will keep a record (the

subject screening log) of subjects who entered screening. See Section 5.3 for screening failures.

Once the subject has been successfully screened and the Investigator has determined that the subject is eligible, the subject will be assigned a randomization number.

Randomization will be performed via a centralized IRT system. Eligible subjects will be randomly assigned to either FKS518 or US-Prolia in a 1:1 ratio, stratified by age (<65 years; ≥65 years), and prior bisphosphonates therapy (Yes; No).

Blinded IP supplies labeled with kit numbers and other information as per Master Label and in line with regulatory requirements will be provided to each study site. Dosing of study drug will be initiated at the site after randomization.

The Investigator will contact the IRT system for each subsequent IP administration, ie, Week 26 and Week 52. At the Week 52 Visit, subjects who were initially randomized to the US-Prolia group will be re-randomized in a 1:1 ratio to receive either FKS518 or US-Prolia at the Week 52 Visit. Subjects who were initially randomized to the FKS518 group will remain on the same treatment with FKS518 for the Week 52 administration. Subjects who discontinue study drug before or at Week 52 will not be re-randomized and will discontinue the study. Re-randomization will not impact the double-blind nature of the study as blinding will be kept.

The same stratification factors will be used for the randomization and re-randomization. The same values of stratification will be maintained for re-randomization.

Randomization will be conducted in permuted blocks.

If a subject withdraws from study participation, her unique identification number cannot be re-used for another subject.

7.4 Dose and Administration

The following IPs will be administered in the study: FKS518 and US-Prolia. The IPs will be administered at a dose of 60 mg by subcutaneous injection at the site on the Day 1 and Weeks 26 and 52 visits.

The IP will be supplied in single-use PFSs and no further preparation is required. The PFSs must be kept in the original outer packaging until administration. The preparation should be carefully inspected before administration. The IP is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if it contains particles.

Prior to administration, the IP must be removed from the refrigerator and must be kept at room temperature (up to 25°C) while remaining in the original container. This generally takes 15 to 30 minutes. The IP should not be warmed in any other way and must not be

put back in the refrigerator. The PFS should not be shaken. The IP should be administered up to 8 hours of removal from the refrigerator.

The injection site should be the abdomen. The IP should be injected slowly.

The IP will be administered by a healthcare professional experienced in giving subcutaneous injections. The exact date and injection time will be recorded in the eCRF. Subjects will be monitored for 2 hours following the IP administration and at the time of post-dose sampling for PK and PD on Day 1 (ie, 5±1 hours post-dose), including ISRs.

Investigators are also requested to look at the injection site thereafter and make note of any findings such as redness (erythema), itching (localized pruritus), injection site pain, swelling, bleeding, bruising, or hematoma. For any injection site findings, the time of onset (ie, when first noticed) and the duration of the ISR should be recorded by the Investigator on the corresponding eCRF page.

7.4.1 Delayed Investigational Product Dose

If for any reason (including a concurrent medical condition that is not an exclusionary criterion or a reason for IP discontinuation) the IP injection cannot be administered on the scheduled day, a ±2-week window is allowed. If the IP injection is not administered within this ±2-week window, the subject may be discontinued from the IP after consultation with the Medical Monitor. The exact date and injection time will be recorded in the eCRF.

7.4.2 Dose Modification

Dose modifications are not allowed in this study.

7.4.3 Intervention After the End of the Study

After subjects leave the study, medical care will be at the discretion of the Investigator following institutional standard of care and the Sponsor will not provide any additional care to subjects.

7.5 Precautions and/or Lifestyle Considerations

All subjects should receive calcium 1000 mg daily and at least 400 IU vitamin D daily during the study. Subjects should be instructed on the importance of calcium and vitamin D supplementation.

Several lifestyle recommendations may improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures. These include a calcium-rich diet (eg, dairy products) and avoiding use of tobacco and excessive use of alcohol.

Patients with osteoporosis may benefit from physical therapy or other activities and other nonpharmacologic measures to improve strength and reduce the risk of falls and fractures.

7.6 Prior and Concomitant Medications and Procedures

At each visit, all concomitant medications or procedures taken by the subject during the study from 4 weeks before the Screening Visit (including all previous treatment for osteoporosis) up to the completion of the final End of Study Visit are to be recorded in the appropriate section of the eCRF, noting the name (generic and tradename), dose/frequency/route, start/stop dates, duration, and indication of each drug. Non-drug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

The Medical Monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

7.6.1 Permitted Medications

All subjects should receive calcium 1000 mg daily and at least 400 IU vitamin D daily during the study.

Any other medications, therapies, or procedures (other than those excluded by the Clinical Study Protocol) that are considered necessary to protect subject welfare and will not interfere with the study drug may be given at the Investigator's discretion. All permitted medication and dose modifications of permitted medication must be recorded in the eCRF. Permitted medication will not be provided by the Sponsor as it is considered standard of care background medication.

While reductions in concomitant medication are allowed for safety reasons, it is important that medication dosages taken during the study remain stable to the extent possible.

COVID-19 vaccination is allowed during study participation. However, to ensure distinction between the adverse reactions caused by vaccination and the IP, it should not occur within 1 week before and after study drug administrations. In addition, to exclude any potential interaction between the study drug and COVID-19 vaccination, it is recommended to perform COVID-19 vaccination as much as possible in between 2 doses of the IP (ie, around Weeks 13 or 39, or after last dose around Week 65).

Any COVID-19 vaccination must be recorded in the eCRF, including all available data (tradename, manufacturer/Marketing Authorization Holder, date and time of vaccination, and batch number whenever available).

7.6.2 Prohibited Medications

The use of prohibited medications during the study will require the subject to be permanently discontinued from the study drug. The use of prohibited medications is also not permitted until the End of Study/Week 78 Visit.

Medication may be administered for the treatment of AEs or emergency treatment at any time during the study and must be recorded in the eCRF.

Table 4 presents a summary of prohibited medications with washout periods (before randomization).

Table 4 Summary of Prohibited Concomitant Medications with Washout Periods (Before Screening)

Prohibited Medications	Washout Period (Before Screening)
Strontium ranelate	Never
Fluoride	5 years
Intravenous bisphosphonates	Never
Oral bisphosphonates	>3 years cumulatively (unless last dose received >5 years) OR 12 months (note: it is allowed to have received less than 1 month of cumulative use between 6 and 12 months prior to screening)
Teriparatide and other PTH analogs within 12 months before screening	12 months
Systemic oral or transdermal estrogen or selective estrogen receptor modulators or tibolone	6 months
Calcitonin or cinacalcet	3 months
Any cathepsin K inhibitor (eg, odanacatib)	18 months
Romosozumab or antisclerostin antibody	Never
Other osteoporotic agents used for the prevention or treatment of osteoporosis	Investigator judgment after consultation with the Medical Monitor
Any medication with known influence on the skeletal system (eg, systemic corticosteroids, heparin, lithium, etc)	3 months

Prohibited Medications	Washout Period (Before Screening)
	A stable dose of systemic prednisone <5 mg or equivalent systemic corticosteroid for >4 weeks before screening is permitted Use of systemic glucocorticosteroids: ≥5 mg prednisone or equivalent per day for more than 14 days within 3 months prior to randomization is not allowed
Another biologic drug	None
Other biologic investigational drugs for the treatment of PMO	Never
Any investigational drugs	30 days or 5 half-lives (whichever is longer)
COVID-19 vaccination	4 weeks before randomization COVID-19 vaccination-related restrictions/recommendations are detailed in Section 7.6.1.

The Medical Monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

7.7 Overdose

There is no experience with overdosage with Prolia.

An overdose is defined as any dose greater than the defined highest daily dose included in a Clinical Study Protocol.

In the event of an overdose, subjects should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Even if it does not meet other criteria for an SAE, any instance of overdose (suspected or confirmed and irrespective of whether or not it involved FKS518 or US-Prolia) must be recorded in the study medication section of the eCRF and reported to the Sponsor or a specified designee in an expedited manner within 24 hours of awareness. Details of any signs or symptoms and their management should be fully recorded including details of any antidote(s) administered.

In the event of a suspected overdose of IP, the Investigator should carefully observe the subject and contact the Medical Monitor immediately, and guidance for next steps will be provided.

Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 8.4).

For overdoses associated with an SAE, the standard SAE reporting timelines apply (ie, 24 hours, see Section 8.4.1).

Overdoses will be reported in the Serious Adverse Event Form whether they are non-serious or serious AEs. The SAE criterion medically significant event is to be selected for overdoses that have been reported as SAEs.

7.8 Compliance

Subjects will be administered IP by the Investigator or site personnel, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF. Treatment compliance will be assured by site reconciliation of all IP supplies.

7.9 Accountability

The IP must not be used for any purpose other than that defined in this protocol. All supplies of IP will be accounted for in accordance with GCP.

The pharmacist or (designee) should maintain accurate records of all IP supplies received during the study. These records should include the dates and amounts of IP that were received at the site, dispensed, and destroyed or returned to the Sponsor (or designee). If errors or damage in the IP shipments occur, the Investigator should contact the Sponsor (or its designee) immediately. Copies of the IP accountability records will be provided by each Investigator for inclusion in the trial master file. The study Monitor will periodically check the supplies of IP held by the Investigator or pharmacist to verify accountability of the IP used.

The Investigator (or designee) will administer the IP only to the identified subjects in this study, according to the procedures described in this study protocol. Details of IP administered to subjects will be recorded in the eCRF. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IP received from the Sponsor (or designee).

After the end of the study, all unused IP and all medication containers should be destroyed at the study center or returned to the Sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the Sponsor. The IP resupply will be managed by the IRT system.

8 ADVERSE EVENTS

8.1 Adverse Events Definitions

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a participating subject regardless of a causal relationship with an administered IP. An AE can therefore be any unfavorable and unintended sign (see Section 8.1.4), symptom, or disease temporally associated with the use of the IP irrespective of a relationship to the exposure.

For surgical or diagnostic procedures, the condition/illness leading up to it is considered the AE rather than the procedure itself.

Any untoward medical occurrence in a participating subject occurring after exposure to IP is defined as a TEAE.

8.1.2 Severity Grading

The intensity or severity of AEs is to be graded by Investigators using the version of the NCI-CTCAE current at the time the Clinical Study Protocol was signed (unless otherwise specified). The NCI-CTCAE provides grading for specific events as well as a general grading scale. If no specific guidance is provided by the NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

8.1.3 Causality Assessment

Investigators must also systematically assess the causal relationship of AEs to IPs using the definitions below. Aspects to be considered when assessing a causal relationship of an AE to the IP include the temporal relationship between the AE and the exposure, the mechanism of action of the IP, the subject's medical history, the course of any underlying disease, any concomitant medications, or performed study procedures.

- Unrelated: Not reasonably related. The AE is not plausibly (pharmacologically/clinically) attributable to the IP under study. In this case a reasonable alternative explanation must be available.

- Related: Reasonably related. The AE is plausibly (pharmacologically/clinically) attributable to the IP under study in this Clinical Study Protocol.

8.1.4 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings or investigational findings (eg, an ECG trace) should not be reported as AEs unless they are clinically significant. Only abnormal laboratory findings or investigational findings that are associated with clinical signs or symptoms, that lead to treatment discontinuation, and/or are considered otherwise medically important by the Investigator, qualify as clinically significant. The corresponding sign, symptom, or medical condition (eg, anemia) must be reported as an AE rather than the abnormal value (eg, low hemoglobin).

8.1.5 Serious Adverse Events

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

- Results in death.

- Is life-threatening. (Note: The term “life-threatening” refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)

- Requires hospitalization or prolongs an existing hospitalization. (This does not include outpatient consultation in an emergency room of a hospital.)

- Results in persistent or significant disability or incapacity.

- Is associated with a congenital anomaly or a birth-defect.

- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. For example, an episode of allergic bronchospasm requiring intensive treatment in an emergency room that does not result in hospitalization.)

    - Confirmed COVID-19 cases should be considered as ‘otherwise medically important’ and accordingly reported as SAEs.

If several untoward medical occurrences have contributed to an SAE, Investigators are asked to identify the leading event that provides the main reason for the classification as an SAE. This event term will be used to assign the corresponding SAE narrative upon study completion.

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described above.

If death occurs, the primary cause of death or the event leading to the subject's death, should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

For the purposes of reporting, any suspected transmission of an infectious agent via an IP is also considered an SAE.

8.1.6 Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (eg, sample collection) are not considered SAEs. Similarly, hospitalization foreseen before enrolment in the study due to an underlying medical condition that did not materially worsen during the study (eg, hip replacement for a pre-existing coxarthrosis) is not considered an SAE. However, all instances of an unplanned hospitalization or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

8.1.7 Events Not to Be Considered as AEs/SAEs

Medical conditions present at the Screening Visit that do not worsen in severity or frequency during the study are categorized as Baseline Medical Conditions (ie, Medical History), and are not to be considered AEs.

8.1.8 Adverse Events of Special Interest

The following are considered pre-defined AESIs for this study:

- Drug-related hypersensitivity/allergic reactions (CTCAE Grade ≥3 or reported as SAEs), and
- AEs leading to IP discontinuation or study withdrawal.

8.2 Methods of Recording and Assessing Adverse Events

At each study visit, the subject will be queried on changes in her medical condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator or site staff.

Complete, accurate, and consistent information on all AEs experienced for the duration of the reporting period is to be reported on an ongoing basis in the appropriate section of the eCRF. In addition, all SAEs must be documented and reported using the appropriate SAE Report Form.

It is important that each AE report includes a description of the event, the onset and resolution dates (and times when the event is occurring in close temporal proximity to the administration – for example in the case of an acute hypersensitivity reaction), its severity, its causal relationship with the study treatment, any other potential causal factors, any treatment given or other action taken, including dose modification, interruption or discontinuation of the IP, and its outcome. In addition, SAEs should be identified and the qualifying seriousness criteria documented.

In case of AEs for which severity changes during the study, it should be recorded as a single AE with severity changes, and the highest severity (grade) will be chosen to document the single AE at the end, instead of having the event recorded as different AEs.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

8.3 Definition of the Adverse Event Reporting Period

The safety reporting period begins when the subject is initially screened for the study (date of signature of the ICF) and continues until completion of the study (Week 78/End of Study Visit) or withdrawal from the study. To complete the AE/SAE report, follow-up AE reporting may extend to the last visit of the subject. Data collected for all subsequent AE follow-up will be recorded only in the source data.

All AEs following ICF signature should be captured in the subject's source data. For randomized subjects, all AEs (serious and non-serious) should also be recorded on the eCRF for the reporting period. AEs that begin or increase in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit are considered TEAEs. All SAEs occurring after the date of the signature of the ICF must be reported as outlined below. See Section 5.3 for AE reporting on screen failures.

8.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest, and Dose Limiting Toxicities

8.4.1 Serious Adverse Events

In the event of a new onset/worsening SAE occurring during the reporting period, the Investigator must immediately (within 24 hours after becoming aware of the event) inform the Sponsor or its designee using the designated SAE Report Form (see SAE contact information on page 6 of this protocol). The form must be completed in accordance with the provided instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form must be provided without delay thereafter.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data with the corresponding information recorded in the eCRF.

The Investigator must respond to requests for follow-up information (eg, further details on the event, information on the outcome, supporting evidence or records) or to questions the Sponsor or designee may have concerning the AE within the same timelines as for initial reports. This is necessary to ensure prompt assessment of the event and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor. A representative from the Clinical Safety & Pharmacovigilance department may in exceptional circumstances contact the Investigator directly to obtain further information or to discuss the event.

8.4.2 Adverse Events of Special Interest

Serious AESIs, ie, that qualify as an SAE, must be reported using the forms and procedures outlined for SAE in an expedited manner according to the timelines outlined above for SAEs (see Section 8.4.1). Non-serious AESIs must be reported using the dedicated AESI form following same expedited timelines outlined for SAEs (Section 8.4.1). No AESI form needs to be completed for AESIs that are also SAEs.

8.4.3 Unexpected Adverse Reactions

An AE that is considered related to the IP qualifies as an adverse reaction. Adverse reactions that are not listed in the Reference Safety Information section of the Investigator's Brochure for FKS518 are considered "unexpected." If this concerns an

event that also qualifies as serious (ie, is an SAE), the event meets the criteria of a SUSAR. For such events, specific reporting requirements to Ethics Committees and Health Authorities apply. Timely clarification of queries is essential in these instances to meet the short regulatory reporting timelines.

Expedited reporting is also required for SUSARs that have arisen in other clinical studies of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the Ethics Committees and Health Authorities.

The CRO is responsible for unexpected suspected adverse reaction reporting to the authorities (Ethics Committees and Health/Competent Authorities).

The CRO will prepare submissions and submit to the authorities by email, fax, courier, local country officer, or hand-carried submission as required by country or local regulations. The Sponsor will perform electronic submissions to E2B to the EMA.

The CRO is responsible for unexpected suspected adverse reaction reporting to ethics committees according to local legislation. The CRO will distribute safety letters to Central Ethics Committees and Institutional Review Boards (IRBs) as required by country or local regulations.

The CRO will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days.

All other SUSARs shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the CRO (in accordance with Article 17(1)(a), (b), and (d) of European Directive 2001/20/EC).

The CRO is responsible for unexpected suspected adverse reaction reporting to the Investigators according to local legislation. The CRO will distribute safety letters to sites as required by country or local regulations.

8.4.4 Pregnancy and In Utero Drug Exposure

The study population includes postmenopausal women and, therefore, no pregnancies are expected. In the event of pregnancy, the procedures described below should be followed:

Only pregnancies considered by the Investigator to be related to study treatment (for example, resulting from a drug interaction with a contraceptive medication) qualify as an AE. However, all pregnancies with an estimated conception date during participation in the study must be recorded by convention in the AE page/section of the eCRF. The

Investigator must notify the Sponsor or designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting.

Investigators must actively follow up, document, and report the outcome of all pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor or designee of these outcomes using the paper Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described for SAE, while normal outcomes must be reported within 45 days after delivery.

If a participant becomes pregnant the IP must be discontinued immediately. The Sponsor or designee must be notified without delay and the subject must be followed as mentioned above.

8.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards, and Investigators

The Sponsor or designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the Independent Ethics Committee (IEC)/IRB that approved the study.

In accordance with International Council for Harmonisation (ICH) GCP, the Sponsor or designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In accordance with regulations, the Sponsor or designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations concerning Safety Report notifications to Investigators must be met.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For clinical studies covered by Directive 2001/20/EC, the Sponsor's responsibilities concerning the reporting of SAEs/SUSARs/Safety Issues will be carried out accordingly and in line with the related Detailed Guidance documents.

9 STATISTICS

9.1 General Procedures

All personnel involved with the analysis of the study will remain blinded until the study database lock, which will occur after the Week 78 data are available and protocol deviations are identified. Analyses will be performed using SAS® software Version 9.4 or higher (SAS Institute, Cary, NC, US).

The Statistical Analysis Plan (SAP) will be approved prior to any lock of the study database and unblinding of the study data. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol.

Descriptive statistics (number of observations, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

If not otherwise specified:

- Data collected before and analyzed at the end of the Core Treatment Period will be summarized per initial treatment group (FKS518 or US-Prolia).
- Data collected or analyzed after the re-randomization during the Transition Period will be summarized for the following 3 treatment groups: FKS518 during the complete study duration, US-Prolia during the complete study duration, and switch from US-Prolia to FKS518.

Baseline is defined as the last nonmissing measurement before the first administration of IP.

9.2 Analysis Populations

The Enrolled Analysis Set will include all subjects who provide informed consent. This analysis set will be used to report disposition and screening failures.

The Intention-to-Treat (ITT) Analysis Set will include all randomized subjects. Subjects will be analyzed according to their randomized treatment. This analysis set will be the primary set used for analyses/summaries of the primary efficacy endpoint, as well as for the co-primary efficacy endpoint (for MAA in the EU and EEA only), all secondary efficacy and other efficacy endpoints.

The Per Protocol (PP) Analysis Set will include all randomized and treated subjects who do not have a clinically important protocol deviation that could affect the assessment of the primary efficacy endpoint (ie, use of prohibited medications during the study). The protocol deviations that could affect the primary endpoint will be defined and agreed upon before unblinding. This analysis set will also be used for the co-primary efficacy

endpoint (for MAA in the EU and EEA only), and for secondary and other efficacy analyses. Subjects will be analyzed according to the actual treatment received.

The PD Analysis Set will include all subjects who receive at least 1 dose of IP, with enough bioanalytical assessments (ie, Baseline and Week 52) of at least 1 PD parameter, and without major protocol deviations affecting PD assessments. These protocol deviations will be defined and agreed upon before unblinding. Subjects will be analyzed according to the actual treatment received.

The Safety Analysis Set will include all subjects who receive at least 1 dose of IP and will be analyzed according to the actual treatment received. This analysis set will be used for summaries of safety and immunogenicity data.

9.3 Sample Size

A sample size of 526 randomized subjects (263 subjects per arm) is chosen to provide approximately 446 subjects (223 subjects per arm) in the PP Analysis Set at Week 52, assuming a 15% drop-out rate (including clinically important protocol deviations).

A total of 446 subjects will provide 90% power to demonstrate equivalence between treatments for the primary endpoint LS-BMD, with equivalence margins of [-1.45%, 1.45%] and a Type I error of 2.5%, assuming a 0.2% difference between FKS518 and US-Prolia and a common SD of 4%. A total of 446 subjects will provide 93.7% power assuming no difference between the 2 treatment groups.

The common SD is based on the Prolia EPAR. The limits of the acceptance range for the primary endpoint, percent change from baseline in LS-BMD at Week 52, are based on the meta-analysis of the following 3 FDA-reviewed studies, which determined the treatment effect of denosumab compared to placebo as 5.35% (95% CI: 4.83% to 5.87%): Bone, 2008; Cummings, 2009; and McClung, 2006.

The limits of the acceptance range will preserve at least 70% of the treatment effect of denosumab. Based on the lower bound of the 95% CI for the pooled denosumab treatment effect in these studies, a 1.45% margin will preserve 70% of the treatment effect (0.3*4.83%).

The drop-out rate/protocol deviation rate will be monitored on blinded data through the first 52 weeks. The number of randomized subjects may be adjusted based on the observed drop-out rate. If larger than anticipated, an investigation on the reasons for dropping out will be conducted.

(For MAA in the EU and EEA only): For the co-primary endpoint AUEC(0-W26) of serum CTX, based on simulated population PK/PD data with equivalence margins of [0.89, 1.12], assuming that the reference population and test population are identical, an analysis of covariance (ANCOVA) of the natural logarithm (log) transformed AUEC (derived in WinNonlin from simulated PD data) controlling for the natural log of the baseline serum CTX, demonstrated that a sample size of n=223 per arm is considered adequate to guarantee >99% power to show equivalence between FKS518 and US-Prolia.

A total of 446 subjects will provide >89% power to demonstrate equivalence between treatments for both the primary endpoint LS-BMD and co-primary endpoint AUEC(0-W26) of serum CTX with a conservative assumption of independence between endpoints.

To calculate suitable equivalence margins for the AUEC(0-W26) of serum CTX, a population PD model for CTX based on a baseline Imax (inhibitory maximum plasma concentration of an inhibitor) model with an IC50 (half-maximal inhibitory concentration) of 0.784 ng/mL (Zheng, 2015), and the PK concentrations resulting from a 60-mg denosumab dose, based on the published target mediated drug disposition model for denosumab (Sutjandra, 2011), with consideration of intra- and intersubject variability, was employed. Based on the considerations presented therein, an equivalence interval of [0.89, 1.12] is proposed for the PD variable AUEC(0-W26) of serum CTX to demonstrate equivalence between FKS518 and US-Prolia.

9.4 Statistical Methods

9.4.1 Primary Efficacy Analyses

9.4.1.1 Percent Change from Baseline in LS-BMD by DXA at Week 52

The primary efficacy objective is to demonstrate equivalence of FKS518 to US-Prolia based on LS-BMD.

The 5 attributes of the primary estimand are defined as follows:

1. Treatment of interest: Treatment (FKS518 or US-Prolia, 60 mg every 26 weeks) as randomized.

2. Population of interest: Women with PMO who were randomized.

3. Primary variable/endpoint of interest: LS-BMD percent change from baseline at Week 52.

4. Potential intercurrent events and strategy to address:

   A treatment policy strategy will be applied for all categories:

   - Permitted concomitant medications with the potential to impact the endpoint of interest.
   - Protocol deviations (prohibited medications, randomization errors, departures from visit windows, etc) with the potential to impact the endpoint of interest.
   - Treatment discontinuation.

5. Population-level summary: Mean difference between the 2 treatment arms in terms of the primary endpoint.

The primary estimator will be the least squares (LS) mean difference between FKS518 and US-Prolia, with its 95% CI, estimated within an ANCOVA framework as described below.

Percent change from baseline at Week 52 in LS-BMD will be analyzed using an ANCOVA with treatment, age (<65 years; ≥65 years) and prior bisphosphonates therapy (Yes/No) as fixed effects, and baseline LS-BMD as a covariate. The difference between treatments will be estimated by the LS mean difference between FKS518 and US-Prolia, with its 95% CI.

FKS518 will be considered equivalent to US-Prolia if the 95% CI for the difference in mean percent change from baseline to Week 52 in LS-BMD lies entirely within the equivalence interval of [-1.45%, 1.45%].

Supportive Estimand (Per Protocol Analysis Set)

The 5 attributes of the supportive estimand are defined as follows:

1. Treatments under evaluation: Treatment (FKS518 or US-Prolia, 60 mg every 26 weeks) as administered.

2. Population of interest: Women with PMO included in the PP Analysis Set.

3. Primary variable/endpoint of interest: LS-BMD percent change from baseline at Week 52.

4. Potential intercurrent events and strategy to address: None, by definition of the population.

5. Population-level summary: Mean difference between the 2 treatment arms in terms of the primary endpoint.

Further supportive estimands will be specified in the SAP.

9.4.1.2 AUEC of Serum CTX up to Week 26 (for MAA in the EU and EEA only)

The co-primary objective is to demonstrate equivalence of FKS518 to US-Prolia based on AUEC(0-W26) of serum CTX.

The 5 main attributes of the co-primary estimand are defined as follows:

1. Treatment of interest: Treatments (FKS518 or US-Prolia, 60 mg every 26 weeks) as randomized.

2. Population of interest: Women with PMO.

3. Variable/endpoint of interest: AUEC(0-W26) of serum CTX.

4. Potential intercurrent events and strategy to address:

   A treatment policy strategy will be applied for all categories:

   - Permitted concomitant medications with the potential to impact the endpoint of interest.

   - Protocol deviation (prohibited medications, randomization errors, departures from visit windows, etc) with the potential to impact the endpoint of interest.

   - Treatment discontinuation.

5. Population-level summary measure: Mean difference between the 2 treatment arms in terms of the endpoint of interest.

The co-primary estimator will be the LS mean difference between FKS518 and US-Prolia with its 95% CI, estimated within an ANCOVA framework as described below.

The natural log transformed AUEC(0-W26) of serum CTX will be analyzed on the PD Analysis Set using an ANCOVA with treatment, age (<65 years; ≥65 years), and prior bisphosphonates therapy (Yes/No) as fixed effects, and the natural log of baseline serum CTX concentration as a covariate.

The difference between treatments will be estimated by the LS mean difference between FKS518 and US-Prolia, with its 95% CI. The point estimate and the limits of the 95% CI will be back transformed on the original scale. FKS518 will be considered equivalent to US-Prolia on CTX if the 95% CI for the ratio of means of AUEC(0-W26) lies entirely within the equivalence interval of [0.89, 1.12].

Supportive Estimand (Per Protocol Analysis Set)

The 5 attributes of the supportive estimand are defined as follows:

1. Treatments under evaluation: Treatment (FKS518 or US-Prolia, 60 mg every 26 weeks) as administered.

2. Population of interest: Women with PMO included in the PP Analysis Set.

3. Variable/endpoint of interest: AUEC(0-W26) of serum CTX.

4. Potential intercurrent events and strategy to address: None, by definition of the population.

5. Population-level summary: Mean difference between the 2 treatment arms in terms of the endpoint of interest.

9.4.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be analyzed on the ITT and PP Analysis Sets.

The secondary efficacy estimands are based on BMD in the femoral neck and total hip. Percent change from baseline at Week 52 in BMD at femoral neck and total hip by DXA will be analyzed using an ANCOVA with study drug, age, and prior bisphosphonates therapy as fixed effects, and baseline BMD at femoral neck and total hip by DXA as a covariate. The difference between treatments will be estimated by the LS mean difference between FKS518 and US-Prolia, with its 95% CI.

9.4.3 Secondary Pharmacodynamic Analyses

The PD estimands are based on CTX and P1NP. The percent change from baseline at Week 52 in CTX and P1NP will be analyzed on the PD Analysis Set using an ANCOVA with treatment, age, and prior bisphosphonates therapy as fixed effects and baseline CTX and P1NP as covariates. The difference between treatments will be estimated by the LS mean difference between FKS518 and US-Prolia, with its 95% CI.

9.4.4 Other Efficacy Analyses

Other efficacy analyses will be outlined in the SAP.

9.4.5 Safety Analyses

The Safety Analysis Set will be used for the analysis of safety data (AEs, ISRs, exposure to the IP, clinical laboratory, physical examination, vital signs, and ECG). Safety data will be summarized for the Core Treatment Period, Transition Period, and overall.

AEs will be coded with MedDRA and will be summarized overall, by severity, and by relationship to FKS518 or US-Prolia. TEAEs are defined as AEs begin or increase in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit. TEAEs will be presented by system organ class and preferred term in frequency tables. Subjects with multiple AEs will be counted only once within each preferred term and system organ class. Key subject information for subjects with an AE with an outcome of death, subjects with SAEs, and subjects with an AE leading to discontinuation of IP will be listed.

Laboratory data (hematology, clinical chemistry, coagulation panel, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively for continuous laboratory variables. Shift tables will be used to present changes in categorical laboratory variables.

Where applicable, hematology and clinical chemistry laboratory results will be graded using the latest version of the NCI-CTCAE criteria. These laboratory NCI-CTCAE toxicity grades will also be summarized by visit and shift from baseline to worst on treatment NCI-CTCAE toxicity grade.

Laboratory data outside study-specific reference ranges will be listed.

Vital signs and ECG assessments will be presented descriptively.

9.4.6 Immunogenicity Analyses

Immunogenicity endpoints will be analyzed descriptively for the Safety Analysis Set. Immunogenicity data will be summarized for the Core Treatment Period, Transition Period, and overall. The proportion of subjects testing positive for ADAs, their titer, and the proportion of subjects with NAbs will be presented, when applicable, by treatment group and by scheduled visit and overall.

9.4.7 Demographic and Baseline Characteristics

If permitted by local regulation, demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics (including height, weight, BMI, and disease characteristics) will be presented descriptively.

[redacted]

9.4.9 Subgroup Analyses

To explore the uniformity of the detected overall treatment effect on the primary efficacy endpoint(s), descriptive subgroup analyses may be performed for the stratification factors as well as ADA and NAb status, if deemed relevant.

Full details of the subgroup analyses will be prespecified in the SAP.

9.4.10 Handling of Missing Values

In the event that the primary endpoint is missing, multiple imputation methodology using a pattern-mixture model assuming a missing-not-at-random mechanism may be applied, with further details on the pattern-mixture model to be provided in the SAP. Additional sensitivity analyses using other imputation methods may also be considered.

9.5 Interim Analysis

No interim analysis is planned.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, in compliance with ICH GCP E6(R2) Guidelines and according to the appropriate regulatory requirements in the countries where the study will be conducted, eg Title 21 of the US Code of Federal Regulations, EU Directives 2001/20/EC, EU Directive 2005/28/EC, and EU Regulation 536/2014.

In addition, this study will adhere to all local regulatory requirements and requirements for data protection.

As per Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human use, and repealing Directive 2001/20/EU, Article 52, a 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor will identify, investigate, and report Serious Breach as required by applicable regulation

FKSBS who is the Sponsor of a clinical trial shall notify in writing the relevant regulatory authority of any serious breach identified during the course of the study within 7 days of becoming aware of that breach.

During a clinical trial, when the Sponsor may become aware of serious breaches of the rules for the conduct of that clinical trial, the Sponsor will report to the Member States concerned in order for action to be taken by those Member States, where necessary.

10.2 Institutional Review Board/Independent Ethics Committee

The conduct of the study is conditioned by an appropriately constituted IRB/IEC approval.

Before initiating a study and enrolling any subject, the Investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the Clinical Study Protocol/amendment(s), ICF and subsequent consent form updates, subject recruitment materials (eg, advertisements), Investigational Brochure, and any written information to be provided to subject.

The Investigator must obtain a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

If required by local regulations, the study should be re-approved by the IEC annually.

10.3 Informed Consent

An unconditional prerequisite for a subject's participation in the study is her written informed consent which must be given before any study-related activities are carried out in compliance with ICH GCP requirements.

The subject will sign the ICF that contains information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions.

In addition to providing this written information to a potential subject, the Investigator or designee will inform the subject verbally of all pertinent aspects of the study. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons. The ICF must be signed and personally dated by the subject and the Investigator (or Sub-investigator[s] to whom this was delegated).

A separate Information Sheet (containing important information about COVID-19, clinical research study participation, and subject consent) will be provided to and signed by each subject to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the subject.

Both the subject and the Investigator or designee will sign an original copy of the ICF. A copy of the signed and dated ICF will remain at the Investigator's site and must be safely archived by the Investigator so that it can be retrieved at any time for monitoring, auditing, and inspection purposes. Another copy of the signed and dated ICF should be provided to the subject prior to participation. Whenever important new information that may be relevant to the subject's consent becomes available, the written ICF and any other written information provided to subjects will be revised by the Sponsor FKSBS or designee (CRO) and be submitted again to the IRB/IEC for review and favorable opinion. The agreed, revised information will be provided to each subject in the study for signing and dating. The Investigator or designee will explain the changes from the previous version to all subjects in the study prior to re-consent.

The Principal Investigator/Investigator(s) at each center will:

- Confirm that each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Confirm that each subject is notified that she is free to discontinue from the study at any time.
- Confirm that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Confirm that each subject provides signed and dated informed consent before conducting any procedure specifically for the study.

- Confirm that a copy of the signed ICF is given to the subject.

- Confirm that any incentives for subject who participate in the study as well as any provisions for subject harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC.

If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

10.4 Financing and Insurance

10.4.1 Study Agreement

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a Clinical Study Agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

The Principal Investigator at each investigational site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between the Sponsor FKSBS/CRO and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

10.4.2 Insurance, Indemnity, and Compensation

The Sponsor will maintain an appropriate clinical study insurance policy.

10.4.3 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

11 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule.
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is related to IP.
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures.
- A general reference to the procedures completed.
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the subject via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the Investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The [redacted] will write a data management plan, which will be finalized prior to performing any data validation.

11.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and

computer printouts, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

The Investigator or designee will record data, derived from the subject source documents, into the eCRF, after having received training both on the electronic data capture (EDC) system and the eCRFs.

The Investigator should complete and maintain all source documents in accordance with the ALCOAC principles (Attributable, Legible, Contemporaneous, Original, Accurate and Complete) in compliance with ICH GCP E6 R2. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

All data derived from the study will remain the property of the Sponsor FKSBS.

Records must be retained in accordance with the current ICH GCP E6 R2 Guidelines. All essential study documents including records of subject, source documents, eCRFs, and IP inventory must be kept on file at the investigational site.

The Investigator should confirm the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

The Investigator must maintain source documents for each subject in the study. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

Blood samples for PD (bone biomarkers), [redacted] and immunogenicity analyses will be sent to the designated qualified laboratory(ies) for processing per the laboratory manual and the results will be transferred electronically according to the data transfer agreement with the CRO.

Blood samples for safety analyses will be sent to the designated laboratory for processing per the laboratory manual and the results will be sent to the Investigator and transferred electronically according to the data transfer agreement with the CRO. The Investigator will maintain the safety laboratory results as part of the subject's source documents.

The EDC system includes password protection and internal quality checks, such as automatic edit checks, to identify data that appear inconsistent, incomplete, or inaccurate.

In addition, CRO staff will monitor the data entered in the eCRFs for completeness and accuracy. Designated investigational site study staff is required to respond to the query and confirm or correct the data in a timely manner.

The data collected by vendors will be electronically transferred to the CRO through datasets. Consistency of these data with the data recorded in the eCRF will be reconciled by the CRO. The CRO will send to the relevant investigational site, the central

laboratory, and the bioanalytical laboratory (or third-party vendor) a request for clarification of data using an electronic data query. All data discrepancies will be resolved prior to database lock.

Concomitant medications entered into the database will be coded using the most current World Health Organization (WHO) Drug Dictionary, which employs the Anatomical Therapeutic Chemical classification system.

Medical history and AEs will be coded using the most current MedDRA dictionary.

All source documents from this study are to be maintained by the Investigator and made available for inspection by authorized persons. The Investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The Sponsor or designee should verify that each subject has consented, in writing, to direct access to her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

11.2 Case Report Form Completion and Data Management

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, Investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

11.3 Study Files and Record Retention

All data derived from the study will remain the property of the Sponsor. The Sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of subjects, source documents, eCRFs, and the IP inventory, must be kept on file.

Essential study documents should be retained 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the proposed biosimilar to denosumab FKS518, but for at least 25 years after the end of the clinical study in line with the requirements set by EU Regulation 536/2014. However, essential study documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

After database lock, the Investigator will receive electronic copies of the subject data for archiving at the study site. The Investigator is not to dispose of any records relevant to this study without written permission from the Sponsor and is to provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

12 AUDITING AND MONITORING

12.1 Monitoring

The CRO will perform the monitoring of the study according to CRO's monitoring plan and applicable Standard Operating Procedures to review that the study is conducted and documented properly in compliance with the protocol, ICH GCP, and all applicable regulatory requirements.

During the study, a CRO representative will have regular contacts with the study site, including remote and on-site visits to:

- Provide study information and support to the Investigator(s).
- Confirm that facilities remain fit for purpose and that the site has appropriate resources available to conduct the study in compliance with the Clinical Study Protocol and are able to collaborate with the CRO monitoring team.
- Confirm that the investigational team is adhering to the Clinical Study Protocol requirements, that data are being recorded in the eCRF in an accurate and timely manner, that biological samples are handled in accordance with the laboratory manual, and that study IP accountability checks are being performed.
- Perform direct source data verification by comparing eCRF data with the subject's source document at the investigational site including verification of informed consent of participating subject.
- Discuss with the Investigator any deviation from the Clinical Study Protocol and other study instruction, and review that there are timely and completely reported accordingly.
- Review with the Investigator any safety events for timely and complete reporting.
- Work closely with the Investigator and site staff to facilitate effective management of the study in compliance with the Clinical Study Protocol, ICH GCP Guidelines, and applicable regulatory requirements.

The CRO representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

12.2 Audits and Inspections

Authorized representatives of the Sponsor FKSBS/CRO, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities

were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, current ICH guidelines, and any applicable regulatory requirements.

If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform the Sponsor or designee immediately that this request has been made.

12.3 Deviation from Study Protocol

The Investigator should conduct the study and perform procedures as defined in the protocol, and collect and record data as instructed by the eCRF completion guidelines. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research-related purpose involving any of the study interventions and/or the study IP.

Protocol deviations will be discussed with the Investigator.

13 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. Substantial protocol amendments will be submitted to the regulatory authorities and/or IRB/IEC as appropriate, and the Investigator must await approval before implementing the changes.

The current version of the ICF will require similar modification if the IRB/IEC, Investigator, and/or Sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the subject and/or impact the subject's involvement as a study subject. In such cases, the ICF will be renewed for enrolled subjects before their continued participation in the study.

14 STUDY REPORT AND PUBLICATIONS

A CSR will be prepared after final database lock.

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The Sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

The publication policy of the Sponsor is discussed in the Investigator's Clinical Research Agreement.

The designated Coordinating Investigator will sign the CSR.

The posting of FKSBS-sponsored study information and tabular study results on the respective public registry and as required any national accessible websites will be done by the CRO.

15 STUDY START AND TERMINATION

The study start date is the date on which the first subject provides informed consent.

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

The Sponsor FKSBS may terminate the study at an individual investigational site if recruitment is poor or if it becomes unjustifiable for medical or ethical reasons.

The Sponsor FKSBS or the CRO will inform Health Authorities and IECs/IRBs about the discontinuation of the study at an individual site and the reasons for discontinuation in accordance with applicable regulations.

16 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor FKSBS. However, authorized representatives from regulatory authorities, IRB/IEC, the Sponsor FKSBS and the CRO are allowed full access to the study records including subjects' source documents (EU General Data Protection Regulation).

17 REFERENCES

Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008;93(6):2149-57.

Cummings SR, San Martin J, McClung MR, et al. FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.

EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), May 2012.

EMA Prolia EPAR Product Information, last update 08/09/2020.

EMA Xgeva EPAR Product Information, last update 07/08/2020.

EU General Data Protection Regulation (https://ec.europa.eu/info/law/law-topic/data-protection_en).

McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354(8):821-31.

Sutjandra L, Rodriguez RD, Doshi S, et al. Population pharmacokinetic meta-analysis of denosumab in healthy subjects and postmenopausal women with osteopenia or osteoporosis. Clin Pharmacokinet. 2011;50(12):793-807.

US Food and Drug Administration, Guidance for Industry. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. 2016.

US Food and Drug Administration, Prolia prescribing information, revised 07/2019.

US Food and Drug Administration, Xgeva prescribing information, revised 05/2019.

Vasikaran S, Cooper C, Eastell R, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. Clin Chem Lab Med. 2011;49(8):1271-4.

Zheng J, van Schaick E, Wu LS, et al. Using early biomarker data to predict long-term bone mineral density: application of semi-mechanistic bone cycle model on denosumab data. J Pharmacokinet Pharmacodyn. 2015;42(4):333-47.

18 APPENDICES

18.1 APPENDIX I – Study Administrative Structure

Sponsor:	Fresenius Kabi SwissBioSim GmbH Terre Bonne Business Park Route de Crassier 23 – Bâtiment A3 CH – 1262 Eysins Switzerland
Sponsor Medical Lead:	[redacted]
Coordinating Investigator:	[redacted]
Contract Research Organization:	[redacted]
Contract Research Organization Medical Lead:	[redacted]

Clinical/Bioanalytical Laboratories:	[redacted]
Central DXA and X-ray Reader:	[redacted]
IRT System:	[redacted]
FKS518 - Proposed Biosimilar Denosumab Manufacturer:	[redacted]
US-licensed Prolia (Denosumab) Manufacturer:	Amgen Inc One Amgen Center Drive Thousand Oaks, CA 91320-1799 US

A log of the name and title of the Investigators who are responsible for conducting the study, and the address and telephone numbers of the study sites will be maintained.

The names and addresses of any other laboratories involved in the study (further to those stated above) will be provided in the laboratory manual.