BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW-

Application Type	BLA 351(k)
Application Number	BLA 761398
Received Date	March 25, 2024
BsUFA Goal Date	March 25, 2025
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology and Nephrology Division of Oncology 1/Office of Oncologic Diseases
Review Completion Date	See DARRTS stamped date
Product Code Name	FKS518
Proposed Nonproprietary Name[1]	Denosumab-bnht
Proposed Proprietary Name[1]	Conexxence (proposed interchangeable biosimilar to US-Prolia); Bomyntra (proposed interchangeable biosimilar to US-Xgeva)
Pharmacologic Class	RANK Ligand (RANKL) Inhibitor
Applicant	Fresenius Kabi USA, LLC
Applicant Proposed Indication(s)	Conexxence (proposed interchangeable biosimilar to US-Prolia): • Treatment of postmenopausal women with osteoporosis at high risk for fracture. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. Bomyntra (proposed interchangeable biosimilar to US-Xgeva):

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

	• Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Recommendation on Regulatory Action	Approval of FKS518 as a biosimilar to US-Prolia and US-Xgeva. Provisional determination that FKS518 is interchangeable with US-Prolia and US-Xgeva. Approval as interchangeable is precluded due to unexpired first interchangeable exclusivity for Jubbonti and Wyost.

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OPQAIII = Office of Product Quality Assessment III
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
OTBB = Office of Therapeutic Biologics and Biosimilars
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OPQAIII	Office of Product Quality Assessment III

OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.-Prolia	U.S.-licensed Prolia
U.S.-Xgeva	U.S.-licensed Xgeva

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1. Executive Summary

1.1. Product Introduction

Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). It is marketed in the United States under the tradenames Prolia (60 mg/1 mL in a pre-filled syringe [PFS]) and Xgeva (120 mg/1.7 mL or 70 mg/mL in a single-dose vial). The indications and strength of US-Prolia are different from the indications and strength of US-Xgeva.

The Applicant proposes FKS518 as an interchangeable biosimilar product to US-Prolia and US-Xgeva, and the proposed proprietary names are Conexxence and Bomyntra, respectively.

The Applicant seeks the same indications for FKS518 as those which are approved for US-Prolia and US-Xgeva. The strengths, dosage form, route of administration, indications, and dosing regimens for FKS518 will be the same as those of US-Prolia and US-Xgeva, which are listed below:

Conexxence:

- Strength: 60 mg/1 mL
- Dosage form: injection
- Route of administration: subcutaneous
- Dosing regimen: 60 mg administered subcutaneously once every 6 months
- Indications:
    - Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
    - Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
    - Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
    - Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures

- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

Bomyntra

- Strength: 120 mg/1.7 mL
- Dosage form: injection
- Route of administration: subcutaneous
- Indications and associated dosing regimen:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors (120 mg injected subcutaneously [SC] every 4 weeks)
  - Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy)
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy).

Bomyntra will be available in two presentations: a single-dose vial and a single-dose pre-filled syringe. US-Xgeva is not currently approved in a PFS presentation.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL (receptor activator of the nuclear factor kappa-B ligand), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclast, the cells responsible for bone resorption thereby modulating calcium release from bone.

This BLA contains sufficient data and information to demonstrate that FKS518 has the same mechanism(s) of action as those of US-Prolia and US-Xgeva. The Applicant performed a comparative analytical assessment of FKS518 and US-Prolia and US Xgeva. The data provided support the conclusion that FKS518 is highly similar to US Prolia and US-Xgeva.

US-Prolia is licensed in 60 mg/1 mL in a pre-filled syringe (PFS) and US-Xgeva is licensed in 120 mg/1.7 mL or 70 mg/mL in a single-dose vial.

FKS518 is proposed as below:

For subcutaneous injection:

- Single-dose prefilled syringe containing 60 mg denosumab-bnht in 1 mL solution.
- Single-dose vial containing 120 mg denosumab-bnht in 1.7 mL (70 mg/mL) solution.
- Single-dose prefilled syringe containing 120 mg denosumab-bnht in 1.7 mL (70 mg/mL) solution.

FKS518 has the same route of administration, strengths, and dosage form as those of US-Prolia and US-Xgeva.

Additionally, the conditions for use for which the Applicant is seeking licensure have been previously approved for US-Prolia and US-Xgeva.

1.4. Inspection of Manufacturing Facilities

An on-site pre-license inspection for the FKS518 drug substance and drug product manufacturing facilities at (b) (4) was conducted on (b) (4), and a 2-item Form FDA 483 was issued to the firm at the end of the inspection. The responses to 483 items were reviewed and found satisfactory.
All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional activity.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

1.6. Biosimilarity and Interchangeability Assessment

Table 1: Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies[2]	
Summary of Evidence	• The comparative analytical assessment included comparisons between FKS518 and US-Prolia and FKS518 and US-Xgeva. • FKS518 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components.

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

	• FKS518 has the same strengths, dosage form, and route of administration as US-Prolia and US-Xgeva.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• No residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• Pharmacokinetic (PK) similarity between FKS518 and US-Prolia was demonstrated in healthy male subjects in Study FKS518-001 and supports demonstration of no clinically meaningful differences between FKS518 and US-Prolia. • Because of demonstrated analytical similarity between FKS518 and US-Xgeva and US-Prolia, PK data from Study FKS518-001 also support the conclusion that FKS518 would be expected to have similar PK as US-Xgeva. Additionally, comparative PK data generated with the 60 mg/1 mL (US-Prolia) strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL (US-Xgeva) strength. • The presence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were compared between FKS518 and US-Prolia in healthy male subjects (Study FKS518-001) and female subjects with postmenopausal osteoporosis (Study FKS518-002). The incidence of immunogenicity was low and comparable across treatment groups in both studies. There was no apparent impact of ADA or NAb on study drug PK, PD, safety, or efficacy.

	• Therefore, the data support that FKS518 has no clinically meaningful differences from US-Prolia and US-Xgeva.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	• The Applicant conducted a randomized, double-blind comparative clinical study (Study FKS518-002) in 553 post-menopausal women with osteoporosis to compare the PK, pharmacodynamics (PD), efficacy, safety, and immunogenicity of FKS518 and US-Prolia. Subjects were randomized to receive FKS518 or US-Prolia 60 mg injected SC every six months for one year (Core Treatment Period). After one year, subjects initially assigned to US-Prolia in the Core Treatment Period were re-randomized to either continue US-Prolia or transition to FKS518. Subjects who received FKS518 during the Core Treatment Period continued their treatment with FKS518. Subjects were followed for six months after the third dose of study drug. • This study demonstrated that FKS518 and U.S.-Prolia have similar efficacy with respect to the percent change from baseline in bone mineral density (BMD) for lumbar spine at Week 52. The 90% confidence interval (CI) for the difference in mean change were within the pre-specified equivalence margin of ±1.45%. • The safety profiles of FKS518 and U.S.-Prolia were comparable. The adverse events observed were consistent with the known safety profile of denosumab (as labeled in the U.S.-Prolia USPI). There were no meaningful differences in the incidence of specific adverse events between FKS518 and U.S.-Prolia, and the small differences in incidences of some of the treatment emergent adverse events (TEAE) that were observed in the FKS518 and U.S.-Prolia arms was likely due to chance. • The study also demonstrated similarity of FKS518 and US-Prolia with respect to the pharmacokinetics of denosumab,

	pharmacodynamic effect on biomarkers of bone turnover, and immunogenicity.
Assessment of Residual Uncertainties	• There are no residual uncertainties.
Switching Study	
Summary of Evidence	• FDA determined that a switching study is unnecessary to support a demonstration of interchangeability for FKS518. • The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of FKS518 and US-Prolia or FKS518 and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	
Summary of Evidence	• The Applicant has provided adequate data and information, including the analytical and clinical data, to support a demonstration that FKS518 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• Division of General Endocrinology (DGE) and the Office of Oncology Drugs (OOD) have determined that the Applicant has provided adequate scientific justification and agrees with the Applicant's justification for extrapolation to the other indications listed in the US-Prolia and US-Xgeva USPIs being sought for licensure based on: 1) the mechanism of action of denosumab, 2) the analysis of the known safety and immunogenicity profiles of denosumab across each of the indications being sought and 3)

	the assessment of any differences in expected toxicities for each indication. • The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of FKS518 as an interchangeable biosimilar to US-Prolia and US-Xgeva for the following indications for which US-Prolia and US-Xgeva have been previously approved: ○ Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. ○ Treatment to increase bone mass in men with osteoporosis, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. ○ Treatment of glucocorticoid-induced osteoporosis who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. ○ Treatment to increase bone mass in men at high for fracture receiving androgen deprivation therapy for prostate cancer ○ Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer ○ Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors

	○ Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity ○ Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of FKS518 as an interchangeable biosimilar to US-Prolia and US-Xgeva for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FKS518 is highly similar to U.S.-Prolia and U.S.-Xgeva, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FKS518 and U.S.-Prolia, or between FKS518 and U.S.-Xgeva, in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that FKS518 can be expected to produce the same clinical result as U.S.-licensed Prolia and U.S.-licensed Xgeva in any given patient. The risk in terms of safety or diminished efficacy of alternating or switching between use of FKS518 and U.S.-Prolia or between FKS518 and U.S.-Xgeva is not greater than the risk of using U.S.-Prolia or U.S.-Xgeva without alternation or switch. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FKS518 is biosimilar to U.S.-Prolia and U.S.-Xgeva and meets the statutory criteria to be an interchangeable with U.S.-Prolia and U.S.-Xgeva as follows:

- FKS518, 60 mg/mL injection for SC use in a single-dose PFS as an interchangeable biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- FKS518, 120 mg/1.7 mL injection for SC use in a single-dose vial and in a single-dose PFS as interchangeable biosimilars to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

for each of the following indications for which US-Prolia and US-Xgeva have been previously approved and for which the Applicant is seeking licensure of FKS518:

US-Prolia:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis

therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

US-Xgeva:
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Healthcare providers administer US-Xgeva to all patient populations. The FKS518 PFS may be licensed as interchangeable with US-Xgeva given that the difference between a vial and a PFS would not be expected to result in any clinically meaningful difference in this case, as healthcare providers can be expected to manage risks associated with administering to patients using a vial or PFS in accordance with the administration instructions in the labeling.

FDA has not identified any deficiencies that would justify a complete response action and has provisionally determined that FKS518 meets the statutory interchangeability criteria for any condition of use as described above. However, pursuant to section 351(k)(6) of the PHS Act, FDA is unable to approve FKS518 as interchangeable because of unexpired first interchangeable exclusivity (FIE) for US-licensed Jubbonti and Wyost. FDA has previously determined that FIE for Jubbonti and Wyost will expire on October 29, 2025. Refer to the Purple Book at https://purplebooksearch.fda.gov/.

Therefore, BLA 761398 will be administratively split to facilitate an approval action for FKS518 as biosimilar to US-Prolia and US-Xgeva (“Original 1”) and a provisional determination that FKS518 would be interchangeable with US-Prolia and US-Xgeva (“Original 2”), but for unexpired exclusivity.

The review team recommends approval of FKS518 as a biosimilar product as follows:

- FKS518, 60 mg/mL injection for SC use in a single-dose PFS is biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- FKS518, 120 mg/1.7 mL injection for SC use in a single-dose vial and in a single-dose PFS are biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

The review team also recommends a Provisional Determination that:

- FKS518, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and

- FKS518, 120 mg/1.7 mL injection for SC use in a single-dose vial and in a single dose PFS meet the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

BLA 761398/Original 2 will receive a Provisional Determination letter. The Applicant is expected to submit an amendment seeking approval no more than six months prior to the expiration of such exclusivity or when the Applicant believes that BLA 761398 Original 2 will become eligible for approval.

The CDTL and Division Signatory agree with the above assessment and recommendation.

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2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

Pre-IND 145897 for this product was opened in November 2019 with the submission of a Biosimilar Biological Product Development (BPD) Type 2 meeting request. The initial pre-IND meeting occurred on February 13, 2020, during which the development of FKS518 as a biosimilar product to US-licensed Prolia and US-licensed Xgeva was discussed.

Key interactions between FDA and the Applicant are summarized in Table 2.

In addition to the FKS518 60 mg/mL pre-filled syringe (PFS) presentation and a FKS518

120 mg/1.7 mL (70 mg/mL) vial presentation, the Applicant proposed a FKS518 120 mg/1.7 mL (70 mg/mL) PFS presentation as well. US-Xgeva is not currently approved in a PFS presentation. Over the course of several meetings and correspondences, FDA discussed the sponsor's proposed FKS518 120 mg/1.7 mL (70 mg/mL) PFS presentation, noting that an assessment of interchangeability would be made during review of the BLA.

Table 2. Regulatory Milestones

Date	Event	Comments
2/13/2020	BPD Type 2 Meeting	Discussed development program. FDA recommended that the Applicant conduct a single-dose PK study in healthy subjects and a comparative efficacy and safety study in women with postmenopausal osteoporosis. FDA stated that a PFS presentation of FKS518 120 mg/1.7 mL (70 mg/mL) may be acceptable provided it meets the statutory standard for biosimilarity, but also requested that the Sponsor submit justification as to why a FKS518 120 mg/1.7 mL (70 mg/mL) PFS presentation would not constitute a new condition of use. In addition, FDA stated that the Sponsor should perform a risk assessment to determine the quality attributes that may be impacted by differences in the FKS518 vial and PFS (120 mg/1.7 mL) manufacturing processes.
6/2/2021	BPD Type 2 Meeting (Written Responses)	Discussed validation of PK, ADA, and Nab assays.
10/26/2021	BPD Type 2 Meeting (Written Responses)	FDA requested the Sponsor provide an explanation of how they propose to meet the statutory standards for licensure of FKS518 120 mg/1.7 mL (70 mg/mL) as a biosimilar to US-Xgeva, including how they will demonstrate that the conditions of use for the proposed PFS have been previously approved for US-Xgeva.
6/7/2022	Advice letter from FDA	FDA communicated that the acceptability of the FKS518 120 mg/1.7 mL (70 mg/mL) PFS presentation will be made during review of the BLA. To support the demonstration of biosimilarity, FDA advised the Sponsor to submit data and information demonstrating that the proposed differences between the 120 mg/1.7 mL PFS FKS518 and US-licensed Xgeva do not result in a clinically meaningful difference between the products in terms of safety, purity, and potency, and that the 120

		mg/1.7 mL PFS FKS518 meets the statutory standards for biosimilarity.
9/26/2022	BPD Type 2 Meeting (Written Responses)	Discussed the Statistical Analysis Plan for the comparative clinical study (FKS518-002).
11/9/2022	Advice letter from FDA	FDA communicated that a switching study would not be necessary to support interchangeability.
7/17/2023	BPD Type 2b Meeting	As the sponsor intended to use US-Prolia as the sole comparator in their PK similarity study (FKS518-001) and comparative clinical study (FKS518-002), FDA stated that the CAA need not include data from EU-Prolia or EU-Xgeva. FDA also recommended the Sponsor conduct an additional comprehensive use-related risk analysis (URRA) to support the interchangeability claim for the vial and PFS presentations of the proposed US-Xgeva biosimilar (single vial and PFS). FDA communicated that a medication guide would not be expected for the proposed FKS518 120mg/1.7mL PFS, but that determination would ultimately be made during the course of BLA review
10/26/2023	BPD Type 2a Meeting (Written Responses)	Statistical Analysis Plan for the comparative clinical study (FKS518-002) found to be acceptable.
1/23/2024	BPD Type 4 Meeting	Discussed planned 351(k) BLA submission. FDA commented that the Sponsor's approach to develop a single USPI for both the presentations of FKS518 70 mg/mL (single dose vial and novel PFS presentation) is acceptable. In response to the Sponsor's inquiry regarding the need for an instruction for use (IFU), FDA noted that the Sponsor may include IFU in the application and the acceptability will be a review issue. However, for drugs administered by health care providers, an IFU is not typically included, as the information is included in the prescribing information. Hence, the Sponsor would need to provide a rationale for why an IFU is necessary for the FKS518 120 mg/1.7 mL (70 mg/mL) PFS.
3/6/2024	Advice letter from FDA	FDA communicated that, given that the approved labeling for Xgeva does not reflect licensure of Xgeva for self- administration, FDA did not anticipate approving the proposed FKS518 120 mg/1.7 mL (70 mg/mL) for self-administration, including the proposed PFS formulation.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

No in vivo nonclinical studies were submitted for FKS518.

Table 3. Relevant Clinical Studies

Study Identity	EudraCT number	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
FKS518-001 (Lumiade-1 Study)	2020-004842-13	Compare the pharmacokinetics, pharmaco-dynamics, safety and immunogenicity of FKS518 and US-Prolia	Double-blind, randomized, 2-arm, single-dose, parallel-group, active-controlled study	Healthy male Subjects	FKS518 60 mg SC once (n=107) US-Prolia 60 mg SC once: (n=106)
Comparative Clinical Study					
FKS518-002 (Lumiade-3 Study)	2020-004422-31	Compare the efficacy, safety, pharmacokinetics and pharmaco-dynamics of FKS518 and US-Prolia	Randomized, multi-center (EU), double-blind study involving two treatment periods	Women with post-menopausal osteoporosis	**Core Period** (52 weeks): o US-Prolia 60 mg SC q6 mo (N=276) o FKS518 60 mg SC q6 mo. (N=277) **Transition Period** (26 weeks): o US-Prolia 60 mg SC q6 mo (N=125) o FKS518 60 mg SC q6 mo. (N=376)

Authors:
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Clinical Reviewer

Shivangi Vachhani, MD
Cross Disciplinary Team Leader

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761398 for Conexxence and Bomyntra manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Conexxence and Bomyntra are well-controlled and lead to products that are safe, pure, and potent. The comparative analytical data support a demonstration that Conexxence and Bomyntra are highly similar to US-licensed Prolia and Xgeva, respectively, notwithstanding minor differences in clinically inactive components. It is recommended that these products be approved for human use under conditions specified in the package inserts. Refer to OPQ memo in DARRTS dated March 14, 2025.

3.2. Devices

Both Conexxence and Bomyntra have preparations that are supplied as drug-device combination products. Each prefilled syringe of Conexxence contains 60 mg of FKS518. Bomyntra is supplied as a prefilled syringe that contains 70 mg of FKS518, as well as in a single-dose vial presentation that is not considered a drug-device combination.

3.2.1. Center for Devices and Radiological Health (CDRH)

The Center for Devices and Radiological Health was consulted for review of the device constituent part of the FKS518 drug-device combination product. The device constituent parts of the FKS518 combination product consist of a fixed-dose and single use pre-filled syringe (PFS) with a needle safety device. The needle safety device uses the off-the-shelf Safe ’n’ Sound Nemera platform.

The CDRH review team concluded that the device constituent parts of the combination product are acceptable. Refer to the CDRH consult review dated December 5, 2024, in DARRTS for additional details.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis 1 (DMEPA-1) evaluated the Use-Related Risk Analysis (URRA) and comparative analyses (CA) to determine if human factors (HF) validation study results and comparative use human factors (CUHF) study results are required to support the marketing application for FKS518 (Conexxence) 60 mg/mL PFS as an interchangeable biosimilar to U.S.-licensed Prolia. The DMEPA-1 review team determined that the Applicant does not need to submit HF validation or CUHF study results to support this marketing application for FKS518 (Conexxence) 60 mg/mL PFS. DMEPA-1 has no HF recommendations. Refer to the

DMEPA-1 review dated January 24, 2025, for additional details.

Additionally, DMEPA-1 evaluated the URRA and CA to determine if CUHF study results are required to support the marketing application for FKS518 (Bomyntra) 120 mg/1.7 mL PFS as an interchangeable biosimilar to U.S.-licensed Xgeva. To note, the Applicant submitted HF validation study results, which included 15 healthcare providers (HCPs) as participants. The DMEPA-1 review team determined that, based on the URRA, CA, and the fact that intended users are only HCPs, the Applicant does not need to submit CUHF study results to support this marketing application for FKS518 (Bomyntra) 120 mg/1.7 mL PFS. DMEPA-1 has no HF recommendations. Refer to the DMEPA-1 review dated January 24, 2025, for additional details.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS conducted a clinical inspection of study FKS518-001 conducted at MTZ Clinical Research, sp. z o. o., Warsaw, Poland. The OSIS reviewer identified one discussion item regarding documentation discrepancies, but this item did not have an impact on reliability of the data or human subject protection for study FKS518-001 conducted at the site. Refer to review dated December 19, 2024, in DARRTS.

3.4. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection of two clinical investigators (CIs) in Poland, Dr. Ewa Krecipro-Nizińska (Site #2305) and Dr. Wojciech Pluskiewicz (Site #2306) for the clinical comparative study FKS518-002.

Based on the overall inspection results of these CIs and the regulatory assessments, OSI concluded that Study FKS518-002 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the application. Refer to OSI review dated January 17, 2025, in DARRTS for additional details.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

FKS518 was developed to be an interchangeable biosimilar to US-licensed Prolia and US-licensed Xgeva (US-Prolia & US-Xgeva, respectively). Denosumab is a recombinant human IgG2 monoclonal antibody targeting RANKL (receptor activator of nuclear factor kappa-B ligand). The applicant seeks licensure for FKS518 and proposes the same therapeutic indications, dosage form, route of administration and dosing regimen as US-Prolia and US-Xgeva.

No animal studies were conducted to compare FKS518 pharmacology and toxicology to US-Prolia or US-Xgeva. In vitro analytical characterization assays were conducted to demonstrate similar pharmacological and biological activity between FKS518 and the reference products because the toxicity of denosumab products, barring differences in clinical pharmacokinetic (PK) parameters, is a direct function of their affinity to RANKL and related activity. The comprehensive battery of in vitro analytical studies is considered more sensitive than animal studies in detecting differences. The acceptability of the analytical characterization studies to demonstrate highly similar biological activity and physico-chemical properties to the listed denosumab products was determined by the OPQ review.

A brief summary of the FKS518 pharmacologic functional assays is shown below:

- **RANKL Binding and Inhibition**: In vitro studies confirmed FKS518 exhibits comparable RANKL binding and downstream RANK inhibition to US-Prolia and US-Xgeva.

- **Fc Receptor Binding:** FKS518 showed similarly low or negligible binding to Fc receptors (FcγRI, FcγRIIIa V158 & F158 and FcγRIIIb), consistent with US-Prolia and US-Xgeva.

In summary, no animal studies with FKS518 and US Prolia or US-Xgeva were needed to support a determination of biosimilarity. Refer to the Quality section of the review for an assessment of the in vitro studies to support biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The FKS518 drug product (DP) is a sterile solution for injection intended for subcutaneous administration. The composition and the quality grade of each component of the drug product are similar to US-Prolia and US-Xgeva, as summarized in Table 4.

Table 4. Composition of the FKS518 Drug Product – Pre-Filled Syringe (PFS)

Ingredient	Function	Quality Grade	DP-60 mg-PFS		DP-120 mg-PFS	
			[redacted] (b) (4)		[redacted] (b) (4)	
			Quantity per mL (mg/mL)	Quantity per Syringe (mg/syringe)	Quantity per mL (mg/mL)	Quantity per Syringe (mg/syringe)
Denosumab (FKS518)	Active ingredient	In-House	60		70	120
Acetic acid, glacial	[redacted] (b) (4)	Ph. Eur., USP	0.23		[redacted] (b) (4)	0.39
Sodium acetate [redacted] (b) (4)		Ph. Eur., USP	[redacted] (b) (4)			[redacted] (b) (4)
Sorbitol		Ph. Eur., USP-NF	47.0			79.9
Polysorbate 20		Ph. Eur., USP-NF	0.10			0.17
Water for injection		Ph. Eur., USP	q.s. to 1.0 mL			q.s. to 1.7 mL

NF = National Formulary; Ph. Eur. = European Pharmacopoeia; q.s. = quantum satis (for as much as required); USP = United States Pharmacopoeia.

Source: Sponsor's submission

Comments on Excipients

There are no novel excipients in the drug product formulation. All excipients are within the levels listed in the FDA Inactive Ingredient Database (IID). The slight variations in the excipient composition and level in the FKS518 drug products compared to US-Prolia and US-Xgeva are not expected to impact the safety profile. There are no nonclinical safety concerns with the proposed drug product composition.

Comments on Impurities of Concern

There are no impurities or degradants of toxicologic concern.

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Nonclinical Reviewer

David Carlson, Ph.D.
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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 5. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• PK similarity between FKS518 and US-Prolia was demonstrated in healthy male subjects (Study FKS518-001). • Comparable study drug exposure between FKS518 and US-Prolia was observed in postmenopausal women with osteoporosis (Study FKS518-002). • PK data from Study FKS518-001 also support the conclusion that FKS518 would be expected to have similar PK as US-Xgeva because comparative PK data generated with the 60 mg/1 mL (US-Prolia) strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL (US-Xgeva) strength. • The results support a demonstration that FKS518 has no clinically meaningful differences from US-Prolia and US-Xgeva.
Immunogenicity	• The incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) observed was very low and comparable across treatment groups in both studies. There was no apparent impact of ADA or NAb on study drug PK, PD, safety, or efficacy. Therefore, immunogenicity data from Study FKS518-001 (healthy male subjects) and Study FKS518-002 (female subjects with postmenopausal osteoporosis) support the demonstration that FKS518 has no clinically meaningful differences from US-Prolia.

The clinical development program of FKS518 included two clinical studies:

1. FKS518-001: A Double-Blind, Randomized, 2-Arm, Single-dose, Parallel-group Study in Healthy Subjects to Compare the Pharmacokinetics, Pharmacodynamics, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with US-Prolia (Lumiade-1 Study).

2. FKS518-002: 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 US-licensed Prolia in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study) have similar efficacy, safety and immunogenicity by the subcutaneous route of administration.

The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Study FKS518-001) and additional PK and immunogenicity data from the comparative clinical study (Study FKS518-002).

PK similarity between FKS518 and US-Prolia was demonstrated given that the 90% confidence intervals (CIs) for the ratios (FKS518/US-Prolia) of geometric means for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} were all completely contained within the pre-specified limits [0.80; 1.25] (Table 6).

Table 6. Summary of statistical analyses for assessment of PK similarity (Study FKS518-001)

Parameter	Geometric Least Squares Mean (95% CI)		Ratio* (90% CI)
	FKS518 (n=105)	US-Prolia (n=103)	FKS518 vs US-Prolia
C_{max} (mcg/mL)	5.36 (4.94,5.81)	5.11 (4.70,5.56)	104.79 (97.04,113.15)
$AUC_{0\text{-last}}$ (h×mcg/mL)	6268 (5792,6783)	5582 (5145,6056)	112.29 (104.17,121.04)
$AUC_{0\text{-inf}}$ (h× mcg/mL)	6411 (5911,6952)	5691 (5232,6189)	112.65 (104.27,121.70)

*Presented as percent. Source: Table 14.2.3, page 162, Study FKS518-001 CSR.

In addition to Study FKS518-001, the Applicant also assessed PK/PD similarity in Study FKS518-002, in which subjects received 60 mg FKS518 or US-Prolia by subcutaneous administration. Refer to Section 6.2 for more detailed information on the design of the study. As shown in Table 7, the primary PK parameters ($AUC_{tau} = AUC_{0\text{-W26}}$) after the first SC dose, met the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) for the comparison.

Table 7. Summary of statistical analyses for assessment of PK similarity (Study FKS518-002)

Parameter	Geometric Least Squares Mean (%CV)		Ratio* (90% CI)
	FKS518 (n=267)	US-Prolia (n=259)	FKS518 vs US-Prolia
AUC_{tau} (h× mcg/mL)	7952.77 (44.23)	7278.99 (40.35)	109.26 (103.06, 115.82)

*Presented as percent. Source: Table 33, page 191, Study FKS518-002 CSR.

Study FKS518-001 and Study FKS518-002 support a demonstration of PK similarity between FKS518 and US-Prolia. In addition, the incidence of ADAs and NAbs was similar between the treatment arms for each study.

Overall, the submitted clinical pharmacology information supports a demonstration that FKS518 has no clinically meaningful differences from US-Prolia. The evidence contributes to the overall totality of evidence supporting biosimilarity between FKS518 and US-Prolia, and between FKS518 and US-Xgeva.

The clinical pharmacology review team recommends approval of BLA 761398.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology perspective.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not Applicable.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

To support a demonstration that FKS518 has no clinically meaningful differences from US-Prolia, the applicant submitted two clinical studies, Studies FKS518-001 and FKS518-002. The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Study FKS518-001) and the additional PK and immunogenicity data from the comparative clinical study (Study FKS518-002). The Applicant collected and analyzed PD data in both clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity or interchangeability.

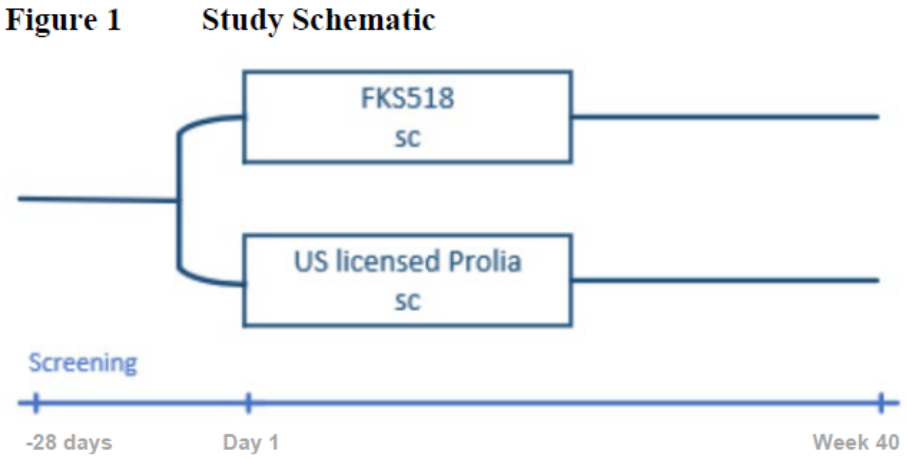
5.3.1. STUDY FKS518-001

Clinical Pharmacology Study Design Features

Study FKS518-001 was a double-blind, randomized, 2-arm, single-dose, parallel-group study to compare the pharmacokinetics, pharmacodynamics, and immunogenicity of FKS518 with US-Prolia after a single s.c. injection of 60 mg in healthy male subjects.

In this study, subjects were randomized in a 1:1 ratio (107 per treatment arm) to receive a single 60 mg s.c. dose of either FKS518 or US-Prolia, with the aim of having a minimum of 170 evaluable subjects (85 per treatment arm) at the end of the study (shown in Figure 1). Randomization was stratified by weight category (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg). The study duration per subject was up to 44 weeks, consisting of a screening period of up to 4 weeks, 1 treatment day and a post-dosing assessment period of 40 weeks.

Figure 1. Schematic overview of the chronological structure of Study FKS518-001



IP = investigational product; sc = subcutaneous

Note: On Day -1, subjects were randomized in a 1:1 allocation ratio into 2 treatment groups: FKS518 or US-Prolia. IP was administered on Day 1.

Source: Figure 1, page 22, Study FKS518-001 CSR.

Of the 424 subjects screened, 214 subjects were randomized to receive one of the 2 treatments (FKS518 or US-Prolia). Of these, 1 subject who had been randomized to receive US-Prolia withdrew his consent prior to dosing. Therefore, 213 subjects were administered 1 dose of FKS518 or US-Prolia; 107 subjects were administered FKS518 and 106 subjects were administered US-Prolia. A total of 208 (97.2%) subjects were included in the PK Analysis Set: 105 subjects in the FKS518 group and 103 subjects in the US-Prolia group. Apart from the 1 subject who had not been dosed, 5 subjects were excluded from the PK analyses because they had several missing visits that resulted in having fewer than 2 consecutive observations after C_{max}.

A total of 206 (96.3%) subjects completed the study as per protocol (103 subjects in each treatment group), and 7 (3.3%) subjects were discontinued early from the study. Of these, 1 subject was withdrawn due to an SAE (bile duct adenocarcinoma, not considered related to the IP), 1 subject was lost to follow-up, 1 subject withdrew his consent, and 4 subjects were discontinued due to other reasons (2 with noncompliance, 1 with subject's request, 1 with sponsor suggestion).

Clinical Pharmacology Study Endpoints

The primary PK endpoints were area under the concentration-time curve (AUC) from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum observed serum concentration (C_{max}). For the comparison of primary endpoints, the 90% confidence intervals (CIs) for the geometric mean ratio (GMR) were derived by exponentiating the 90% CI obtained for the difference between the 2 treatments least-square (LS) means resulting from the analysis of the log-transformed PK primary endpoints. To demonstrate PK similarity, if the 90% CIs for the GMR of all PK primary endpoints were

entirely within the 80.00% to 125.00% similarity margins, then PK similarity between the 2 treatments could be declared.

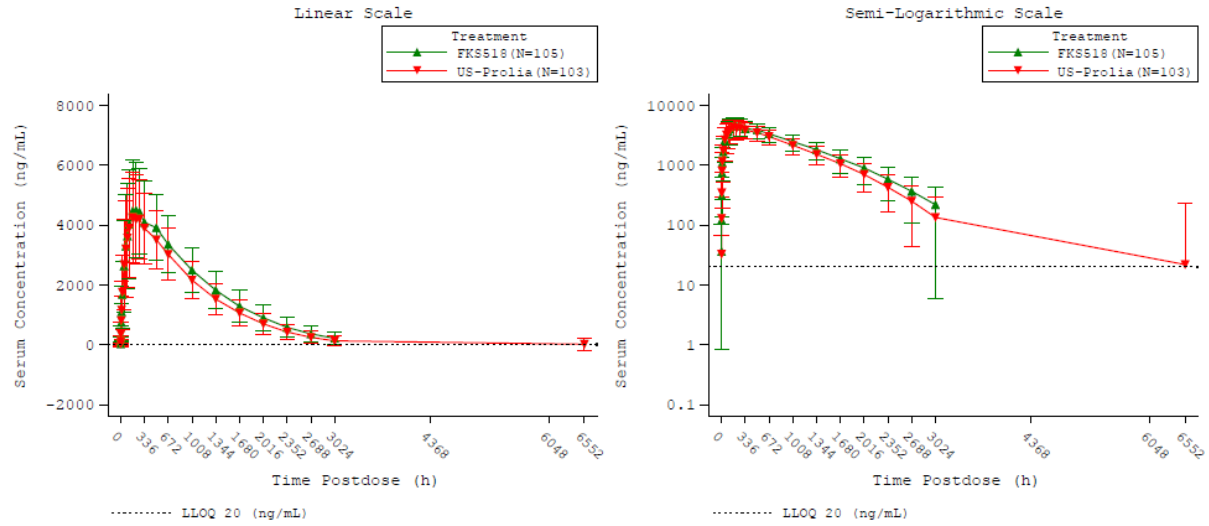
Bioanalytical PK Method and Performance

A electrochemiluminescence (ECL) immunoassay method ICD 857 was used to quantify free study drug in serum of healthy subjects in Study FKS518-001. In this method, anti-denosumab antibody coated in 96-well plate was used to capture serum FKS518 and US-Prolia, and biotinylated anti-denosumab (primary detection) and Streptavidin-Sulfo-TAG (secondary detection) were used to detect the bound analytes. The method was fully validated over a range of 20 to 800 ng/mL for study drug in accordance with the Bioanalytical Method Validation Guidance from the agency. Refer to the Appendix 14.4.1 for more detailed information on method validation.

PK Similarity Assessment

The mean study drug serum concentration-time profiles are similar for all treatment groups (Figure 2). For the primary PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}), the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (Figure 3).

Figure 2. Study drug serum concentrations vs. time profile (Study FKS518-001)



Source: Figure 14.2.6

Abbreviations: H = Hours; LLOQ = lower limit of quantification; PK = pharmacokinetic; SD = standard deviation

The planned time points were Predose, H 1.00, H 2.00, H 4.00, H 8.00, H 12.00, H 24.00, H 48.00, H 72.00, H 96.00, H 120.00, H 168.00, H 216.00, H 264.00, H 336.00, H 504.00, H 672.00, H 1008.00, H 1344.00, H 1680.00, H 2016.00, H 2352.00, H 2688.00, H 3024.00, H 4368.00, H 6048.00, H 6552.00.

Note: Some of the time points such as H 1.00, H 2.00, H 4.00, H 8.00, H 12.00, H 24.00, H 48.00, H 72.00, H 96.00, H 120.00, H 168.00, H 216.00, H 264.00 and H 504.00 are not presented on the X axis due to space constraints.

Note: The mean denosumab concentration at H 6552 for the US-Prolia treatment is impacted by the outlying concentration value at this time point for Subject 1010222 (Listing 16.2.6.1).

Source: Figure 2, page 64, Study FKS518-001 CSR.

Figure 3. Geometric least-square mean ratio and confidence interval for primary PK parameters to compare treatments (Study FKS518-001)

	FKS518 (Test) (N = 105)		US-Prolia (Reference) (N = 103)		Ratio (%) (Test/Reference)
Parameter	**n**	**GLSM (95% CI)**	**n**	**GLSM (95% CI)**	**GLSM (90% CI)**
C_{max} (µg/mL)	105	5.36 (4.94,5.81)	103	5.11 (4.70,5.56)	104.79 (97.04,113.15)
$AUC_{0\text{-last}}$ (h·µg/mL)	105	6268 (5792,6783)	103	5582 (5145,6056)	112.29 (104.17,121.04)
$AUC_{0\text{-inf}}$ (h·µg/mL)	105	6411 (5911,6952)	102	5691 (5232,6189)	112.65 (104.27,121.70)

Source: Table 14.2.3
Abbreviations: AUC = area under the concentration-time curve; CI = confidence interval; C_{max} = maximum observed serum concentration; GLSM = geometric least-squares mean; n = number of subjects included in the analysis; PK = pharmacokinetic.
The analyses were performed on ln-transformed parameters using an analysis of variance model with treatment and weight strata (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg) as fixed effects.
There were no intercurrent events for PK.

Source: Table 9, page 67, Study FKS518-001 CSR.

Bioanalytical PD Method and Performance

C-terminal cross-linking telopeptide of Type 1 collagen (CTX) and procollagen Type 1 N-terminal propeptide (P1NP) in human serum were quantified using ELISA and immunoassay, respectively. The CTX and P1NP sample analysis was performed for all subjects in the study using validated methods by a qualified laboratory under the responsibility of FKSBS. Bioanalytical reports were generated, one for each CTX and P1NP analysis, by the bioanalytical laboratory and are included in Appendix 16.1.13 of Study FKS518-001 CSR. All validation parameters passed the acceptance criteria and the assays are considered appropriate for the quantification of CTX and P1NP in human serum.

PD Assessment

The Applicant collected and analyzed PD data in the clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity or interchangeability.

For the PD parameter in Study FKS518-001, the response of CTX serum levels and P1NP serum levels in terms of PD parameters %CfB and AUEC0-W40 was similar between FKS518 and US-Prolia. (Table 8).

Table 8. Statistical Analysis of CTX and P1NP PD Parameters of FKS518 versus US-Prolia (Study FKS518-001)

	FKS518 (Test) (N = 107)		US-Prolia (Reference) (N = 107)		Ratio (%) (Test/Reference)
Parameter	**n**	**GLSM (95% CI)**	**n**	**GLSM (95% CI)**	**GLSM (90% CI)**
CTX $AUEC_{0\text{-}W40}$ for %CfB (h·%)	107	519120 (500762,538151)	106	507427 (488555,527029)	102.30 (98.72,106.02)
P1NP $AUEC_{0\text{-}W40}$ for %CfB (h·%)	107	382004 (368982,395486)	106	378252 (364817,392182)	100.99 (97.59,104.52)

Source: Table 14.2.24
Abbreviations: AUEC = area under the effect curve; CfB = change from baseline; CI = confidence interval; CTX = C-terminal cross-linking telopeptide of Type 1 collagen; GLSM = geometric least-squares mean; IE = intercurrent event; n = number of subjects was included in the analysis; P1NP = procollagen Type 1 N-terminal propeptide; PD = pharmacodynamic.
Analytes: CTX (ng/L); P1NP (µg/L).
Subjects with missing/censored data were imputed by multiple imputation, n = 9 (n = 5 had IEs) for FKS518 and n = 10 (n = 7 had IEs) for US-Prolia. Subject (b) (6) is not included in the analysis as the subject did not have baseline values to be used for imputation.
The analyses were performed on ln-transformed parameters using an analysis of variance model with treatment and weight strata (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg) as fixed effects and log baseline concentration as a covariate.

Source: Table S2, page 7, Study FKS518-001 CSR.

5.3.2. STUDY FKS518-002

Study FKS518-002 was 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 US-licensed Prolia in postmenopausal women with osteoporosis (LUMIADE-3 Study), to establish that the two drugs have similar efficacy, safety and immunogenicity by the subcutaneous route of administration.

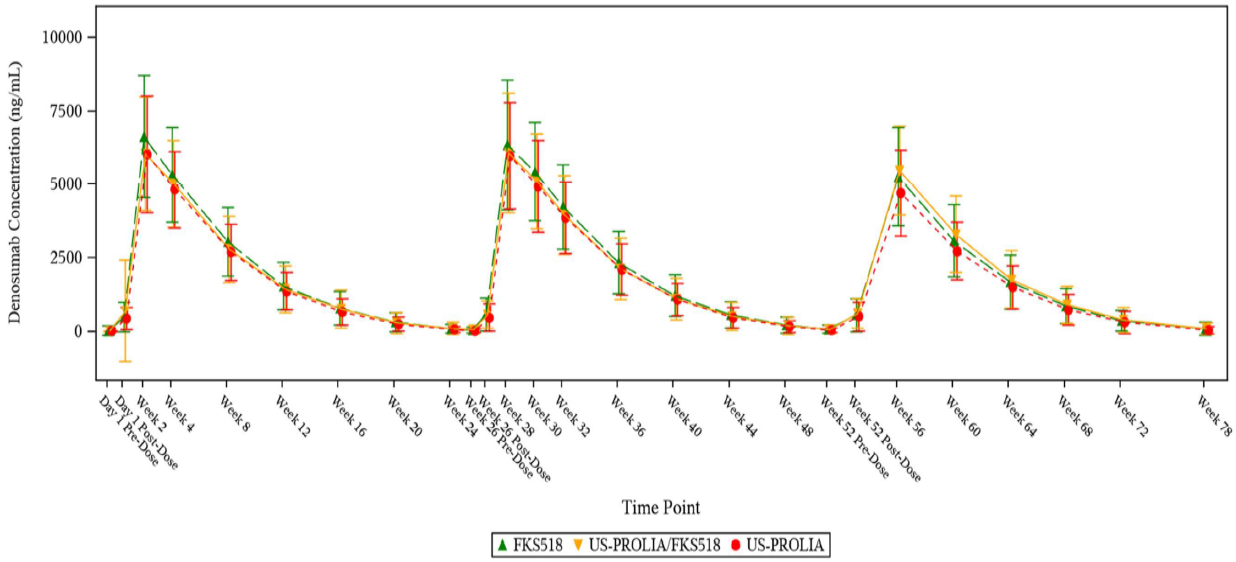
Patients were randomized in a 1:1 ratio to receive either FKS518 or Prolia subcutaneously at Months 0 and 6. Study visits occurred at weeks 0, 2, 4, 8, 12, 16, 20, 24, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples for PK were collected at each visits. Blood samples for immunogenicity were collected at weeks 0, 2, 4, 8, 12, 26, 32, 40, and 52.

At week 52, patients who received Prolia in the core period were randomized again in a 1:1 ratio to either continue on Prolia (Prolia+Prolia) or were transitioned to FKS518 (Prolia+FKS518). Patients who received FKS518 in the core period continued to receive FKS518 (FKS518+FKS518), but they also followed the randomization procedure to maintain blinding. Patients were followed up to week 78. (Refer to Sections 6.2. for more detailed information on the design of the study).

PK Assessment

A total of 530 patients were included in the core period PK analysis dataset (269 patients from the FKS518 and 261 patients from the Prolia treatment groups). The mean study drug concentration-time profiles are similar between FKS518 and US-Prolia (Figure 4).

Figure 4. Mean Denosumab Concentration over Time (Linear Scale) – Overall Period (PK Analysis Set)



Source: Figure 17, page 188, Study FKS518-002 CSR.

PD Assessment

Serum CTX and P1NP concentrations were analyzed by treatment group and visit. Blood samples for PD were collected at weeks 0, 2, 4, 8, 12, 16, 20, 24, 26, 28, 36, 40, 44, 48, and 52.

The results of the statistical analysis of the co-primary endpoint (EMA only) Estimand 2.2 (hypothetical estimand) demonstrated PD equivalence of FKS518 and US-Prolia, with the 95% CIs of the FKS518/US-Prolia ratio of geometric least squares means for AUEC(0-W26) CTX fully included within the predefined equivalence interval (see Table 9).

Table 9. Analysis of Ratio of Means of AUEC (ng*h/L) of Serum CTX up to Week 26 – Estimand 2.2 (ITT Analysis Set)

Variable Statistic	FKS518 (N=277)	US-Prolia (N=276)	Ratio FKS518 / US-Prolia
Mean AUEC of Serum CTX up to Week 26[a]			
Geometric LS Mean	1895	1875	
95% Confidence Interval	(1849, 1941)	(1828, 1923)	
Number of Imputed Values [n (%)]	27 (9.7)	31 (11.2)	
Ratio of Geometric LS Means[a]			
Point Estimate			1.01
95% Confidence Interval			(0.99, 1.04)**

Source: Table 14.2.2.2.3.
AUEC = Area Under the Effect Curve; CTX = C-Terminal Cross-Linking Telopeptide of Type 1 Collagen; EEA = European Economic Area; EU = European Union; IE = Intercurrent Event; IRT = Interactive Response Technology; ITT = Intention-to-Treat; LS = Least Squares; MAA = Marketing Authorization Application.
** Indicates that equivalent efficacy was achieved.
a. LS means, ratio of LS means and confidence intervals were from an ANCOVA model on the natural log transformed AUEC of Serum CTX up to Week 26 with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for natural log of baseline serum CTX concentration. Fixed effects as entered in IRT. For the MAA in the EU and EEA: FKS518 was considered equivalent to US-Prolia on CTX if the 95% Confidence Interval for the ratio of means of AUEC up to Week 26 laid entirely within the equivalence interval of [0.89; 1.12].
Note: Estimand 2.2: Comparison made as per hypothetical strategy, an imputation model using a multiple imputation approach to impute any data point if patient had any changes to medications/ bone-affecting interventions, or had adverse events affecting bone assuming missing at random.
Note: Censored and missing AUEC up to Week 26 values were imputed from the pool of patients for whom AUEC up to Week 26 was available and for whom an IE had not occurred.

Source: Table S6, page 17, Study FKS518-002 CSR.

At Week 52, similar reductions in percent change from baseline in serum CTX and P1NP were observed between the FKS518 and US-Prolia groups in the analyses of Estimands for serum CTX and for serum P1NP (data not shown).

5.4. Clinical Immunogenicity Studies

5.4.1. STUDY FKS518-001 and FKS518-002

5.4.1.1. Design features of the clinical immunogenicity assessment

Refer to Sections 5.3 and 6.2 for more detailed information on the design of the study.

5.4.1.2. Immunogenicity endpoints

Immunogenicity assessment was proposed as the secondary study endpoints in the following studies:

- Study FKS518-001: Incidences of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

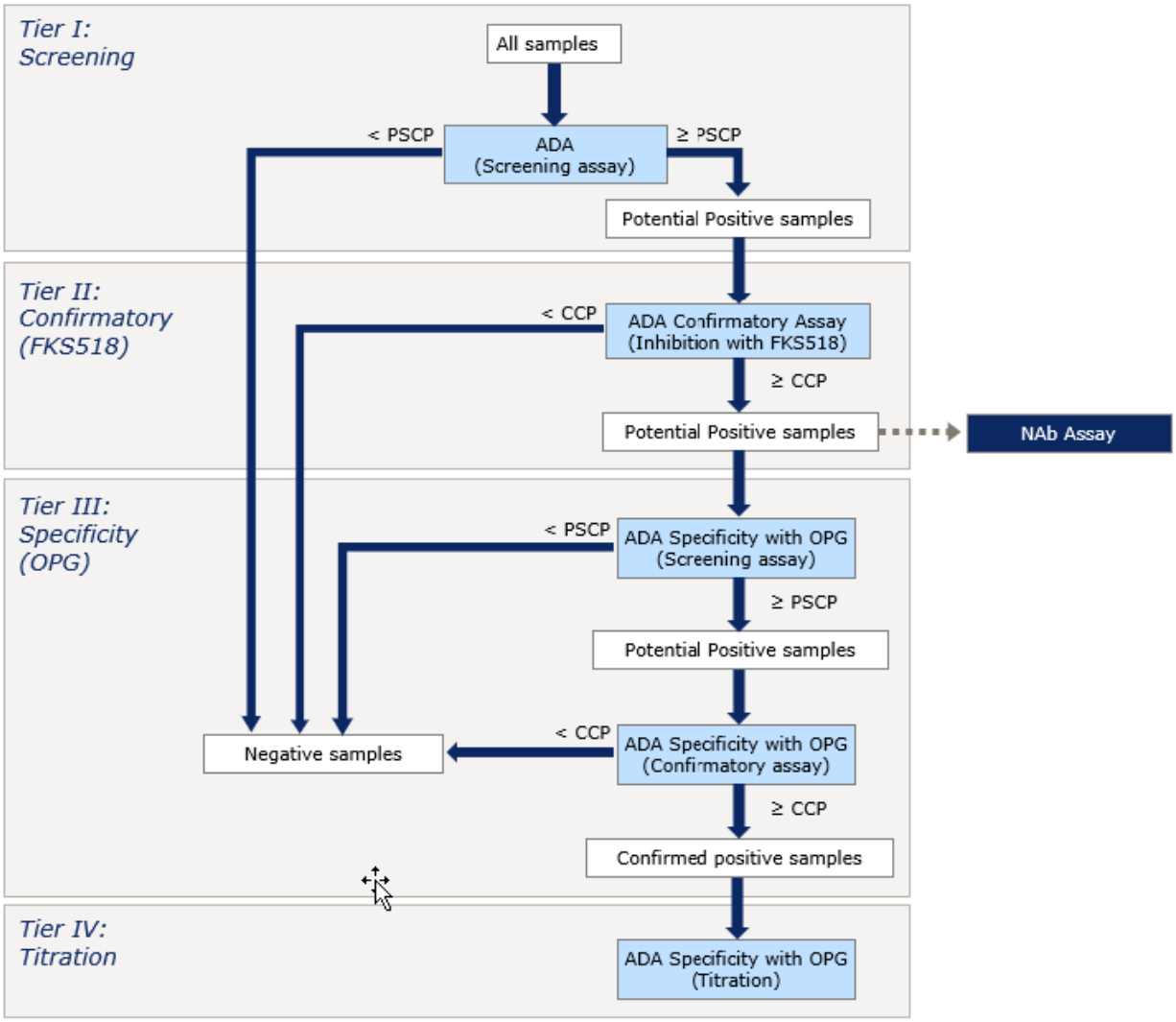
- Study FKS518-002: Incidence of ADAs and NAb up to month 18.

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

Anti-drug antibodies (ADA) against denosumab/FKS518 in human serum were detected using an electro-chemiluminescent (ECL) method. Samples collected from study FKS518-001 and FKS518-002 were analyzed with a multi-tiered approach（Figure 5）.

All study samples were initially tested in the screening tier (Tier 1). The resulting screening positive samples were tested in the confirmatory tier (Tier 2). Subsequently, samples with a percentage of inhibition greater than or equal to the Confirmatory Cut Point (CCP) were further tested in the specificity tier (i.e. in the presence of OPG) to exclude false positive results due to sRANKL interference (Tier 3). The confirmed positive samples from the specificity tier, if observed, are finally titrated in the presence of OPG (Tier 4).

Figure 5. Tiered Approach in the FKS-518 Anti-drug Antibody, Neutralizing Antibody and Titer Assays



Abbreviations: PSCP = Plate-Specific Cut Point, CCP = Confirmatory Cut Point, ADA = Anti-drug antibody, Nab = Neutralizing antibody, OPG = Osteoprotegerin.

Note: The assessment of the neutralizing activity of ADAs was performed prior the implementation of the specificity tier.

Source: section 5.3.5.3 Integrated Summary of Immunogenicity, Figure 3.

The overall ADA and NAb incidences using the original ADA assay are much higher than reported for US-Prolia (e.g., > 90 % vs < 10 % for ADA; ~ 40 % vs < 1 % for NAb). The very high ADA/NAb incidences triggered an investigation of the ADA assay by the applicant. Following the identification of interference of RANKL in the original ADA assay, to mitigate the interference, the applicant modified the ADA assay, and a specificity tier was included in the ADA testing scheme. All the samples that tested positive initially using the original ADA assay, were reanalyzed using the modified ADA assay. Based on validation reports, OPQAIII review team agrees that the modified ADA

assay is adequately validated with drug tolerance and is suitable for its intended use. OPQAIII team also agrees that the level of sRANKL required to cause interference in the NAb assay are much higher than the ones interfering in the ADA assay. Therefore, the original Nab assay is also suitable for its intended use.

Additionally, the mean maximum serum concentration of study drugs in the PK Similarity Study FKS518-001 (~4000 ng/mL) and the Comparative Clinical Study FKS518-002 (~6000 ng/mL) are significantly lower or approximately to the drug tolerance of the ADAs/NAbs assay (6000 ng/mL), indicating minimal interference with the ADAs/NAbs assay in the presence of study drugs in the serum at different sampling timepoints.

Refer to OPQAIII's review dated March 14, 2025, for an assessment of bioanalytical method validation and performance of the ADAs/NAbs assays.

5.4.1.3. Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

In Study FKS518-001, ADA samples were collected at pre-dose, Day 15, Day 29, Day 85, Day 127, Day 183 and Day 274 (EOS). In Study FKS518-002, ADA samples were collected at pre-dose, week 2, 4, 8, 12, 26, 32, 40, 52, 64 and 78 (EOS).

The immunogenicity assessment schedules in Studies FKS518-001 and FKS518-002 are deemed appropriate. These schedules include ADA sampling at baseline (pre-dose) and at multiple post-dose timepoints, extending beyond 5 half-lives of denosumab. This comprehensive sampling strategy allows for a thorough evaluation of the immunogenic response over time.

Furthermore, the study design incorporates concurrent measurement of drug concentrations at the same timepoints as immunogenicity sample collection. This parallel assessment of drug levels and ADA formation enhances the ability to interpret the immunogenicity data in the context of drug exposure.

The inclusion of baseline samples, multiple post-dose timepoints, and corresponding drug concentration measurements provides a robust framework for evaluating the immunogenicity profile of the study drug.

5.4.1.4. Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

The incidence of ADA and NAb in Studies FKS518-001 and FKS518-002 are shown in Table 10, Table 11 and Table 12, respectively.

The incidence of ADAs and NAbs was low and comparable between treatment groups

for each study. There was no NAb detected in all treatment groups in Study FKS518-001. The incidence of NAbs was low in all treatment groups in Study FKS518-002. Pre-treatment of US-Prolia and transitioning to FKS518 did not influence the incidence of ADAs and NAbs in FKS518 group after the transition (Table 12).

Table 10. Immunogenicity results for binding ADA and NAb in Study FKS518-001

	N	Anti-Drug Antibody		NAb
		Baseline	Treatment-Induced	
FKS518	105	0/105 (0.0%)	0/105 (0.0%)	0/105 (0.0%)
US-Prolia	105	0/105 (0.0%)	0/105 (0.0%)	0/105 (0.0%)

Source: Section 5.3.3.1 CSR Study FKS518-001, Table 14.3.5.4

Table 11. Immunogenicity results for binding ADA and NAb in Study FKS518-002 (Week 0 to Week 52)

	N	Anti-Drug Antibody		NAb
		Baseline	Treatment-Induced	
FKS518	277	1/276 (0.4%)	3/274 (1.1%)	1/274 (0.4%)
US-Prolia	276	0/276 (0.0%)	6/276 (2.2%)	1/276 (0.4%)

Source: Section 5.3.5.3, Table 40; Section 5.3.5.1 CSR, Study FKS518-002, Table 31

Table 12. Immunogenicity results for binding ADA and NAb in Study FKS518-002 Transition Period (Week 52 to Week 78)

	N	Anti-Drug Antibody	NAb
FKS518/FKS518	252	2/247 (0.8%)	1/247 (0.4%)
US-Prolia/FKS518	124	1/124 (0.8%)	1/124 (0.8%)
US-Prolia/US-Prolia	125	2/124 (1.6%)	1/124 (0.8%)

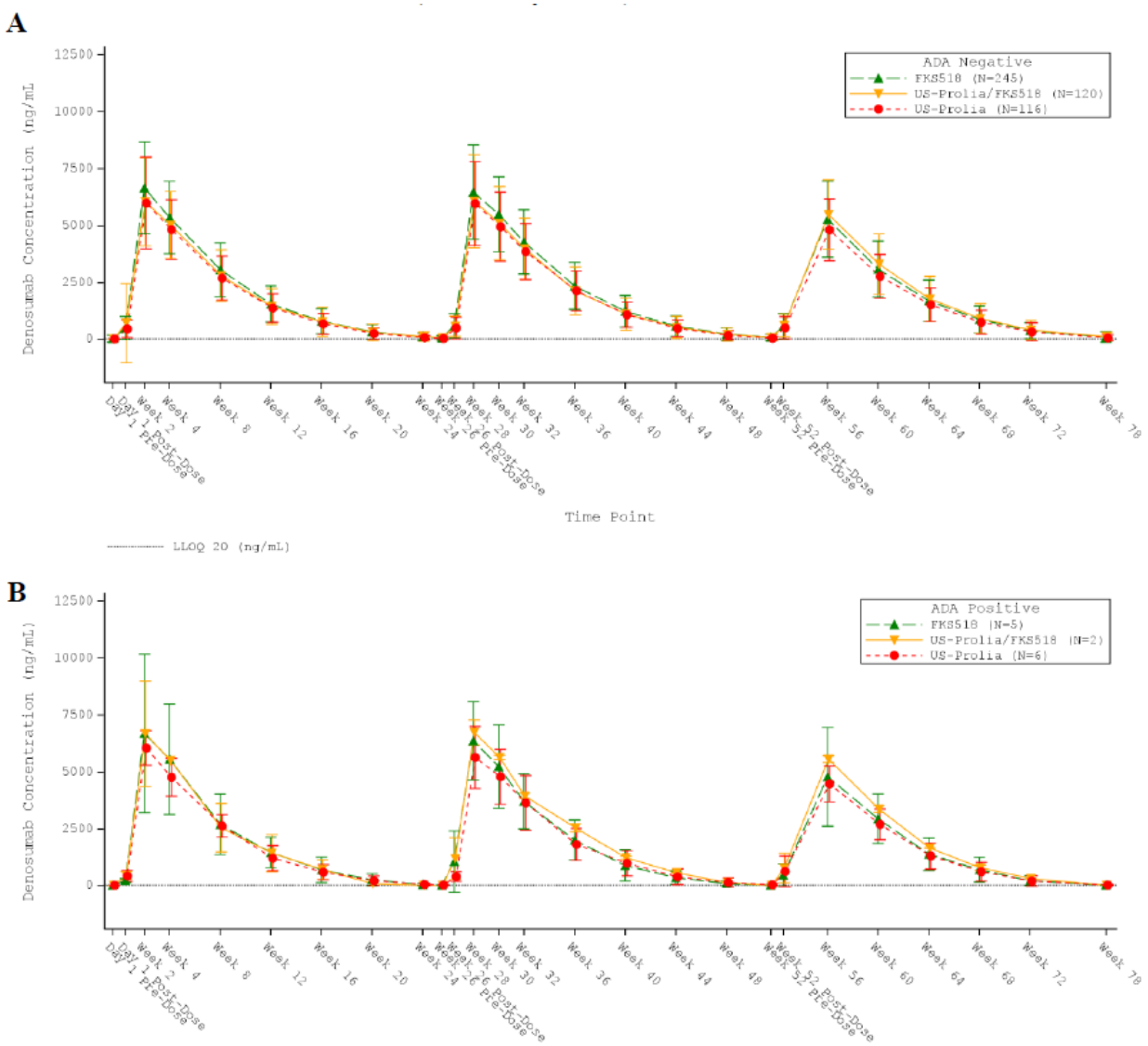
Source: Section 5.3.5.3, Table 41; Section 5.3.5.1 CSR, Study FKS518-002, Table 32

5.4.1.5. Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

In Study FKS518-001, no ADA positive and ADA negative subgroup analysis was performed as none of the samples were found to be ADA positive.

In Study FKS518-002, following multiple administrations of FKS518 or US-Prolia, despite the low numbers of ADA positive patients, the PK profiles by ADA status for the overall period overlapped during the duration of the study (Figure 6), this indicated comparable PK between FKS518 and US-Prolia groups regardless of ADA status. In addition, the PK profiles are comparable between ADA positive and ADA negative patients in both FKS518 and US-Prolia groups (see panel A vs. B). These results support the lack of impact of immunogenicity on the PK following multiple administrations (FKS518 or US-Prolia) and following a single transition from US-Prolia to FKS518, which is consistent with the low titer (e.g., median ADA titer: 50) and transient ADA response.

Figure 6. Impact of the ADA status on the denosumab concentration (arithmetic mean ± SD) during the overall period in the PK analysis set of the FKS518-002 Study. (A: ADA negative subgroups. B: ADA positive subgroups.)

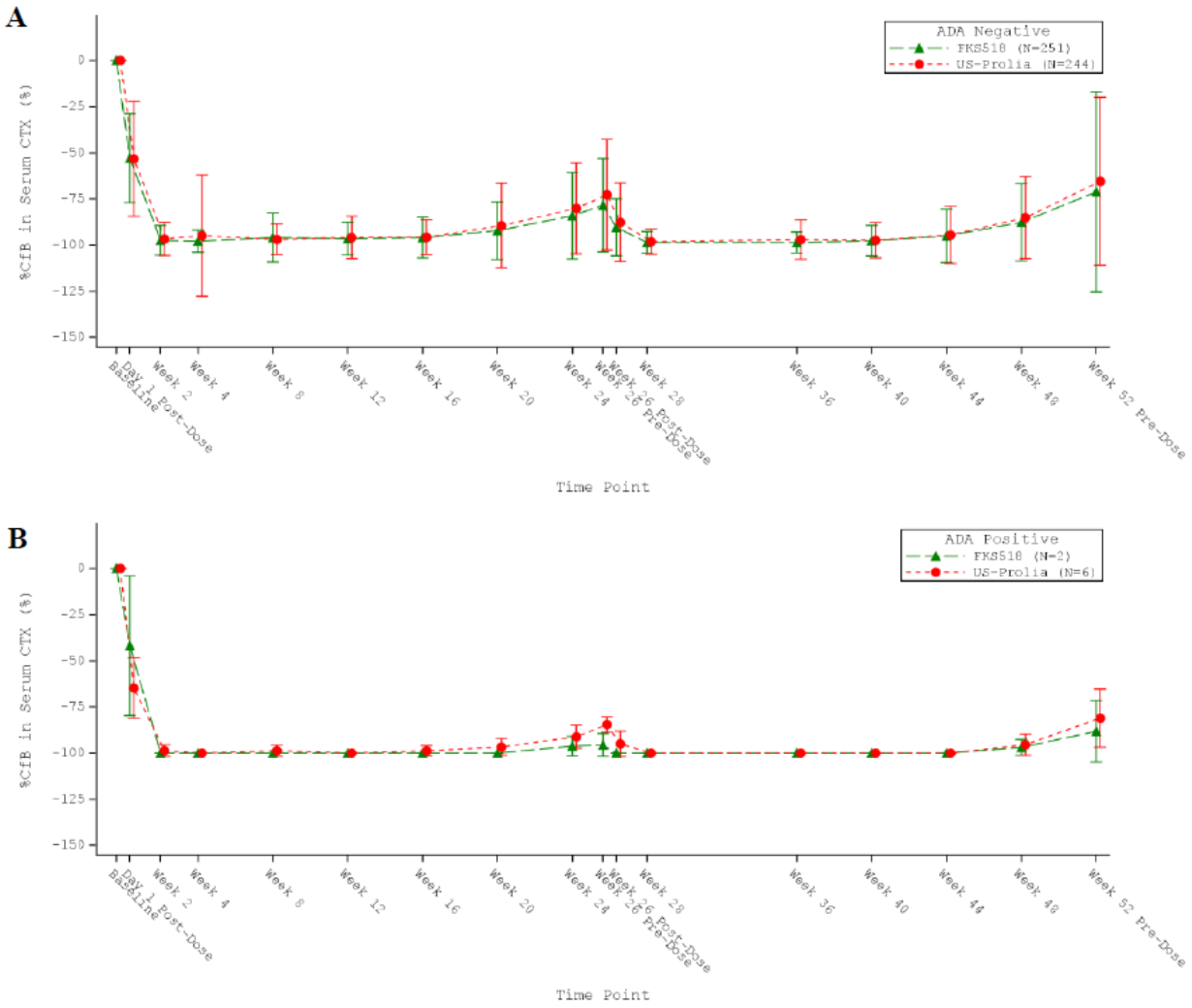


Source: Section 5.3.5.3, Figure 13; Section 5.3.5.1, CSR FKS518-002, Table 14.2.6.3.1 and Listing 16.2.6.1.1.

The Applicant states the proportion of patients with an ADA and NAb positive status was lower than 10%, thus the sensitivity analyses of the efficacy and PD parameters based on ADA/NAb status were not performed as defined in the SAP. Nevertheless, the Applicant provided ad-hoc analysis showing the percent change from baseline (%CfB) of CTX and P1NP in serum by ADA status to support the assessment of the impact of the immunogenicity on these PD parameters. The mean profiles of the %CfB of CTX in serum from patients treated with FKS518 or US-Prolia by ADA status during the core period are shown in Figure 7, and the mean profiles of the %CfB of P1NP in serum from patients treated with FKS518 or US-Prolia stratified by ADA status during the core

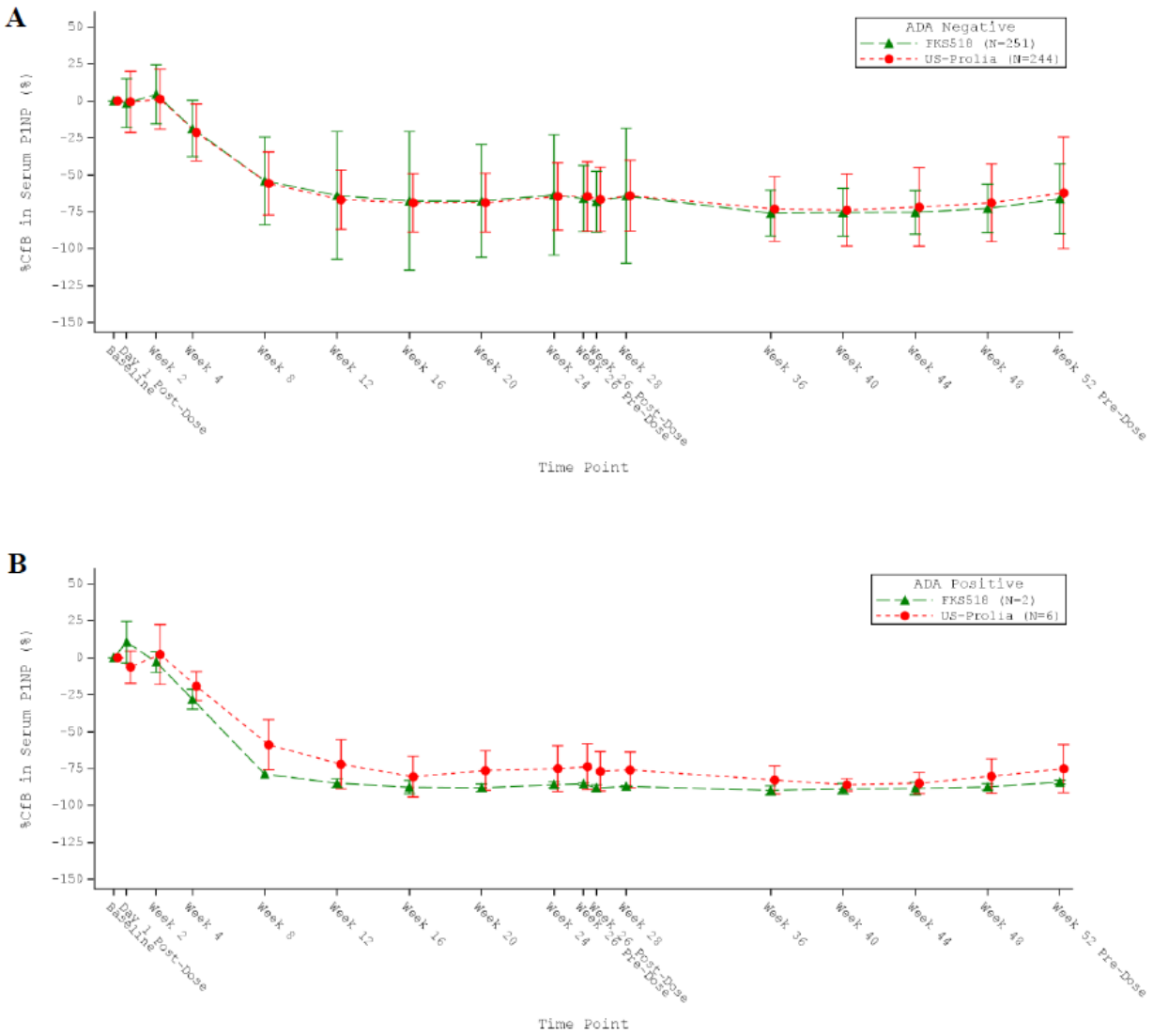
period are shown in Figure 8. The profiles were comparable between ADA positive and ADA negative subgroups, supporting that the ADA status had no notable impact on the biomarker responses as assessed by the %CfB of CTX or P1NP in serum. In addition, given the NAb incidences were very low (1 subject in each treatment group), the impact of NAbs on the PK and PD profiles of FKS518 and US Prolia cannot be assessed for this study.

Figure 7. Impact of the ADA status on the %CfB (arithmetic mean ± SD) of serum CTX levels during the core period in the PD analysis set of the FKS518-002 Study. (A: ADA negative subgroups. B: ADA positive subgroups.)



Source: Section 5.3.5.3, Figure 11; Section 5.3.5.1, CSR FKS518-002, Listing 16-02-06-02-01-02

Figure 8. Impact of the ADA status on the %CfB (arithmetic mean ± SD) of serum P1NP levels during the core period in the PD analysis set of the FKS518-002 Study. (A: ADA negative subgroups. B: ADA positive subgroups.)



Source: Section 5.3.5.3, Figure 12; Section 5.3.5.1, CSR FKS518-002, Listing 16-02-06-02-01-02

Impact of ADA and NAb on Safety

Study FKS518-002

When analyzing the ADA positivity of subjects treated during study FKS518-002, titer levels were evaluated according to the reference range of the assay. Both the lower and upper limits of the analysis range were 50, so subjects with ADA level above 50 were considered to have high titers, subjects with ADA level at 50 were considered to have mid-level titers, and subjects with ADA level below 50 were considered to have low titers.

Core Period

No subjects developed high levels of ADA titers during the Core Period. The incidence of mid-level ADA titers (i.e., 50) during the Core Period was low in both the FKS518 (N=4/277, 1.4%) and US-Prolia (N=7/276, 2.5%) treatment groups.

During the Core Period, these 11 subjects developed 38 adverse events. When examining the most common adverse events in subjects with mid-level ADA titers, three subjects developed *COVID-19* (all in the US-Prolia group), three subjects experienced a *urinary tract infection* (two in the US-Prolia group and one in the FKS518 group), two subjects experienced a *vaccine complication* (one in the US-Prolia group and one in the FKS518 group), and two subjects developed *upper respiratory tract infection* (both in the US-Prolia group). Otherwise, only one subject with mid-level ADA titers developed each adverse event.

Table 13 depicts the frequency of the most common TEAEs for the entire study population compared to subjects with mid-level ADA titers. Though numerically the incidence of some of these events may be higher in the mid-level titer subjects compared to the entire study population, because few subjects developed mid-level titers during the Core Period, any difference between the populations is unlikely to be clinically meaningful.

Table 13. Most common treatment emergent adverse events (i.e., incidence >5%) in subjects with ADA titer = 50 compared to entire study population, Core Period, Study FKS518-002

	FKS518		US-Prolia	
	Titer = 50 (N=4)	Entire dataset (N=277)	Titer = 50 (N=7)	Entire dataset (N=276)
COVID-19	1 (25)	32 (12)	3 (43)	41 (15)
Nasopharyngitis	0	27 (10)	0	33 (12)
Upper respiratory tract infection	0	23 (8)	2 (29)	30 (11)
Urinary tract infection	1 (25)	18 (7)	2 (29)	23 (8)
Systemic hypertension (FMQ)*	0	14 (5)	0	8 (3)
Headache	0	13 (5)	1 (14)	15 (5)
Diarrhea	0	13 (5)	0	9 (3)
Arthralgia	0	10 (4)	0	15 (5)

Source: clinical reviewer analysis
FMQ = FDA medical query
*All events under systemic hypertension (FMQ): blood pressure increased, hypertension
After the FDA review team evaluated and provided modifications to the Applicant's translation of adverse event verbatim terms to dictionary derived terms, there is now a small discrepancy in the number of some adverse events. As none of the changes resulted in a difference in adverse event incidence of 1.5% or more, this discrepancy is unlikely to result in the FDA analysis to be significantly different from the Applicant's analysis

No subjects with mid-level titers experienced hypersensitivity-related reactions as defined by the hypersensitivity FDA Medical Query (FMQ). Three subjects in the Core Period experienced an injection site reaction, and none of these subjects had mid-level ADA titers.

Transition Period

No subjects developed high levels of ADA titers during the Transition Period. The incidence of mid-level ADA titers (i.e., 50) during the Transition Period was low in all treatment groups: 2/252 (0.8%) in the FKS518/FKS518 group, 2/124 (1.6%) in the US-Prolia/FKS518 group, and 4/125 (3.2%) in the US-Prolia/US-Prolia group. There was no significant increase in immunogenicity after a single transition.

During the Transition Period, these 8 subjects developed 16 adverse events. When examining adverse events in subjects with mid-level ADA titers during the Transition Period, no adverse events occurred in more than 1 subject. The sample size of subjects with mid-level titers was too small to make a meaningful comparison of TEAEs compared to the overall treatment group.

No subjects with mid-level titers experienced hypersensitivity-related reactions as defined by the hypersensitivity FDA Medical Query (FMQ). Two subjects in the Transition Period experienced an injection site reaction, and neither of these subjects had mid-level ADA titers.

Overall, it does not appear that development of anti-drug antibodies had a meaningful impact on safety, and there was no clinically meaningful difference between treatment groups in occurrence of immunogenicity.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The Applicant conducted a single comparative clinical study comparing the efficacy and safety of FKS518 and US-Prolia in postmenopausal women with osteoporosis (Study FKS518-002). The demographic and disease characteristics of the population at baseline was similar between the two treatment groups.

The primary efficacy endpoint was the percentage change in lumbar spine bone mineral density (LS-BMD) assessed by DXA at week 52 compared to baseline. At the end of the Core Treatment period (i.e., week 52), the difference in the mean percentage change from baseline in LS-BMD between the FKS518 group and the US-Prolia group was 0.46 under the non-inferiority null imputation and 0.69 under the non-superiority null imputation of missing data , with the 90% confidence interval within the pre-defined equivalence margin of +/-1.45% (see section 6.2.7). Therefore, this study demonstrated that there is no clinically meaningful difference between the two products with respect to efficacy. There was also no meaningful difference between FKS518 and US-Prolia with respect to the nature or frequency of treatment emergent adverse events.

The single transition from US-Prolia to FKS518 showed maintenance of efficacy (see Table 21) and was not associated with any increase in the nature or frequency of adverse events or evidence of immunogenic response.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

Study FKS518-002: 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

6.2.1. Data and Analysis Quality

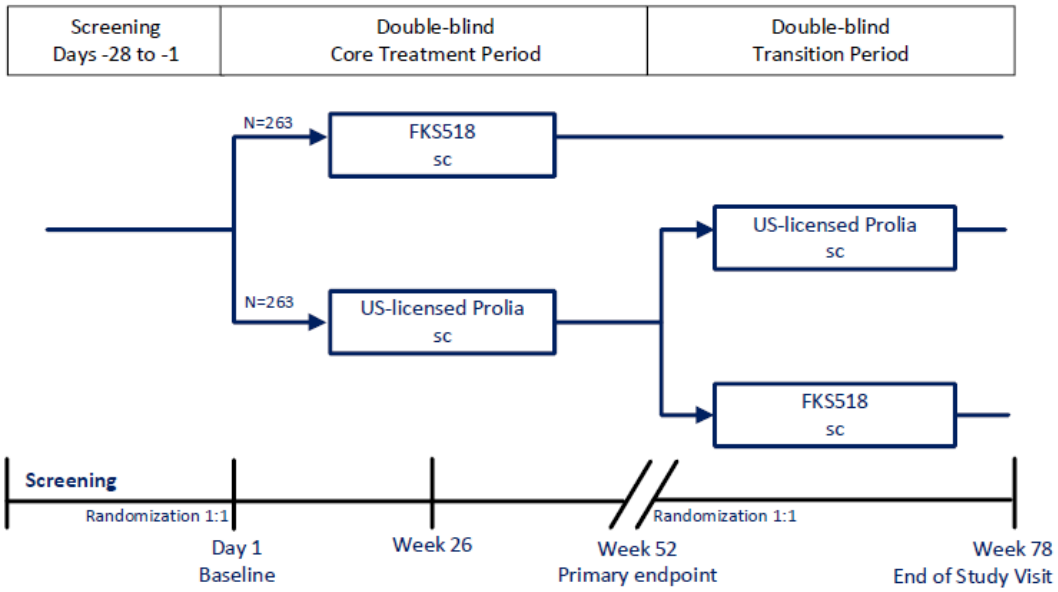
There are no concerns regarding data quality and integrity.

6.2.2. Study Design and Endpoints

Study FKS518-002 was an international, multicenter, randomized, double-blind study, consisting of two treatment periods. For the first treatment period (i.e., Core Treatment Period), a total of 553 female subjects with post-menopausal osteoporosis (PMO) were randomized in a 1:1 ratio to receive either FKS518 60 mg or US-Prolia 60 mg on Day 1 and at Week 26. Randomization on Day 1 was stratified by age group (<65 years/ ≥65 years) and prior bisphosphonates use (yes/ no).

At Week 52, subjects entered the Transition Period. All subjects in the FKS518 group continued treatment with a third dose of FKS518 60 mg SC. Subjects who had received US-Prolia during the Core Treatment Period were re-randomized in a 1:1 ratio to either continue on US-Prolia 60 mg SC or switch to FKS518 60 mg SC. Subjects were followed for an additional 26 weeks. The study design is shown in Figure 9.

Figure 9. FKS518-002 Study Design



sc=subcutaneous
Source: Figure 1, page 499 of FKS518-002 protocol

To qualify for study participation, subjects had to be post-menopausal, aged 55 to 85 years and have osteoporosis according to bone mineral density (BMD) criteria on DXA scan (absolute lumbar spine BMD T-score ≤ -2.5 and ≥ -4.0). Subjects also had to be naïve to denosumab. Use of medications with bone effects, or presence of underlying conditions that could impact bone quality or density were additional exclusion criteria. Refer to Section 13.5.2 for complete list of entry criteria.

FKS518 or US-Prolia were administered by blinded study staff, and the SC injection was only administered in the abdomen. The dose used in the study is the same as the dose of US-Prolia indicated for treatment of postmenopausal osteoporosis [i.e. 60 mg injected subcutaneously (SC) every 6 months]. All subjects were instructed to take 1000 mg of calcium and at least 400 IU vitamin D daily.

The primary efficacy endpoint was the percentage change in lumbar spine bone mineral density (LS-BMD) assessed by DXA at Week 52 compared to baseline. The same DXA scanner was to be used for a particular subject for all study procedures, and all DXA scans were submitted to a central imaging vendor for analysis.

The key secondary endpoint was the percentage change from baseline in BMD at femoral neck and total hip assessed by DXA at Week 52.

The study duration was 78 weeks, including 24 visits to the study clinic. Assessments included periodic testing of vital signs, ECG, and laboratory tests for safety. DXA scan was performed at screening and again at treatment weeks 52 and 78. Immunogenicity assessment consisted of antidrug antibody and neutralizing antibody testing and

evaluation for injection site reactions. The complete schedule of assessments is shown in Table 40 and Table 41.

6.2.3. Statistical Methodologies

The sponsor's primary analysis set, the Intent-to-Treat (ITT) analysis set, consisted of all subjects who were randomized. Subjects were analyzed according to their randomized treatment.

Reviewer's Preferred Analysis Population

The statistical reviewer's preferred analysis population is the same as the applicant's - all randomized subjects. Note that the primary endpoint, percent change from baseline in lumbar spine (LS) bone mineral density (BMD), requires a corresponding baseline measure in order for the percent change from baseline to be calculated. All randomized subjects had baseline lumbar spine BMD measures in this study.

Primary Efficacy Analysis

The statistical hypotheses tested to assess similarity between FKS518 and Prolia using the primary endpoint, percent change from baseline in LS-BMD by DXA at Week 52, was as follows:

$$H0: |\text{FKS518} - \text{Prolia}| \geq \Delta$$
$$\text{versus}$$
$$H1: |\text{FKS518} - Prolia| < \Delta$$

Similarity was considered confirmed if the two-sided 90% confidence interval (CI) for the difference |FKS518 – Prolia|, in the primary efficacy endpoint is contained within the margins of (-1.45%, 1.45%).

The Applicant's prespecified primary analysis was an Analysis of Covariance (ANCOVA) model. The ANCOVA model included treatment, age (<65 years,>=65 years), and prior bisphosphonates therapy (yes/no) as factors, and baseline LS BMD value as the covariate. The imputation model was a regression model with the following covariates: treatment group, baseline lumbar spine BMD, and percent change from baseline in lumbar spine BMD at Month 6 and Month 12. Two multiple imputations were performed. Missing data was first imputed as missing at random. Then a shift of -1.45% was applied for testing the non-inferiority null, and a shift of 1.45% was applied for testing the non-superiority null. These shifts were applied to the FKS518 arm.

6.2.4. Subject Disposition

The majority of subjects in both treatment groups completed both the Core Period and the Treatment Period (see Table 14, Table 15). The primary efficacy analysis for the primary endpoint (percent change from baseline in LS-BMD at week 52) was conducted

on the Intention to Treat Analysis Set, which includes all randomized subjects. The most common reason for premature discontinuation in both treatment periods was patient withdrawal of consent.

Three subjects discontinued the study early due to reason classified as “other”. During the Core Period, Subject (b) (6) (in FKS518 group) was discontinued from the study by Sponsor request due to being non-compliant with the protocol, and Subject (b) (6) (in FKS518 group) was discontinued from the study due to concomitant treatment with another biologic medication, which met criteria for study exclusion. During the Transition Period, Subject (b) (6) (in the FKS518/FKS518 group) was discontinued from the study due to being out of the country.

Table 14. Subject disposition, Study FKS518-002 Core Period

Disposition Status	FKS518 (N=277) n (%)	US-Prolia (N=276) n (%)
Randomized	277	276
Subjects Treated as Randomized	277 (100)	276 (100)
Discontinued before Week 52	25 (9)	27 (9.8)
Primary Reason for study discontinuation		
Adverse event	0	6 (2.2)
Death	0	0
Investigator decision	1 (0.4)	0
Withdrawal of Consent	20 (7.2)	21 (7.6)
Lost to Follow up	2 (0.7)	0
Other	2 (0.7)	0
Subjects Completing Core Period	252 (91)	249 (90)

Source: FKS518-002 study report, Table 14.1.1.3.1, page 250-251

Table 15. Subject disposition, Study FKS518-002 Transition Period

Disposition Status	FKS518/FKS518 (N=252) n (%)	US-Prolia/FKS518 (N=124) n (%)	US-Prolia/US-Prolia (N=125) n (%)
Re-Randomized	252	124	125
Subjects Treated as Randomized	252 (100)	124 (100)	125 (100)
Discontinued prematurely	7 (2.8)	2 (1.6)	3 (2.4)
Primary Reason for study discontinuation			
Adverse event	0	1 (0.8)	1 (0.8)
Death	0	0	0
Withdrawal of study consent	6 (2.4)	1 (0.8)	2(1.6)
Other	1 (0.4)	0	0
Completed Transition Period	245 (97.2)	122 (98.4)	122 (97.6)

Source: FKS518-002 study report, Table 14.1.1.3.2, page 253

6.2.5. Demographics and Baseline Characteristics

Demographic characteristics were overall well-balanced between the two treatment groups (see Table 16). Baseline disease characteristics were also similar (see Table 17). In cases when there were slight differences in baseline characteristics, it is unlikely that these differences had a significant impact on the study findings.

Table 16. Demographic characteristics, Study FKS518-002

Demographic variable	FKS518 (N=277) n (%)	US-Prolia (N=276) n (%)
Age		
Mean (SD) years	65.2 (6.4)	65.8 (6.5)
N(%) < 65 years	128 (46)	126 (46)
N(%) ≥ 65 years	149 (54)	150 (54)
Race – N(%)		
White	277 (100)	276 (100)
Baseline weight		
Mean (SD) kg	63.5 (10)	62.3 (9)
BMI, N(%) < 25 kg/m^2	153 (55)	166 (60)
BMI, N(%) ≥ 25 kg/m^2	124 (45)	110 (40)
Region– N (%)		
Poland	137 (50)	143 (52)
Bulgaria	47 (17)	34 (12)
Georgia	36 (13)	36 (13)
Czech Republic	26 (9)	24 (9)
Hungary	20 (7)	25 (9)
Estonia	11 (4)	14 (5)

Source: FKS518-002 clinical study report, adapted from Table 14, pg 122

Table 17. Baseline disease characteristics, Study FKS518-002

Demographic variable	FKS518 (N=277) n (%)	US-Prolia (N=276) n (%)
Prior bisphosphonate use – N (%)		
Yes	32 (12)	34 (12)
No	245 (88)	242 (88)
History of fracture – N (%)		
Yes	74 (27)	78 (28)

Demographic variable	FKS518 (N=277) n (%)	US-Prolia (N=276) n (%)
No	202 (73)	198 (72)
Unknown	1 (0.4)	0
Baseline LS BMD (g/cm^2)		
Mean (SD)	0.79 (0.09)	0.79 (0.06)
Min, Max	0.62, 0.92	0.62, 0.91
Baseline LS T-score		
Mean (SD)	-3.02 (0.41)	-3.01 (0.39)
Min, Max	-4.03, -2.21	-4.33, -2.19

Source: FKS518-002 clinical study report, adapted from Table 14, Table 15, and Table 16, pg 122-126

6.2.6. Potential Effects of Missing Data

There were 277 randomized treated patients on the FKS518 arm, and 276 randomized treated patients on the Prolia arm. There were 22 (7.9%) of patients with missing final assessments on the FKS518 arm, and 24 (8.7%) patients with missing final assessments on the Prolia arm. Analysis results using different methods for imputing missing data were consistent and supportive of biosimilarity. The Applicant's tipping point analyses also indicated that the conclusion of no clinically meaningful difference would only be overturned under unlikely scenarios of missing data.

6.2.7. Analysis of Primary Clinical Endpoint(s)

The primary analysis for the primary endpoint was an ANCOVA (Analysis of Covariance) model. Percent change from baseline in LS-BMD at Week 52 was the response variable, and treatment, Tanner stage (stages 2/3/4 vs. stage 5), and presence of weight-related comorbidities age (< 65 years; ≥ 65 years) and prior bisphosphonate therapy (Yes/No) were factors. Baseline LS-BMD-DXA was included as a covariate. (Note the Baseline LS_BMD-DXA have exactly the same measurements as Baseline BMD. However Baseline BMD has some missing measurements, whereas LS_BMD-DXA, which is in the ADSL dataset, has no missing measurements.)

The Applicant imputed missing data in both treatment groups based on observed data within each group. The imputed values in the test product group were subsequently subtracted by the margin 1.45% for testing non-inferiority (**Table** 18) and added by the margin for testing non-superiority (**Table** 19), respectively. The imputed datasets were then each analyzed using the same ANCOVA model as the primary analysis. The analyses results (using 200 imputations for missing data) were combined using Rubin's method. Results from the two one-sided tests supported the similarity in LS BMD at month 12 between the two treatment groups. The 90% confidence limits were all within the similarity margin.

Table 18. Percent Change in BMD from Baseline to Week 52

Variable Statistic	FKS518 [N=277]	US-Prolia [N=276]	Difference (FKS518 - Prolia)
LS Mean (SE)	5.52 (0.292)	5.07 (0.297)	0.46 (0.306)
90% Confidence Interval	(5.04, 6.00)	(4.58, 5.55)	(-0.05, 0.96)

Applicant's analysis; Note- missing values were first imputed under missing at random (MAR) assumption; the imputed values in the FKS518 arm were then subtracted by 1.45%.

Table 19:Percent Change in BMD from Baseline to Week 52

Statistic	FKS518 [N=277]	US-Prolia [N=276]	Difference (FKS518 – Prolia)
LS Mean (SE)	5.73 (0.292)	5.03 (0.297)	0.69 (0.306)
90% Confidence Interval	(5.24, 6.21)	(4.55, 5.52)	(0.19, 1.20)

Applicant's analysis- missing values were first imputed under missing at random (MAR) assumption; the imputed values in the FKS518 arm were then added by 1.45%.

6.2.8. Analysis of Additional Clinical Endpoint(s)

Secondary Clinical Endpoints: BMD at femoral neck and total hip Week 52

Although not controlled for type I error or subject to hypothesis testing, BMD values for femoral neck and total hip were assessed by DXA at Week 52, coinciding with the completion of twelve months of treatment prior to the single transition dose.

The difference between FKS518 and US-Prolia was estimated by the difference in the least squares means of percent change from baseline to Week 52, with 95% confidence intervals. At Week 52, the increase in percent change from baseline in femoral neck and total hip BMD was similar between the FKS518 and US-Prolia groups (see Table 20). These data do not suggest a clinically meaningful difference between FKS518 and US-Prolia in efficacy at multiple skeletal locations.

Table 20. Analysis of percent change from baseline in femoral neck and total hip BMD (g/cm^2) at Week 52, ITT Analysis Set, Study FKS518-002

	Treatment	LS Mean (SE)	Difference	
			LS Mean (SE)	95% CI
Femoral Neck BMD	**FKS518**	2.07 (0.284)	0.22 (0.301)	[-0.37, 0.81]
	US-Prolia	1.85 (0.291)		
Total Hip BMD	**FKS518**	2.97 (0.217)	0.10 (0.230)	[-0.35, 0.55]
	US-Prolia	2.88 (0.223)		

CI = confidence interval; LS mean = least squares mean; SE = standard error

Source: Adapted from Clinical Study Report FKS518-002, Table 26 and 27, page 167-170

Other Clinical Endpoint: Lumbar spine BMD Week 78

Lumbar spine BMD values were assessed by DXA at Week 78, coinciding with six months after the single transition dose. The mean percent change from baseline in lumbar spine BMD at Week 78 was similar among the three treatment groups (see Table 21). This endpoint was not controlled for type I error or subject to hypothesis testing. Nevertheless, these data do not suggest a clinically meaningful difference in efficacy after transitioning from US-Prolia to FKS518.

Table 21. Mean (SE) percent change from baseline to Week 78 in lumbar spine BMD, ITT Analysis Set, Study FKS518-002

	FKS518+FKS518 (N=252)	US-Prolia+US-Prolia (N=125)	US-Prolia+ FKS518 (N=124)
LS Mean (SE)	7.1 (0.32)	5.9 (0.41)	6.7 (0.41)
95% CI	[6.47, 7.73]	[5.09, 6.69]	[5.91, 7.54]

LS mean = least squares mean; SE = standard error; CI = Confidence Interval

Source: Adapted from Clinical Study Report FKS518-002, Table 30, page 179

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The evaluation of safety is based primarily on the comparative clinical study (study FKS518-002), which evaluated safety and efficacy of FKS518 and US-Prolia use in post-menopausal women with osteoporosis. However, safety data from the comparative clinical pharmacology study (study FKS518-001), which enrolled healthy adult males, were also examined for known risks of denosumab (e.g., hypersensitivity reactions, hypocalcemia) and to further evaluate any new safety signals that become apparent during review of the data from study FKS518-002. Safety analysis was conducted using

the safety population, defined as subjects who received at least one dose of the study drug. The size of the safety database was agreed upon with the Agency during the clinical development program.

Categorization of Adverse Events

In both study FKS518-001 and FKS518-002, an adverse event (AE) was defined as any untoward medical occurrence in a participating subject regardless of a causal relationship with an administered investigational product. Any untoward medical occurrence in a participating subject occurring after exposure to an investigational product is defined as a treatment emergent adverse event (TEAE). Adverse events were categorized by severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Abnormal laboratory values or test results constituted adverse events only if they were associated with clinical signs or symptoms, led to treatment discontinuation, or are considered otherwise medically important by the Investigator. The corresponding sign, symptom, or medical condition was reported as an AE rather than the abnormal laboratory value.

Serious adverse events (SAEs) were defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was associated with a congenital anomaly or birth defect, or was otherwise considered to be medically important. For both study FKS518-001 and FKS518-002, all confirmed COVID-19 cases qualified as SAE due to being classified as ‘otherwise medically important.’ This resulted in an increase in SAEs due to confirmed COVID-19 cases, though these AEs did not necessarily result in a serious or severe outcome.

Pre-defined adverse events of special interest (AESIs) for study FKS518-002 included drug-related hypersensitivity/allergic reactions (CTCAE Grade ≥3 or reported as SAE) and AEs leading to investigational product discontinuation or study withdrawal.

Safety Analyses

Safety data were not combined because the study populations and design of the two studies differed.

Study FKS518-002 consisted of two treatment periods; the first period (Core Period) compared FKS518 to US-Prolia, and the second period (Transition Period) was designed to evaluate the safety of a transition from US-Prolia to FKS518 compared to continuing on US-Prolia. Safety data from the two treatment periods are presented separately.

Adverse events were coded using MedDRA version 24.0. The FDA review team identified several cases where the coding of the MedDRA preferred term from the

verbatim term was inaccurate or resulted in adverse events being dropped off due to inappropriate lumping of terms. Hence, the review team modified the Applicant's translation of adverse event verbatim terms to dictionary derived terms, when needed. This led to discrepancies in the number of some adverse events compared to the data provided by the Applicant. Any occurrence when FDA modification of the Applicant's translation of event verbatim term to dictionary derived term led to a difference in adverse event rates is notated in the safety results.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Study FKS518-001 enrolled healthy adult male volunteers, who do not reflect the population for whom denosumab is indicated. Nonetheless, the population was considered appropriate and sensitive given the primary objectives of the study.

Study FKS518-002 enrolled post-menopausal women with osteoporosis, which is one of the targeted populations for denosumab. Demographic and baseline disease characteristics of the study population are shown in Table 16 and Table 17, respectively.

Deaths

There were no deaths in either study FKS518-001 or FKS518-002.

Serious Adverse Events

Study FKS518-001

A total of 23 subjects experienced a serious adverse event as defined by the Applicant-14 (13.1%) in the FKS518 group and 9 (8.5%) in the US-Prolia group. However, all but two of these events were COVID-19 infections, as discussed below.

One subject in the FKS518 group experienced a suicide attempt and one subject in the FKS518 group experienced biliary duct adenocarcinoma. Neither of these events appear to be related to the study drug

Study FKS518-002

Core Period:

During the Core Period, serious adverse events occurred in 43/277 (15.5%) of subjects receiving FKS518 and 50/276 (18.1%) of subjects receiving US-Prolia (refer

to Table 22). The slight excess SAE incidence in the US-Prolia group was driven by an excess number of subjects with confirmed COVID-19 infection.

In both groups, the most frequently reported serious adverse event was COVID-19, which was designated as an 'otherwise medically important' serious adverse event regardless of severity. Of the 43 subjects with SAEs in the FKS518 group, 35/277 (12.6%) had COVID-19, and of the 50 subjects with SAEs in the US-Prolia group, 43/276 (15.6%) had COVID-19. None of the COVID-19 events resulted in death, and just two were associated with hospitalization (and hence, met the standardized definition of an SAE). One of the subjects with COVID-19 associated with hospitalization (in the FKS518 group) had COVID-related pneumonia, and the other subject (in the US-Prolia group) had COVID-induced atrial fibrillation exacerbation. In this study, COVID-19 infection was not strongly associated with events that are typically considered serious, such as hospitalization and death. Therefore, the incidence of SAEs driven by COVID-19 infection, which largely comprises events that the review team does not consider to be truly SAEs as they do not meet the standard definition of an SAE, does not indicate a clinically significant safety signal.

Of the remaining SAEs, there was a higher incidence of new malignancies in the US-Prolia treatment group compared to the FKS518 treatment group (2.5% [7/276] in the US-Prolia group compared to 0.7% [2/277] in the FKS518 group). Though new malignancies are included as an adverse event in the Prolia label, the frequency of malignancy was lower in study FKS518-002 than the frequency of new malignancy noted in the Prolia label. This observed treatment difference is likely due to chance, and unlikely to be clinically meaningful.

Table 22. Serious adverse events, Core Period, Study FKS518-002

	FKS518 (N=277) n (%)	**US-PROLIA (N=276)** n (%)
Total number of subjects with SAEs (%)	43 (15.5)	50 (18.1)
COVID-19*	35 (12.6)	43 (15.6)
Malignancy (FMQ)**	2 (0.7)	7 (2.5)
Vestibular disorder	1 (0.4)	0
Balance disorder	1 (0.4)	1 (0.4)
Loss of consciousness	1 (0.4)	0
Foot deformity	1 (0.4)	0
Hydrometra	1 (0.4)	0
Rectocele	1 (0.4)	0
Asthma	1 (0.4)	0
Hypertension	1 (0.4)	0
Device dislocation	0	1 (0.4)

Source: clinical reviewer analysis

FMQ = FDA medical query
*Of the reported SAEs due to COVID-19, the review team considered just two of these events to be true SAEs, as they resulted in hospitalization: in the FKS518-treated group, one subject had COVID-related pneumonia, and in the US-Prolia group, one subject had COVID-induced atrial fibrillation exacerbation.
**Malignancy FMQ includes the following preferred terms: bladder transitional cell carcinoma, squamous cell carcinoma (in the FKS518 treatment group); bladder neoplasm, glioblastoma, lung adenocarcinoma, metastases to lymph nodes, nasopharyngeal cancer, neuroendocrine tumour of the lung metastatic, oral papilloma, ovarian cancer (in the US-Prolia treatment group)

One event of *COVID-19* in subject (b) (6) was considered by the investigator as possibly related to the investigational product. The event occurred on Day 256 of the trial, 73 days after the second administration of FKS518. This infection did not result in hospitalization or death and resolved after four days with oral azithromycin and inhaled budesonide. COVID-19 was a common adverse event across all treatment groups and more likely due to the pandemic rather than a causal relationship with FKS518.

Overall, none of the SAEs in the Core Period appear to be related to the study drug.

Transition Period

During the Transition Period, 8/252 (3.2%) subjects in the FKS518+FKS518 group, 6/124 (4.8%) subjects in the Prolia+FKS518 group, and 6/125 (4.8%) subjects in the Prolia+Prolia group experienced treatment-emergent serious adverse events (refer to Table 23). As was found during the Core Period, the most frequently reported serious adverse event in all treatment groups was COVID-19. Six subjects in the FKS518+FKS518 group, 4 subjects in the Prolia+FKS518 group, and 3 subjects in the Prolia+Prolia group experienced COVID-19 infections. None of the subjects with COVID-19 were hospitalized or died, therefore, the review team does not consider these events to be SAEs as they do not meet the standard definition of an SAE.

Table 23. Serious adverse events, Transition Period, Study FKS518-002

	FKS518 + FKS518 (N=252) n (%)	US-PROLIA + FKS518 (N=124) n (%)	US-PROLIA + US-PROLIA (N=125) n (%)
Total number of subjects with SAEs (%)	8 (3.2)	6 (4.8)	6 (4.8)
COVID-19*	6 (2.4)	4 (3.2)	3 (2.4)
Angina pectoris	1 (0.4)	0	0
Thrombocytosis	1 (0.4)	0	0
Pancreatitis acute	0	1 (0.8)	0
Bladder cancer recurrent	0	1 (0.8)	0
Spinal osteoarthritis	0	0	1 (0.8)
Nervous system disorders	0	0	1 (0.8)
Dizziness	0	0	1 (0.8)

Source: clinical reviewer analysis
FMQ = FDA medical query

*Of the reported SAEs due to COVID-19, the review team did not consider any to be true SAEs, as none resulted in hospitalization, death, or otherwise qualified as a serious adverse event.

Subject (b) (6) was diagnosed with *pancreatitis* on Day 388, 22 days after administration of FKS518. This subject was hospitalized on Day 388 for severe stomachache with associated weakness and was discharged on Day 406 upon resolution of the event. The subject discontinued the study on Day 449 due to adverse event, leading this adverse event being classified as an adverse event of special interest.

Pancreatitis was reported in 4 subjects (0.1%) in the placebo and 8 subjects (0.2%) in the Prolia groups in the original registration trial for Prolia, and is included in Section 6 of the Prolia label. With an occurrence in only a single subject during study FKS518-002, the event was too infrequent to draw conclusions.

During the Transition Period, none of the SAEs in any of the treatment groups were considered related to study drug. Review of the narratives yields the same conclusion. Across the study, there were no significant patterns in the SAEs reported to indicate a potential safety signal.

Common Treatment Emergent Adverse Events

Study FKS518-002

Core Period

The most common treatment emergent adverse events (i.e., occurring in >2% of subjects in either treatment group) were similar between treatment groups, and is largely consistent with the known safety profile of denosumab (see Table 24).

Table 24. Most common treatment emergent adverse events (incidence >2%), Core Period, Study FKS518-002

	FKS518 (N=277) n (%)	US-PROLIA (N=276) n (%)
Any TEAE, N (%)	185 (66.8)	189 (68.5)
COVID-19	32 (11.6)	41 (14.9)
Nasopharyngitis	27 (9.7)	33 (12.0)
Upper respiratory tract infection	23 (8.3)	30 (10.9)
Urinary tract infection	18 (6.5)	23 (8.3)
Systemic hypertension (FMQ)*	14 (5.1)	8 (2.9)
Headache	13 (4.7)	15 (5.4)
Diarrhea	13 (4.7)	9 (3.3)
Arthralgia	10 (3.6)	15 (5.4)
Spinal pain	10 (3.6)	10 (3.6)

Bronchitis	8 (2.9)	9 (3.3)
Pyrexia	8 (2.9)	0
Oropharyngeal pain	7 (2.5)	6 (2.2)
Cough	7 (2.5)	3 (1.1)
Back pain	6 (2.2)	9 (3.3)
Gamma-glutamyl transferase increased	6 (2.2)	3 (1.1)
Vitamin D deficiency	6 (2.2)	3 (1.1)
Conjunctivitis	5 (1.8)	6 (2.2)
Osteoarthritis	4 (1.4)	9 (3.3)
Pharyngitis	3 (1.1)	10 (3.6)
Dizziness	3 (1.1)	8 (2.9)
Abdominal pain upper	2 (0.7)	7 (2.5)

Source: clinical reviewer analysis
FMQ = FDA medical query
*Systemic hypertension FMQ includes the following preferred terms: blood pressure increased, hypertension
After the FDA review team evaluated and provided modifications to the Applicant's translation of adverse event verbatim terms to dictionary derived terms, there was a small discrepancy in the incidence of some adverse events. As none of the changes resulted in a difference in adverse event incidence of 1.5% or more, this discrepancy is unlikely to result in the FDA analysis to be significantly different from the Applicant's analysis.

The most common TEAEs in the Core Period were *COVID-19*, *nasopharyngitis*, and common infections including *upper respiratory infection* and *urinary tract infection*. These most common TEAEs were largely more common in the US-Prolia group compared to the FKS518-treated group. For all TEAEs in which more subjects in the FKS518 group than the US-Prolia group were affected, the difference between incidences of the TEAEs was small and likely due to chance rather than meaningful differences between the products.

Transition Period

The adverse event profile during the Transition Period was also largely consistent with the known safety profile of denosumab. The most common TEAEs during the Transition Period were infectious in etiology, which is a labeled adverse effect of Prolia (see Table 25).

Table 25. Most common treatment emergent adverse events (incidence >2%), Transition Period, Study FKS518-002

	FKS518 + FKS518 (N=252) n (%)	**US-PROLIA + FKS518 (N=124)** n (%)	**US-PROLIA + US-PROLIA (N=125)** n (%)
Any TEAE (%)	106 (42.1)	58 (46.8)	47 (37.6)
Nasopharyngitis (FMQ)*	30 (11.9)	26 (21)	15 (12)
Nasopharyngitis	11 (4.4)	17 (13.7)	8 (6.4)

Upper respiratory tract infection	12 (4.8)	8 (6.5)	7 (5.6)
Viral infection (FMQ)**	20 (7.9)	7 (5.6)	5 (4)
Bacterial infection (FMQ)***	20 (7.9)	5 (4)	3 (2.4)
Bronchitis	7 (2.8)	1 (0.8)	1 (0.8)
Arthralgia	6 (2.4)	2 (1.6)	0
Spinal Pain	1 (0.4)	1 (0.8)	3 (2.4)
Dizziness	1 (0.4)	0	3 (2.4)
Rash	0	3 (2.4)	0

Source: clinical reviewer analysis
FMQ = FDA medical query
*Nasopharyngitis FMQ includes the following preferred terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, pharyngitis bacterial, rhinitis, rhinitis allergic
**Viral infection FMQ includes the following preferred terms: COVID-19, COVID-19 pneumonia, hepatitis E, herpes zoster, influenza, oral herpes, skin papilloma, viral infection, viral upper respiratory infection
***Bacterial infection FMQ includes the following preferred terms: abscess limb, bronchitis bacterial, cystitis, Lyme disease, periodontitis, pharyngitis bacterial pulpitis dental, urinary tract infection

Total treatment emergent adverse events were balanced overall between the treatment groups. Events that occurred more commonly in the group transitioning from Prolia to FKS518 than in the other treatment groups were *nasopharyngitis* and *rash*. However, the total number of subjects effected are small overall and differences between the treatment groups is more likely due to chance than a meaningful difference between the products. In addition, this difference is unlikely to be clinically significant as all nasopharyngitis cases were either grade 1 or 2 CTCAE in severity without requiring significant intervention.

Dropouts and/or Discontinuations

Study FKS518-002

Core Period

During the Core Period of the study, a similar number of subjects withdrew from the study in each group (25/277 [9%] subjects in the FKS518 group, and 27/276 [9.8%] subjects in the US-Prolia group). Most of these subjects discontinued the study due to withdrawal of consent (20 subjects in the FKS518 group and 21 subjects in the US-Prolia group).

No subjects in the FKS518 group discontinued the study due to an adverse event, while 6 subjects (2.2%) in the US-Prolia group discontinued prematurely due to an adverse event (refer to Table 26). Several of the subjects who discontinued early due to an adverse event related to newly diagnosed malignancies.

Table 26. Adverse events (by preferred term) leading to premature discontinuation of Study FKS518-002, Core Period

	FKS518 (N=277) n (%)	US-PROLIA (N=276) n (%)
Total number of subjects who discontinued from the study prematurely due to adverse events	0	6 (2.2)
Periodontal disease	0	1 (0.4)
Pulpitis dental	0	1 (0.4)
Arrhythmia	0	1 (0.4)
Nasopharyngeal cancer	0	1 (0.4)
Metastasis to lymph nodes	0	1 (0.4)
Ovarian cancer	0	1 (0.4)
Arthralgia	0	1 (0.4)
Spinal osteoarthritis	0	1 (0.4)
Intercostal neuralgia	0	1 (0.4)
Glioblastoma	0	1 (0.4)

Source: clinical reviewer analysis

Transition Period

Only two subjects discontinued the study due to an adverse event during the Transition Period. Subject (b) (6) (in the Prolia+Prolia treatment group) discontinued the study on Day 422 due to the diagnosis of *lung adenocarcinoma*, though onset of the adverse event occurred on Day 321, prior to the subject's third dose of Prolia. Subject (b) (6) (in the Prolia+FKS518 treatment group) discontinued the study due to *pancreatitis acute*.

In conclusion, study dropouts were rare throughout the study, but they were unbalanced during the Core Period; 6 subjects taking Prolia discontinued the study due to AEs while no subjects taking FKS518 discontinued due to AEs. Most discontinuations were due to newly diagnosed malignancies, which, though they occurred more frequently in the Prolia group, were at a lower frequency than is noted in the Prolia label. This therefore does not appear to be a clinically significant signal. Overall, none of the TEAEs leading to study discontinuation appear to be related to the study drug. There is no evidence that the safety profile of FKS518 is different than that of Prolia.

6.3.3. Additional Safety Evaluations

Laboratory Findings

Calcium and Minerals

Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorous and magnesium). The US-Prolia prescribing information advises that calcium, phosphorous and magnesium be monitored within 14 days of injection, as the nadir for serum calcium occurs within the first two weeks following administration of denosumab.

Abnormal labs were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE toxicity grading scale for hypomagnesemia, hypocalcemia, and hypophosphatemia is shown in Table 27. Toxicity for derangements in magnesium and calcium are based on laboratory values. For phosphorous, toxicity is graded based on clinical symptoms and requirement for intervention rather than on specific laboratory findings.

Table 27. CTCAE Toxicity Grading Scale for Hypomagnesemia, Hypocalcemia and Hypophosphatemia

	Toxicity Grade				
	1	2	3	4	5
Hypomagnesemia	<LLN – 1.2 mg/dL	<1.2 – 0.9 mg/dL	<0.9 – 0.7 mg/dL	<0.7 mg/dL	Death
Hypocalcemia	<LLN – 8 mg/dL	<8 – 7 mg/dL	<7 – 6 mg/dL	<6 mg/dL	Death
Hypophosphatemia	No intervention indicated	Noninvasive intervention indicated	Severe/ medically significant but not immediately life-threatening; hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death

Source: US Department of Health and Human Services. (Nov. 27, 2017). Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Hypocalcemia

Study FKS518-001

Safety laboratory testing occurred at screening, post-injection days 2 and 6, and post-injection weeks 3, 5, 13, 19, 27, 37, and 40. Safety laboratory testing consisted of hematology, clinical chemistry (including serum calcium) and urinalysis checked throughout the study.

There were no meaningful differences in treatment groups in median change in chemistry parameters over time, and shift analysis revealed no concerns or notable differences among the treatment groups. No subjects in any treatment group had serum calcium levels below the lower limit of normal (8.58 mg/dL) throughout the study.

Study FKS518-002

Core Period

During the 12-month Core Period, subjects received study drug (i.e., either FKS518 or US-Prolia) injection at study day 1 and study day 183 (week 26). Safety laboratory testing (including hematology, serum chemistry, and urinalysis) was performed at screening, at baseline, and at 2, 4, 12, 26, 28, 30, 36, and 52 weeks after treatment initiation. There were no clinically meaningful differences between treatment groups in median change in chemistry parameters over time during the Core Period.

Subjects were instructed to take 1000 mg calcium and at least 400 IU vitamin D supplementation daily.

As the nadir for serum calcium occurs within the first two weeks following study drug administration, serum calcium was measured at baseline and 2 weeks after both investigational product injections (i.e., week 2 and week 28). The risk of hypocalcemia is greater in patients with severe renal impairment (i.e., glomerular filtration rate <30 mL/min), and this study excluded subjects with a creatinine clearance <30 mL/min at screening or receiving dialysis.

The Clinical Study Report presented results for both serum calcium and albumin-corrected serum calcium. Because approximately 40% of total body calcium is protein bound, serum calcium may be artificially low in the setting of hypoalbuminemia. In those situations, a correction formula to account for the low albumin is used to estimate actual serum calcium levels. Ionized calcium is the preferred measurement but is not readily available in all laboratories.[3] However, as low albumin results were very rare and mild in severity in this study, and there are reported inaccuracies with various correction formulas and the role for such formulas when albumin levels are normal is unclear, this review examines only serum calcium measurements, not the corrected calcium values. Only 5 subjects developed hypoalbuminemia during the trial. All subjects had only a single low albumin reading (with values ranging from 32 to 34 g/L; normal range 35 to 55 g/L).

[3] Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. BMJ Open. 2018 Apr 7;8(4):e017703.

All low albumin levels in the study were CTCAE toxicity Grade 1, and all were isolated with no additional low levels.

The median change from baseline in serum calcium during the Core Period was comparable in both treatment groups at all measurements following the initial and second study drug administration (see Table 28).

Table 28. Median (min, max) change from baseline in serum calcium (mg/dL) following first and second study drug administration

	FKS518	US-Prolia
Change from baseline to Week 2 Median (min, max)	-0.4 (-1.6, 0.92) N=266	-0.4 (-1.68, 0.8) N=271
Change from baseline to Week 4 Median (min, max)	-0.4 (-1.72, 1.28) N=267	-0.4 (-1.6, 0.88) N=271
Change from baseline to Week 12 Median (min, max)	-0.2 (-1.4, 1.2) N=264	-0.2 (-1.4, 1.4) N=264
Change from baseline to Week 26 Median (min, max)	0 (-1.6, 1.6) N=255	0 (-0.92, 1) N=248
Change from baseline to Week 28 Median (min, max)	0 (-1.4, 1.52) N=260	-0.08 (-1.2, 1) N=250
Change from baseline to Week 30 Median (min, max)	-0.08 (-1.32, 1.2) N=255	0 (-1.12, 1) N=254
Change from baseline to Week 36 Median (min, max)	0 (-1.08, 1.2) N=253	0 (-1.12, 1.4) N=254
Change from baseline to Week 52 Median (min, max)	0.8 (-1.4, 1.4) N=254	0.8 (-1.52, 1.2) N=250

Source: FKS518-002 Clinical study report, adapted from Table 14.3.3.2.1.1, pg 5727-5731

All subjects had normal serum calcium level at screening. The incidence of hypocalcemia (i.e., serum calcium below the lower limit of normal: 8.5 mg/dL) during treatment was similar between the two treatment groups. Most of the shifts occurred following the first dose of study drug (see Table 29). After the second dose of study drug at week 26, the incidence of hypocalcemia was rare.

Table 29. N (%) of subjects with shift in serum calcium to below the lower limit of normal (<LLN) after the first and second study drug administration during Study FKS518-002, Core Period

	FKS518 (N=277) n (%)	US-Prolia (N=276) n (%)
Hypocalcemia at any time during Core Period	30 (10.8%)	34 (12.3%)
Following first study drug injection (Day 1)		
First 2-week period post-injection (Week 2)	13 (4.7%)	12 (4.3%)
Between 4 weeks and 26 weeks post-injection	18 (6.5%)	20 (7.2%)
Following second study drug injection (Week 26)		
First 2-week period post-injection (Week 28)	0	2 (0.7%)
Between 4 weeks and 26 weeks post-injection (Week 30 to Week 52)	2 (0.7%)	3 (0.7%)

Source: clinical reviewer analysis

Among the subjects with laboratory evidence of serum hypocalcemia, the degree of hypocalcemia was mild in the majority of cases. Calcium values below 8 mg/dL occurred once in two subjects. Two subjects in the Prolia-treated group had a single serum calcium level of 7.9 mg/dL; one was drawn during the Week 2 visit (subject [redacted]) and one was drawn during the Week 4 visit (subject [redacted]). Both subjects were asymptomatic on the day of the low calcium reading.

One subject with hypocalcemia (subject [redacted] in Prolia treatment group) reported a TEAE of leg cramps on study Day 22; the subject had a serum calcium level of 8.3 mg/dL on Day 15 and 8.2 mg/dL on Day 29. The event was Grade 1 in severity and resolved after one day with no concomitant or additional treatment required.

During the Core Period, one subject ([redacted], in the FKS518 treatment group) reported an adverse event of hypocalcemia that was classified as a CTCAE Grade 1 toxicity grade. The associated serum calcium level was 8.2 mg/dL. No associated symptoms were reported.

Transition Period

The Transition Period commenced at the Week 52 study visit when subjects received their third and final dose of study drug. Subjects who had received US-Prolia during the Core Period were re-randomized in a 1:1 ratio to received either US-Prolia or FKS518 for their final dose. Laboratory evaluation of hematology, clinical chemistry, and urinalysis occurred prior to denosumab injection at the Week 52 visit, the Week 56 visit, the Week 68 visit, and at the end-of-study visit (week 78, or early termination).

There were no meaningful differences between treatment groups in median change in chemistry parameters over time during the Transition Period. There was also no meaningful difference in median change from the Transition Period baseline (Week

52) in serum calcium to the End of Study visit (Month 78) between the three groups (see Table 30).

Table 30. Median (min, max) change in serum calcium (mg/dL) from Transition Period baseline (Week 52) to End of Study (Week 78), Study FKS518-002

	FKS518+FKS518	US-Prolia+FKS518	US-Prolia + US-Prolia
Change from baseline to week 56			
Median (min, max)	-0.08 (-1.4, 1.4) N=243	0 (-1.4, 1.32) N=121	-0.08 (-1.12, 1.12) N=123
Change from baseline to week 68			
Median (min, max)	-0.08 (-1.48, 1.32) N=242	-0.12 (-1.92, 1) N=121	-0.08 (-1.2, 1) N=123
Change from baseline to week 78			
Median (min, max)	0 (-1.4, 1) N=245	-0.08 (-1.2, 1.08) N=121	0 (-1.2, 1.28) N=122

Source: FKS518-002 Clinical study report, Table 14.3.3.2.1.3, pg 5906-5907
Baseline value is defined as the last non-missing assessment taken prior to or on the Week 52 visit.

During the Transition Period, there was a higher incidence of hypocalcemia in the US-Prolia to FKS518 transition group compared to the other two treatment groups (see Table 31). However, the number of subjects with hypocalcemia was low overall (5 subjects in the FKS518+FKS518 treatment group, 6 subjects in the US-Prolia+FKS518 treatment group, and zero subjects in the Prolia+Prolia treatment group), and this difference in incidence is unlikely to be meaningful and likely to be due to statistical chance. In addition, subjects with hypocalcemia were asymptomatic and hypocalcemia events were mild in severity. No subject had a serum calcium level <8 mg/dL.

Table 31. N (%) of subjects with a shift in serum calcium from normal or elevated at Transition Period baseline (i.e., Month 12) to below the lower limit of normal (< LLN) during Study FKS518-002, Transition Period

	FKS518+ FKS518 (N=252) n (%)	US-Prolia + FKS518 (N=124) n (%)	US-Prolia + US-Prolia (N=125) n (%)
Number of subjects with normal or elevated serum calcium at Week 52	250	124	125
Shift to Calcium < LLN during transition period	5 (2%)	6 (4.8%)	0
Shift to Calcium < 8 mg/dL during transition period	0	0	0

Source: clinical reviewer analysis

There were no reported TEAEs of hypocalcemia during the Transition Period.

Hypomagnesemia and hypophosphatemia

Study FKS518-001

There were no meaningful differences in treatment groups in median change in any chemistry parameters over time, including magnesium and phosphate, and shift analysis revealed no concerns or notable differences among the treatment groups.

Study FKS518-002

The incidence of transitions from normal at baseline to below the normal range for magnesium and phosphate were similar between treatment groups during both the Core Period (Table 32) and the Transition Period (Table 33). Small differences between treatment groups are most likely due to chance rather than differences between the drug products.

Table 32. Incidence of shifts from normal to below the limit of normal in magnesium and phosphate, at any point during the Core Period in Study FKS518-002

Laboratory parameter	FKS518 (N=277) n (%)	US-Prolia (N=276) n (%)
Magnesium	34 (12.3%)	33 (12%)
Phosphate	15 (5.4%)	24 (8.7%)

Source: clinical reviewer analysis

Table 33. Incidence of shifts from normal to below the limit of normal in magnesium and phosphate, Study FKS518-002, Transition Period

Laboratory parameter	FKS518+ FKS518 (N=252) n (%)	US-Prolia+ FKS518 (N=124) n (%)	US-Prolia+ US-Prolia (N=125) n (%)
Magnesium	14 (5.6%)	12 (9.7%)	9 (7.2%)
Phosphate	8 (3.2%)	7 (5.6%)	1 (0.8%)

Source: clinical reviewer analysis

Hemoglobin

Denosumab was associated with a higher incidence of anemia in the US-Prolia post-menopausal osteoporosis indication registration trial. Therefore, this review includes an analysis of changes in hemoglobin levels.

The CTCAE toxicity grading scale for anemia is shown in Table 34, with toxicity levels based on laboratory values.

Table 34. CTCAE Toxicity Grading Scale for Anemia

	Toxicity Grade				
	1	2	3	4	5
Anemia	<LLN – 10 g/dL	<10 – 8 g/dL	<8 g/dL; Transfusion indicated	Life-threatening consequences, urgent intervention needed	Death

Source: US Department of Health and Human Services. (Nov. 27, 2017). Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Study FKS518-001

There were no meaningful differences in treatment groups in median change in hematology parameters over time, and shift analysis revealed no concerns or notable differences among the treatment groups.

Study FKS518-002

Core Period

There were no clinically meaningful differences between treatment groups in median change in hematology parameters over time during the Core Period.

The incidence of transitions from normal at baseline to below the normal range for serum hemoglobin was slightly more frequent in the FKS518 group during the Core Period of the study (refer to Table 35). However, these differences were overall not clinically meaningful, as 40 of the 43 subjects transitioned from normal hemoglobin level to Grade 1 anemia, corresponding to a hemoglobin level between the lower limit of normal and 10.0 g/dL according to CTCAE criteria. There were few transitions from normal to Grade 2 anemia (3/277 (1%) subjects in the FKS518 group and none in the Prolia group) and no subjects had Grade 3 anemia. Any differences in development of anemia, in addition to being mild and not clinically significant, are unlikely due to a meaningful difference between the products due to the small number of subjects enrolled.

Table 35. Incidence of shifts from normal to below the limit of normal in hemoglobin, Study FKS518-002, Core Period

Laboratory parameter	**FKS518 (N=277)** n (%)	**US-Prolia (N=276)** n (%)
Hemoglobin	43 (15.5%)	27 (9.8%)

Source: clinical reviewer analysis

Transition Period

There were no meaningful differences between treatment groups in median change in hematology parameters over time during the Transition Period. Though the incidence of

shifts from normal to low hemoglobin during the study was less frequent in both the FKS518 and the transition treatment groups compared to the US-Prolia group (refer to Table 36), given the small population size of the Transition Period treatment groups, small differences between treatment groups are most likely due to chance rather than differences between the drug products.

Table 36. Subjects with a shift in hemoglobin from normal to below the lower limit of normal during Study FKS518-002, Transition Period

Laboratory parameter	FKS518+ FKS518 (N=252) n (%)	US-Prolia+ FKS518 (N=124) n (%)	US-Prolia+ US-Prolia (N=125) n (%)
Hemoglobin	15 (6%)	6 (4.8%)	9 (7.2%)

Source: clinical reviewer analysis

Other Laboratory Findings

During the Transition Period, one subject (FKS518-[redacted] (b) (6)) experienced elevations in liver enzymes after transitioning from US-Prolia to FKS518. At the Week 56 laboratory evaluation, four weeks after administration of the first dose of FKS518 and previously treated with Prolia for two doses, the subject had elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) over 3 times the upper limit of normal (AST of 136 U/L, ALT of 400 U/L, GGT of 391 U/L). The Investigator recorded adverse events of ALT increased, AST increased, and GGT increased on the same date (study day 393). These adverse events were not considered serious, no additional actions or hospitalizations were noted, and there were no additional diagnoses included as adverse events. There were no accompanying bilirubin abnormalities or jaundice, so the event does not meet Hy's Law criteria. All three laboratories normalized by Week 68, and AST and ALT remained normal at Week 78.

This subject has no medical history of liver disease, and concomitant medications at the time of the laboratory abnormalities included calcium, vitamin D, and hydrochlorothiazide/losartan. Previous concomitant medications included amoxicillin/clavulanic acid, administered from Day 385 to Day 392, which is notably immediately prior to the date of the liver enzyme elevations (Day 393).

The amoxicillin/clavulanic acid US Prescribing Information includes a warning that hepatic dysfunction, including hepatitis and cholestatic jaundice, has been associated with the use of amoxicillin and clavulanate potassium tablets. The Prolia label does not include a similar warning. Therefore, the review team considers the use of amoxicillin/clavulanic acid to be a more likely cause of this subject's liver enzyme elevation than the study drug.

Injection Site Reactions (ISRs)

Per protocol, in both study FKS518-001 and FKS518-002, study drug was injected subcutaneously in the abdomen. For both studies, local tolerance at the injection site was evaluated by inspection of the skin and appendages in proximity to the site of administration. The Investigator or designee assessed for the presence of erythema, rash, tenderness, swelling, itching, bruising, pain, extravasation, phlebitis, or other types of reaction. The severity of all ISRs were graded according to the National Cancer Institute (NCI)-CTCAE criteria.

Study FKS518-001

In study FKS518-001, local tolerance at the injection site was evaluated prior to study drug administration on Day 1, and at 48 hours, 72 hours, 96 hours, and 120 hours after study drug administration.

Injection site reactions were documented in 6/106 subjects (5.7%) in the US-Prolia group and in 1/107 subject (0.9%) in the FKS518 group. All reactions consisted of injection site bruising and were of grade 1 severity.

Study FKS518-002

In study FKS518-002, evaluation for ISRs occurred on the day of study drug administration and at follow up visits as shown in the Assessment Schedule (refer to Table 40 and Table 41).

Injection site reactions were overall rare, mild in severity, and balanced between treatment groups throughout the study. During the Core Period, one subject in the FKS518 group had grade 2 itching and pain and two subjects in the US-Prolia group had grade 1 itching, bruising, and pain. During the Transition Period, 1 subject in the FKS518+FKS518 group experience grade 1 bruising and 1 subject in the Prolia+Prolia group experienced grade 1 erythema. There were no ISRs reported in the Prolia+FKS518 group.

Overall, for both clinical studies, ISR incidence was low in all treatment groups and mild severity. Therefore, there was no clinically meaningful significant difference between the treatment groups with respect to injection site reactions.

Hypersensitivity Reactions

The clinical reviewer searched the safety dataset for adverse event preferred terms coding to the Anaphylaxis FDA Medical Query (FMQ) and Hypersensitivity Reaction FMQ to evaluate for events of anaphylaxis and hypersensitivity in the clinical studies.

Notably, the Applicant's safety analysis resulted in what they determined to be more frequent hypersensitivity reactions compared to this reviewer. However, the Applicant classified subjects as having a hypersensitivity reaction by using broad Standardized MedDRA Queries (SMQ), leading to the categorization of nonspecific events, such as *cough*, *allergic rhinitis*, and *seasonal allergy*, to be considered hypersensitivity

reactions. Therefore, the FMQ approach to defining hypersensitivity event is more specific to occurrence of drug hypersensitivity and more meaningful for the purpose of this review.

Study FKS518-001

There were no events of anaphylaxis or hypersensitivity during this study, according to a search of the safety dataset for adverse event preferred terms coding to the Anaphylaxis FMQ and Hypersensitivity Reaction FMQ.

Study FKS518-002

Core Period

There were no events of anaphylaxis in either treatment group during the Core Period. Hypersensitivity reactions were rare overall, with one event of *hypersensitivity* and one event of *allergic oedema* occurring in one subject each. Both of these subjects were in the US-Prolia group. No subjects in the FKS518 group experienced a hypersensitivity reaction according to the Hypersensitivity FMQ.

Transition Period

During the Transition Period, there were no events of anaphylaxis or hypersensitivity according to a search of the safety dataset for adverse event preferred terms coding to the Anaphylaxis FMQ and Hypersensitivity Reaction FMQ. Therefore, there was no evidence that transitioning from US-Prolia to FKS518 was associated with an increase in hypersensitivity reactions.

Overall, there were no clinically significant hypersensitivity findings in either clinical study.

Fractures

Study FKS518-002

Thoraco-lumbar spine X-rays were performed at screening and were read centrally. Additional spine X-rays were performed if there was a suspicion of a fracture; these X-rays were assessed locally. A severe vertebral fracture was defined as vertebral height loss >50%, and moderate fracture was defined as height loss from 25% to 50%.

All fractures that occurred during the study were either a 1 or 2 grade in severity.

Core Period

During the Core Period, non-vertebral fractures occurred in two subjects in the FKS518 group compared to nine subjects in the US-Prolia group (see Table 37). The increase in incidence of fractures in the Prolia group appears to be driven by tooth fractures rather than skeletal fractures.

Table 37. N(%) of subjects experiencing Treatment Emergent Adverse Events of Fracture, Core Period, Study FSK518-002

	FKS518 (N=277) n (%)	US-PROLIA (N=276) n (%)
Subjects with Fractures (%)	3 (1.1)	9 (3.3)
Tooth fracture	0	4 (1.4)
Radius fracture	1 (0.4)	1 (0.4)
Femur fracture	0	1 (0.4)
Foot fracture	0	1 (0.4)
Tibia fracture	0	1 (0.4)
Humerus fracture	0	1 (0.4)
Patella fracture	1 (0.4)	0
Fractured sacrum	1 (0.4)	0

Source: clinical reviewer analysis

One event of vertebral fracture (*fractured sacrum*, subject (b) (6), FKS518 group) occurred during the Core Period of the study. This subject had a personal history of hip fracture but otherwise no prior history of vertebral fracture at baseline. Notably, this subject experienced a decrease in both lumbar spine bone mineral density (LS-BMD) and T-score at 52 weeks compared to baseline (LS-BMD of 0.731 g/cm^2 at baseline and 0.719 g/cm^2 at Week 52; LS-BMD T-score -3.75 at baseline and -3.79 and -3.91 at week 52), so lack of bone mineral density response was the likely etiology of the fracture.

Transition Period

Non-vertebral fractures occurred in 1 subject in the FKS518+FKS518 group, 1 subject in the Prolia+FKS518 group, and 2 subjects in the Prolia+Prolia group (see Table 38).

Table 38. N (%) of subjects experiencing Treatment Emergent Adverse Events of Fracture, Transition Period, Study FKS518-002

	FKS518 + FKS518 (N=252) n (%)	US-PROLIA + FKS518 (N=124) n (%)	US-PROLIA + US-PROLIA (N=125) n (%)
Subjects with Fractures (%)	2 (0.8)	1 (0.8)	2 (1.6)
Clavicle fracture	0	0	1 (0.8)
Foot fracture	0	0	1 (0.8)
Forearm fracture	1 (0.4)	0	0
Lumbar vertebral fracture	1 (0.4)	0	0
Rib fracture	0	0	1 (0.8)
Tooth fracture	0	1 (0.8)	0

Source: clinical reviewer analysis

One vertebral fracture (*lumbar vertebral fracture*, subject (b) (6), FKS518/FKS518 group) occurred during the Transition Period of the study. This subject had a personal history of patellar fracture and wrist fracture but otherwise no prior history of vertebral fracture at baseline. No information was available regarding the circumstances associated with the events, such as whether they were associated with trauma or fragility fractures. Both vertebral and non-vertebral fractures were rare events throughout both treatment periods in the trial. Therefore, any difference in incidences between the treatment groups is more likely due to chance rather than meaningful differences between the products.

Osteonecrosis of the jaw

Osteonecrosis of the jaw is identified as a potential adverse reaction under the Warnings and Precautions section of the USPI for Prolia. No subjects in either Study FKS518-001 or FKS518-002 had a TEAE of osteonecrosis of the jaw.

6.4. Clinical Conclusions on Immunogenicity

The assessment of immunogenicity occurred in the comparative pharmacokinetic Study FKS518-001 and the comparative clinical Study FKS518-002. There was no meaningful difference between the treatment arms in either study with respect to development of anti-drug antibodies (ADAs) or neutralizing antibodies (NAbs). Furthermore, presence of ADAs or Nabs had no apparent impact on efficacy or safety outcomes. Refer to Section 5.4 for complete details of the immunogenicity assessment and conclusions from the Clinical Pharmacology review team.

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6.5. Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant's development program established that FKS518, US-Prolia, and US-Xgeva share identical primary structures and comparable secondary and tertiary structures. Functional assays showed similarity between FKS518, US-Prolia, and US-Xgeva with respect to pharmacologic activity. There were no meaningful differences in pharmacokinetics between FKS518 and US-Prolia in the PK similarity study.

The comparative clinical study showed no meaningful difference in PK, efficacy, safety, or immunogenicity between FKS518 and US-Prolia in the treatment of post-menopausal women with osteoporosis. Presence of ADAs had no impact on PK, efficacy, or safety. Although some numerical differences were observed between FKS518 and US-Prolia in

terms of incidences of certain adverse events, the absolute differences were not large and not considered clinically meaningful. Importantly, the adverse event profile of both products was comparable.

A transition from US-Prolia to FKS518 was well tolerated with no meaningful impact on PK, efficacy, or safety. At six months post-transition (i.e., Month 18), the LS mean percentage change from baseline in lumbar spine BMD was comparable in the two treatment groups. There was no meaningful increase in ADA titers or incidence of NAbs after transitioning from US-Prolia to FKS518.

The Applicant provided sufficient justification that FKS518 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

Mechanism of Action

Across all approved indications for US-Prolia and US-Xgeva, the clinical efficacy is based on denosumab binding to RANKL and prohibiting its binding to the RANK receptor. Functional assays established that FKS518 exhibits the same pharmacologic activity as US-Prolia and US-Xgeva and has identical primary structure to US-Prolia and US-Xgeva. Furthermore, there was no clinically meaningful difference in the effect of FKS518 and US-Prolia on the bone turnover marker CTX and lumbar spine bone mineral density, which further supports a shared mechanism of action.

The Applicant provided adequate justification to support that FKS518 has the same, known, and potential mechanisms of action, as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Pharmacokinetics

The applicant provided adequate justification that FKS518 is expected to have a similar PK profile as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Immunogenicity

In the FKS518 development program, immunogenicity was evaluated in populations considered sensitive for detecting clinically meaningful differences: female subjects with post-menopausal osteoporosis (PMO) and healthy subjects. Immunogenicity was found to be similar when comparing FKS518 and US-Prolia in the PK Similarity Study, FKS518-001 in healthy subjects, and between FKS518 and US-Prolia in the comparative clinical study, Study FKS518-002. The Applicant provided adequate justification that FKS518 is expected to have a similar immunogenicity as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Toxicity

Comparative safety was assessed in the comparative clinical study FKS518-002, which was conducted in female subjects with PMO. Supportive safety information was also available from the PK similarity study, Study FKS518-001. The Applicant provided

adequate justification that FKS518 is expected to have a similar safety profile as US-Prolia and US-Xgeva for each indication being sought for licensure.

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of FKS518 and US-Prolia or US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of FKS518 and US-Prolia and US-Xgeva and the results from the comparative clinical study (FKS518-002) to support their justification. The Applicant also described that the results from the single transition included in Study FKS518-002 provided supportive evidence of a low immunogenic risk and no safety concerns with switching between FKS518 and US-Prolia or US-Xgeva.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between FKS518 and US-Prolia or US-Xgeva to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess whether there could be diminished efficacy or safety issues associated with alternating or switching between use of FKS518 and US-Prolia or US- Xgeva was considered unnecessary to support a demonstration of interchangeability for FKS518.

Conclusion

In summary, the data and information provided by the Applicant are sufficient to demonstrate that FKS518 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that the risk, in terms of safety or diminished efficacy of alternating or switching between use of FKS518 and US-Prolia, or FKS518 and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without alternation or switch.

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6.6. Extrapolation

6.6.1. Division of General Endocrinology and Office of Oncology Drugs

The Applicant submitted data and information in support of a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between FKS518 and US-Prolia, or FKS518 and US-Xgeva, in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that FKS518 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of FKS518 and US-Prolia or FKS518 and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alteration or switch.

The Applicant is seeking licensure of FKS518 for the following indication(s) for which US-Prolia and US-Xgeva have been previously licensed and for which FKS518 has not been directly studied:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of FKS518 as an interchangeable biosimilar for each such indication for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved.

Therefore, the totality of the evidence provided by the Applicant supports licensure of FKS518 as a biosimilar to and interchangeable with US-Prolia and US-Xgeva for each of the following indication(s) for which the Applicant is seeking licensure of FKS518 and for which US-Prolia and US-Xgeva have been previously approved:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Conclusions

The Division of General Endocrinology and the Office of Oncology Drugs 1 conclude that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of FKS518 for all indications for which US-Prolia and US-Xgeva are licensed.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, denosumab-bnht, was found to be conditionally accepted by the Agency.

7.2. Proprietary Name

The proposed proprietary names for FKS518 are conditionally approved as "Conexxence" (denosumab-bnht in a 60 mg/mL PFS) and "Bomyntra" (denosumab-bnht in a 120 mg/1.7 mL vial and 120 mg/1.7 mL PFS). These names have been reviewed by DMEPA, who concluded the names were acceptable.

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Applicant also submitted unbranded biological product labeling for FKS518 60 mg/mL in a PFS and FKS518 120 mg/1.7 mL in a vial and 120 mg/1.7 mL in a PFS. The Applicant proposed inclusion of the statement, "This product is Conexxence (denosumab-bnht)" and "This product is Bomyntra (denosumab-bnht)" in the labeling for the unbranded biological products for Conexxence and Bomyntra, respectively. The review team considered whether there is a potential safety concern that such labeling statements would mitigate. Due to the fact that US-Prolia and US-Xgeva have different dosing regimens, different strengths, different indications, and because both are healthcare provider administered, the review team concluded that there is no potential safety concern that would need to be mitigated by such labeling statements.

For Conexxence (and its unbranded biological product) and Bomyntra (and its unbranded biological product), text throughout the Full Prescribing Information were made to align with the reference product Prolia and Xgeva, respectively, and language used when referring to a denosumab biosimilar. 'Conexxence', 'Bomyntra', 'Denosumab-bnht', 'denosumab', or 'denosumab products' were used in place of Prolia or Xgeva as applicable.

For Conexxence (and its unbranded biological product), major changes to the draft labeling were made to the following sections of the Prescribing Information:

- 2 DOSAGE AND ADMINISTRATION/ 2.3 Recommended Dosage: “PROPRIETARY NAME should be administered by a healthcare professional” was updated to “Conexxence (Denosumab-bnht) should be administered by a healthcare provider” to include the approved tradename and terminology commonly used in labeling when referring to healthcare individuals or prescribers.

- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration/ *Instructions for Administration of Conexxence Prefilled Syringe with Needle Safety Guard*: To concisely show the retraction of the needle within the needle guard, the figure was updated to show a side-by-side illustration of before and after use in lieu different views of the prefilled syringe for the before and after use. The applicant included many illustrations with corresponding text for subcutaneous injection. Healthcare providers are familiar with subcutaneous administration; therefore, the section was simplified by removing common knowledge and redundancy.

- 3 DOSAGE FORMS AND STRENGTHS: added identifying characteristics “clear, colorless to pale yellow” for the solution, per 21 CFR 201.57(c)(4).

- 5 WARNINGS AND PRECAUTIONS/ 5.2 Drugs with Same Active Ingredient: “Patients receiving Conexxence (denosumab-bnht) should not receive other denosumab products concomitantly.”

- 6 ADVERSE REACTIONS/ 6.3 Immunogenicity: moved to Section 12 Clinical Pharmacology/ 12.6 Immunogenicity per FDA’s Draft Guidance for Industry: Immunogenicity Information in Human Prescription Therapeutic Protein and Select Product Labeling – Content and Format (February 2022)

- 8 USE IN SPECIFIC POPULATIONS/ 8.4 Pediatric Use: the following additions were added to the Conexxence PI to align with Prolia, which summarized the terminated pediatric studies submitted to Prolia (S-213; approved 3/4/2024). The safety and effectiveness of Prolia (denosumab) were not established in pediatric patients; therefore, a summary of studies and any differences in adverse reactions should be included in subsection 8.4 Pediatrics Use per the Pediatric Labeling Guidance.
  - “In one multicenter, open-label study with denosumab conducted in 153 pediatric patients with osteogenesis imperfecta, aged 2 to 17 years, evaluating fracture risk reduction, efficacy was not established.”
  - “Clinical studies in pediatric patients with osteogenesis imperfecta were terminated early due to the occurrence of life-threatening events and hospitalizations due to hypercalcemia.”

(b) (4)

(b) (4)

(b) (4)

- 11 DESCRIPTION: revised the inactive ingredient list by using established names per USP/NF monograph titles, listed inactive ingredients in alphabetical order, and revised the quantity from percent to mg amount.

- 12 CLINICAL PHARMACOLOGY/ 12.3 Pharmacokinetics: included main subheadings Absorption, Distribution, and Elimination per the FDA's Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016).

- 16 HOW SUPPLIED/STORAGE AND HANDLING: included NDC numbers 6521966801

- 17 PATIENT COUNSELING/ Drug Products with Same Active Ingredient: "Advise patients that if they receive Conexxence (denosumab-bnht), they should not receive other denosumab products concomitantly *[see Warnings and Precautions (5.2]*."

For Bomyntra (and its unbranded biological product), major changes to the draft labeling were made to the following sections of the Prescribing Information:

- 2 DOSAGE AND ADMINSTRATION/ 2.1 Important Administration Instructions: added the statement, "[Bomyntra/Denosumab-bnht] should be administered by a healthcare provider" to provide specific direction for the administration of this product (see 21 CFR 201.57(c)(3)(iv)).[4] Refer to the Memorandum to File dated 03/24/2025 in DARRTS for this BLA for additional information about this statement.

- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration/ *Instructions for Administration of Bomyntra Prefilled Syringe with Needle Safety Guard*: To concisely show the retraction of the needle within the needle guard, the figure was updated to show a side-by-side illustration of before and after use in lieu different views of the prefilled syringe for the before and after use. The applicant included many illustrations with corresponding text for subcutaneous injection. Healthcare providers are familiar with subcutaneous administration; therefore, the section was simplified by removing common knowledge and redundancy.

[4] Separately, a prior approval supplement request letter was sent to Amgen identifying that a statement should be added in Section 2.1 of the Xgeva (denosumab) Prescribing Information and carton and container labeling that the product should be administered by a healthcare provider. See DARRTS for BLA 125320.

- 3 DOSAGE FORMS AND STRENGTHS: added identifying characteristics “clear, colorless to pale yellow” for the solution, per 21 CFR 201.57(c)(4).

- 5 WARNINGS AND PRECAUTIONS/ 5.1 Drugs with Same Active Ingredient: “Patients receiving Bomyntra (denosumab-bnht) should not receive other denosumab products concomitantly.”

- 6 ADVERSE REACTIONS/ 6.3 Immunogenicity: Replaced [redacted] with “The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of denosumab or of other denosumab products.”
    - o The updated language provides important background and context to the immunogenicity section, per FDA’s Draft Guidance for Industry: Labeling for Biosimilar and Interchangeable Biosimilar Products, Revision 1 (September 2023)

- 11 DESCRIPTION: revised the inactive ingredient list by using established names per USP/NF monograph titles, listed inactive ingredients in alphabetical order, and revised the quantity from percent to mg amount.

- 16 HOW SUPPLIED/STORAGE AND HANDLING: included NDC numbers 6521967001 (120 mg/1.7 mL vial) and 6521967201 (120 mg/1.7 mL prefilled syringe)

  17 PATIENT COUNSELING/ Drug Products with Same Active Ingredient: “Advise patients that if they receive Bomyntra (denosumab-bnht), they should not receive other denosumab products concomitantly *[see Warnings and Precautions (5.1]*.”

Authors:

LaiMing Lee, PhD
Associate Director for Labeling, DGE

Shivangi Vachhani, MD
Cross Discipline Team Leader, DGE

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.1 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:
Carly Gordon, MD
Clinical Reviewer

Shivangi Vachhani, MD
Cross Disciplinary Team Leader

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:
Carly Gordon, MD
Clinical Reviewer

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required

unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a “new active ingredient” for purposes of PREA.

At the time of this review, other denosumab products, Jubbonti and Wyost, have been approved as interchangeable biosimilars and have qualified for FIE. FKS518 will be approved as a biosimilar product, as discussed in Section 1.7, and therefore is considered to have a new active ingredient for the purposes of PREA. The Applicant submitted the initial Pediatric Study Plan (iPSP) on December 17, 2021, and an agreement letter was issued on July 17, 2022.

For the following indications and populations, PREA requirements were either waived for, or inapplicable to, US-Prolia or US-Xgeva, and therefore the Applicant is not required to submit a pediatric assessment for them:

Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer,
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and
- Treatment of glucocorticoid-induced osteoporosis in pediatric patients <5 years of age at high risk for fracture.

Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of hypercalcemia of malignancy of refractory to bisphosphonate therapy
- Treatment of pediatric patients who are not skeletally mature (0-12 years of age) with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The applicant submitted a pediatric assessment for giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity in skeletally mature adolescents (aged 13 to 17 years) based on a demonstration of biosimilarity and providing adequate scientific justification to support extrapolation of data and information to support licensure. Refer to Section 6.6 for review of the assessment.

US-Prolia has a PREA post-marketing requirement (PMR) to conduct a study to evaluate the safety and efficacy of denosumab in pediatric patients aged 5-17 years old with glucocorticoid-induced osteoporosis (final report submission date: May 2024). A PREA PMR is required for the assessment of FKS518 for the treatment of

glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age and can be deferred until the pediatric data from US-Prolia becomes available.

PeRC discussed this application on January 28, 2025, and concurred with the Division's recommendations.

Authors:

Carly Gordon, MD
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Shivangi Vachhani, MD
Cross Disciplinary Team Leader

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The most recent modification to the Prolia REMS was on March 5, 2024.The Prolia REMS consists of a communication plan (CP) and timetable for submission of assessments.

On March 25, 2024, the Applicant submitted a BLA with an incomplete proposed REMS for Conexxence that consisted of a CP and timetable for submission of assessments but did not include a Supporting Document. The Agency sent comments to submit a complete REMS proposal. The Applicant submitted amendments on June 14, 2024, October 8, 2024, February 18, 2025, and February 21, 2025in response to the Agency's comments.

The Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the amended REMS and found the Conexxence REMS, as submitted on February 21, 2025, acceptable. The Conexxence REMS is comparable to the Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety. The requirements of the Conexxence REMS will also apply to any unbranded Denosumab-bnht distributed by the Applicant.

The Conexxence REMS goal and objective are:

> The goal of the Conexxence REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Conexxence. The following describes the objective associated with the REMS:
>
> Objective 1: Inform healthcare providers on:
> - Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2)

- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Conexxence in patients with advanced chronic kidney disease

The REMS elements consist of a communication plan (CP) and timetable for submission of assessments.

The communication plan elements include:

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- Patient Guide
- REMS Website

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. The Conexxence REMS assessment plan was reviewed by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and found to be acceptable.

11.2. Recommendations for Postmarket Requirements and Commitments

The following post-marketing requirement (PMR) and post-marketing commitment (PMC) will be requested:

PMR: Provide an assessment of Conexxence (denosumab-bnht) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

Authors:

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Courtney Cunningham, PharmD
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12. Division Director Comments

12.1. Division Director (OND – Clinical) Comments

I concur with the review team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that FKS518 is

biosimilar to US-Prolia and US-Xgeva. I also concur with the team's recommendation to provisionally determine that FKS518 meets the standards for interchangeability under section 351(k)(4) of the PHS Act. We have not identified any deficiencies that would justify a complete response action. Although we have provisionally determined that FKS518 meets the requirements for licensure as interchangeable biosimilar product, pursuant to section 351(k)(6) of the Public Health Service Act, we are unable to make such a determination because of unexpired first interchangeable exclusivity for US-licensed Jubbonti and Wyost, as discussed in Section 1.7 above. Accordingly, I also concur with the review team's recommendation to provisionally determine that:

- FKS518, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- FKS518, 120 mg/1.7 mL injection for SC use in a single-dose vial and in a single dose PFS meet the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

These FKS518 products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have previously been approved and for which the applicant is seeking licensure:

U.S.-Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

U.S.-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

When action is taken for this BLA, it will be administratively split to facilitate an approval action for FKS518 as a biosimilar product (“Original 1”) and a provisional determination that FKS518 is an interchangeable biosimilar product, as described in Section 1.7 above (“Original 2”). The Applicant is expected to submit an amendment seeking approval of BLA 761398/Original 2 no more than six months prior to the expiration of exclusivity, or when the Applicant believes that BLA 761398/Original 2 will become eligible for approval.

Author:
Theresa Kehoe, M.D.
Division Director, Division of General Endocrinology

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study FKS518-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 16		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study FKS518-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 250		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.2. Nonclinical Appendices

Not Applicable

13.3. Clinical Pharmacology Appendices

13.3.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For both the PK similarity study FKS518-001 and the phase 3 study FKS518-002 (clinical study in female subjects with PMO), serum FKS518 and US-Prolia concentrations were measured using a validated electrochemiluminescence (ECL) immunoassay (method ICD 857). Both the method validation entitled “method ICD 857” and sample analysis for the study were performed at (b) (4)

(b) (4) In this method, anti-denosumab antibody (Cat. No. HCA-280, (b) (4) (b) (4) Lot 154126) coated in 96-well plate was used to capture serum FKS518 and US-Prolia, and biotinylated anti-denosumab (primary detection using HCA-283, (b) (4); prepared from human anti-denosumab HCA-283, (b) (4), Lot 1805) and Streptavidin-Sulfo-TAG (secondary detection, (b) (4), Lot W0019250S) were used to detect the bound analytes. Table 39 shows the summary of bioanalytical method ICD 857 performance in quantification of FKS518 and US-Prolia during the method validation.

Table 39. Summary of the bioanalytical method validation and in-study performance for measurement of FKS518 and US-Prolia

Bioanalytical method review summary	An electrochemiluminescent (ECL) immunoassay where human anti-denosumab antibodies are absorbed overnight onto (b) (4) plates. Denosumab from standards, QCs and samples tested is captured on the coated plates. After incubation and washing, the plate is incubated with biotinylated anti-denosumab antibodies as primary detection reagent followed by ruthenylated streptavidin with wash steps between the incubations. After the final wash, the plate is read using an (b) (4) instrument. The ECL signal generated is relative to the amount of denosumab present in the standards, QCs and samples tested.		
Materials used for calibration curve & concentration	Material: FKS518 (Batch 4S1905) Concentrations: 10 (anchor), 20, 30, 40, 100, 250, 500, 600, 800, and 1000 (anchor) ng/mL		
Validated assay range	20 ng/mL to 800 ng/mL		
Material used for QCs & concentration	Material: FKS518 (Batch 4S1905), US-Prolia (Batch 1108794), EU-Prolia (Batch 1110620A) Concentrations: 20, 30, 60, 200, 650, and 800 ng/mL		
Minimum required dilutions (MRDs)	1:20 in assay diluent		
Source & lot of reagents (LBA)	Capture: Human Anti-denosumab Antibody (HCA-280) – Lot: 154126– Source: (b) (4) Detection: Primary Detection: Biotinylated Human Anti-denosumab Antibody (HCA-283) – Lot: 1805 – Source: (b) (4), labelled by (b) (4) Secondary Detection: Streptavidin-Sulfo-TAG (Cat. No. R32AD-1) – Lot: W0019250S – Source: (b) (4)		
Regression model & weighting	5-parameter logistic (5-PL) curve fitting with 1/x2 weighting		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ FKS518	-4.14 to 3.94%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ FKS518	≤ 3.84%	Yes

LBA: ±20% bias (±25% at lower limit of quantitation (LLOQ)), ≤ 20%CV			
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in 6 QCs US-Prolia FKS518 EU-Prolia	 -5.46 to 3.44% ≤ 9.07% -4.59 to 1.62%	Yes
	Inter-batch %CV US-Prolia FKS518 EU-Prolia	 ≤ 7.49% ≤ 7.19% ≤ 8.26%	Yes
	Percent total error (TE) US-Prolia FKS518 EU-Prolia	 ≤ 13.0% ≤ 14.4% ≤ 9.88%	Yes
Selectivity & matrix effect	No effect observed		Yes
Interference & specificity	Target and decoy receptor interference: No effect up to 1000 pg/mL of RANKL and OPG Antibody interference (polyclonal ADA) for different QC levels: ULOQ (800 ng/mL) No interference in the presence of ≤ 1000 ng/mL ADA HQC (650 ng/mL) No interference in the presence of ≤ 250 ng/mL ADA LQC (60 ng/mL) No interference in the presence of ≤ 100 ng/mL ADA LLOQ (20 ng/mL) No interference in the presence of ≤ 50 ng/mL ADA Blank (0 ng/mL) No false positives noted		Yes
Hemolysis effect	No effect observed		Yes
Lipemic effect	No effect observed		Yes
Dilution linearity & hook effect	Acceptance criteria met up to 128-fold dilution using Dil QC 10000 ng/mL. (%CV ≤ 3.73) No hook effect observed at concentrations up to 10000 ng/mL. (%CV ≤ 11.9)		Yes
Bench-top/process stability	FKS518, US-Prolia and EU-Prolia: up to 24 hours at RT.		Yes
Freeze-Thaw stability	FKS518, US-Prolia and EU-Prolia: up to 6 freeze-thaw cycles.		Yes
Long-term storage	Analyte stability: At -25°C: - FKS518: 995 days - US-Prolia: 986 days - EU-Prolia: 985 days At -80°C: - FKS518: 1040 days		Yes

	- US-Prolia: 986 days - EU-Prolia: 985 days	
Parallelism	In healthy normal matrix: 10 out of 10 samples met criteria. In disease state matrix: 20 out of 20 samples met criteria.	Yes
Carry over	Not applicable	
Method Performance in Study FKS518-001		
Assay passing rate	257 out of 267 runs (96.3%) met acceptance criteria	Yes
Standard curve performance	Cumulative accuracy (%RE): -2.21 to 4.60% Cumulative precision (%CV): ≤ 5.45%	Yes
QC performance	Cumulative accuracy (%RE): -11.6 to -3.26% Cumulative precision (%CV): ≤ 9.64% Cumulative total error (%): ≤ 18.43%	Yes
Method reproducibility	Incurred sample reanalysis was performed in 6.69% (378 out of 5648) of study samples and 96.0% of samples met the criteria	Yes
Study sample analysis/ stability	Samples were stored at -80°C. All samples analyzed within the established 986 days long-term stability (longest interval from collection to analysis: 420 days).	
Method Performance in Study FKS518-002		
Assay passing rate	564 out of 598 runs (94.3%) met system suitability criteria	Yes
Standard curve performance	Cumulative accuracy (%RE): -4.07 to 5.95% Cumulative precision (%CV): ≤ 6.48%	Yes
QC performance	Cumulative accuracy (%RE): -2.80 to 3.39% Cumulative precision (%CV): ≤ 9.37% Cumulative total error (%): ≤ 12.8%	Yes
Method reproducibility	Incurred sample reanalysis was performed in 5.47% (731 out of 13351) of study samples and 97.5% of samples met the criteria	Yes
Study sample analysis/ stability	Samples were stored at -80°C. All samples analyzed within the established 986 days long-term stability (longest interval from collection to analysis: 681 days).	

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

13.3.2. Other Clinical Pharmacology Information

Not applicable

13.4. Clinical Appendices

13.4.1. Schedule of Assessments, Study FKS518-002

The schedule of assessments for Study FKS518-002 is shown in Table 40 and Table 41.

Table 40. Schedule of Assessments, Study FKS518-002 (Screening to Week 52)

	Screening		Core Treatment Period (1:1 FKS518 versus 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)
LS-BMD by DXA [j]	X																	X [u]

	Screening		Core Treatment Period (1:1 FKS518 versus 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)**
Femoral neck and total hip BMD by DXA [k]	X																	X [u]
FSH (patients ≤ 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
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; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; 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 was obtained from each patient prior to performing any screening assessments. Note: A separate Information Sheet (containing important information about COVID-19, clinical research study participation, and patient consent) was given to and signed by each patient to provide information on the general risks of study participation related to COVID-19 and to document that it was understood by the patient.

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

[c] Patients were 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 had to be recorded.

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

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

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

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

[h] If a chest X-ray or radiograph had been taken within 2 months prior to screening and showed no clinically significant abnormality, and there were no signs and symptoms suggestive of pulmonary disease that would have excluded the patient from the study, then a chest X-ray or radiograph did not need to be repeated at screening.

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

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

[k] The same DXA system (i.e., Lunar or Hologic) had to be used for all study procedures for a particular patient for the duration of the study. All DXA scan data were submitted electronically to the central imaging vendor for analysis. For proximal femur DXA scans, the left side had to be used for all scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it had to be used consistently throughout the study. If a patient fractured the hip that had been scanned during the study up to the time of fracture, no further scans would be obtained for the affected location.

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

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

[n] Bone biomarkers: serum CTX and P1NP. Blood sampling had to 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 were obtained for bone biomarkers: predose (between 8:00 and 10:00 am and fasting) and 5 ± 1 hours postdose (not fasting). On the third dosing day (Week 52), only the predose sample (between 8:00 and 10:00 am and fasting) was obtained.

[o] PK samples had to be collected prior to the immunogenicity sampling. On dosing days (Day 1, Week 26, and Week 52), 2 PK samples were obtained: predose and 5 ±1 hours postdose.

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

[q] Eligibility check included COVID-19 eligibility and was performed by the Investigator and the Medical Monitor.

[r] On Day 1, patients were randomized in a 1:1 allocation ratio into 2 treatment groups: US-Prolia or FKS518. At Week 52, the patients in the US-Prolia group were 1:1 randomized into 2 separate groups to either continue with US-Prolia or to transition to FKS518.

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

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

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

Source: FKS518-002 Clinical Study Report, page 55-57

Table 41. Schedule of Assessments, Study FKS518-002 (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 were to be performed for the End of Study Visit and the Early Termination Visit. In case of premature discontinuation from the study, the Investigator was to make every effort to ensure the patient completes the Early Termination visit as soon as possible, but not earlier than 4 weeks after last injection (for immunogenicity assessment).
If a patient discontinued IP prior to Week 52, the patient was to remain in the study up to the completion of the Week 52 assessments. If a patient discontinued IP during the Transition Period, the patient was to remain in the study up to the completion of the End of the Study Visit.

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

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

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

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

[f] Additional spine X-rays were performed if there was a suspicion of a fracture (e.g., new onset of persistent or pronounced back pain or material worsening of back pain); these were assessed locally.

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

[h] The same DXA system (i.e., Lunar or Hologic) had to be used for all study procedures for a particular patient for the duration of the study. All DXA scan data were submitted electronically to the central imaging vendor for analysis. For proximal femur DXA scans, the left side had to be used for all scans at all study visits. If the right side had to be used (e.g., due to implants) or was inadvertently used at baseline, then it had to be used consistently throughout the study. If a patient fractured the hip that had been scanned during the study up to the time of fracture, no further scans were to be obtained for the affected location.

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

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

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

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

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

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

Source: FKS518-002 Clinical Study Report, page 58-59

13.4.2. Entry Criteria, Study FKS518-002

Inclusion Criteria

1 Women aged 55 to 85 years of age, inclusive.

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

3 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 bone mineral density 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 to L4 region and at least 1 hip joint were 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 have posed a risk to patient safety or interfere with study evaluations or procedures.

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

Exclusion Criteria

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 (e.g., tooth extraction, dental implants, or oral surgery in the previous 6 months), poor oral hygiene, periodontal, and/or preexisting 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.

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 (e.g., histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infestations) within 6 months before screening.

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

c. A positive test for human immunodeficiency virus (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 was allowed to confirm active disease if HCV or HBV antibodies were 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 patient was 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: patients with resected cutaneous basal cell or squamous cell carcinoma, or carcinoma of cervix in situ that had been treated with no evidence of recurrence could be included.

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

16 Any ongoing or recent (i.e., at the time of screening) medical condition that could have interfered with the study conduct, interpretation of study data, and/or otherwise put the patient at an unacceptable risk or could have led to noncompliance with requirements of the study; e.g., patients with rheumatoid arthritis or other autoimmune conditions were not eligible. The Investigator had to specifically evaluate the patient's eligibility taking into consideration COVID-19 risk factors and situation.

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 was excluded if:

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

b. Any dose within 12 months before screening, except if the patient had received < 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 (e.g., 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 were 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 (e.g., systemic corticosteroids, heparin, lithium, etc). Patients with a stable dose of systemic prednisone < 5 mg or equivalent systemic corticosteroid for > 4 weeks before screening were eligible. However, use of systemic glucocorticosteroids ≥ 5 mg prednisone or equivalent per day for > 14 days within 3 months before randomization was 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 Had received a COVID-19 vaccine within 4 weeks before randomization or COVID-19 vaccination was ongoing at the time of screening. COVID-19 vaccination was considered ongoing if a multidose regimen had been started but had not been completed.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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03/25/2025 08:36:57 AM

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03/25/2025 09:02:40 AM