22 May 2025
EMA/210370/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Conexxence

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006268/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
(%)CfB	(Percent)Change from baseline
ADA	Antidrug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the serum concentration-time curve
AUC0-inf	AUC from time zero to infinity
AUC0-last	AUC from time zero to the last quantifiable concentration
AUEC	Area Under the Effect Curve
BMD	Bone Mineral Density
BMI	Body Mass Index
C1q	Complement component C1q
CDC	Complement-dependent cytotoxicity
CfBmax	Maximum Change from Baseline
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence Interval
CL/F	Apparent total clearance
CLBA	Competitive ligand binding assay
Cmax	Maximum Concentration
COVID-19	Coronavirus SARS-Cov-2
CRF	Case report form
CSR	Clinical Study Report
CSs	Calibrators
CTCAE	Common Terminology Criteria for Adverse Events
CTX C	Terminal Cross-Linking Telopeptide of Type 1 Collagen
CTx-1	C-Terminal Telopeptide of Type 1 Collagen
CV	Coefficient of Variation
DP	Drug Product
DS	Drug substance
DXA	Dual Energy X-Ray Absorptiometry
EC50	Half-maximal effective concentration
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eCRF	Electronic case report form
EEA	European Economic Area
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EoS	End of study
ESC	Endogenous Serum Control
EU	European Union
F	Female
Fab	Fragment antigen-binding
Fc	Fragment crystallizable
FcRn	Neonatal Fc Receptor
FcγRI	Fc gamma receptor I
FcγRIIa	Fc gamma receptor IIa
FcγRIIb	Fc gamma receptor IIb
FcγRIIIa	Fc gamma receptor IIIa
FcγRIIIb	Fc gamma receptor IIIb
FcγRs	Fc gamma receptors
FDA	Food and Drug Administration
GB	Great Britain
GCP	Good Clinical Practice
Geo	Geometric

GeoMean	Geometric mean
GGT	Gamma-Glutamyl Transferase
GLSM	Geometric least squares mean
GLSMs	Geometric Least Squares Means
GMR	Geometric mean ratio
h/H	Hours
HQC	High QC
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE	Intercurrent Events
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
IP	Investigational Product
IRT	Interactive Response Technology
IRT	Interactive response technology
ISR	Injection Site Reaction
ITT	Intention to Treat
KD	Equilibrium dissociation constant
LLOQ	Lower limit of quantification
Ln	Natural log
LQC	Low QC
LS	Least Square
LS-BMD	Lumbar Spine Bone Mineral Density
M	Male
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
max	Maximum
MI	Multiple Imputation
min	Minimum
MNAR	Missing Not at Random
MoA	Mechanism of action
MQX	Mid QC
MRD	Minimum Required Dilution
MSD	Meso Scale Discovery
N/n	Number of subjects
NA	Not Applicable
NAb	Neutralizing Antibody
NC	Not calculated
NCI	National Cancer Institute
P1NP	Procollagen Type 1 N-Terminal Propeptide
PD	Pharmacodynamics
PFS	Pre-Filled Syringe
PIND	Pre-Investigational New Drug
PK	Pharmacokinetics
PMO	Postmenopausal Osteoporosis
PP	Per Protocol
PT	Preferred Term
PTH	Parathyroid Hormone
QCs	Quality Controls
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RE	Relative Error
RMP	Reference medicinal product (ie, EU-RMP)
RP	Reference product (ie, US-RP)
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBP	Similar Biotherapeutic Products
SC	Subcutaneous
SD	Standard Deviation
SDSP	Standard Data Standardisation Plan
SE	Standard Error
SmPC	Summary of Product Characteristics

SMQ	Standardised Medical Dictionary for Regulatory Activities Queries
SOC	System Organ Class
SPR	Surface plasmon resonance
sRANKL	Soluble RANKL
t1/2	Terminal elimination half-life
TA	Threshold Analysis
TEAE	Treatment-Emergent Adverse Events
Tmax	Time to Cmax
tmax	Time to maximum observed concentration
tmRANKL	Transmembrane RANKL
ULOQ	Upper Limit of Quantitation
USPI	United States Prescribing Information
Vz/F	Volume of distribution during the terminal phase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 29 May 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Conexxence, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication(s):

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than /6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Prolia 60 mg solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26-05-2010
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/10/618/003

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Prolia 60 mg solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26-05-2010
- Marketing authorisation granted by:
  - Union

- Marketing authorisation number: EU/1/10/618/003

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
25 June 2020	EMEA/H/SA/4510/1/2020/III	*Andrea Laslop, Elina Rönnemaa*
14 January 2021	EMEA/H/SA/4520/2020/III	*Clarification on EMEA/H/SA/4510/1/2020/III*
22 July 2021	EMA/SA/0000061878	*Andrea Laslop, Elina Rönnemaa*
11 November 2021	EMA/SA/0000069139	*Jens Reinhardt, Jan Sjöberg*
15 September 2022	EMA/SA/0000095042	*Bruno Delafont, Sif Ormarsdóttir*
22 June 2023	EMA/SA/0000136524	*Elina Rönnemaa, Sheila Killalea, Livia Puljak*

The applicant received scientific advice on the development of denosumab biosimilar (FKS518) for treatment in the same indications as the reference product Prolia/Xgeva from the CHMP on 25 June 2020 (EMEA/H/SA/4510/1/2020/III). The scientific advice pertained to the following quality and clinical aspects:

- Panel of analytical methods selected for similarity assessment; approach of combining the target ranges established on Prolia and Xgeva reference products for analytical similarity assessment of FKS518 to Prolia/Xgeva; quality range target setting and general quality programme development of FKS518; Xgeva biosimilar presentations; approach to developing a ligand-binding assay format for assessing neutralizing antibodies to denosumab.
- Clinical development plan for FKS518 including the study designs, population, dose, endpoints, sample size, stratification factors and equivalence margins; extrapolation of clinical study data to all authorised indications of Prolia and Xgeva.

The applicant received scientific advice on the development of denosumab biosimilar (FKS518) for treatment in the same indications as the reference product Prolia/Xgeva from the CHMP on 22 July 2021 (EMA/SA/0000061878). The scientific advice pertained to the following clinical aspects:

- Equivalence margin for the secondary endpoint (area under the effect curve of serum carboxy terminal telopeptide) in the efficacy equivalence study in women with postmenopausal osteoporosis.

The applicant received scientific advice on the development of denosumab biosimilar (FKS518) for treatment in the same indications as the reference product Prolia/Xgeva from the CHMP on 11 November 2021 (EMA/SA/0000069139). The scientific advice pertained to the following quality aspects:

- Adequacy of the proposed comparability strategy following drug substance and drug product manufacturing process technology transfer.

The applicant received scientific advice on the development of denosumab biosimilar (FKS518) for the treatment in the same indications as the reference products Prolia and Xgeva from the CHMP on 15 September 2022 (EMA/SA/0000095042). The scientific advice pertained to the following clinical aspects:

- Estimands and statistical analyses (including COVID-19 related data) of a multicentre, randomised, double-blind, parallel-group, two-arm study to demonstrate equivalent efficacy of FKS518 and US-Prolia in women with postmenopausal osteoporosis.

The applicant received scientific advice on the development of denosumab biosimilar (FKS518) for the treatment in the same indications as the reference products Prolia and Xgeva from the CHMP on 22/06/2023 (EMA/SA/0000136524). The scientific advice pertained to the following quality and clinical aspects:

- Strategy for the criticality assessment of quality attributes; criticality risk ranking; data analysis plan for similarity; analytical tests for the release panel of FKS518.
- Marketing authorisation application data submission approach.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner Co-Rapporteur: Hjalti Kristinsson

The application was received by the EMA on	28 May 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 September 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 September 2024

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 January 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 March 2025
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	27 March 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Conexxence on	22 May 2025

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.2. About the product

Conexxence was developed as a biosimilar product to Prolia (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation:

• Prolia: 60 mg/mL PFS (pre-filled syringe)

The applicant is claiming all the indications approved for the reference product.

Prolia indications:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

2.3. Type of application and aspects on development

During the development of FKS518, the applicant sought CHMP scientific advice four times. All critical aspects during these advice procedures that are deviating from the final study designs will be discussed in the respective methods or result sections of this report.

GMP

Name, address, responsibilities and certificates of all manufacturers involved in manufacture, quality control, and stability testing of FKS518 drug substance (DS) as well as manufacturing and storage sites of cell banks (MCB, WCB) are listed. Valid GMP certificates are available.

Name, address, responsibilities and certificates of all manufacturers involved in manufacture (including secondary packaging and assembly with safety device), quality control, stability testing of FKS518 drug product (DP) are listed. Valid GMP certificates are available.

No pre-approval inspection is required.

GLP

Not applicable (no studies were submitted in Module 4).

GCP

In study FKS518-001, data quality assurance measures put in place are considered adequate. In study FKS518-002, there was a mis-stratification of 17 patients due to discrepant information on prior bisphosphonate use in the IRT system and the eCRF. A sensitivity analysis on the treatment policy

estimand 1.0 of the primary efficacy endpoint was performed to account for the mis-stratification of 17 patients due to discrepant information about prior bisphosphonate therapy recorded at randomisation in the IRT system and that recorded in the eCRF. When eCRF information on prior bisphosphonate use was used in the analysis, the results were similar to the main analysis, indicating that mis-stratification did not impact the results relevantly. Thus, although it is not totally clear how this discrepancy could have happened, it seems as if this mis-stratification does not impact the efficacy analysis. Therefore, no concern on GCP compliance is raised.

2.4. Quality aspects

2.4.1. Introduction

Conexxence (laboratory code FKS518, denosumab) has been developed as a similar biological medicinal product to the reference medicinal product Prolia.

The finished product is presented as a solution for injection in a pre-filled syringe (PFS) containing 60 mg of denosumab as active substance.

Other ingredients are: acetic acid, sodium acetate trihydrate, sorbitol (E420), polysorbate 20 (E432) and water for injections (wfi).

The product is available in a single use pre-filled syringe made from type I glass with stainless steel 29-gauge needle closed with a plunger stopper (fluoropolymer coated elastomeric) and a rigid needle shield. The pre-filled syringe is assembled with a passive needle safety guard.

2.4.2. Active substance

General information

FKS518 is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G2 (IgG2) subclass, composed of 2 heavy chains (HCs) and 2 light chains (LCs) of the kappa subclass. The 4 polypeptide chains are linked by 12 intrachain and 6 interchain disulfide bonds (36 total cysteine residues). Each LC contains 215 amino acids, with 2 intrachain and 1 interchain disulfide bonds, one variable domain (VL) and one constant domain (CL). Each HC contains 448 amino acids, with 4 intrachain and 5 interchain disulfide bonds, one variable domain (VH) and three constant domains (CH1, CH2 and CH3). LC and HC variable domains are composed of three complementarity-determining regions (CDR 1 to 3) involved in RANKL binding. The CH2 domain on the HC contains the C1q and the Fc gamma receptor (FcgR) binding regions, both being influenced by glycosylation at the consensus glycosylation site asparagine 298 (N298). However, denosumab was developed as an IgG2 known to have minimal Fc effector activities via FcgRs and C1q. The FcRn binding region is located at the junction between CH2 and CH3 domains and FcRn binding influences antibody pharmacokinetic.

Denosumab has a molecular weight of approximately 147 kDa (based on primary sequence) for the four polypeptide chains of 1326 amino acids. Microheterogeneity of denosumab is observed due to variable processing of carboxy-terminal lysine and glycan structure variation at the N-linked glycosylation site.

The main structure is a complex, biantennary type, core fucosylated oligosaccharide with zero (G0F), one (G1F) or two (G2F) galactose residues. Other glycans are also present in smaller amounts (high mannose, sialylated, afucosylated and complex).

Denosumab binds with high affinity and specificity to receptor activator of nuclear factor-κB ligand (RANKL), preventing activation of its receptor, receptor activator of nuclear factor-κB (RANK), on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Manufacture, process controls and characterisation

Name, address, and responsibilities of all manufacturers involved in manufacture, quality control, and stability testing of FKS518 active substance (AS) as well as manufacturing and storage sites of cell banks are listed in the dossier. Active substance manufacture takes place at WuXi Biologics Co., Ltd., 108 Meiliang Road, Mashan, Binhu District, Wuxi, Jiangsu, 214092, China.

Adequate information has been provided in support of GMP compliance.

Description of manufacturing process and process controls

The active substance is expressed in a CHO cell line. Manufacture of a batch starts from a single vial of the working cell bank (WCB). After thawing, cells are expanded through serial sub-cultivations followed by expansion in the production bioreactor. After fermentation, the cell culture is harvested and purified by a series of chromatography and filtration steps as well as additional steps for removal and inactivation of potential adventitious viral contaminants.

The applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts showing the upstream and downstream steps including the process parameters and In-process controls (IPCs). For further information on Critical process parameter (CPP), Key process parameters (KPP), Critical performance attributes (CPA) and Key performance attributes (KPA) of the respective process steps, it is referred to the controls of critical steps and intermediates section, this is acceptable.

In conclusion, the applicant provided a detailed description of the manufacturing process and controls that is in line with regulatory expectations.

Control of materials

Materials

Raw materials used for the cell culture and purification process are listed together with their quality standard (compliant with Ph. Eur., USP/NF, or in-house specification). Acceptable in-house specification tests are provided for the non-compendial raw materials. The qualitative composition of the cell culture media and solutions is adequately described. An agreement is in place with the cell culture media supplier to notify the MAH in case of changes to the culture media.

No animal-derived materials are used for manufacture of FKS518 AS.

Cell substrate

The construction of the expression plasmids and their genetic elements are described in sufficient detail. The information provided on origin and history of the host cell line and generation and selection of the stable-transfected production cell line clone is satisfactory. The leading clone was selected, and pre-master cell banks (pre-MCB) were established. The cells of the pre-MCB were tested as sterile and negative for mycoplasma. Upon request, the lead clone selection and the approach to prove monoclonality were described in sufficient detail including a short summary of results from the imaging of plates/visual inspection and mRNA profiling of the selected clone.

Cell banking system, characterisation and testing

A two-tiered cell bank system with MCB and WCB has been established starting from the research cell bank. MCB and WCB were successfully tested for the absence of adventitious agents in accordance with ICH Q5A (R1). Cell line identities were tested, cross contamination could be excluded. Phenotypic characterisation is provided. Genotypic characterization of MCB, WCB and extended cell bank (ExCB) were provided for both LC and HC, confirming plasmid integrity.

Overall, the cell banking system is adequately described with sufficient details on manufacture and storage of the MCB and WCB. A protocol has been provided for preparation of future WCBs.

Overall, the description of cell banking system, including relevant testing, is considered satisfactory.

Control of critical steps and intermediates

Classifications of each parameter into KPP, CPP, IPC, and proven acceptable range (PAR) are listed for each analysed parameter.

For in-process controls, respective action limits are in place and have been justified.

Test procedures are listed for each of the parameters; these are mostly the same as for AS release and/or are compendial tests. Analytical method validation data were provided to demonstrate suitability of the methods for their intended purpose.

Overall, surveillance of critical steps is adequately described including information on process holds/ intermediates.

The applicant plans to begin development of an endotoxin assay, eliminating the need for animal derived material. This is fully supported.

Process validation and/or evaluation

Process performance qualification (PPQ)

PPQ including the IPC limits and AS release limits based on process development and characterisation was carried out considering data from representative, consecutive commercial scale batches at the proposed commercial AS manufacturing site and facilities, at WuXi Biologics Co., Ltd.–Jiangsu, China.

Further, the monitoring of process is controlled via constant ongoing process verification to ensure a state of control over the product quality. The qualification and validation activities are divided in PPQ, resin and membrane lifetime study, hold-time studies of process intermediates, buffers and media, mixing studies, AS homogeneity in storage containers, impurity clearance and validation of AS transfer to the finished product (FP) facility. The PPQ delivered acceptable results, with all batches meeting the pre-defined acceptance criteria that evolved during process characterisation studies. For one of the used batches, maximum cell expansion and maximum cumulated hold time of intermediates was applied. No differences in results were observed, the acceptance criteria were met.

In conclusion, the PPQ results demonstrate that the AS manufacturing process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions. Adequate and consistent performance of the cell culture and purification processes has been confirmed during the PPQ campaign.

Resin and membrane lifetime studies

The applicant performed studies on resin lifetime and cleaning effectiveness at small-scale. The complementing studies at commercial scale are still partially on-going and any out of specification results will be reported to the authorities.

Confirmation is expected by on-going large manufacturing scale studies, so far the results confirm the small-scale studies.

Process intermediates hold time

Several process hold steps are foreseen during manufacture of FKS518 active substance. Stability-indicating quality attributes were monitored aiming to confirm that the process holds have no detrimental impact on product quality. Overall, only minor insignificant changes appeared when pre- and post- hold attributes were compared after the study. The proposed hold-times are considered acceptable.

Media and buffer hold-time and respective microbial studies have been conducted using growth-promoting surrogate solutions for challenging the integrity of the storage containers under worst-case conditions. These studies substantiate the proposed hold-times, are considered adequate and are acceptable.

Mixing studies and AS homogeneity validation

Proper dissolution and homogenisation were validated using a risk-based approach for the different used solutions/media, an approach which is acceptable and endorsed. AS homogeneity in storage containers was validated. All acceptance criteria valid at time of testing were met.

Impurity clearance

The clearance of process related impurities and cell-culture process derived impurities were validated by using analysis results of large-scale batches, or by using qualified scale-down spiking models.

The overall clearance factor for certain impurities was given. Clearance studies of product related impurities are considered of acceptable quality and acceptable reduction has been demonstrated.

For completeness, brief information on the used scale down model was provided upon request.

Shipping validation is described, a shipping study was conducted.

Overall, the AS manufacturing process is considered appropriately validated.

Manufacturing process development

The manufacturing process was generated through a combination of traditional and enhanced approaches as per ICH Q11 and is further described as outlined in ICH Q8. A quality target product profile (QTPP) is defined and considered adequate, as it considers the route of administration, dosage form, bioavailability, strength and stability of the product. Critical quality attributes were assigned, including a respective control strategy. The risk ranking of attributes is considered meaningful and developed following state-of-the-art principles. Scale-down models during process characterisation studies are described in sufficient detail. The applicant has elaborated on process parameters that can have high risk of impact on product quality according to ICH Q8. Evolvement of the material control strategy is described and considered of acceptable quality.

Demonstration of comparability between the different process versions is not necessary, as all clinical batches were manufactured at the intended commercial scale. A comparability exercise was done between two on-site facilities.

The comparability approach is described in sufficient detail. Overall, and following adequate responses to questions raised during the procedure, the pre- and post-change batches and consequently, manufacturing processes on former and new facility are considered comparable.

Characterisation

The applicant characterised physicochemical and biological properties of FKS518 using orthogonal, state-of-the art analytical methods. FKS518 batches manufactured at the former facility and at the intended commercial facility have been characterised, with all of them being AS batches. Brief descriptions of the used batches were presented.

Structural and Physicochemical characterisation

Primary and higher order structure, as well as post-translational modifications have been investigated using an appropriate battery of analytical methods. The analytical results are consistent with the proposed structure.

Biological characterisation

Biological characterisation was carried out by In Vitro Bioassay. Relative potencies were comparable throughout all batches.

Impurities

The applicant has identified product-related impurities, process-related impurities as well as other impurities.

The validation results on the clearance of process-related impurities showed a successful removal of all potential impurities in the active substance during the purification steps of the manufacturing process. Other impurities could be shown to be well below levels of concern.

Nitrosamine impurities risk assessment

The applicant presented a nitrosamine risk assessment both for the active substance and the finished product (1mL PFS and vial) separately. All raw materials (filters, bags, media, buffers, chemicals) have been extensively controlled and grouped for their risk of introducing nitrosating agents/nitrosamines into the AS and FP manufacturing processes.

The used raw materials are not including sodium nitrite or other nitrosating agents. Further, the manufacturing processes do not employ high temperature unit operations. The water used is purified water, tested for nitrates/nitrites. Certificates/statements on nitrosamine assessment of vendors of raw materials are also provided.

In summary, the applicant could satisfyingly show that the nitrosamine introduction/formation risk to the manufacturing process of FKS518 AS and FP is negligible.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The proposed release specification for the active substance includes compendial tests for degree of opalescence and clarity of solution, coloration, pH and osmolality (EP 2.2.1, 2.2.2, 2.2.3 and 2.2.35 respectively). Microbial tests include bioburden (TAMC and TYMC) and Endotoxins by EP 2.6.12 and 2.6.14 respectively. Non-compendial tests comprise identity, biological activity, purity, product-related substances, impurities and process-related impurities.

The overall set of test methods for specification and acceptance criteria are chosen in compliance with ICH topic Q6B, Ph. Eur and EMA/CHMP/BWP/532517/2008 and are considered acceptable.

The acceptance criteria were set using a statistical approach. The specification limits are clinically justified. Based on the provided data, the specifications are acceptable.

In sum, presented data on specifications are acceptable.

Analytical procedures and Validation of analytical procedures

The general and microbial attributes are tested according to the respective Ph. Eur. monographs. All other attributes are tested using in-house analytical methods. The analytical methods are considered adequate for their intended purpose and overall, the implemented system suitability tests and sample acceptance criteria appear suitable to provide adequate control over analytical method performance.

Method validation reports have been provided for all methods. The validation results demonstrate suitability of the analytical procedures for their intended use. The relevant parameters have been assessed in accordance with ICH Q2(R1).

Batch analyses

Batch analyses data are presented for several batches manufactured at commercial scale at either the former and the new (commercial) facilities.

All results comply with the specifications valid at time of testing and later with the proposed commercial specifications. In summary, the presented results demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

Reference standards

The applicant started the implementation of a one-tiered reference standard system by introducing interim reference standards.

Later, a two-tiered reference standard was implemented, consisting of a primary reference standard and a secondary house standard.

Complete testing and extensive analytical characterisation during the qualification experiments is described that was carried out in the course of reference standards establishment, which is endorsed. Results are overall acceptable, and the history of reference standards is well described, comprehensible and thus regarded meaningful and acceptable. Finally, a system of future reference system characterisation is in place, including the method panel that is foreseen for testing.

Container closure system

The active substance is stored frozen in bags. The bag is compliant with Ph. Eur. 5.2.8.

Based on the results from the presented leachables study, no concern for the patient is arising and the active substance container is considered suitable for its intended use.

Stability

A shelf-life of 36 months at -70 ± 10°C is claimed for the active substance.

Stability data has been provided for long-term (-70 ± 10°C), accelerated (5 ± 3°C) and stressed (25 ± 2°C/60 ± 5% relative humidity (RH) and 40 ± 2°C/75 ± 5% RH) conditions.

Under the proposed long-term storage conditions of -70 ± 10°C all results were within the stability acceptance criteria and within the limits defined for the commercial specification. No quality attributes showed significant stability trends under long-term storage conditions.

A Post-Approval Stability Protocol and Stability Commitment is in place and is acceptable.

Based on the data provided, the proposed active substance shelf life of 36 months at -70 ± 10°C is acceptable.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a sterile solution for injection intended for subcutaneous administration, presented at an active substance concentration of 60 mg/mL in a pre-filled 1.0 mL type I glass syringe combined with a 29 Gauge stainless steel needle protected by a rigid needle shield, closed with a plunger stopper. The naked PFS is further assembled with the safety device (1.0 ml), designed to prevent needle stick injuries.

Each PFS is designed to allow delivery of 60 mg of active ingredient in a 1.0 mL of solution.

The assembled products are labelled with the device label and secondary packaged in blisters. The pack size is of 1 pre-filled syringe (glass) with needle guard. Specifications, technical drawings and certificates of Analysis of Primary Packaging Components and safety device are provided.

The qualitative and quantitative composition of the finished product, including the respective function is provided. The excipients are of compendial quality and controlled in compliance with tests and acceptance criteria of compendial monographs. Certificates of analyses of the excipients are provided. There are no novel excipients, and no excipients of human or animal origin.

Formulation development

The formulation of the finished product is identical to Prolia´s formulation.

Manufacturing process development

Manufacturing of the finished product based on standard fill/finish operations (dilution, sterile filtration, and filling) was performed at a former manufacturing line and afterwards transferred to a new manufacturing line at the same site. Differences between the manufacturing lines are listed, and a risk assessment has been performed for differences in equipment, raw materials/consumables and process parameters. Comparability of post-change batches manufactured with the intended commercial manufacturing process to pre-change batches has been demonstrated. The history of the release specifications, applied during development and proposed for commercial, including justification for the changes is provided.

Raw materials, equipment, utilities and single-use materials used during the finished product manufacturing process, and primary packaging materials are properly controlled.

In-process compatibility study confirmed compatibility between the diluted active substance and in-process materials used in the finished product manufacturing (In-process Compatibility)

Container closure

The suitability of the container closure system to protect from microbial contamination without altering the physicochemical properties of the finished product during storage, transportation and use has been demonstrated during long-term stability studies, process characterisation and shipping validation studies, and further investigated by extractables and leachables, and integrity of the container closure. The materials used for the container closure system comply with the relevant Pharmacopeial monographs.

Details of the sterilisation process are provided. *Medical device*

The naked PFS is assembled with the safety device (1.0 ml), which consists of a plunger rod and a needle guard, designed to prevent needle stick injuries. In accordance with Article 117 of the Regulation (EU) 2017/745 on medical devices (the Medical Device Regulation, MDR), the conformity of

the device part with the relevant General Safety and Performance Requirements (GSPRs) has been reviewed by an appropriately designated notified body. The notified body opinion has been provided (Section 3.2.R.2).

Manufacture of the product and process controls

The finished product manufacturing and testing sites are GMP compliant. Final batch release is done at Fresenius Kabi Austria GmbH (Austria).

The finished product manufacturing process represents a standard process consisting of thawing of frozen active substance, preparation and filtration of formulation buffer, compounding of active substance with formulation buffer, filtration, filling, stoppering, visual inspection, intermediate labelling and packaging of naked PFS, shipping to the assembly site, assembly with device, labelling and secondary packaging and finished product storage.

The manufacturing process is sufficiently described. All hold times and process steps duration are provided.

The manufacturing process has been developed with defined manufacturing procedures, CPPs, IPCs, and release specifications. Identification of CPPs and establishment of PARs, and the information on the control of the critical quality attributes are properly discussed. Analytical procedures used for IPCs have been properly validated.

Process validation

Process validation was undertaken with several consecutive commercial scale batches.

The manufacturing and release data, including IPC, release testing, maximum process and holding times obtained on the validation batches were within the acceptance criteria defined, therefore robustness and reproducibility of the manufacturing process of the finished product was demonstrated and the manufacturing process of the naked PFS manufacture is considered successfully validated.

Validation of the assembly of naked PFS with the safety Device has been done with a biosimilar product, having the same device presentation and assembled at the same site using the same equipment.

Validation of the aseptic process activities were performed, Results provided confirm that aseptic process activities have been satisfactorily validated. Filter extractable studies were performed by the supplier and it has been concluded that the worst-case exposure of patients with the extractable compounds identified is below the substance specific PDE values. Validation of the media fills has been performed to confirm that the aseptic process employed in the vial filling area provide a high degree of aseptic assurance. Several consecutive qualification runs were completed using the commercial container closure systems 1.0 mL syringes. Results met the required specification, and no contamination was observed. The integrity of the container closure system has been confirmed during process performance qualification and stability testing.

Shipping has been properly validated.

Product specification, analytical procedures, batch analysis

A comprehensive panel of release specifications has been set for the finished product in naked PFS, including general properties (appearance, clarity and degree of opalescence, pH, osmolality, subvisible particles and extractable volume), identity, protein content, biological activity, polysorbate 20, purity/impurities and product-related substances, and microbiological quality. Shelf-life specifications

differ from release specifications with less stringent acceptance criteria applied for end of shelf-life only for selected stability indicating attributes. The proposed release and shelf-life specifications are in line with ICH Q6B and Ph.Eur. requirements.

Release specifications for finished product in the assembled PFS include extractable volume and device performance tests. Shelf-life specifications of finished product in assembled PFS include additional device performance testing. Specifications for the finished product assembled in the safety device are defined based on the performance of the safety device designed by the device supplier and following the standards ISO 11608-1, ISO 11608-3 and ISO 23908.

Acceptance ranges have been set based on release data encompassing the development history and including engineering and good manufacturing practice (GMP) batches, clinical pharmacokinetic (PK) as well as efficacy and safety and PPQ batches.

For quantitative quality attributes tested by in-house developed methods, such as biological activity, as well as purity/ impurities and product-related substances, the acceptance criteria have been set by statistical analysis and considering product and process knowledge, process variability and capability as well as prior knowledge for similar molecules.

The applicant performed a risk assessment in line with ICH Q3D to evaluate the potential presence of elemental impurities considering the potential sources included in the finished product manufacturing process. Several components that had the potential to transfer elemental impurities into the finished product were identified, but in a level far below the PDE. Based on the risk assessment and the presented data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A Risk assessment was performed to evaluate the risk of the presence of nitrosamine impurities in the finished product, and results show that the risk of nitrosamines, vulnerable amines, or nitrosating agents is negligible.

Analytical procedures

Testing has been done using a combination of compendial and non-compendial methods. Relevant pharmacopoeia references are provided for the compendial test methods. Methods have been properly validated.

Batch analysis

Batch analysis results are provided for several finished product batches. All batches met the acceptance criteria of release in place at the time indicating consistency and uniformity of the finished product among the batches.

Reference standards

The reference standard used in the testing and release of the finished product is the same as the one used for the testing and release of the active substance.

Stability of the product

A shelf life of 36 months at long-term storage conditions (5°C ±3°C) is claimed for the finished product.

The stability programme includes testing at long-term condition (5°C ± 3°C), accelerated condition (25°C ± 2°C/60% ± 5% RH) and stress condition (40°C ± 2°C/75% ± 5% RH), a photostability study,

a temperature excursion study and forced degradation studies. Studies have been performed according to ICH Q5C.

PPQ batches of PFS assembled with safety device and several batches from engineering and development runs were placed on stability under long-term, accelerated and stressed conditions.

The methods applied in the stability studies are identical to the methods for release testing.

Long-term studies are ongoing. Available long-term stability data show that under the proposed long-term storage conditions tested all results were within the stability acceptance criteria and within the limits defined for the commercial specification.

Comparability between development batches (pre-change finished product batches) to PPQ batches (post-change, commercial manufacturing process) has been demonstrated, therefore the shelf-life of 36 months could be extrapolated from the development batches.

A photostability study has been performed to demonstrate protection from light when the product is stored in the commercial secondary packaging.

The temperature excursion study performed simulating deviations from the recommended storage conditions confirmed stability under temperature conditions that may be experienced during shipment, storage, and handling.

The comparative forced degradation studies confirmed the comparable degradation profiles of FKS518 finished product and reference product under the stress conditions applied.

In-use stability studies were not performed since no dilution or re-constitution is requested for FKS518. The available data supports that the PFS can be stored up to 25°C for up to 30 days (protected from light) and this is reflected in the SmPC.

The applicant has provided appropriate post-approval commitments in relation to the stability studies.

In conclusion, based on the data provided a shelf life of 36 months at 5°C ±3°C is supported for the finished product.

Biosimilarity

FKS518 has been developed as proposed biosimilar of EU-approved Prolia/Xgeva (denosumab) for subcutaneous (SC) use in two presentations, i.e. PFS (Conexxence, 60 mg/1 mL of solution) and Vial (Bomyntra, 120 mg/1.7 mL of solution, at a nominal concentration of 70.0 mg/mL). Additionally, Bomyntra has been developed as 120 mg/1.7 mL of solution in PFS. Xgeva 120 mg PFS (120 mg/1.0 ml) was not yet approved when Bomyntra was developed and the 120 mg PFS of Bomyntra has not been directly compared with the Xgeva 120 mg PFS.

FKS518 PFS and Vial have the same pharmaceutical form, protein concentration, route of administration and indication of the EU-approved Prolia and Xgeva, respectively.

The analytical similarity assessment is properly described.

All batches used for similarity assessment were within the shelf life at the time of testing and were stored and handled as recommended by the label. Batches were chosen to reflect a range of product ages and expiration dates, which is endorsed. The batches of US/EU Prolia/Xgeva were chosen to cover a range of expiry dates and product ages and were otherwise sourced from those available on the market at the time.

Since FKS518 batches were relatively young in comparison to Prolia/Xgeva batches, studies were performed to determine whether the age of batches affect the conclusions of the analytical similarity studies. Lower HMWs, slightly lower acidic variants and LMWs levels are found in the batches tested soon after manufacturing, which is in line with results of the stability studies.

The similarity assessment has been done testing multiple batches of FKS518 60 mg PFS, FKS518 120 mg Vial, EU-Prolia, EU-Xgeva, US-Prolia and US-Xgeva. Not all batches of each product were tested using all methods. For attributes heavily influenced by process changes and sensitive to storage conditions, larger number of batches were tested. The number of batches included in the similarity assessment is considered acceptable.

A range of state-of-the-art, orthogonal techniques were used to compare the physicochemical properties including the primary structure and post-translational modifications, higher order structure, purity and impurities, product variants, and biological activity. Fab-dependent binding and biological activity of denosumab were evaluated by measuring the ability of denosumab to inhibit the sRANKL-induced IkB degradation, the binding affinity to soluble RANKL (sRANKL) and transmembrane RANKL (tmRANKL) and the ability of denosumab to inhibit osteoclastogenesis in a cell-based bioassay. The therapeutic efficacy of denosumab is based on the ability to block the receptor activator of nuclear factor kappa-B ligand (RANKL) from binding the receptor activator of nuclear factor-kappa B (RANK) and Fc-dependent effector activities are not part of the mode of action (MoA) of denosumab, and no or very low binding to FcγRI and FcγRIII, and minimal Fc effector activities are expected for a monoclonal antibody (mAb) of the IgG2 subclass. Nevertheless, to ensure that the products are comparable, head-to-head testing of FKS518 and EU/US Xgeva/Prolia batches was performed to evaluate Fc effector activities: FcγRI binding, FcγRIIIa (V158 & F158) binding, FcγRIIIb binding, C1q binding, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

A step-wise approach was applied to evaluate comparative analytical data. The first step was to undertake a criticality assessment of quality attributes according to the risk of potential impact on activity, pharmacokinetic (PK), safety, efficacy, and immunogenicity. The subsequent step of the comparative analytical assessment was to determine and justify the approach for analysis of data on each attribute or from each method, considering the risk ranking of the quality attributes, as well as other factors, thus supporting the data analysis plan for the comparative analytical assessment. The results of criticality ranking for each quality attribute and biological activity are summarised with brief descriptions of the prior knowledge and FKS518 in-house studies which support the ranking. The criticality ranking (very low, low, moderate, high, very high), together with the nature, distribution, abundance, sensitivity of assay (variability), quantitative or qualitative nature of measurement and publicly available information serves as a basis to determine the approach to statistical analysis (similarity criteria). The comparative analytical data have been analysed using quality range (QR) or descriptive assessment (DA).

The quality range approach has been applied to attributes of moderate to very high criticality. The acceptance criteria for the QR approach uses the Mean ± x SD, where the choice of the multiplier x was done in relation to the criticality of an attribute as to control risks of wrong decision.

The descriptive assessment has been applied to e.g., 1) Quality attributes with "low" to "very low" criticality scores or; 2) attributes for which statistical analysis is not feasible., such as qualitative test methods or where there is no variability in the reference product or where all values are below the LOQ; 3) Orthogonal test methods, where the attribute is also assessed by statistical analysis of data from a primary test method. To allow comparison, data tables with individual batch data and graphical data, such as spectra and/or descriptive statistics (Mean and minimum to maximum ranges) are presented and, depending on the attribute, are evaluated by visual comparison. If batches do not fall within the quality range or differences between products are observed as part of the descriptive

assessment, a scientific justification based on additional information or on additional studies is provided.

Results for FKS518 in biosimilarity assessment refer to both FKS518 60 mg PFS and 120 mg vial.

Primary Structure and Post-Translational Modifications

FKS518 has the expected amino acid sequence, and no amino acid substitutions were detected in the samples. The mass of the intact molecule is similar for both FKS518 and Prolia/Xgeva. Post-translational modifications (PTMs) were investigated, showing similar levels of PTMs, notwithstanding minor differences that do not preclude that products are similar. Results provided confirm that FKS518 and Prolia/Xgeva are identical in primary amino acid sequence and contain the same types of post-translational modifications.

Higher Order Structure

The higher order structure of FKS518 was found to be highly similar to Prolia/Xgeva in terms of secondary and tertiary structure, notwithstanding minor differences not impacting safety and efficacy of the molecule. The data also support that EU and US Prolia/Xgeva are highly similar in higher order structure.

Purity and Impurities

FKS518 is highly similar to Prolia/Xgeva in terms of purity and size heterogeneity. in the amount and nature of LMW species (Non-reduced CE-SDS), highly similar to Prolia/Xgeva in electrophoretic purity as sum of heavy chain and light chain and have similar levels of NGHC (Reduced CE-SDS). SE-HPLC shows that the high molecular weight species have similar profile and distribution, and that the monomer is the predominant species with low levels of HMW (dimer) species. FKS518 is highly similar to Prolia/Xgeva in HMW species and monomer content. The slightly lower levels of HMW species and higher purity for FKS518 batches is attributed to the different batch age at testing and overall lower levels of aggregates in FKS518. The AUC sedimentation coefficient profiles show FKS518 batches contained slightly higher levels of monomer and slightly lower levels of dimer and higher aggregates than Prolia/Xgeva, although the slightly better impurity profile of FKS518 is unlikely to be clinically significant, particularly given the overlapping values for each species in the products. These results support the conclusions by SE HPLC and FKS518 and Prolia/Xgeva can be considered to have similar levels of monomeric purity, dimer and higher aggregates species by AUC. SEC-MALS data demonstrates that FKS518 and Prolia/Xgeva have similar molecular weight values for monomer and dimer, and that FKS518 have slightly higher levels of monomer and lower levels of levels of HMW species. Thus, analysis by non-reduced and reduced CE-SDS, SE-HPLC, AUC and SEC-MALS show that FKS518 and Prolia/Xgeva are similar in terms of % Purity and size heterogeneity. The data also support that EU and US Prolia/Xgeva are highly similar.

Product Variants

FKS518 size and charge variants were shown comparable to reference product.

FKS518 and Prolia/Xgeva contain similar charge variants, disulfide bridge variants and glycans, and slight differences in the levels of these variants in the products are not considered clinically meaningful.

Protein Content and Extractable Volume

The analysis of protein concentration demonstrated that FKS518 60 mg-PFS is highly similar to that of EU/US Prolia, and that protein concentration of FKS518 120 mg-vial is highly similar to that of EU/US

Xgeva. US and EU Prolia, as well as US and EU Xgeva batches are highly similar to each other in this attribute.

FKS518 have slightly higher extractable volumes than Prolia/Xgeva. Similar values are shown for US and EU Prolia batches, as well as for US and EU- Xgeva batches. The slightly higher extractable volume of the FKS518 batches will not impact the dose delivered to patients as demonstrated by the comparable values of gross content of FKS518 60 mg-PFS and US and EU Prolia, and of FKS518 120 mg-vial and US and EU Xgeva.

Fab Binding and Potency

The applicant applied different methods to investigate the inhibition of RANKL activity and Fab binding to soluble and to membrane-bound RANKL. The data show that FKS518 and Prolia/Xgeva are highly similar in inhibition of sRANKL-induced IκB degradation and in binding to sRANKL. FKS518 and Prolia/Xgeva were also highly similar in inhibition of sRANKL-induced osteoclastogenesis and in binding to tmRANKL. Due to the high similarity demonstrated in inhibition of sRANKL-induced IκB degradation and sRANKL-induced osteoclastogenesis and in binding to sRANKL and tmRANKL, FKS518 is expected to have the same therapeutic effect as Prolia/Xgeva *in vivo*, and the minor physicochemical differences detected during analytical similarity assessment do not have an adverse impact on the biological activities that are key to the mechanism of action of denosumab.

Fc Binding

FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in FcRn, FcγRIIa and FcγRIIb binding. Therefore, the products can be expected to have the same PK profile and to share similar FcγRII binding in the clinic.

Absence of ADCC and CDC was also demonstrated for FKS518 and Prolia/Xgeva batches, thus confirming that FKS518 and Prolia/Xgeva were similarly unable to induce Fc effector activities, and that Fc effector activities are not part of the mechanism of action of denosumab and of no clinical significance *in vivo*.

Denosumab was developed as an IgG2 known to have minimal effector activities, to neutralise RANKL without inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Therefore, the activity of denosumab is based solely on the ability to block RANKL from binding to RANK and Fc effector functions are not part of the mechanism of action of denosumab. Nevertheless, the interaction of the Fc domain of denosumab with Fc receptors involved in effector activities and with C1q was investigated together with the absence of ADCC and CDC activities.

No or very low binding of the denosumab Fc region to FcγRI and FcγRIII variants and to C1q, and absence of ADCC and CDC were confirmed for FKS518 and Prolia/Xgeva batches. In conclusion, FKS518 and Prolia/Xgeva were similarly unable to induce Fc effector activities, thus confirming that Fc effector activities are not part of the mechanism of action of denosumab and are of no clinical significance *in vivo*.

The conclusions of the comparative analytical assessment of FKS518 and Prolia/Xgeva are listed in Table 1.

Table 1. Summary of analytical similarity assessment

Attribute	Method	Conclusions
Primary amino acid sequence	Peptide mapping by LC-MS/MS	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have identical amino acid sequences.
	Edman chemistry	The N-terminal sequences matched the expected sequence for denosumab and were the same for all FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP batches, showing that the N-terminal sequences are identical.

Attribute	Method	Conclusions
Deamidation and isomerisation	Peptide mapping by LC-MS/MS	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in deamidation and succinimide levels.
Oxidation	Peptide mapping by LC-MS/MS	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in oxidation and HC K126 hydroxylation levels.
Glycation	Peptide mapping by LC-MS/MS	Whilst FKS518 60 mg-PFS and FKS518 120 mg-vial had slightly higher levels of total glycation than RP and RMP, the difference does not preclude that products are similar.
N-Glycosylation site occupancy	Peptide mapping by LC-MS/MS	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP were similar in glycosylation site occupancy at HC Asn 298.
N- and C-terminal extension/ truncations	Peptide mapping by LC-MS/MS	FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP had similar levels of HC C-terminal lysine variants, HC C-terminal proline amidation and of LC and HC N-terminal pyroglutamate variants.
Secondary structure	FTIR	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar secondary and tertiary structure.
Secondary & tertiary structure	CD	
Tertiary structure	Fluorescence spectroscopy	The fluorescent scan data show that FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar emission wavelengths, suggesting that the fluorescent aromatic amino acids within each product have similar microenvironments and therefore that all products have similar secondary and tertiary structures.
Thermal stability	DSC	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in thermal stability and thus, have similar higher order structures.
Disulfide bridge variants	Peptide mapping by LC-MS/MS	The same disulfide linked peptides are present in FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP, supporting that the products have the same disulfide bonds, without rearrangements. The data support that FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar tertiary structures.
Free thiol content	Ellman's assay	The free thiols analysis suggests that FKS518 60 mg-PFS, FKS518 120 mg-vial have slightly higher levels of free thiols compared to the RP and to the RMP. The main quantitative difference is localized to the intrachain disulfide bond within the CH2 domain, with no observed impact on biological activity data. Moreover, literature describes the presence of significant and variable levels of unpaired disulfide bonds in both recombinant and serum-derived IgG1 and IgG2 which are mostly related to incomplete disulfide bond formation during protein folding, well tolerated under physiological conditions, and intra-domain disulfide bonds can reform from unpaired cysteines when exposed to serum. Thus, the slightly higher levels of free thiols in FKS518 are unlikely to impact safety and efficacy of the molecule.
LMW species (non-assembled forms/ fragments)	CE-SDS (Non-Reduced)	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in purity (Intact IgG) and LMW species.
	CE-SDS (Reduced)	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in electrophoretic purity and have similarly low levels of NGHC.
Monomer and HMW species/ aggregates	SE-HPLC	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in monomer content and levels of HMW species.
	AUC	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar monomeric purity, dimer and higher aggregates species.
	SEC-MALS	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar monomer and dimer molecular weight.

Attribute	Method	Conclusions
Charge variants	icIEF (with CPB)	icIEF (after CPB) data suggest that FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP contain the same charge variant species profile. Overall, FKS518 DP, RP and RMP contain similar levels of acidic and basic variants but are at the lower end of the RP/RMP range. FKS518 DP batches generally contained higher levels of main species than RP or RMP. The higher levels of main species in some FKS518 DP batches would not adversely affect efficacy, safety or immunogenicity and are considered desirable quality characteristics. In parallel, the comparative variant characterisation demonstrated that samples enriched in basic, acidic or main species do not demonstrate a difference in potency or FcRn binding.
	icIEF (w/o CPB)	The icIEF (without CPB) peak profiles and pI values of FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP are very similar with consistent pI values, suggesting that FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP contain similar charge variant species. The icIEF data demonstrate that FKS518 DP, RP and RMP contain similar levels of acidic variants, basic variants and main species although, as observed by icIEF after CPB treatment, few FKS518 60 mg-PFS and FKS518120 mg-vial batches contain slightly higher levels of main species than RP. The higher levels of main species in some FKS518 DP batches would not adversely affect efficacy, safety or immunogenicity and are considered desirable quality characteristics.
	AEX-HPLC (with CPB)	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar levels of acidic variants, basic variants and main species.
Disulfide bridge variants	RP-UPLC (non-reduced)	The RP-UPLC chromatograms demonstrate that FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP contain the same disulfide bridges variants. Overall, FKS518 DP, RP and RMP contain similar levels of disulfide bridge variants B, B x A/B, A/B, A, AA* and A*, with few FKS518 120 mg-PFS batches containing slightly higher levels of AA* variant than RMP. However, the slightly higher levels of disulfide bridge variant AA* are highly unlikely to impact safety and efficacy, as supported by the natural occurrence of disulfide structural heterogeneity in IgG2 antibodies and the conversion of disulfide bridge variants in human blood.
Glycosylation	2AB-HILIC UPLC glycan mapping	Glycan mapping (2AB HILIC UPLC) chromate-grams demonstrate that the glycan profiles of FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP are similar and that the same glycan peaks are present in all batches. The chromatograms also show that G0F, G1F, G1F iso, M5, G0 and G2F are the predominant glycans in all FKS518 DP, RP and RMP. The data from glycan mapping demonstrate that FKS518 60 mg-PFS and FKS518 120 mg-vial are similar to RP and RMP in galactosylated, afucosylated and sialylated glycan levels. Although FKS518 60 mg-PFS and FKS518 120 mg-vial contained lower levels of high mannose glycans than RP and RMP, the small difference in high mannose glycans is highly unlikely to have an adverse effect in the clinic and to impact efficacy, PK or immunogenicity.
	DMB-UPLC	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar levels of sialic acid capped glycans.
Protein content	Slope spectroscopy	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in protein concentration. The products can be expected to have the same efficacy and PK profiles upon administration to patients.
Extractable volume	Gravimetric volume determination	For FKS518 60 mg-PFS, extractable volume is slightly higher than Prolia RP and is comparable to the Prolia RMP. The engineering and first two FKS518 60 mg-PFS GMP batches had slightly higher extractable volume than targeted. Hence the target filling volume was adjusted at this time to improve similarity to the RP/RMP range. All later batches, including batches used in clinical studies and PPQ batches) had extractable volume within reference product quality ranges. The results of the statistical analysis support the conclusion that the extractable volume of FKS518 60 mg-PFS from the intended commercial process is similar to that of Prolia RP and RMP.
		FKS518 120 mg-vial are slightly higher than Xgeva RP/RMP in extractable volume. Slightly higher extractable volume results would not impact the dose delivered to patients as demonstrated by comparable values of gross content between FKS518 120 mg-vial and US-licensed and EU-approved Xgeva. Excess volume of FKS518 120 mg-vial is within the limits recommended by <1151> for all PPQ batches and would thus not allow for misuse of leftover drug product or pooling of vials to obtain a single dose.

Attribute	Method	Conclusions
Inhibition of sRANKL-induced IκB degradation	sRANKL-induced IκB degradation by *in vitro* bioassay	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in Inhibition of sRANKL-induced IκB degradation (%EC50), the key mechanism of action of denosumab and thus, FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP can be expected to mediate the same therapeutic effect in the clinic.
Affinity to sRANKL	sRANKL binding by SPR	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in affinity to sRANKL (KD) and thus, can be expected to have similar binding to sRANKL *in vivo*.
Inhibition of sRANKL-induced osteoclastogenesis	sRANKL-induced osteoclasto-genesis by *in vitro* bioassay	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in inhibition of sRANKL-induced osteoclastogenesis and can be expected to have similar activity *in vivo*.
Binding to tmRANKL	tmRANKL binding by flow cytometry	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in binding to tmRANKL ($\%EC_{50}$) and can be expected to have similar binding to tmRANKL *in vivo*.
Affinity to FcRn	FcRn binding by SPR	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP are highly similar in binding affinity to neonatal FcR (KD), supporting that the products can be expected to have similar PK profiles in the clinic.
Affinity to FcγRIIa (H131 & R131)	FcγRIIa (H131 & R131) binding by SPR	FKS518 60 mg-PFS, FKS518 120 mg-vial and RP/RMP have similar binding affinities to FcγRIIa R131, FcγRIIa H131 and FcγRIIb. The products can be expected to share similar FcγRII binding *in vivo*.
Affinity to FcγRIIb	FcγRIIb binding by SPR	
Affinity to FcγRI	FcγRI binding by SPR	FKS518 60 mg-PFS, FKS518 120 mg-vial, RP and RMP tested head-to-head showed no binding to FcγRI, FcγRIIIb and C1q, and very low binding to FcγRIIIa F158 and V158 for which no quantitative determination of KD can be made. These data confirm that Fc effector activities are not playing a role in the MoA or are not contributing to the therapeutic effect *in vivo*.
Affinity to FcγRIIIa (F158 & V158)	FcγRIIIa (F158 & V158) binding by SPR	
Affinity to FcγRIIIb	FcγRIIIb binding by SPR	
Binding to C1q	C1q binding by ELISA	
ADCC	ADCC-induced cell death by luminescence	FKS518 60 mg-PFS and RP/RMP similarly lack ADCC and CDC activities, confirming that Fc effector activities are not playing a role in the MoA or are not contributing to the therapeutic effect *in vivo*.
CDC	CDC-induced cell death by luminescence	

In conclusion, the strategy presented to assess analytical similarity of FKS518 (PFS/Vial) and the reference product EU-Prolia/Xgeva is supported. An appropriate scientific bridge has been established between the EU reference medicinal product and the US comparator used in clinical studies. The US-licenced batches and the FKS518 batches used in the clinical studies have been included in the analytical similarity studies. For most of the quality attributes tested, the proposed biosimilar FKS518 (PFS/Vial) was demonstrated to be analytically similar to EU-approved Prolia/Xgeva. Minor differences were properly discussed, justified, and are not expected to have an impact on the clinical performance of FKS518. Forced degradation studies confirmed comparable degradation profiles of FKS518 (PFS/Vial) and Prolia/Xgeva. From a quality perspective, it can be concluded that FKS518 (PFS/Vial) is similar to EU-approved Prolia/Xgeva.

Adventitious agents

The applicant presented an exhaustive evaluation on the risk of adventitious agents contaminating the manufacturing process and consequently the product itself.

Multiple complementing measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks and unprocessed bulk harvest for microbial and viral contaminants. Testing of microbial attributes, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction.

No raw materials of animal origin were used during preparation of MCB, WCB and ExCB and during the active substance and finished product manufacturing. Based on the information provided, it is agreed that the overall risk with regard to TSE is minimal.

MCB, WCB, and ExCB were tested for the absence of bacterial/fungal contamination and mycoplasma according to Ph. Eur. Absence of mycoplasma is routinely confirmed for the unprocessed bulk material. Bioburden testing is performed at the unprocessed bulk step of the active substance manufacturing process. At the release stage, active substance and finished product are tested for bioburden or sterility, respectively, as well as for endotoxin content. In conclusion, the risk for microbial contamination is adequately controlled.

Adventitious viruses

The MCB, WCB, and ExCB were analysed and confirmed to be free of viral adventitious agents. The testing programme for the cell banks applied could demonstrate the absence of non-viral and viral adventitious agents. Testing is in line with ICH Q5A and relevant Ph. Eur. Monographs.

Virus clearance studies

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using small-scale models. The design of the studies appears to be largely in line with the guidance documents ICH Q5A (R2) and CPMP/BWP/268/95. Thus, orthogonal manufacturing steps were evaluated in virus clearance studies (solvent/detergent treatment, protein A affinity chromatography, anion- and cation exchange chromatography) using relevant model viruses (MMV, PRV, Reo-3, X-MuLV). Tabular comparisons of the process parameters for the manufacturing scale and small-scale process steps have been provided.

In conclusion, the virus clearance steps in combination with the chromatography steps provide an effective and robust overall clearance capacity for adventitious viruses.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Extensive analytical similarity studies have demonstrated that the finished product is similar to the EU reference product Prolia. In addition, an appropriate scientific bridge has been established between the EU reference product and the US comparator used in clinical studies.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.5. Non-clinical aspects

2.5.1. Introduction

This Marketing Authorization Application did not contain any study reports in Module 4, which is acceptable by the CHMP.

2.5.2. Pharmacology

Analytical and functional similarity studies of Bomyntra (FKS518, denosumab of Fresenius Kabi Deutschland GmbH) were submitted in Module 3 and are therefore described and discussed in the Quality Assessment. No additional non-clinical pharmacodynamic studies, neither in vitro nor in vivo, were performed and included in Module 4 of this MAA, which is acceptable by the CHMP.

2.5.3. Pharmacokinetics

No pharmacokinetic studies were conducted and filed in Module 4 of this Marketing Authorization Application, which is acceptable by the CHMP.

2.5.4. Toxicology

No non-clinical toxicology studies were conducted and filed in Module 4 of this Marketing Authorization Application, which is supported by the CHMP.

2.5.5. Ecotoxicity/environmental risk assessment

In the case of products containing proteins as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) should be provided, whereby this ERA may consist of a justification for not submitting ERA studies, e.g. that due to the nature of particular pharmaceuticals they are unlikely to result in a significant risk to the environment (EMEA/CHMP/SWP/4447/00 corr 2 issued 01 June 2006).

The applicant provided a valid justification for the absence of ERA studies with Bomyntra, which is deemed acceptable by the CHMP.

2.5.6. Discussion on non-clinical aspects

Pharmacology

A series of in vitro studies were conducted for analytical and functional characterisation and comparison of FKS518 and the reference medicinal product and were submitted in Module 3.

The key biological assays (Fab binding and complement/Fc binding) showed similar biological activities for FKS518 and EU-Xgeva.

No *in vivo* PD studies, secondary pharmacodynamics studies, safety pharmacology or pharmacodynamic drug interactions studies were conducted with FKS518, which is in line with the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005 Rev 01).

Pharmacokinetics

No pharmacokinetic studies were conducted and filed in Module 4 of this Marketing Authorization Application, which is accepted as in line with appropriate guidelines for biosimilars (e.g. EMEA/CHMP/BMWP/42832/2005 Rev1).

Toxicology

No animal toxicity testing (*in vivo* comparison) is required for biosimilar medicinal products in the EU [EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/05 Rev.1)], since a stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product, as *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, and therefore these assays can be considered as paramount for the non-clinical biosimilar comparability exercise.

Environmental Risk Assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Bomyntra (denosumab) is not expected to pose a risk to the environment.

Furthermore, denosumab is already used in existing marketed products (Xgeva) and no significant increase in environmental exposure is anticipated.

Therefore Bomyntra (denosumab of Fresenius Kabi Deutschland GmbH) is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Not applicable.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical *in vitro* functional activity data support the biosimilarity between FKS518 and the EU (and US) reference medicinal products Prolia and Xgeva.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study FKS518-001

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s): Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Comparative PK/PD study in Healthy Subjects (Phase I)	FKS518-001	5.3.3.1	The primary objective was to demonstrate PK equivalence of 60 mg FKS518 with 60 mg US-Prolia. The secondary objectives were to compare the safety, tolerability, and immunogenicity of FKS518 with US-Prolia as well as the biomarker responses (serum CTX, and P1NP) The study also aimed to explore exposure-response relationship between %CfB in CTX and P1NP biomarker and denosumab concentrations.	Double-blind, randomized 2-arm, single dose, parallel group, study to compare the PK, PD, safety, tolerability, and immunogenicity of SC administration of FKS518 with US-Prolia	Test product: FKS518 Reference product: US-Prolia Single dose of 60 mg PFS for SC injection	Randomized: 214 subjects Subjects treated: 213 subjects FKS518: 107 US-Prolia: 106	Healthy adult male subjects	Single dose	Completed CSR available

Study FKS518-002

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s): Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Comparative efficacy and safety study in women with PMO (Phase III)	FKS518-002	5.3.5.1	The primary objective of the study was to demonstrate equivalent efficacy and PD of the proposed biosimilar denosumab FKS518 to US-Prolia in women with PMO. The secondary objectives were to compare the safety, tolerability, PD, and immunogenicity of FKS518 to US-Prolia. The study also aimed to: - evaluate the effects of a single treatment transition on safety and immunogenicity. - describe the PK parameters of FKS518 and US-Prolia. - explore the long-term efficacy of FKS518	Double-blind, randomized, multicenter, 2-arm, multiple-dose, parallel group study with a transition period, to compare the efficacy, PD, safety, tolerability, and immunogenicity of FKS518 with US-Prolia in women with PMO.	Test product: FKS518 Reference product: US-Prolia 3 doses of 60 mg IP were administered SC to women with PMO every 6 months (Week 0, 26, and 52) At week 52 (after 2 doses), subjects treated with US-Prolia were partially switched (1:1 ratio) to FKS518. End of Study Visit was performed at Week 78.	Randomized: 553 subjects Core Treatment Period: 553 treated FKS518: 277 US-Prolia: 276 Transition Period: 501 treated FKS518: 252 US-Prolia to FKS518: 124 US-Prolia: 125 Overall Period – Including Safety Follow-up Period: FKS518: 277 US-Prolia to FKS518: 124 US-Prolia: 152	Adult female patients with PMO	78 weeks	Completed CSR available

2.6.2. Clinical pharmacology

The clinical pharmacology of FKS518 and the reference product has been investigated in two studies:

Study FKS518-001: a double-blind, randomised, single centre, 2-arm, single-dose, parallel-group study in healthy subjects to compare the pharmacokinetics, pharmacodynamics, safety and immunogenicity of FKS518 – proposed biosimilar to denosumab with US-Prolia.

Study FKS518-002: a double-blind, randomised, multicentre, 2-arm, multiple-dose, parallel-group study with a transition period, to compare efficacy, safety, tolerability, and immunogenicity of the proposed biosimilar to denosumab FKS518 with US-Prolia (denosumab) in ambulatory women with PMO. Bone biomarkers (PD) and PK were also assessed.

Apart from the above-mentioned studies, no other clinical pharmacology studies (i.e., drug interaction studies, or studies in special populations such as hepatic or renal impairment) were performed.

FKS518-001 is the main study to investigate the clinical pharmacology and its methods and results are presented in details below.

FKS518-002 is the main study to investigate efficacy and only PK/PD results are presented below. The main design and results of this study are presented in section 2.6.5 Clinical Efficacy.

2.6.2.1. Pharmacokinetics

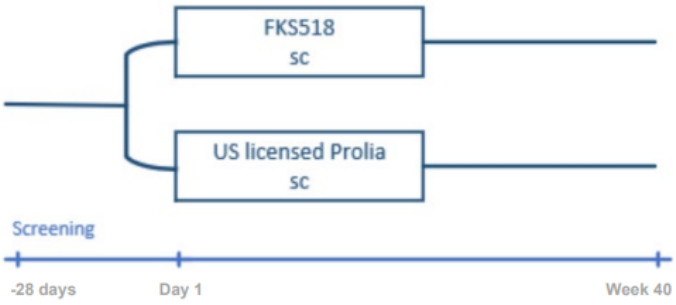
Main study FKS518-001

Study FKS518-001: 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 Prolia® (Lumiade-1 Study)

The study had a duration of up to 44 weeks, including a screening period of up to 4 weeks prior to IP administration on Day 1 and a follow-up period of 40 weeks, consisting of 1 week of confinement in the clinic from Day -1 to Day 6 and 16 ambulatory visits up to Day 274. Blood samples for PK, PD, and immunogenicity were collected at predose (0 hours) and at scheduled time points up to Day 274 (EOS).

Eligible healthy male volunteers were randomised in a 1:1 ratio on Day -1 to receive either 60 mg of FKS518 or US-Prolia as single-use PFS on Day 1. Randomisation was performed via a centralised interactive response technology (IRT) system and was stratified by weight (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg). A total of 214 healthy male subjects (107 per group) aged ≥ 28 to ≤ 55 years, with a body weight between 50.0 and 110.0 kg and body mass index (BMI) between 18.0 and 32.0 kg/m2, inclusive, were planned to be enrolled to target a minimum of 170 evaluable subjects.

The study design is outlined in the figure below.



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.

Figure 1. Study schema

Methods

Study participants

Inclusion criteria

The following inclusion criteria must have been met for a patient to be eligible for inclusion in the study:

1. Healthy male subject, between 28 and 55 years of age, inclusive, at screening.

2. Body weight between 50.0 and 110.0 kg, inclusive, at admission, and body mass index (BMI) between 18.0 and 32.0 kg/m2, inclusive.

3. Male subjects were either surgically sterile (vasectomy with documented confirmation of aspermia) or willing to use a condom in addition to having their female partner of childbearing potential use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive (e.g., implant, injectable, patch, or oral pill) from Day 1 until 39 weeks after dosing, unless their partners were infertile or surgically sterile. Total abstinence, in accordance with the lifestyle of the subject, was also acceptable. Men had to agree to refrain from donating sperm from the time of the IP administration and for at least 3 months after the IP administration.

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

5. Normal electrocardiogram (ECG) or, if abnormal, considered nonsignificant by the Investigator.

6. Subjects voluntarily gave written informed consent before any study-related activities were performed. Subjects had to read and fully understand the ICF and the requirements of the trial and were willing to comply with all trial visits and assessments.

Exclusion Criteria:

A patient who met any of the following exclusion criteria was not eligible for inclusion in the study:

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

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

3. Osteonecrosis of the jaw, or risk factors for osteonecrosis of the jaw such as invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery in the past 6 months), poor oral hygiene, periodontal, and/or pre-existing dental disease.

4. Evidence of hypocalcaemia (albumin-adjusted serum calcium < 2.13 mmol/L or < 8.5 mg/dL) or hypercalcaemia (albumin adjusted serum calcium > 2.6 mmol/L or > 10.5 mg/dL) as assessed by the clinical laboratory at screening.

5. Known vitamin D deficiency (25-hydroxy vitamin D levels < 12 ng/mL) as assessed by the clinical laboratory at screening (no retest allowed).

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

7. Medical evidence of current or history of primary or secondary immunodeficiency as per Investigator’s judgment.

8. 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 (more than 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 [HBcAb]) at screening.

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

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 randomisation.

9. Subject underwent noteworthy surgical intervention within 8 weeks before administration of the IP or scheduled to have a surgical procedure during the study.

10. History of clinically significant alcohol abuse within the last year prior to randomisation, or current alcohol abuse or excessive intake of alcohol, defined as an average weekly intake of > 15 units for men (1 unit = 10 g of pure alcohol equivalent to 330 mL of beer, 100 mL of wine, or 30 mL of spirits), or positive alcohol screen at screening and/or admission to the clinical research centre.

11. History of clinically significant drug abuse within the last year prior to randomisation, or positive drug screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, and tricyclic antidepressants) at screening and admission to the clinical research centre.

12. Judgment by the Investigator that the subject should not participate in the study if they had any ongoing or recent (i.e., at the time of screening) medical condition that could interfere with the study conduct or the interpretation of study data and/or otherwise put the subject at an unacceptable risk or could result in non-compliance with requirements of the study. The Investigator should specifically evaluate the subject's eligibility taking into consideration COVID-19 risk factors and situation.

13. A positive PCR test for SARS-CoV-2 prior to admission to the clinical research centre on Day -1.

14. Unsuitable veins for blood sampling.

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

16. Prior use of any medications that can influence bone metabolism were excluded according to the Investigator's judgment after consultation with the Medical Monitor.

17. Use of any prescribed or nonprescribed medication (other than ibuprofen and paracetamol/acetaminophen), dietary supplements, or herbal medication within 2 weeks prior to IP administration or longer if the medication has a long half-life.

18. Participation in a drug study within 60 days prior to IP administration in the current study, or planned intake of an investigational drug during the course of this study.

19. Subject donated or lost 450 mL or more of blood within 8 weeks prior to the administration of IP.

20. Any abnormal skin conditions or potentially obscuring tattoos, pigmentation, or lesions in the areas intended for SC injection that, in opinion of Investigator, did not allow assessment of local tolerability.

21. Smoking more than the equivalent of 10 cigarettes, 2 cigars, or 1 pipe daily and/or the inability to refrain from smoking or consuming nicotine-containing products during the confinement at the study site.

22. Use of caffeine or methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, or energy drinks) within 24 hours of IP administration.

23. Vigorous exercise within 72 hours of IP administration, verified by creatine phosphokinase (CPK) blood level, assessed as clinically significant by the Investigator.

24. Employee of the clinical site, or the Sponsor.

25. Had received a COVID-19 vaccine within 4 weeks prior to randomisation or COVID-19 vaccination was ongoing at the time of screening. COVID-19 vaccination was considered ongoing if a multidose regimen was started but not completed.

Treatments

Test Product	Active Comparator
IP/non-IP: IP	IP/non-IP: IP
Name: FKS518 (proposed denosumab biosimilar)	Name: US-licensed Prolia (denosumab)
Dose: 60 mg single dose	Dose: 60 mg single dose
Route of administration: Subcutaneous injection	Route of administration: Subcutaneous injection
Manufacturer:	Manufacturer: Amgen Inc, US
Batch numbers:	Batch numbers:

Objectives

Primary objective

To demonstrate PK equivalence of 60 mg FKS518 with 60 mg US-Prolia in healthy male subjects

Secondary objectives

- To compare safety, tolerability, and immunogenicity of FKS518 with US-Prolia in healthy male subjects
- To compare biomarker responses with serum C-terminal cross-linking telopeptide of Type 1 collagen (CTX), and procollagen Type 1 N-terminal propeptide (P1NP)

Endpoints

Primary endpoints

- Area under the concentration-time curve from time zero to infinity (AUC0-inf)
- Area under the concentration-time curve from time zero to the last quantifiable concentration (AUC0-last)
- Maximum serum concentration (Cmax)

Secondary endpoints

Pharmacokinetics:

- Time to Cmax (tmax)
- Volume of distribution during the terminal phase (Vz/F)
- Terminal half-life (t1/2)
- Total apparent clearance (CL/F)
- Partial AUC: Week 1-19, Week 19-27, Week 27-40, or another interval as justified by PK profile

Pharmacodynamics:

- Area under the effect curve (AUEC0-Wk40) for percent change from baseline (%CfB) of CTX and P1NP in serum
- %CfB at all time points post-dose for CTX and P1NP
- Maximum percent change from baseline (%CfBmax) for CTX and P1NP

Safety and tolerability:

- Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) Injection site reactions (ISRs; local tolerability)
- Adverse Events of Special Interest (AESI): hypersensitivity/allergic reactions (common terminology criteria for adverse events [CTCAE] Grade 23 or reported as serious events), and adverse events (AEs) leading to study withdrawal (AEs) leading to study withdrawal
- Clinically significant laboratory abnormalities
- Clinically significant vital sign abnormalities (blood pressure, respiratory rate, pulse rate, or temperature)
- Clinically significant 12-lead electrocardiogram (ECG) abnormalities

Immunogenicity:

- Antidrug antibody (ADA) status ADA titre
- Neutralizing antibody (Nab) status

Exploratory Endpoints:

- %CfB in CTX and P1NP bone biomarker and denosumab concentrations

Sample size

A sample size of 214 randomised subjects (107 subjects per arm) was chosen to provide 170 subjects (85 subjects per arm) in the PK Analysis Set, assuming a 20% drop-out rate (including important protocol deviations leading to exclusion from the PK Analysis Set).

A total of 170 subjects was computed to provide 90% power to demonstrate bioequivalence between the 2 treatments for the PK primary endpoints with a bioequivalence margin of [0.8, 1.25] and a Type I error rate of 5%, assuming a maximum 5% difference between treatment groups on the geometric mean ratio (GMR), a drop-out rate of 20% and a maximum coefficient of variation of 40% for the PK

primary endpoints (AUC0-inf, AUC0-last, and Cmax). A total of 170 subjects was computed to provide 96.6% power assuming no difference between the 2 treatment groups.

The drop-out rate/protocol deviation rate was planned to be monitored on blinded data throughout the study. The number of randomised subjects may have had to be adjusted accordingly in case of deviation from the initial assumption. If larger than anticipated, an investigation on the reasons for dropping out was planned be conducted.

Randomisation and blinding (masking)

Subjects who met all eligibility criteria were to be randomised on Day -1. Randomisation was performed via a centralised IRT system. Eligible subjects were randomly assigned to either FKS518 or US-Prolia in a 1:1 ratio, stratified by weight (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg).

Randomisation was planned to be conducted in permuted blocks. If a subject withdrew from study participation, his unique identification number(s) was not to be re-used for another subject.

The study was planned and conducted double blinded with the subjects, the Investigator, and the Sponsor being blinded to the IP administered until the end of the study. Randomisation data were to be kept strictly confidential, accessible only to authorized staff, until the time of unblinding.

To maintain this blind, qualified, unblinded members of the site staff not otherwise involved in the study procedures were responsible for IP administration according to the randomisation list. The unblinded study staff was not to be involved in any other assessments or safety reporting.

Subjects were planned to blinded to treatment as well. To maintain blinding of subjects, a visual blind was in place during dose administration.

Breaking of the blinding was only allowed in the case of an emergency, when knowledge of the IP was essential for the clinical management of the subject. Should any unblinding have happened, it would have been organized through the IRT system.

Statistical methods

The study analysis sets were defined as follows:

The **enrolled analysis set** was to include all subjects who provide informed consent. This analysis set was to be used to report disposition and screening failures.

The **randomised analysis set** was to include all subjects who were assigned a randomisation number in the study. This set was to be used for all data listings except for the PK/PD, TEAE, laboratory and screen failure listings.

The **Safety Analysis Set** was to include all subjects who receive any dose (partial or complete) of the IP, and were to be analysed according to the actual treatment received. This analysis set was to be used for summaries of baseline characteristics, laboratory, safety and immunogenicity data.

The **PK Analysis Set** was to include all subjects who receive a complete dose of the IP, with enough PK assessments to calculate reliable estimates of at least 1 PK parameter, and without important protocol deviations affecting PK assessments. These protocol deviations were planned to be defined and agreed upon before unblinding. Subjects were to be analysed according to the actual treatment received. This set was to be used for the serum concentration and PK parameter summaries and primary analysis.

The **PD Analysis Set** was to include all subjects who receive a complete dose of IP, with enough PD assessments, including a baseline concentration value, to calculate reliable estimates of at least 1 PD parameter, and without important protocol deviations affecting PD assessments. These protocol deviations were planned to be defined and agreed upon before unblinding. Subjects were to be analysed according to the actual treatment received.

Standard statistical methods had been planned for descriptive and summarising analyses of all PK-, PD-, Safety- and Immunogenicity-endpoints defined.

For the primary Analyses, the natural log-transformed PK primary endpoints (ie, AUC0-inf, AUC0-last, and Cmax) was planned to be analysed on the PK-Analysis Set using an ANOVA model with treatment and weight strata as fixed effects. For the comparison of primary endpoints, the 90% confidence intervals (CIs) for the GMR were planned to be derived by exponentiating the 90% CI obtained for the difference between the 2 treatments least squares (LS) means resulting from the analysis of the log-transformed PK primary endpoints. If the 90% CIs for the GMR of all PK primary endpoints were found entirely within the 0.8 to 1.25 equivalence margins, then PK equivalence between the 2 treatments was planned to be declared.

The trial protocol contained information regarding the statistical analysis approach making use of the estimands framework:

The 4 attributes of the 3 primary estimands were defined as follows:

- Population of interest: healthy subjects fulfilling the inclusion/exclusion criteria
- Primary variables/endpoints of interest: AUC0-inf, AUC0-last, and Cmax
- Potential intercurrent events and strategy to address: for subjects with events leading to exclusion from the PK Analysis Set, a principal stratum strategy will be applied such that these subjects will not be included in the primary analysis
- Population level summary: GMR of the 2 treatments for the 3 primary variables

The SAP contained the following plan information in this regard:

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

1. Treatment of interest: SC injection of FKS518 as compared to US-Prolia

2. Population of interest: healthy male subjects fulfilling the inclusion/exclusion criteria and being included in the PK analysis set.

3. Primary variables/endpoints of interest: AUC0-inf, AUC0-last, and Cmax

4. Potential intercurrent events and strategy to address:

- Occurrence of adverse events affecting one of the 3 primary PK parameters (e.g. vomiting, diarrhoea)
- Use of concomitant medications with the potential to impact one of the 3 PK parameters.
- Strategy used to address these IEs: The concerned concentration will be set to missing and the PK parameter will be determined using all other concentrations as described in the SAP

5. Population level summary: GMR of the 2 treatments and respective 90% CI, for each of the 3 primary PK parameters

Furthermore, the SAP contained a plan for tentative subgroup analyses evaluating primary outcome separately according to body weight classes and ADA/NAb status.

Results

Participant flow

Study initiation date: 06 May 2021 (first subject signed informed consent)

Study completion date: 02 September 2022 (last subject last visit)

The study subjects were enrolled from one investigative site in Poland.

Patient disposition is summarised below.

Table 2. Summary of subject disposition

	FKS518 n (%)	US-Prolia n (%)	Overall n (%)
Enrolled Set (Subjects Screened)			424
Subjects Enrolled, but not Randomized			210
Reason Enrolled but not Randomized			
Subject did not meet all eligibility criteria			210
Death			0
Other			0
Subjects Randomized, but not Dosed	0	1	1
Randomized Analysis Set	107 (100)	107 (100)	214 (100)
Safety Analysis Set	107 (100)	106 (99.1)	213 (99.5)
PK Analysis Set	105 (98.1)	103 (96.3)	208 (97.2)
PD Analysis Set	105 (98.1)	104 (97.2)	209 (97.7)
Completed Study	103 (96.3)	103 (96.3)	206 (96.3)
Discontinued Study	4 (3.7)	3 (2.8)	7 (3.3)
Primary Reason for Study Discontinuation			
Adverse Event	1 (0.9)	0	1 (0.5)
Lost to Follow-up	1 (0.9)	0	1 (0.5)
Death	0	0	0
Withdrawal by Subject	0	1 (0.9)	1 (0.5)
Other	2 (1.9)	2 (1.9)	4 (1.9)
Is the premature discontinuation related to COVID-19			
Yes	0	0	0
No	4 (3.7)	3 (2.8)	7 (3.3)

Sources: Table 14.1.1 and Listing 16.2.1.1.
Abbreviations: COVID-19 = coronavirus disease 2019; PD = pharmacodynamic; PK = pharmacokinetic.
Note: Percentages are based on the number of subjects in the Randomized Set.

Important protocol deviations were recorded for 8 (3.8%) subjects; 5 (4.7%) subjects in the FKS518 group and 3 (2.8%) subjects in the US-Prolia group. The most common category of important protocol deviation was "missing a study visit," recorded for 7 of the 8 subjects with important protocol deviations.

Conduct of the study

Two amendments were made to the original protocol (V1.0, dated 06 Nov 2020). The key features of each amendment are as follows:

Amendment 1 (dated 18 February 2021) was issued to comply with a request from the IEC to further clarify the inclusion of only male subjects in this study. Also, time restrictions were implemented related to denosumab administration and COVID-19 vaccination. The description of the laboratory performing determination of bone biomarkers was changed.

Amendment 2 (dated 12 July 2021) was issued to clarify when abnormal laboratory findings and other abnormal investigational findings should be reported as AEs by the Investigator to the Sponsor.

Baseline data

Demographic characteristics are summarised below for the Safety Analysis Set.

Table 3. Summary of demographics (Safety Analysis Set)

		FKS518 (N = 107)	US-Prolia (N = 106)	Overall (N = 213)
	Category or Statistic	n (%)	n (%)	n (%)
Sex [n (%)]	Male	107 (100)	106 (100)	213 (100)
Race [n (%)]	White	107 (100)	106 (100)	213 (100)
Ethnicity [n (%)]	Not Hispanic or Latino	107 (100)	106 (100)	213 (100)
Age (yrs)	n	107	106	213
	Mean	38.9	38.8	38.8
	SD	7.05	5.93	6.50
	Median	37.0	39.0	38.0
	Min, Max	28, 55	29, 52	28, 55
Baseline Weight (kg)	n	107	106	213
	Mean	84.21	83.46	83.83
	SD	12.104	11.598	11.833
	Median	84.00	84.00	84.00
	Min, Max	58.0, 109.0	53.5, 107.0	53.5, 109.0
Baseline Weight Category	≥ 50.0 to ≤ 70.0 kg	15 (14.0)	14 (13.2)	29 (13.6)
	> 70.0 to ≤ 110.0 kg	92 (86.0)	92 (86.8)	184 (86.4)
Height (cm)	n	107	106	213
	Mean	179.8	179.2	179.5
	SD	6.86	6.40	6.62
	Median	180.0	179.0	180.0
	Min, Max	162, 199	161, 194	161, 199
Baseline BMI	n	107	106	213
	Mean	26.00	25.95	25.97
	SD	2.958	3.202	3.074
	Median	25.90	26.35	26.00
	Min, Max	19.6, 31.7	18.2, 31.7	18.2, 31.7

Source: Table 14.1.3.1
Abbreviations: BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation.
Note: Height was determined at screening.

Similar proportions of subjects in the FKS518 (65.4%) and US-Prolia (67.0%) groups had at least 1 medical history condition. Medical history findings ongoing at baseline were of mild or moderate severity. Overall, the medical history findings did not meet any of the CSP-specified exclusion criteria, with the exception of one patient, whose diagnosis of schizophrenia was not known during subject's screening.

The subjects used no prior medications that were prohibited according to the exclusion criteria.

All subjects had negative drug and alcohol screen results at screening and first admission. Serology was negative for all subjects at screening.

The number of subjects who used concomitant medications or therapies during the study was balanced across both treatments. A total of 180 (84.5%) subjects used concomitant medications or therapies

during the study; this included 91 (85.0%) subjects who were administered FKS518 and 89 (84.0%) subjects who were administered US-Prolia.

Numbers analysed

Patient analysis sets are summarised in the table below.

Table 4. Summary of subject disposition for study FKS518-001

	FKS-518 n (%)	US-Prolia n (%)	Total n (%)
Safety Analysis Set [a]	107 (100)	106 (99.1)	213 (99.5)
PK Analysis Set [b]	105 (98.1)	103 (96.3)	208 (97.2)
PD Analysis Set [c]	105 (98.1)	104 (97.2)	209 (97.7)

Abbreviations: PK = pharmacokinetic, PD = pharmacodynamic

[a] All subjects who received Investigational Medicinal Product (IMP)

[b] All subjects who had received IMP and had at least 1 of the primary PK parameters without clinically important protocol deviations or events which may significantly affect PK assessments.

[c] All subjects who had received IMP and had at least 1 of the secondary PD parameters without clinically important protocol deviations or events which may significantly affect PD assessments.

Source: Refer to Module 5, Section 5.3.3.1, CSR FKS518-001, Table 6.

Outcomes

When comparing the primary PK parameters of denosumab between FKS518 and US-Prolia using an ANOVA model, the 90% CIs for the geometric least-squares mean (GLSM) of the ratio test/reference for these PK parameters were fully contained within the predefined bioequivalence limits of [80.00% to 125.00%]. The 90% CIs for the GLSM ratios were [97.04, 113.15] for Cmax, [104.17, 121.04] for AUC0-last, and [104.27, 121.70] for AUC0-inf. A summary of the statistical analysis is provided below.

Table 5. Statistical analysis of the bioequivalence of FKS518 versus US-Prolia – Primary estimand (PK Analysis Set)

	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)

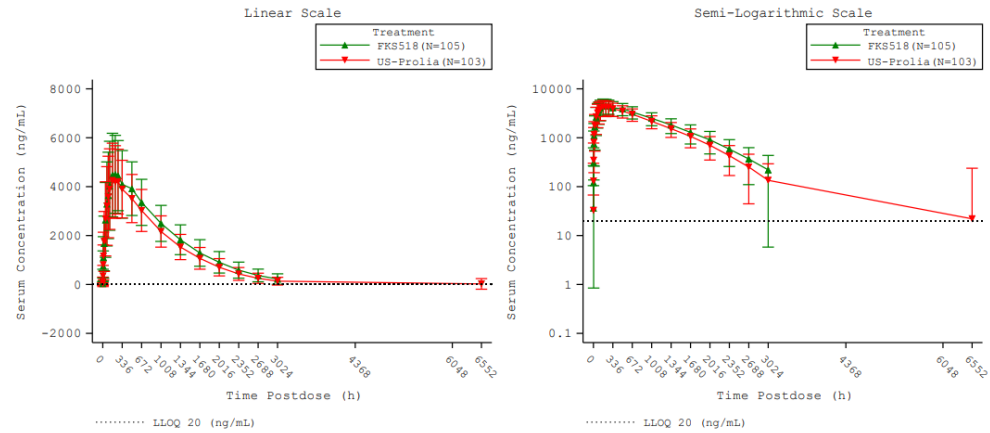
Source: Table 14.2.3

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.

The denosumab serum concentration time profiles (linear scale and semi-logarithmic scale) are provided in the figure below.



Source: Figure 14.2.6
Abbreviations: H = Hours; LLOQ = lower limit of quantification; PK = pharmacokinetic; SD = standard deviation

Figure 2. Plot of arithmetic mean (+/-SD) denosumab serum concentrations versus time on a linear scale and semi-logarithmic scale (PK Analysis Set, Analyte: denosumab ng/mL)

Individual denosumab serum concentrations vs time profiles were provided for all subjects. In some plots, a sudden concentration drop is recorded, as can be seen in the following example.

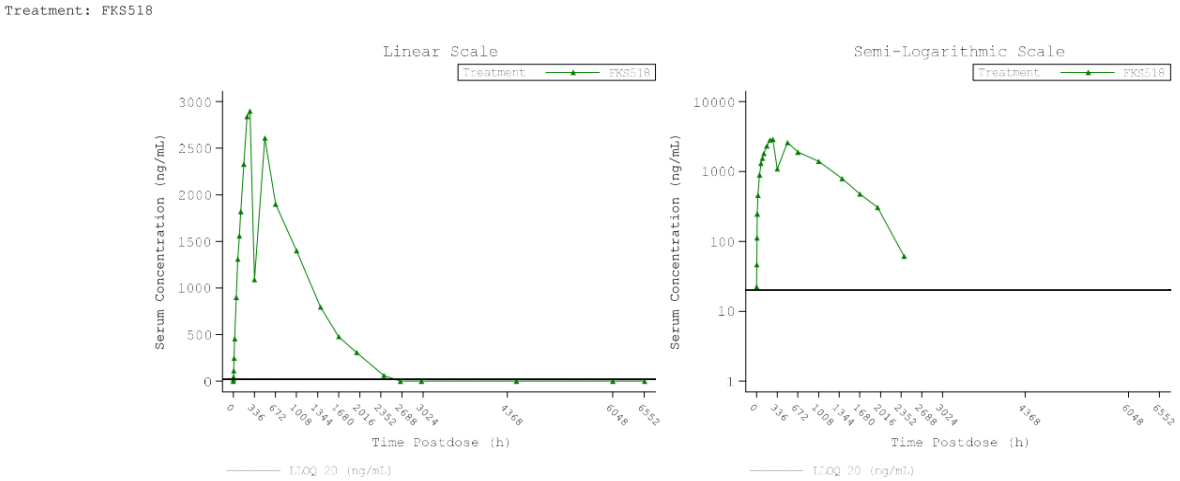
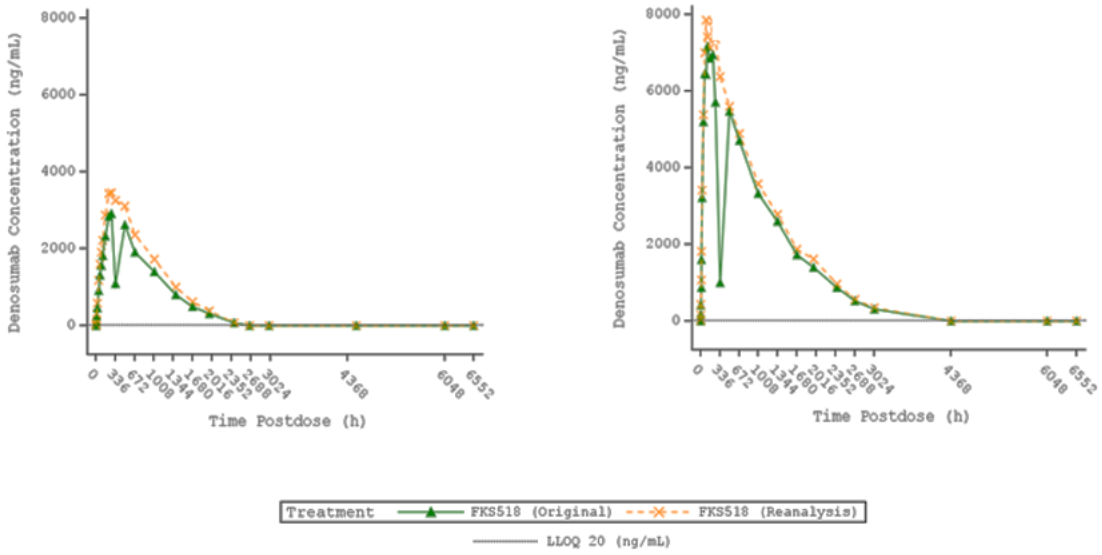


Figure 3. Plot of individual denosumab serum concentrations versus time on linear and semi-logarithmic scales (PK Analysis Set, analyte: denosumab ng/mL) as an example

The PK concentration analyses for the whole profiles of the 12 subjects with PK concentration fluctuations were re-analysed, as requested by the CHMP during the evaluation. These 324 samples were re-analysed following the same method and applicable SOPs as in the initial concentration determination.

To confirm the robustness of the data reported in the CSR, the PK concentrations determined for the re-analysed samples were compared to the original PK concentration. When a re-analysis result was significantly different from the original result (more than 30% relative difference), the sample was re-analysed again to obtain a third result. In such cases the final reporting of the concentration result followed a decision tree delineated in the relevant SOP.



Abbreviations: H = Hours; LLOQ = Lower Limit of Quantification (20 ng/mL); PK = Pharmacokinetic.
Source: FKS518-001_PK_27Mar2025, ADPC, FKS518-001 CSR Listing 16.2.6.1.

Figure 4. Original versus re-analysis PK profiles (example of two depicted subjects)

Post hoc Sensitivity analyses to assess the impact of the major drops in drug concentration on PK equivalence

In addition, sensitivity analyses were subsequently submitted during the evaluation where the bioequivalence test for AUC parameters was repeated:

a) Using all subjects in the PK analysis set, including the 12 subjects with an unexpected PK profile. However, the 13 concentrations considered as major fluctuations were set to missing and the $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were calculated without these concentration data points using the linear up/ log-down trapezoidal rule.

b) Excluding the 12 subjects with unexpected PK concentration fluctuations from the bioequivalence analysis.

Results are presented below:

Table 6. FKS518-001 – Statistical analysis of the bioequivalence of FKS518 versus US-Prolia-treating major fluctuations as missing concentrations (PK Analysis Set)

Parameter	FKS518 (N=105) GLSM (95% CI)	US-Prolia (N=103) GLSM (95% CI)	Ratio (FKS518/US-Prolia) GLSM (90% CI)
N	105	103	
C_{max} (µg/mL)	5.33 (4.91, 5.78)	5.12 (4.71, 5.57)	104.04 (96.34, 112.35)
N	105	103	
$AUC_{0\text{-last}}$ (h*µg/mL)	6298 (5823, 6811)	5608 (5171, 6081)	112.30 (104.24, 121.00)
N	105	102	
$AUC_{0\text{-inf}}$ (h*µg/mL)	6440 (5941, 6981)	5716 (5259, 6214)	112.66 (104.33, 121.66)

Abbreviations: CI = Confidence Interval; GLSM = Geometric Least Squares Mean; n = Number of subjects that was 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. For derivation of AUC - Treating unexplained drops as missing, the following assessments have been set to missing: Subject (Day-nominal time) [redacted] (Day 10-H216), [redacted] (Day 10-H216), [redacted] (Day 12-H264), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336), [redacted] (Day 15-H336).
Source: FKS518-001_AUC_D180_2sub, FKS518-001_AUC_Q106_Q88, ADPC, ADPP.

Table 7. FKS518-001 – Statistical analysis of the bioequivalence of FKS518 versus US-Prolia-excluding subjects with major fluctuations (PK Analysis Set)

Parameter	FKS518 (N=105) GLSM (95% CI)	US-Prolia (N=103) GLSM (95% CI)	Ratio (FKS518/US-Prolia) GLSM (90% CI)
N	97	99	
C_{max} (µg/mL)	5.29 (4.86, 5.76)	5.13 (4.70, 5.59)	103.25 (95.46, 111.66)
N	97	99	
$AUC_{0\text{-last}}$ (h*µg/mL)	6277 (5789, 6806)	5632 (5187, 6116)	111.44 (103.38, 120.13)
N	97	98	
$AUC_{0\text{-inf}}$ (h*µg/mL)	6414 (5901, 6971)	5739 (5271, 6248)	111.77 (103.44, 120.78)

Abbreviations: CI = Confidence Interval; GLSM = Geometric Least Squares Mean; n = Number of subjects that was 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.
The following subjects are excluded from the analysis: Subjects [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].
Source: ADPP.

Secondary PK parameters

Summary statistics of the PK parameters for the treatment groups are presented below.

Table 8. Summary of secondary PK parameters for denosumab in serum (PK Analysis Set)

Parameter (unit)	Statistic	60 mg Denosumab FKS518 (N = 105)	60 mg Denosumab US-Prolia (N = 103)
t_{max} (h)	n	105	103
	nmiss	0	0
	Mean	250.188	228.362
	%CV	44.5	42.4
	Median	217.450	216.030
	Min, Max	72.00, 673.60	96.00, 672.95
$t_{1/2}$ (h)	n	105	102
	nmiss	0	1
	Mean	428	391
	SD	178	188
	%CV	41.5	48.1
	Median	385	337
	Min, Max	170, 858	156, 1076
	Geo Mean (95% CI)	392 (361, 426)	352 (322, 385)
	%GeoCV	44.6	47.4
Vz/F (L)	n	105	102
	nmiss	0	1
	Mean	6.66	6.83
	SD	2.67	2.59
	%CV	40.2	37.9
	Median	6.39	6.51
	Min, Max	2.95, 22.1	2.91, 18.2
	Geo Mean (95% CI)	6.25 (5.84, 6.68)	6.39 (5.95, 6.87)
	%GeoCV	35.8	37.9
CL/F (L/h)	n	105	102
	nmiss	0	1
	Mean	0.0120	0.0135
	SD	0.00579	0.00566
	%CV	48.4	42.0
	Median	0.0105	0.0121
	Min, Max	0.00550, 0.0480	0.00592, 0.0458
	Geo Mean (95% CI)	0.0110 (0.0103, 0.0119)	0.0126 (0.0117, 0.0135)
	%GeoCV	39.3	37.2
$AUC_{0\text{-}3024}$ (h·µg/mL)	n	105	103
	nmiss	0	0
	Mean	5626	4942
	SD	1826	1580
	%CV	32.4	32.0
	Median	5598	4891
	Min, Max	1232, 9805	1297, 9272
	Geo Mean (95% CI)	5301 (4939, 5689)	4676 (4369, 5003)
	%GeoCV	37.8	35.7
$AUC_{3024\text{ - }4368}$ (h·µg/mL)	n	105	103
	nmiss	0	0
	Mean	86.4	54.0
	SD	133	84.6
	%CV	154.3	156.7
	Median	44.8	21.9
	Min, Max	0, 765	0, 473
	Geo Mean (95% CI)	NC	NC
	%GeoCV	NC	NC
$AUC_{4368\text{ - }6552}$ (h·µg/mL)	n	105	103
	nmiss	0	0
	Mean	9.52	4.42
	SD	37.9	27.2
	%CV	397.8	614.6
	Median	0.000402	0.0000822
	Min, Max	0, 245	0, 260
	Geo Mean (95% CI)	NC	NC
	%GeoCV	NC	NC

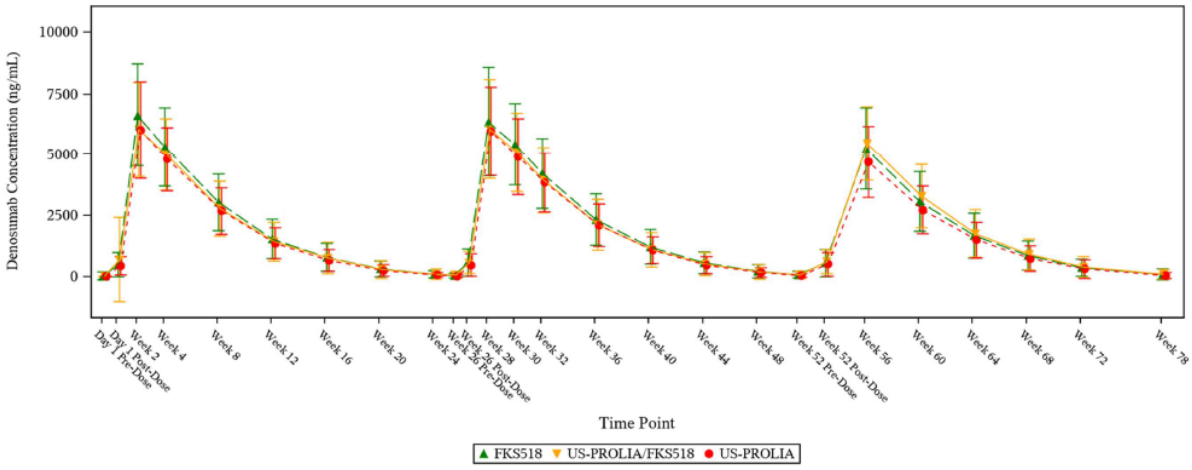
Source: Table 14.2.2.1
Abbreviations: AUC = area under the concentration-time curve; CI = confidence interval; CL/F = apparent total clearance; CV = coefficient of variation; Geo = geometric; Max = maximum; Min = minimum; n = number of subjects; NC = not calculable; nmiss = number of missing observations; PK = pharmacokinetic(s); SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; tmax = time to maximum observed serum concentration; VzF = volume of distribution during terminal phase.
For T_{max}, only median, minimum, maximum, mean, and %CV are presented.

Study FKS518-002 in postmenopausal women with osteoporosis

Individual and mean concentrations at each sampling time point for denosumab were listed and summarised. Serum concentrations that were below the level of quantification (BLQ) were set to lower limit of quantification (LLOQ)/2 in the computation of mean concentration values. If the mean at a given time point was BLQ then the descriptive statistics were not presented and were instead displayed as BLQ for the mean and minimum. With the exception of the number of patients (n) and the maximum value, all other statistics would be missing. The plots matched the summary table results and did not have an observation at a given time point if the mean was BLQ.

PK parameters AUCtau and partial AUCs for 0 to 16 weeks, 0 to 20 weeks, and 16 to 26 weeks were calculated using noncompartmental analysis with Phoenix WinNonlin (Version 8.3.4) to further characterise the elimination profile in patients. For the calculation of the AUCs, linear up log down was used. Summary statistics of PK parameters were presented. Geometric means ratio and 90% CIs for AUCs including partial areas between treatment groups were calculated descriptively using an exploratory analysis of variance model without predefined margins for comparison.

Plots of mean denosumab serum concentrations over time in the PK Analysis Set are presented for the Overall Period in the figure below.



Source: Figure 14.2.6.1.1.1.
LLOQ = lower limit of quantification; PK = Pharmacokinetic.
Note: Values below the LLOQ were imputed as ½LLOQ.
Note: Missing values due to no sample, insufficient sample volume for analysis, no result or result not valid were excluded from the analysis.

Figure 5. Mean denosumab concentration over time (linear scale) – Overall period (PK Analysis Set)

Denosumab PK parameters were calculated for the first IP dose only. A summary of denosumab PK parameters (AUCs) in the PK Analysis Set is presented for the core treatment period in the table below.

Table 9. Denomsumab PK parameters – Core treatment period (PK Analysis Set)

PK parameter (unit) Statistic	FKS518 (N=269)	US-Prolia (N=261)
AUC_{tau} (h*ug/mL)		
n (missing)	267 (2)	259 (2)
Mean (std)	8605.96 (3171.328)	7810.73 (2861.666)
CV	36.850	36.638
Geometric Mean	7952.77	7278.99
Geometric CV	44.23	40.35
Median	8439.69	7327.96
Min, Max	1461.8, 18595.6	1798.4, 18546.0
Geometric Means Ratio FKS518/US-Prolia (90% CI)	1.0926 (1.0306, 1.1582)	
$AUC_{0\text{-}W16}$ (h*ug/mL)		
n (missing)	269 (0)	261 (0)
Mean (std)	8071.54 (2790.003)	7358.57 (2512.883)
CV	34.566	34.149
Geometric Mean	7526.42	6910.45
Geometric CV	41.43	38.11
Median	8045.46	7010.71
Min, Max	1460.9, 16468.8	1775.6, 15296.5
Geometric Means Ratio FKS518/US-Prolia (90% CI)	1.0891 (1.0309, 1.1506)	
$AUC_{0\text{-}W20}$ (h*ug/mL)		
n (missing)	269 (0)	261 (0)
Mean (std)	8419.87 (3027.547)	7662.53 (2730.824)
CV	35.957	35.639
Geometric Mean	7808.13	7160.45
Geometric CV	43.16	39.62
Median	8288.32	7280.42
Min, Max	1461.8, 17795.6	1792.5, 17009.4
Geometric Means Ratio FKS518/US-Prolia (90% CI)	1.0905 (1.0300, 1.1544)	
$AUC_{W16\text{-}26}$ (h*ug/mL)		
n (missing)	267 (2)	259 (2)
Mean (std)	516.10 (460.103)	444.81 (432.004)
CV	89.149	97.120
Geometric Mean	301.08	274.76
Geometric CV	209.21	152.44
Median	389.45	314.21
Min, Max	1.1, 2126.8	8.6, 3249.5
Geometric Means Ratio FKS518/US-Prolia (90% CI)	1.0958 (0.9219, 1.3024)	

Source: Table 14.2.6.5.1.
AUC = Area Under the Curve; CI = Confidence Interval; CV = Coefficient of Variation; PK = Pharmacokinetic; std = Standard Deviation.
Note: Geometric means ratio and 90% CIs for AUCs were calculated descriptively using exploratory analysis of variance model without predefined margins for comparison.

2.6.2.2. Pharmacodynamics

Mechanism of action

RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone destruction in metastatic bone disease and multiple myeloma. Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.

Giant cell tumours of bone are characterised by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis

is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

Primary and Secondary pharmacology

Study FKS518-001

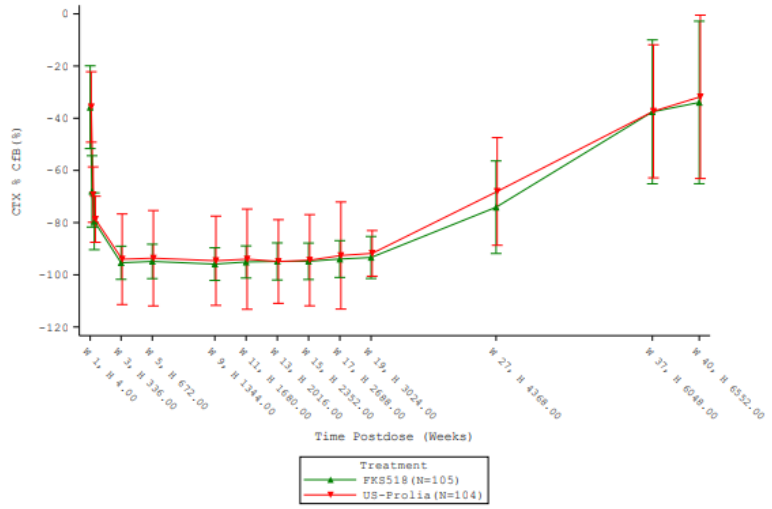
All PD analyses were performed on the PD Analysis Set. PD parameters included the parameters of CTX and P1NP defined in the table below:

Table 10. PD parameters

Parameter	Description	Biomarker
%CfB	Percent change from baseline in biomarker concentrations for measured time points.	CTX, P1NP
%CfBmax	Maximum percent change from baseline.	CTX, P1NP
$AUEC_{0\text{-}W40}$ for %CfB	Area under the effect curve for percent change from baseline in biomarker concentrations over the entire study period. Any possible rebound effect where biomarker concentrations rose above baseline was not taken into account and only the area below baseline was considered in this parameter.	CTX, P1NP
Net $AUEC_{0\text{-}W40}$ for %CfB	Area under the effect curve for percent change from baseline in biomarker concentrations over the entire study period where the percent changes from baseline were negative. For any possible rebound effect where biomarker concentrations rise above baseline, the area above baseline was subtracted from the area below baseline. This parameter was determined only as a sensitivity analysis parameter.	CTX, P1NP
$AUEC_{0\text{-}W26}$	Area under the effect curve for the (untransformed) biomarker concentrations from baseline up to Week 26. Any possible rebound effect where biomarker concentrations rose above baseline was not taken into account and only the area below baseline was considered in this parameter.	CTX

Abbreviations: CTX = C-terminal cross-linking telopeptide of Type 1 collagen; P1NP = procollagen Type 1 N-terminal propeptide

Plots of arithmetic mean %CfB of CTX and P1NP in serum versus time are presented below.



Source: Figure 14.2.14

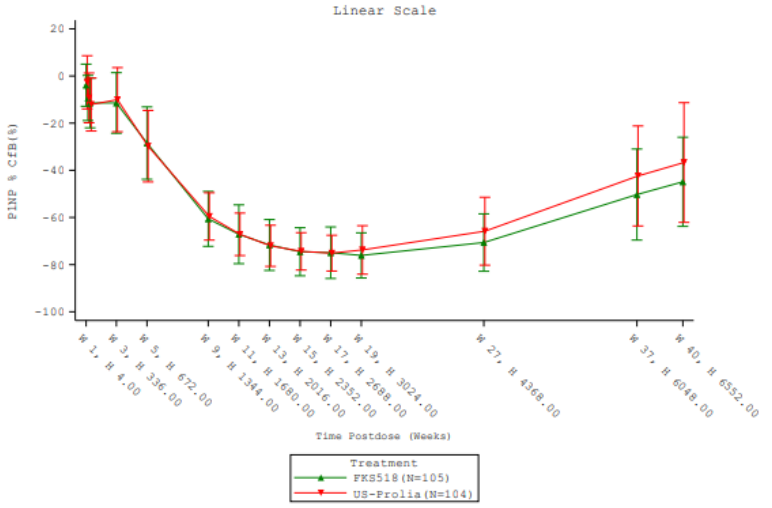
Abbreviations: CfB = change from baseline; CTX = C-terminal cross-linking telopeptide of Type 1 collagen; H = hours; LLOQ = lower limit of quantification; PD = pharmacodynamic; SD = standard deviation; W = Week.

The planned time points were Predose, H 4.00, H 24.00, H 48.00, H 336.00, H 672.00, H 1344.00, H 1680.00, H 2016.00, H 2352.00, H 2688.0, H 3024.00, H 4368.00, H 6048.00, H 6552.00.

Note: Some of the Week 1 time points such as H 24.00 and H 48.00 are not presented on the X axis due to space constraints.

Values below LLOQ were imputed as zero.

Figure 6. Plot of arithmetic mean (+/- SD) CTX % CfB values versus time (PD Analysis Set, analyte CTX)



Source: Figure 14.2.21

Abbreviations: CfB = change from baseline; H = Hours; PD = pharmacodynamic; P1NP = procollagen Type 1 N-terminal propeptide; SD = standard deviation; W = Week.

The planned time points were Predose, H 4.00, H 24.00, H 48.00, H 336.00, H 672.00, H 1344.00, H 1680.00, H 2016.00, H 2352.00, H 2688.0, H 3024.00, H 4368.00, H 6048.00, H 6552.00.

Note: Some of the Week 1 time points such as H 4.00, H 24.00 and H 48.00 are not presented on the X axis due to space constraints.

Figure 7. Plot of arithmetic mean (+/- SD) P1NP % CfB values versus time (PD Analysis Set, analyte P1NP)

A summary of CTX and P1NP serum PD parameters in the PD Analysis Set is presented by treatment below.

Table 11. Summary of PD parameters for CTX in serum (PD Analysis Set)

		60 mg Denosumab	
Parameter (unit)	**Statistic**	**FKS518 (N = 105)**	**US-Prolia (N = 104)**
$\%CfB_{max}$ (%)	n	105	104
	nmiss	0	0
	Mean	97.83	98.81
	SD	4.397	3.480
	%CV	4.5	3.5
	Median	100.00	100.00
	Min, Max	81.6, 100.0	84.8, 100.0
	Geo Mean (95% CI)	97.73 (96.85, 98.62)	98.74 (98.03, 99.46)
	%GeoCV	4.7	3.7
$AUEC_{0\text{-}W26}$ (pg·h/mL)	n	103	102
	nmiss	2	2
	Mean	2384061	2147662
	SD	943256	895817
	%CV	39.6	41.7
	Median	2312050	2077530
	Min, Max	690928, 5296106	596568, 4639981
	Geo Mean (95% CI)	2199655 (2028587, 2385148)	1964941 (1804157, 2140053)
	%GeoCV	43.3	45.6
$AUEC_{0\text{-}W40}$ for %CfB (h·%)	n	103	103
	nmiss	2	1
	Mean	509604	497021
	SD	63545	71227
	%CV	12.5	14.3
	Median	515460	501934
	Min, Max	336659, 626898	202354, 618588
	Geo Mean (95% CI)	505490 (492831, 518475)	491154 (475798, 507005)
	%GeoCV	13.0	16.4
Net $AUEC_{0\text{-}W40}$ for %CfB (h·%)	n	103	103
	nmiss	2	1
	Mean	508058	494241
	SD	65922	80907
	%CV	13.0	16.4
	Median	515456	501934
	Min, Max	315871, 626898	30162, 618588
	Geo Mean (95% CI)	503561 (490314, 517166)	480844 (452637, 510808)
	%GeoCV	13.7	31.7

Source: Table 14.2.12
Abbreviations: AUEC = area under the effect curve; CfB = change from baseline; CI = confidence interval; CTX = C-terminal cross-linking telopeptide of Type 1 collagen; CV = coefficient of variation; Max = maximum; Min = minimum; n = number of subjects; nmiss = number of missing observations; PD = pharmacodynamic; SD = standard deviation.
The AUECs are calculated using the linear trapezoidal linear interpolation calculation method; calculations are based on the actual sampling times in hours relative to denosumab dosing.

Table 12. Summary of PD Parameters for P1NP in Serum (PD Analysis Set)

		60 mg Denosumab	
Parameter (unit)	**Statistic**	**FKS518 (N = 105)**	**US-Prolia (N = 104)**
$\%CfB_{max}$ (%)	n	105	104
	nmiss	0	0
	Mean	78.82	77.47
	SD	8.350	9.573
	%CV	10.6	12.4
	Median	80.60	78.80
	Min, Max	45.2, 94.5	7.4, 92.3
	Geo Mean (95% CI)	78.33 (76.58, 80.12)	76.11 (72.54, 79.86)
	%GeoCV	11.7	25.1
$AUEC_{0\text{-}W40}$ for %CfB (h·%)	n	103	103
	nmiss	2	1
	Mean	385222	365876
	SD	65122	62954
	%CV	16.9	17.2
	Median	397138	378546
	Min, Max	221961, 511277	150940, 519669
	Geo Mean (95% CI)	379237 (365923, 393035)	359730 (346409, 373563)
	%GeoCV	18.4	19.5
Net $AUEC_{0\text{-}W40}$ for %CfB (h·%)	n	103	103
	nmiss	2	1
	Mean	384601	364355
	SD	66016	66044
	%CV	17.2	18.1
	Median	397066	377525
	Min, Max	202510, 511277	99629, 519669
	Geo Mean (95% CI)	378385 (364803, 392473)	356968 (342005, 372586)
	%GeoCV	18.9	22.2

Source: Table 14.2.19

Abbreviations: AUEC = area under the effect curve; CfB = change from baseline; CI = confidence interval; CV = coefficient of variation; Max = maximum; Min = minimum; n = number of subjects; nmiss = number of missing observations; PD = pharmacodynamic; P1NP = procollagen Type 1 N-terminal propeptide; SD = standard deviation.

The statistical analysis of the AUEC0-W40 for %CfB of CTX and P1NP PD parameters of FKS518 versus US-Prolia is presented in the table below. An ANOVA model was used for the comparison between treatment groups in terms of these PD parameters, and 3 estimands (Treatment Policy estimand, Trial Product estimand, Hypothetical estimand) were defined for that purpose.

Table 13. Statistical analysis of the CTX and P1NP PD parameters of FKS518 versus US-Prolia

	FKS518 (Test)		US-Prolia (Reference)		Ratio % (Test/Reference)
Parameter	**n**	**GLSM (95% CI)**	**n**	**GLSM (95% CI)**	**GLSM (90% CI)**
Estimand: Treatment Policy (Randomized Analysis Set)					
		(N = 107)		**(N = 107)**	
CTX $AUEC_{0\text{-}W40}$ for %CfB (h·%)	103	518845 (500929,537401)	103	507284 (489365,525860)	102.28 (98.91,105.76)
P1NP $AUEC_{0\text{-}W40}$ for %CfB (h·%)	103	382264 (368253,396809)	103	376908 (362688,391686)	101.42 (97.84,105.13)
Estimand: Trial Product (PD Analysis Set)					
		(N = 105)		**(N = 104)**	
CTX $AUEC_{0\text{-}W40}$ for %CfB (h·%)	103	518845 (500929,537401)	103	507284 (489365,525860)	102.28 (98.91,105.76)
P1NP $AUEC_{0\text{-}W40}$ for %CfB (h·%)	103	382264 (368253,396809)	103	376908 (362688,391686)	101.42 (97.84,105.13)
Estimand: Hypothetical (Randomized Analysis Set) [a]					
		(N = 107)		**(N = 107)**	
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

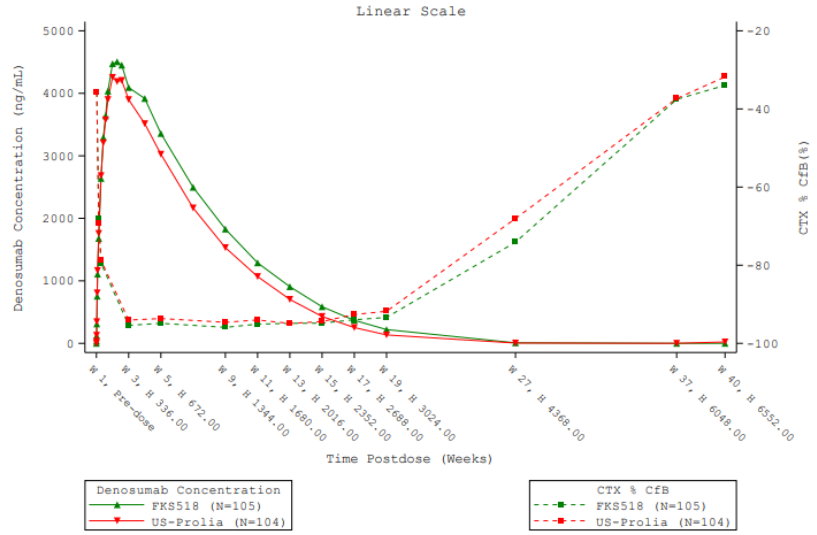
Abbreviations: AUEC = area under the effect curve; CfB = change from baseline; CI = confidence interval; CTX = C-terminal cross-linking telopeptide of Type 1 collagen; GLSM = geometric least-squares mean; IE = intercurrent event; n = number of subjects was included in the analysis; P1NP = procollagen Type 1 N-terminal propeptide; PD = pharmacodynamic.

Analytes: CTX (ng/L); P1NP (µg/L).

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.

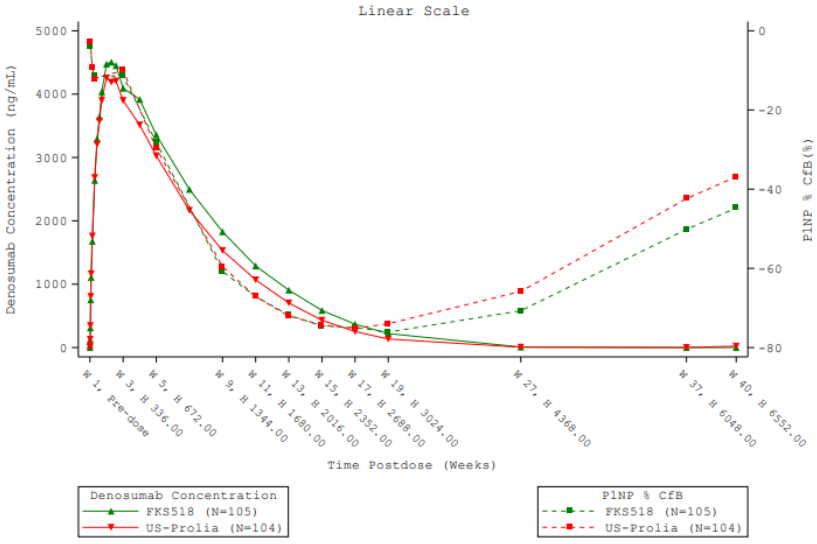
[a] Subjects with missing/censored data were imputed by multiple imputation, n = 9 (n = 5 had IEs) for FKS518 and n = 10 (n = 7 had IEs) for US-Prolia. Subject [redacted] is not included in the analysis as the subject did not have baseline values to be used for imputation.

Mean denosumab concentrations and CTX/ P1NP %CfB values are shown below.



Source: Figure 14.2.15
Abbreviations: CfB = change from baseline; CTX = C-terminal cross-linking telopeptide of Type 1 collagen; H = Hours; PD = pharmacodynamic; W = Week.

Figure 8. Plot of arithmetic mean denosumab concentrations and CTX % CfB values (PD Analysis Set)



Source: Figure 14.2.22
Abbreviations: CfB = change from baseline; H = Hours; PD = pharmacodynamic; P1NP = procollagen Type 1 N-terminal propeptide; W = Week.

Figure 9. Plot of arithmetic mean denosumab concentrations and P1NP % CfB values (PD Analysis Set)

Study FKS518-002

PD parameters included the parameters of CTX and P1NP defined in the table below:

Table 14. PD parameters

Parameter	Description	Biomarker
%CfB	Percent change from baseline in biomarker concentrations for measured time points.	CTX, P1NP
$AUEC_{0\text{-}W26}$	Area under the effect curve for the (untransformed) biomarker concentrations from baseline up to Week 26. Any possible rebound effect where biomarker concentrations rose above baseline was not taken into account, and only the area below baseline was considered in this parameter.	CTX

CTX = C-terminal cross-linking telopeptide of Type 1 collagen; P1NP = procollagen Type 1 N-terminal propeptide

The percent change from baseline for reduction in bone biomarkers CTX and P1NP concentrations was calculated relative to baseline, and values were expected to be negative at least up to the time drug effect was present.

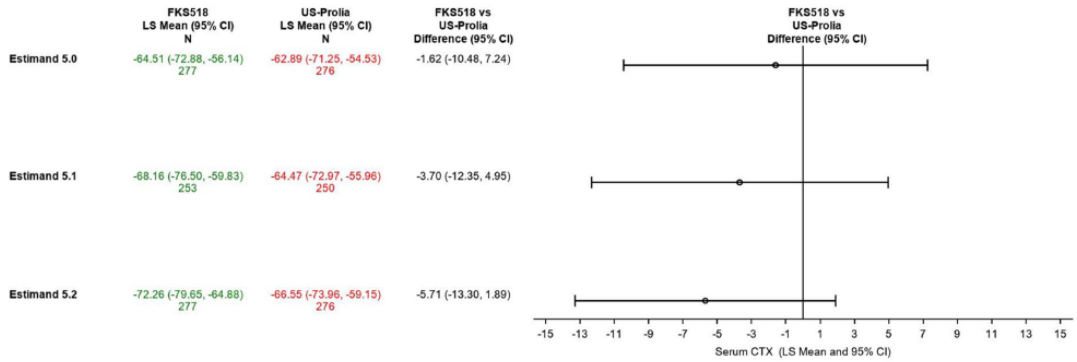
The analysis of the ratio of means of AUEC(0-W26) CTX for estimand 2.2 (co-primary estimand) is presented for the ITT Analysis Set in the table below. The comparison was made as per a hypothetical strategy, where missing AUEC(0-W26) CTX was imputed as if the patient had continued to follow the protocol and did not have an IE.

Table 15. 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.

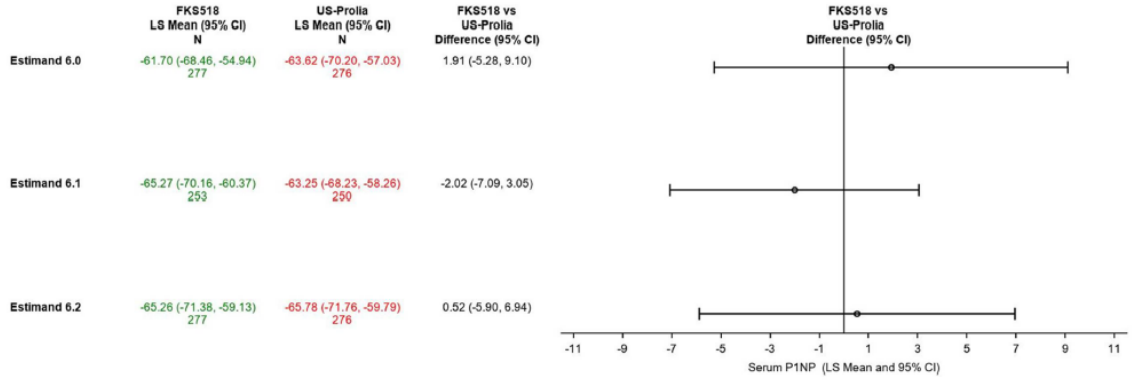
A forest plot for the percent change from baseline in serum CTX at Week 52 is presented for estimand 5.0, estimand 5.1, and estimand 5.2 in the figure below.



Source: Figure 14.2.3.2.1.
CI = Confidence Interval; CTX = C-Terminal Cross-Linking Telopeptide of Type 1 Collagen; LS = Least Squares.
Note: LS means, standard errors, and CIs were from an ANCOVA model on the percent change from baseline in CTX with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline CTX measurement. Fixed effects as entered in IRT.

Figure 10. Serum CTX percent change from baseline at Week 52 – Estimands 5.0,5.1 and 5.2- Forest plot

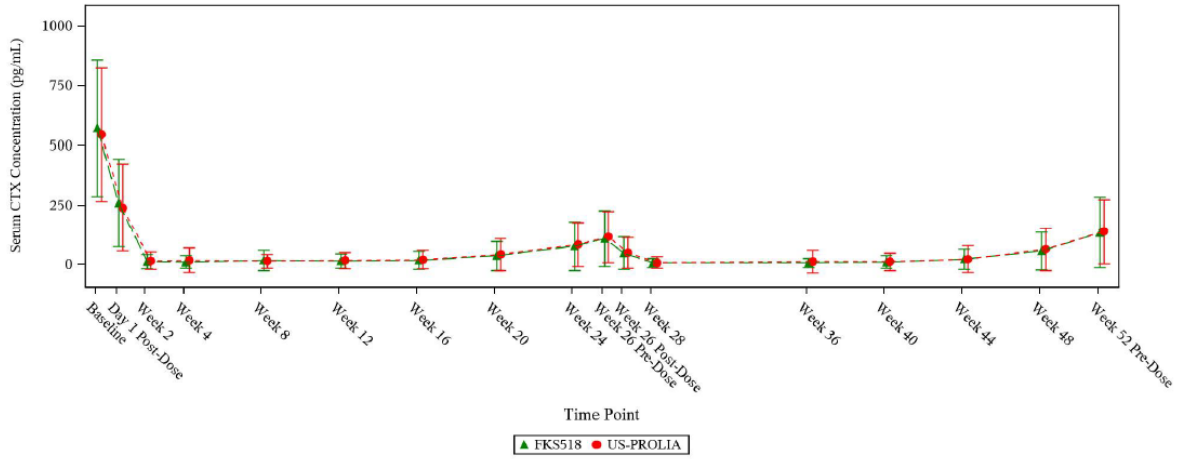
A forest plot for the percent change from baseline in serum P1NP at Week 52 is presented for estimand 6.0, estimand 6.1, and estimand 6.2 in the figure below.



Source: Figure 14.2.3.2.2.
CI = Confidence Interval; IRT = Interactive Response Technology; LS = Least Squares; P1NP = Type 1 N-Terminal Propeptide.
Note: LS means, standard errors, and CIs were from an ANCOVA model on the percent change from baseline in serum P1NP with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline P1NP measurement. Fixed effects as entered in IRT.

Figure 11. Serum P1NP percent change from baseline at Week 52 – Estimands 6.0,6.1 and 6.2- Forest plot

The serum CTX concentration over time for both groups is provided in the figure below.



PD = Pharmacodynamics; SD = Standard Deviation.
Note: Serum concentrations that are BLQ are set to 0 in the computation of mean concentration values.
Note: Missing values due to no sample, insufficient sample volume for analysis, no result or result not valid were excluded from the analysis.
Source: Table 14.2.5.5.1.1, Dataset: ADBMPD, Program: f-mean-deno-con.sas, Output: F-14-02-03-02-05-mean-ctx.rtf, Generated on: 2023-12-20T05:47
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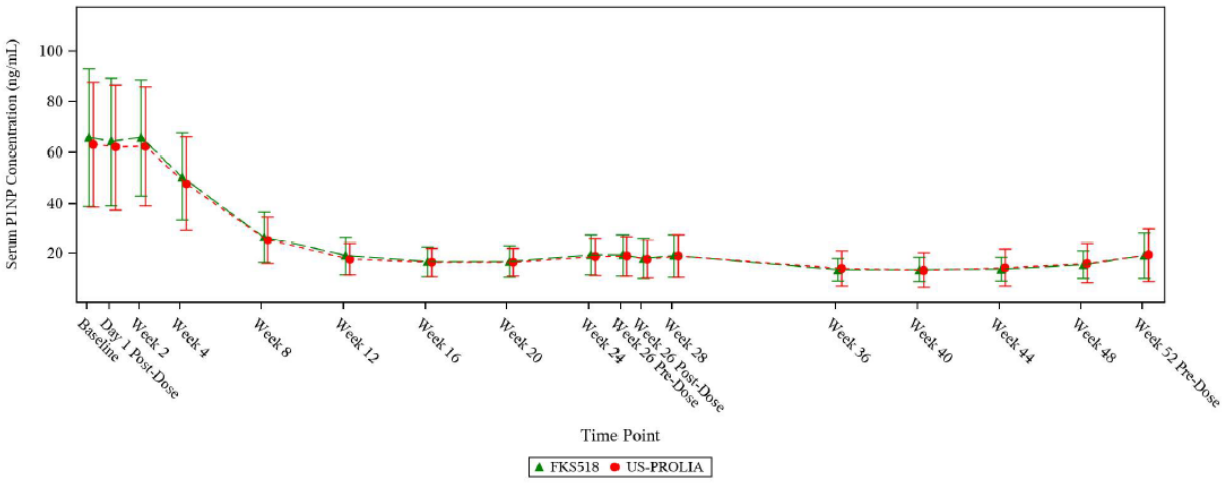
Figure 12. Mean (+/- SD) serum CTX (pg/mL) concentration over time (linear scale) – Core period (PD Analysis Set)

The serum P1NP concentration over time for both groups is provided in the figure below.



PD = Pharmacodynamic.
Note: Serum concentrations that are BLQ are set to 0 in the computation of mean concentration values.
Note: Missing values due to no sample, insufficient sample volume for analysis, no result or result not valid were excluded from the analysis.
Source: Table 14.2.5.5.2.1, Dataset: ADBM, Program: f-mean-deno-con.sas, Output: F-14-02-03-02-06-mean-p1np.rtf, Generated on: 2023-12-20T05:47
Page 1 of 1

Figure 13. Mean (+/- SD) serum P1NP (ng/mL) concentration over time (linear scale) – Core period (PD Analysis Set)

2.6.3. Discussion on clinical pharmacology

The PK/PD characteristics of FKS518 were investigated in one pivotal PK study (Study FKS518-001) and one pivotal efficacy and safety study (Study FKS518-002). No drug interaction studies, or studies in special populations, such as hepatic or renal impairment, were performed. This is acceptable for biosimilars.

The applicant used US-Prolia as comparator in the pivotal Phase 1 and Phase 3 trials and no comparison is made at the clinical level between the EU- and US-comparators, but this is acceptable as a robust data package was submitted for analytical comparability with EU-licensed Prolia.

Bioanalytical Methods

An electrochemiluminescence (ECL) bridging immunoassay to quantitate denosumab in serum samples was validated by the contract lab validated for its accuracy/precision, LOQ, selectivity (matrix interference), dilutional linearity, prozone (hook) effect, specificity, and stability.

The validation of the assay by a third party laboratory is as described in line with the requirements of the guideline on validation of such assays in all important areas of accuracy, precision, LOQ, linearity, specificity and stability. Some of the PK results, mainly from study FKS518-001 are unexpected with a sudden drop in value for some individuals. The performance of the QCs for the runs, which included the samples from subjects with a major drop in their concentration in the PK profiles, was however in line with the QC performance of all runs during sample analysis and is consistent with the QC performance during assay validation.

Osteoporosis biomarkers CTX-1 and P1NP were determined from human serum. CTx-1 quantitation was determined in serum samples using an (CTx-1) ELISA kit which was modified and validated . P1NP analysis was performed and validated in serum samples using an automated analyser. The assays were validated with respect to accuracy, precision, interference & specificity, prozone effect and stability.

Incurred sample re-analysis for the respective assays were within pass rate. Taken together, presented assays are considered validated for their intended use, given the resolution of the above described concern.

Study FKS518-001

Design and Conduct

The pivotal Phase 1 study FKS518-001 was a randomised, double-blind, two-arm, parallel group, single dose study in healthy male subjects. Overall, the design of the study was discussed in the CHMP Scientific Advice procedure EMEA/H/SA/4510/1/2020/III and recommendations from CHMP were implemented into the study design.

The study had a duration of up to 44 weeks, including a screening period of up to 4 weeks prior to IP administration on Day 1 and a follow-up period of 40 weeks. The EOS visit was at Day 274. The study duration covers a period sufficiently long to capture the entire PK and PD profiles.

Due to the long half-life of denosumab (mean half-life 28 days), a parallel design rather than a cross-over design is considered appropriate. The subjects received a single s.c. injection of 60 mg dose of FKS518 or US-Prolia at Day 1. A sub-therapeutic dose was scientifically preferred by the CHMP (e.g., a dose of 35 mg using Xgeva vial as reference), however, the use of a 60 mg dose was also considered acceptable, provided that partial AUCs reflecting the different elimination pathways (non-target-mediated vs. target-mediated) or PK modelling were considered (PK Q&A, EMA/CHMP/SAWP/338801/2019). An analysis of partial AUCs (pAUC0-w19, pAUCw19-27 and pAUCw27-40) was included reflecting the different elimination routes of denosumab.

On the basis of the provided CQAs, the protein content of the used FKS518 batch has been 61.8 mg/ml and the protein content of the used US-Prolia batch has been 61.5 mg/ml. Consequently, the protein contents of the used batches in the study FKS518-001 have been similar.

The enrolled study population consisted of healthy male subjects. The main inclusion criteria were an age between 28 and 55 years, a body weight between 50.0 and 110.0 kg and a BMI between 18.0 and 32.0 kg/m2. The exclusion criteria were chosen to recruit a healthy subject population without a history of bone disease or any medical condition that could have affected bone metabolism. Overall, the selected study population appears to be suitable for conducting a biosimilar study with denosumab as it is considered a sensitive population to identify, or exclude, differences between the test and the reference product, if existent.

The primary study objective was to demonstrate PK similarity between FKS518 and US-Prolia. The secondary objectives included additional PK, PD, safety, and immunogenicity aspects. This is endorsed by the CHMP. The primary PK endpoints were AUC0-inf, AUC0-last and Cmax after a single s.c. dose of 60 mg denosumab. According to the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)", in case of s.c. administration, AUC0-inf and Cmax should be evaluated as co-primary parameters. AUC0-last was added as a co-primary endpoint, which is likely based on an intended global marketing authorization. The choice of the primary endpoints is considered adequate.

The secondary PK endpoints (including tmax, Vz/F, t1/2, CL/F, and pAUCs) are considered appropriate for the demonstration of PK similarity of FKS518 and US-Prolia. The secondary PK parameters AUC%ext. and λz were not measured according to the CSR, which is generally not of concern as the terminal elimination phase is considered to be very variable and prone to measurement dependencies, and therefore less informative for biosimilarity assessment. The PD endpoints were AUEC0-W40 for %CfB of CTX and P1NP in serum, %CfB at all time points post dose for CTX and P1NP and Maximum %CfBs for CTX and P1NP. For immunogenicity, ADA status, ADA titre and NAb status were evaluated. The choice of the endpoints is agreed.

The sampling timepoints for PK are deemed acceptable to reflect the characteristics of denosumab and to provide respective data for a comparative evaluation of the critical PK parameters of denosumab. The timepoints for PD sampling as well as immunogenicity sampling are also considered appropriate.

A sample size of 214 randomised subjects (107 subjects per arm) was chosen to provide 170 subjects (85 subjects per arm) in the PK Analysis Set, assuming a 20% drop-out rate (including important protocol deviations leading to exclusion from the PK Analysis Set). Sample size calculations can be followed from the computational perspective.

Subjects who met all eligibility criteria were randomised on Day -1. Randomisation was performed via a centralised IRT system. Eligible subjects were randomly assigned to either FKS518 or US-Prolia in a 1:1 ratio, stratified by weight (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg). This is generally supported.

The data quality assurance measures for the study FKS518-001, including study monitoring, data management as well as quality assurance audits, are considered adequate.

The measures planned and taken to maintain the double-blind nature of the trial are sufficiently described. According to the study report, there was no need for emergency-related unblinding during trial conduct. From the methodological perspective, there is no concern regarding noteworthy bias related to unblinding issues.

Definition of analysis sets and specifications for the ANOVA models are considered reasonable. The applicant made use of the estimand framework for the planning of the statistical equivalence testing of

PK (and PD) data. A subject is included in the PK analysis set if sufficient data are available to reliably calculate at least one PK parameter and aim to limit the amount of excluded data.

Results

The study was conducted at one study centre in Poland. The study recruitment started on 06 May 2021 and the study was completed on 02 Sep 2022. The database was locked on 30 Jan 2023. No concerns arise from this. The study protocol was amended two times. Amendment 1 (dated 18 February 2021) was introduced before the first subject was randomised and amendment 2 was performed after study start (dated 12 July 2021), specifying when abnormal laboratory findings and other abnormal test results should be reported by the investigator to the sponsor as AE. No changes were made to the original protocol that would have affected the study analysis as the Protocol Amendment 2 was a clarification of the wording and did not result in missing information when reporting abnormal laboratory results or other corresponding TEAEs. The protocol amendments are regarded appropriate.

Of the 214 randomised subjects, 213 subjects were dosed (n = 107 subjects in the FKS518 group and n = 106 subjects in the US-Prolia group) and were included in the Safety Analysis Set (99.5% of subjects in total). Overall, a comparable and large proportion of randomised subjects were included in the PK and PD Analysis Sets (97.2% and 97.7%, respectively). Important protocol deviations were recorded for 8 (3.8%) subjects, whereas 5/8 subjects were excluded from PK and/or PD analysis sets as they had fewer than 2 consecutive observations after Cmax and/or did not achieve maximum PD inhibition. During the evaluation, the applicant justified that for these 5 subjects neither Cmax nor AUC could be reliably measured due to lacking PK concentration information. Their exclusion from the primary analysis is justified and found to be in line with prespecified plans and applicable regulatory guidance. No intercurrent events (adverse events or use of concomitant medications with the potential to impact one of the 3 co-primary PK parameters) were observed, hence all concentrations of subjects included in the PK analysis could be used for the derivation of PK parameters.

Additional minor deviations occurred during the study with a similar number of events between the treatment groups.

Overall, demographics and baseline characteristics were similar between the two treatment groups (median age 38 years, median BMI 26 kg/m2). Subjects were stratified according to body weight (< 70 kg vs. ≥ 70 kg) on Day -1, with most subjects belonging to the higher weight category (13.6% vs. 86.4%, respectively). The medical history data were generally balanced across both treatment groups based on the Safety Analysis Set. The use of concomitant medication was generally comparable, except for paracetamol use, which was more common in the FKS518 than in the US-Prolia group (33.6% vs. 23.6% of subjects, respectively). This may be due to a higher proportion of subjects with headaches in the FKS518 treatment arm (22.4% in the FKS518 group vs 14.2% in the US-Prolia group).

Pharmacokinetic Results

Denosumab serum concentration was slightly higher for the FKS518 treatment arm on average, however the PK-profiles within the PK-analysis set were overall comparable between FKS518 and US-Prolia groups. The geometric LSMean ratios (90% CI) for FKS518 and US-Prolia for Cmax, AUC0-last, and AUC0-inf were 104.79% (97.04% and 113.15%), 112.29% (104.17% and 121.04%), and 112.65% (104.27% and 121,70%), respectively. It is noted that the upper bounds of the 90% CI of AUC0-inf and AUC0-last were close to 125% and unity was not included, suggesting significant higher exposure with FKS518 compared to US-Prolia.

In some of the subjects' individual serum concentration profiles, a sudden drop in concentration was observed at time point 264h or 336h. A brief review of all individual PK curves revealed that a similar pronounced drop can be seen for at least 11 more subjects. In addition, there are several PK curves

that show a less pronounced PK concentration fluctuation at the same time point. All of those drops recovered at the next evaluation time point. These data patterns lead to a concern regarding validity of the PK-concentration read-outs. The applicant investigated possible root causes during the procedure. Prior to unblinding and data analysis, the applicant had already initiated some investigations in this area, independent of the regulatory assessment. This points towards the fact that there is a common understanding that the validity of (some of) the PK measurements was in question due to huge magnitudes of short-term fluctuations. Using sample data from those identified subjects, the applicant conducted data verification activities and could not find any root causes for the observed phenomenon. A further thorough review of the validity of the PK-concentration data was performed by a root cause analysis at the clinical study site and at the bioanalytical laboratory . This included blood sample collection, processing/storage and shipping conditions, laboratory operations including method validation, sample analysis and data processing as well as data management activities. Also in this reviewing steps, the applicant did not identify any errors related to clinical conduct or sample analysis that could explain the observed PK fluctuations. An FDA inspection of the clinical site was recently conducted (2024). According to the applicant, the inspector's preliminary feedback indicates that no significant findings were identified and no issues with sample management were reported, which is reassuring with regards to concerns on study conduct at the site.

As no cause of experimental error was identified, no corrective action was taken after the first root cause search in preparation for the data analyses. This decision to take all concentration data as measured into the PK-data analysis can be followed, given the guideline recommendations mentioned in the answer. Nevertheless, re-analysis of the samples in question was requested that could potentially contribute as relevant information for the current assessment, as reproducibility of PK concentrations profiles would reduce the level of uncertainty related to the observed phenomenon. Thereby, 324 single samples were re-analysed using the same methods as the original analysis. The applicant used a method allowing a second re-measurement if the first re-measurement differed by 30% or more from the original value. The median of three values was taken as the reported concentration. This approach is not considered appropriate to establish true data for PK profiles used in subsequent statistical analysis of primary PK endpoints. Extensive deviations in PK concentrations indicate methodological issues with the assay itself.

According to the applicant, the assay performed robustly, with ISR results being satisfactory and comparable (96% and 97.2%) between the original and re-analysis. In 307 samples, the results were indeed close to the original value, but in 17 samples the re-analysis did not confirm the original result, with 10 samples directly associated with the sampling times where the described large concentration fluctuation occurred. Notably, in 10 out of the 12 PK profiles identified for re-evaluation, the formerly observed short-term fluctuations were not reproducible upon sample reanalysis. Re-measurement profiles, however, favourably show rather smooth concentration time-courses comparable to the shapes of the majority of other study participants. From these observations it is concluded that failure to reproduce original concentration levels is strongly associated to the observed incidences (sampling time points) of large short-term PK fluctuations. This points towards experimental errors during the "original" PK-concentration data measurement. However, as all previously conducted root cause analyses could not identify procedural/methodological errors in experimental conduct including assay handling, the exact reason for the phenomenon of the originally observed fluctuations remains unexplained.

A relationship between the demographic parameters of the subjects (as well as medical history, concomitant medications, AEs, protocol deviations and laboratory abnormalities) and the PK concentration fluctuations could not be detected. However, during the applicant's search for potential root causes an association between high serum volumes and (sampling time point of) major drops in concentration was observed. At this stage of assessment, this reported signal seems strong enough

from the methodological perspective to further pursue the quest for the phenomenon's root cause. However, as volume information is not fully informative to completely separate those samples with "dropped" concentrations from the others, it is difficult to suggest specific further investigations to be carried out. It is important to note that similar phenomena of huge short-term PK fluctuations were discussed by Reijers *et al*. (Clin Pharmacokinet, 2017). The paper shows that the plasma concentration–time course of selected monoclonal antibodies can show considerable fluctuations with no straightforward explanations based on physiology or assay variability. Nonetheless, causal hypotheses are discussed in this publication which might support the assumption that the observed fluctuations in the trial at hand may indeed result from valid measurements. Since most of the observed fluctuations in PK concentration were not reproducible, it is not possible at present to hypothesize that physiologically induced fluctuations contribute to the variability of free drug levels. Rather, it can be assumed that the originally observed fluctuations are due to experimental errors that were not identified during the root cause analysis.

Sensitivity analyses were performed for Cmax and AUC parameters to assess a potential impact of drug concentration fluctuations on PK equivalence in these endpoints. Results have shown that, after treating the impacted timepoints as missing or excluding the 12 profiles with PK concentration fluctuations from the analysis, the 90% CIs for the geometric least-squares means (GLSMs) of the ratio FKS518/ US-Prolia for all PK parameters (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}Inf}$) were still fully contained within the predefined bioequivalence limits of 80.00% to 125.00%.

As already mentioned, re-measuring the affected denosumab serum concentration-time curves lacked full reproducibility, a data discrepancy that is considered indicative for an (analytical) measurement error in the first place. The likelihood however, to discover the exact reasons for the originally observed/debated large short-term fluctuations is considered low at this stage. Given the totality of information generated on this issue, it is nevertheless considered unlikely that the outcome of additional elaboration/investigation would eventually jeopardise the conclusion of PK-equivalence between the biosimilar candidate and the originator product. Since merely 12 out of 208 subjects are identified as affected by the phenomenon of PK concentration fluctuations, it can be concluded that the impact of these limited number of cases is overall limited and an assessment of PK equivalence and a conclusion on biosimilarity based on the available data is possible. In addition, the 12 profiles were found across both treatment arms (8 profiles from the FKS518 and 4 profiles from the US-Prolia group), showing that these observations are not treatment arm specific. Moreover, the outcome of the two already performed additional sensitivity analyses supports the assumption that the remaining uncertainty in relation to the conclusion on PK-equivalence is sufficiently low. Despite the unexplained background of the phenomenon, further pursuit of the issue is therefore not considered necessary.

The means of secondary PK parameters (i.e., tmax, t1/2, Vz/F, CL/F and pAUCs) were indicative of similarity among the treatment groups FKS518 and US-Prolia. Moreover, the primary and secondary PK parameters were similar between FKS518 and US-Prolia across body weight categories.

Pharmacodynamic results

The biomarkers s-CTX and P1NP were evaluated as secondary endpoints. The geometric means for s-CTX AUEC over the study period were 505490 h*% and 491154 h*% inhibition for the FKS518 and US-Prolia group, respectively and the geometric means for s-CTX Net AUEC over the study period were 503561 h*% and 480844 h*% for the FKS518 and US-Prolia group, respectively. The means for s-CTX were generally comparable between treatment arms.

The geometric means for P1NP AUEC over the study period were 379237 h*% and 359730 h*% inhibition for the FKS518 and US-Prolia group, respectively and the geometric means for P1NP Net AUEC over the study period were 378385 h*% and 356968 h*% for the FKS518 and US-Prolia group,

respectively. The Net AUEC (where the rebound area is subtracted) is comparable between the two treatment arms FKS518 and US-Prolia and is also comparable with the primary PD results.

The maximum %CfB for serum CTX and P1NP as well as the exploratory PD parameter AUEC0-W26 for CTX were comparable after a single s.c. injection of FKS518 and US-Prolia in healthy male subjects.

When comparing FKS518 and US-Prolia using an ANOVA model, the hypothetical estimand strategy is considered to reveal the analysis of primary interest here. Resulting 90% CIs for the GLSMs of the ratio test/reference of the AUEC0-W40 for %CfB were [98.72, 106.02] for CTX and [97.59, 104.52] for P1NP. As the 90% CIs for the GLSMs of the ratio (FKS518/US-Prolia) were similar to those observed in the main analysis when following Treatment Policy (Randomized Analysis Set) or Trial Product (PD Analysis Set) estimand analysis strategies, robustness of these results is accepted.

In order to finally conclude on PD-equivalence, it is necessary to assess the 95% CIs instead of 90% CI. However, the data are in good support of equivalence and as importantly, PD is appropriately assessed as co-primary in study FKS518-002, the PD results of study FKS518-001 are considered supplemental and in support of these primary results.

The median percent change from baseline for serum concentration of s-CTX and P1NP was comparable between the FKS518 and US-Prolia groups being practically overlapping at visit timepoints throughout the whole treatment period for the s-CTX and up to week 17 for the P1NP parameter. The curves depicting %CfB at each study visits for P1NP separate at the terminal elimination phase starting from W17 visit up to the EOS visit. The P1NP concentration returned to its initial value more quickly in the US-Prolia group. However, terminal elimination phase is considered to be less sensitive for biosimilarity as the measurement errors and variability increases, and hence this is not pursued further. Moreover, PK-PD profiles were similar for both treatments.

Overall, PD results of study FKS518-001 support the PD similarity of FKS518 and US-Prolia.

Study FKS518-002

FKS518-002 is the main study to investigate efficacy and only PK/PD results are discussed below. The main design and results of this study are discussed in section 2.6.5 Clinical Efficacy.

Pharmacokinetic Results

For study FKS518-002, the applicant provided the mean denosumab concentration time profiles for the whole study period. The profiles were similar for the treatment groups, supporting PK similarity of the test and reference product. However, the PK results from FKS518-002 are only considered supplemental in this application and cannot replace the need for a firm conclusion on PK equivalence from study FKS518-001. Furthermore, the applicant also provided the individual serum concentration-time profiles for each subject up to week 78. This is acknowledged by the CHMP.

Several PK parameters were calculated for the first IP dose in study FKS518-002. AUCtau was 8605.96 h*µg/mL for the FKS518 group and 7810.73 h*µg/mL for the US-Prolia group. Partial AUCs were also calculated. AUC0-W16 was 8071.54 h*µg/mL for the FKS518 group and 7358.57 h*µg/mL for the US-Prolia group. AUC0-W20 was 8419.87 h*µg/mL for the FKS518 group and 7662.53 h*µg/mL for the US-Prolia group. AUC16-W26 was 516.10 h*µg/mL for the FKS518 group and 444.81 h*µg/mL for the US-Prolia group. Thus, there was an approximately 10% higher exposure in the evaluated PK parameters in the FKS518 group. Nevertheless, the PK parameters were similar between the groups and support the PK similarity of the test and reference product.

Pharmacodynamic Results

In study FKS518-002, the AUEC(0-W26) of serum CTX was the co-primary endpoint. The pharmacodynamic data analysis is principally adequate to assess similarity for the test and the reference product.

For the co-primary hypothetical estimand, the mean AUEC of serum CTX up to week 26 was 1895 ng*h/L for the FKS518 group and 1875 ng*h/L for the US-Prolia group. The point estimate of the geometric LS means ratio (FKS518/US-Prolia) for AUEC was 1.01 with the corresponding 95% CI being (0.99; 1.04). Thus, the 95% CI was within the pre-specified and accepted equivalence range of [0.89, 1.12] and the co-primary PD endpoint was met. For the supportive treatment policy estimand, the mean AUEC of serum CTX up to week 26 was 1884 ng*h/L for the FKS518 group and 1862 ng*h/L for the US-Prolia group. The point estimate of the geometric LS means ratio (FKS518/US-Prolia) for AUEC was 1.01 with the corresponding 95% CI being (0.99; 1.04). For the supportive trial product estimand, the mean AUEC of serum CTX up to week 26 was 1936 ng*h/L for the FKS518 group and 1920 ng*h/L for the US-Prolia group. The point estimate of the geometric LS means ratio (FKS518/US-Prolia) for AUEC was 1.01 with the corresponding 95% CI being (0.99; 1.03). Thus, the results of the treatment policy and trial product estimand support the results of the co-primary hypothetical estimand. In conclusion, the results observed for co-primary endpoint AUEC(0-W26) of serum CTX indicate PD similarity of the test and reference product.

Additionally, the applicant provided several sensitivity analyses for the co-primary endpoint AUEC(0-W26) of serum CTX. The results of the sensitivity analyses support the robustness of the results of the co-primary analysis.

Furthermore, subgroup analyses by age (< 65 years and ≥ 65 years) and prior bisphosphonate therapy (Yes/No) were provided for using a hypothetical estimand strategy. These are generally consistent with the main co-primary endpoint analysis and the 95% confidence intervals for all of the subgroup analyses were contained within the pre-specified and accepted margin of [0.89, 1.12] for the co-primary analysis. Thus, the predefined subgroup analyses support the conclusion of the co-primary analysis and no concerns arise from these subgroup analyses.

For the definition of the AUEC 0-W26 any possible rebound effect where biomarker concentrations rose above baseline was not taken into account and only the area below baseline was considered. Thus, the calculation of the AUEC0-W26 for serum CTX would not capture different extent of rebound in the treatment arms. The applicant was therefore asked to repeat the analysis for the pharmacodynamic parameter using netAUEC0-6M, thus also considering a possible rebound. The applicant provided the requested net AUEC0-W26 for serum CTX. 6.1% of the patients in the FKS518 group and 10.1% of the patients in the US-Prolia group had CTX values above baseline. The mean net AUEC0-W26 was 2298.76 h*ug/L for the FKS518 group and 2147.04 h*ug/L for the US-Prolia group. This is, as expected, slightly lower than the mean AUEC0-W26 for both groups, which was 2299.51 h*ug/L for the FKS518 group and 2149.60 h*ug/L for the US-Prolia group. Therefore, there was only a minimal impact on AUEC0-W26 in both groups if the areas above baseline were subtracted.

The percent change from baseline in serum CTX/P1NP at Week 52 were evaluated as secondary PD endpoints in study FKS518-002. The percent change from baseline in serum CTX at Week 52 for the hypothetical estimand was -72.26% for the FKS518 group and -66.55% for the US-Prolia group. The difference between the groups was -5.71% with the 95% CI being (-13.3; 1.89). Similar results were achieved for the treatment policy and the trial product estimand. The percent change from baseline in serum P1NP at Week 52 for the hypothetical estimand was -65.26% for the FKS518 group and -65.78% for the US-Prolia group. The difference between the groups was 0.52% with the 95% CI being (-5.9; 6.94). Similar results were achieved for the treatment policy and the trial product estimand. Thus, the percent change from baseline in serum CTX/serum P1NP at Week 52 was similar between the groups and support the PD similarity of the test and reference product.

The serum CTX/P1NP concentration over time is also comparable for the FKS518 and US-Prolia group, supporting the PD similarity of the test and reference product.

2.6.4. Conclusions on clinical pharmacology

In the pivotal Phase I study, the 90% CIs for the GLSM of the ratio test/reference for the primary PK parameters (AUC0-inf, AUC0-last, and Cmax) were fully contained within the predefined bioequivalence limits of [80.00% to 125.00%]. Additional sensitivity analyses support a conclusion on PK equivalence between FKS518 and Prolia.

In the Phase III study FKS518-002, PK sampling was only sparse. Nevertheless, the PK profiles from the osteoporosis patients were similar between the FKS518 and US-Prolia group and support PK similarity of the test and reference product.

The PD results of study FKS518-001 support the PD similarity of the denosumab biosimilar candidate FKS518 and the reference product US-Prolia. In study FKS518-002, the AUEC(0-W26) for serum CTX concentration was a co-primary endpoint and was met. Secondary PD endpoints of this study also support the PD similarity of the test and reference product.

Taking into account the common mechanism of action across all indications and the known comparable PK profile of Prolia and Xgeva, the CHMP considers that the results of the studies using Prolia as comparator are relevant for the demonstration of comparable PK and PD between FKS518 and Prolia/Xgeva.

2.6.5. Clinical efficacy

During the clinical development programme of FKS518 as a proposed denosumab biosimilar of Prolia and Xgeva, one comparative clinical efficacy and safety trial (Study FKS518-002) was performed in postmenopausal women with osteoporosis, an approved indication for the reference product (RP) Prolia, to establish similar efficacy, safety, immunogenicity and pharmacodynamics (PD) between FKS518 and the reference product.

2.6.5.1. Dose response studies

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

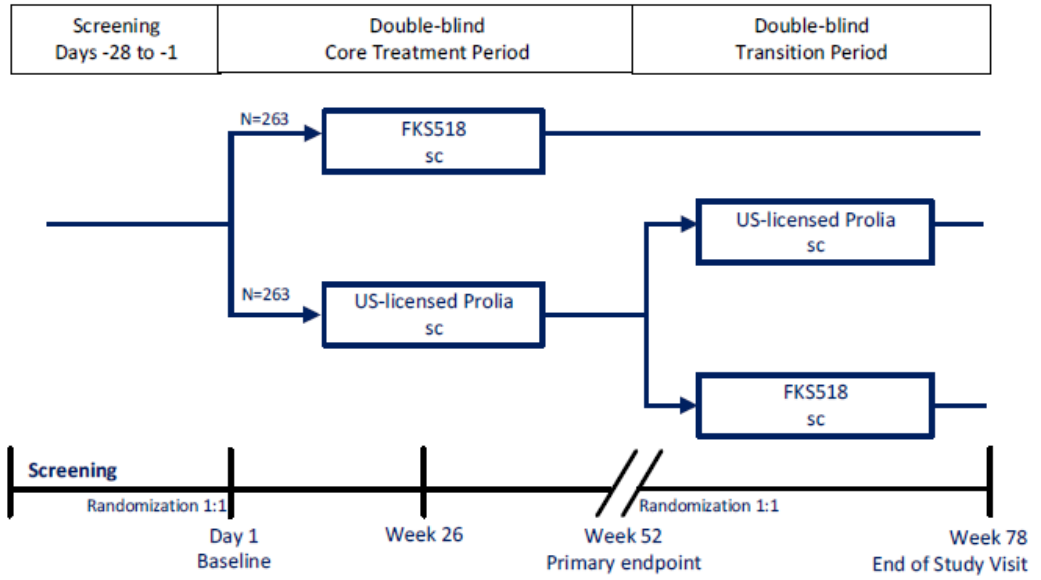
2.6.5.2. Main study(ies)

FKS518-002: Double-Blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)

The study enrolled patients from 64 investigative sites in Bulgaria, Czech Republic, Estonia, Georgia, Hungary, and Poland. The study included a Screening Period of maximum 4 weeks (28 days) prior to first drug administration, a double-blind core treatment period up to Week 52, and a double-blind single transition period from Week 52 up to Week 78, with administration of the study drug on Day 1, Week

26 (Month 6), and Week 52 (Month 12). An End of Study Visit was performed 26 weeks (6 months) after the last administration of study drug (at Week 78). Total study duration was up to 82 weeks (including up to 4 weeks of screening).

The study design is outlined in the figure below.



sc = subcutaneous
Note: Following screening, 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 transition to FKS518.

Figure 14. Study schema

Methods

- **Study participants**

Inclusion criteria

The following inclusion criteria must have been met for a patient to be eligible for inclusion in the study:

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

2. Body mass index (BMI) ≥ 18 to ≤ 32 kg/m2.

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

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

6. Clinically acceptable physical examinations and laboratory tests (haematology, 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:

A patient who met any of the following exclusion criteria was not eligible for inclusion in the study:

Disease-related

1. History and/or presence of 1 severe or > 2 moderate vertebral fractures or hip fracture confirmed by X-ray.

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 hypocalcaemia (albumin-adjusted serum calcium < 2.13 mmol/L or < 8.5 mg/dL) or hypercalcaemia (albumin-adjusted serum calcium > 2.6 mmol/L or > 10.5 mg/dL), as assessed by the central laboratory at screening.

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

7. Known intolerance to calcium or vitamin D supplements.

Other Medical Conditions

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

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

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

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

12. Infection-related exclusions:

a. Severe herpes zoster (disseminated, multidermatomal, herpes encephalitis, or ophthalmic herpes) or recurrent herpes zoster (defined as 2 episodes within 2 years), or any opportunistic invasive infection (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 hospitalisation or treatment with intravenous antibiotics within 8 weeks before randomisation.

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 randomisation.

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 randomisation.

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.

Prior or Concomitant Therapy

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

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

19. Any current or prior use of strontium ranelate.

20. Any current or prior use of intravenous bisphosphonates. Prior use of oral bisphosphonates 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 oestrogen or selective oestrogen 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 randomisation 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 randomisation 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.

- **Treatments**

Test Product	Active Comparator
IP/non-IP: IP Name: FKS518 (proposed denosumab biosimilar) Dose: 60 mg every 26 weeks (6 months) Route of administration: Subcutaneous injection Manufacturer: Batch numbers:	IP/non-IP: IP Name: US-licensed Prolia (denosumab) Dose: 60 mg every 26 weeks (6 months) Route of administration: Subcutaneous injection Manufacturer: Amgen Inc, US Batch numbers:

Concomitant and rescue therapies

Permitted Medications

All patients had to take calcium 1000 mg daily and at least 400 IU vitamin D supplementation daily during the study, as required by the Prolia Product/Prescribing Information. Non-compliance with this requirement was closely monitored during the study, and deviations were assessed as important, but not clinically important protocol deviations.

COVID-19 vaccination was allowed during study participation. However, to ensure distinction between the adverse reactions caused by vaccination and the IP, vaccination had to occur > 1 week before or

after study drug administrations. In addition, to exclude any potential interaction between the study drug and COVID-19 vaccination, it was recommended to perform COVID-19 vaccination as much as possible in between 2 doses of the IP (i.e., around Weeks 13 or 39, or after the last dose around Week 65). COVID-19 vaccination was recorded in the eCRF.

Prohibited Medications

A summary of prohibited medications with washout periods (before randomisation) is presented in the table below.

Table 16. Summary of prohibited concomitant medications with wash out periods (before screening)

Prohibited Medications	Washout Period (Before Screening)
Strontium ranelate	Never
Fluoride	5 years
Intravenous bisphosphonates	Never
Oral bisphosphonates	>3 years cumulatively (unless last dose received >5 years) OR 12 months (note: it is allowed to have received less than 1 month of cumulative use between 6 and 12 months prior to screening)
Teriparatide and other PTH analogues within 12 months before screening	12 months
Systemic oral or transdermal estrogen or selective estrogen receptor modulators or tibolone	6 months
Calcitonin or cinacalcet	3 months
Any cathepsin K inhibitor (eg, odanacatib)	18 months
Romosozumab or antisclerostin antibody	Never
Other osteoporotic agents used for the prevention or treatment of osteoporosis	Investigator judgment after consultation with the Medical Monitor
Any medication with known influence on the skeletal system (eg, systemic corticosteroids, heparin, lithium, etc)	3 months A stable dose of systemic prednisone <5 mg or equivalent systemic corticosteroid for >4 weeks before screening is permitted Use of systemic glucocorticosteroids: ≥5 mg prednisone or equivalent per day for more than 14 days within 3 months prior to randomization is not allowed
Another biologic drug	None
Other biologic investigational drugs for the treatment of PMO	Never
Any investigational drugs	30 days or 5 half-lives (whichever is longer)

- **Objectives**

Primary objectives

The primary objectives were to demonstrate equivalent efficacy and PD of the proposed biosimilar denosumab FKS518 to US-Prolia in women with PMO.

Equivalence hypotheses to be tested:

For the primary endpoint LS-BMD by DXA:

H_0: $(\mu_T - \mu_R) \leq -1.45\%$ or $(\mu_T - \mu_R) \geq 1.45\%$.

H_1: $-1.45\% < (\mu_T - \mu_R) < 1.45\%$

where

1. μ_T = mean percent change from baseline in LS-BMD to Week 52 for FKS518
2. μ_R = mean percent change from baseline in LS-BMD to Week 52 for US-Prolia

Calculation and justification of the equivalence margin for the LS-BMD endpoint was based on the lower bound of an 95% confidence interval for a pooled denosumab treatment effect over placebo (70% retention).

The limits of the acceptance range for the primary endpoint, percent change from baseline in LS-BMD at Week 52, are based on the meta-analysis of the following 3 FDA-reviewed studies, which determined the treatment effect of denosumab compared to placebo as 5.35% (95% CI: 4.83% to 5.87%): Bone, 2008; Cummings, 2009; and McClung, 2006. The limits of the acceptance range will preserve at least 70% of the treatment effect of denosumab. Based on the lower bound of the 95% CI for the pooled denosumab treatment effect in these studies, a 1.45% margin will preserve 70% of the treatment effect (0.3*4.83%).

For the coprimary endpoint AUEC(0-W26) CTX

H_0: $\mu_T^{G(CTX)} / \mu_R^{G(CTX)} \leq 0.89$ *or* $\mu_T^{G(CTX)} / \mu_R^{G(CTX)} \geq 1.12$

H_1: $0.89 < \mu_T^{G(CTX)} / \mu_R^{G(CTX)} < 1.12$

where

1. $\mu_T^{G(CTX)} / \mu_R^{G(CTX)}$ is the ratio of geometric means of the FKS518 product ($\mu_T^{G(CTX)}$) over the US-Prolia product ($\mu_R^{G(CTX)}$) of the AUEC(0-W26) CTX

Calculation and justification of the equivalence margin for the AUEC(0-W26) of serum CTX was based on a population PD model for CTX (Zheng, 2015, Sutjandra, 2011), as briefly described in the trial protocol, and discussed during CHMP scientific advice procedures.

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

Secondary objectives

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

Other objectives:

To evaluate the effects of a single treatment transition (ie, in subjects who transitioned from US-Prolia to FKS518) on safety and immunogenicity.

To explore the long-term efficacy of FKS518.

To describe pharmacokinetic (PK) parameters of FKS518 and US-Prolia.

- **Outcomes/endpoints**

Primary endpoints:

Percent change from baseline in LS-BMD by DXA at Week 52

AUEC of serum CTX up to Week 26

Secondary endpoints:

Efficacy:

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

Pharmacodynamics:

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

Percent change from baseline in serum CTX at Week 52.

Safety and tolerability:

Occurrence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) during core treatment period, transition period, and overall.

Occurrence of treatment-emergent adverse events of special interest (AESIs): drug-related hypersensitivity/allergic reactions (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3 or reported as SAEs), and adverse events (AEs) leading to IP discontinuation or study withdrawal during core treatment period, transition period, and overall.

Occurrence of injection site reactions (ISRs) during core treatment period, transition period, and overall (local tolerability).

Immunogenicity:

Antidrug antibody (ADA) incidence during core treatment period, transition period, and overall.

ADA titre during the core treatment period and transition period.

Neutralizing antibody (NAb) incidence during the core treatment period, transition period, and overall.

Other Endpoints:

Efficacy:

Percent change from baseline in LS-BMD by DXA at Week 78/End of Study.

Percent change from baseline in BMD at femoral neck and total hip by DXA at Week 78/End of Study.

Safety:

Changes in clinical laboratory values (haematology, clinical chemistry, and urinalysis), vital sign measurements (blood pressure, respiratory rate, pulse rate, and temperature), abnormalities in 12-lead electrocardiogram (ECG) assessment, and physical examination during the core treatment period, transition period, and overall.

Pharmacokinetics:

Denosumab concentrations and area under the concentration-time curve (AUC) tau and partial AUCs related to different phases of denosumab elimination.

Estimands for the primary objectives

Table 17. Primary endpoint estimands and attributes- Percent change from baseline in LS-BMD by DXA at Week 52

Clinical Question of Interest	Estimand	Endpoint	Treatment	Population	Potential intercurrent events/strategy to address	Population level summary
Do the two treatments have equivalent efficacy in the target population of women with postmenopausal osteoporosis (PMO) regardless of treatment discontinuation or changes in concomitant/background medications (or interventions) or adverse events (AEs) (affecting bone)?	1.0 Treatment Policy Estimand **(Primary Estimand for FDA)**	LS-BMD percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	A treatment policy strategy for all IEs (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have equivalent efficacy in the target population of women with PMO who take treatment as prescribed and only take permitted concomitant medications?	1.1 Trial Product Estimand	LS-BMD percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as administered	Women with PMO in the PP Analysis Set	A treatment policy strategy for all IEs (all observed data will be used).	Mean difference between the 2 treatment arms
Would the two treatments have equivalent efficacy in the target population of women with PMO had they all taken treatment as prescribed and had no changes to concomitant/background medication or intervention (affecting bone) or AEs affecting bone?	1.2 Hypothetical Estimand **(Primary Estimand for EMA)**	LS-BMD percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	Hypothetical continuing per protocol strategy: 1. Treatment discontinuation[1] 2. Changes in concomitant medication or interventions 3. AEs affecting bone	Mean difference between the 2 treatment arms

1.Excluding reason "Withdrawal of consent from treatment".

Table 18. Co-primary endpoint estimands and attributes- AUEC (0-W26) CTX (for MAA in the EU and EEA only)

Clinical Question of Interest	Estimand	Endpoint	Treatment	Population	Potential intercurrent events/strategy to address	Population level summary
Do the two treatments have equivalent pharmacodynamics (PD) in the target population of women with postmenopausal osteoporosis regardless of changes in concomitant medications or bone-affecting AEs?	2.0 Treatment Policy Estimand	AUEC (0-W26) CTX	FKS518 or US-Prolia, 60 mg at baseline and Week 26, as prescribed	Women with PMO in the ITT Analysis Set	A treatment policy strategy for all IEs (all observed data will be used).	Geometric mean ratio of the 2 treatment arms
Do the two treatments have equivalent Pharmacodynamics in the target population of women with postmenopausal osteoporosis who take treatment as prescribed and only take permitted concomitant medications?	2.1 Trial Product Estimand	AUEC (0-W26) CTX	FKS518 or US-Prolia, 60 mg at baseline and Week 26, as administered	Women with PMO in the PD analysis set	A treatment policy strategy for all IEs (all observed data will be used).	Geometric mean ratio of the 2 treatments
Would the two treatments have equivalent Pharmacodynamics in the target population of women with postmenopausal osteoporosis had they not had any changes in concomitant medications or interventions and had no bone affecting AEs?	2.2 Hypothetical Estimand **(Co-primary Estimand for EMA)**	AUEC (0-W26) CTX	FKS518 or US-Prolia, 60 mg at baseline and Week 26, as prescribed	Women with PMO in the ITT Analysis Set	Hypothetical continuing per protocol strategy: 1. Changes in concomitant medication or interventions 2. AEs affecting bone	Geometric mean ratio of the 2 treatments

Estimand 1.2 – Hypothetical estimand (LS-BMD, Hypothetical continuing per-protocol ITT) – Primary estimand for EMA

Missing baseline BMD were to be imputed assuming missing at random (MAR) by using baseline BMD of all available subjects and multiple imputation using Markov Chain Monte Carlo (MCMC) with "impute=monotone".

LS-BMD assessments were censored for data affected by intercurrent events and were imputed. For all intercurrent events an 'hypothetical' strategy was followed where measurements are projected as a per protocol scenario as if the subject had followed the protocol and had no intercurrent events.

Censored and missing data were to be imputed using data from subjects with similar baseline characteristics (within the same treatment group) who had no intercurrent events. This strategy for dealing with data affected by intercurrent events has the underlying clinically valid assumption that if subjects had continued treatment, had no change in concomitant medication or interventions and had no bone affecting adverse events, their LS-BMD at Week 52 would be similar to that of patients in the study (with a similar profile) who had no intercurrent events. This is due to the fact that denosumab is expected to have a marked effect after 2 doses are administered (McClung et al, 2006).

The analysis was planned to incorporate multiple imputation for missing and censored data as follows:

Step 1: Impute baseline if missing using multiple imputation.

Step 2: Censored and missing LS-BMD Week 52 data will be imputed using multiple imputation (using PROC MI) from the pool of subjects with similar subject profiles, for whom LS-BMD Week 52 is available and for whom an intercurrent event has not occurred.

Step 3: Each imputed complete dataset will then be used to determine percent change from baseline and then analysed using the following ANCOVA model: Percent change from baseline at Week 52 in LS-BMD will be analysed using an ANCOVA with treatment, age (< 65 years; ≥ 65 years) and prior bisphosphonates therapy (Yes/No) as fixed effects, and baseline LS-BMD as a covariate. Stratification variables will be used as entered in IRT. The difference between treatments will be estimated by the LS mean difference between FKS518 and US-Prolia.

Step 4: The results of the analysis will be combined by PROC MIANALYZE in SAS. 90% and 95% CIs will be calculated for the combined results.

Estimand 2.2 -Hypothetical estimand (AUEC(0-W26) CTX, Hypothetical continuing per-protocol ITT) – Co-Primary estimand for EMA

CTX data points were planned to be censored for the duration of the intercurrent events before the derivation of AUEC(0-W26) CTX. For all AUEC(0-W26) CTX that cannot be calculated, these were planned to be set to missing.

An 'hypothetical' strategy was be followed where missing AUEC(0-W26) CTX were to be imputed as a per protocol scenario (as if the subject had continued to follow the protocol and did not have an intercurrent event).

Assuming MAR, missing AUEC(0-W26) CTX were imputed by multiple Imputation from AUEC parameters calculated for subjects for whom this parameter could be reliably calculated and for whom an intercurrent event has not occurred. All imputations were to be performed on the log scale. Imputed AUEC(0-W26) CTX values will be restricted such that the values are greater than zero.

For the estimation, the following ANCOVA model was planned to be applied: The natural log transformed AUEC(0-W26) CTX was to be analysed using an ANCOVA with treatment, age (< 65 years; ≥ 65 years), and prior bisphosphonates therapy (Yes/No) as fixed effects, and the natural log of

baseline serum CTX concentration as a covariate. The difference between treatments were to be estimated by the LSmeans ratio between FKS518 and US-Prolia, with its 95% CI. The point estimate and the limits of the 95% CI were to be back transformed to the original scale to obtain the geometric mean ratio and corresponding 95% CI.

Estimands for the secondary efficacy and PD objectives

Table 19. Secondary endpoint estimands and attributes

Clinical Question of Interest	Estimand	Endpoint	Treatment	Population	Potential intercurrent events/strategy to address	Population level summary
Do the two treatments have similar femoral neck BMD in the target population of women with postmenopausal osteoporosis (PMO) regardless of treatment discontinuation or changes in concomitant/background medications (or interventions) or adverse events (AEs) (affecting bone)?	3.0 Treatment Policy Estimand	BMD Femoral neck percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	A treatment policy strategy for all IEs impacting secondary efficacy endpoint (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have similar Femoral neck BMD in the target population of women with PMO who take treatment as prescribed and only take permitted concomitant medications?	3.1 Trial Product Estimand	BMD Femoral neck percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as administered	Women with PMO in the PP Analysis Set	A treatment policy strategy for all IEs impacting secondary efficacy endpoint (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have similar femoral neck BMD in the target population of women with postmenopausal osteoporosis (PMO) had they continued treatment, had any changes in concomitant medications or interventions and had no AEs affecting bone?	3.2 Hypothetical Estimand	BMD Femoral neck percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	Hypothetical continuing per protocol strategy: 1. Treatment discontinuation1 2. Changes in concomitant medication or interventions 3. AEs affecting bone	Mean difference between the 2 treatment arms
Do the two treatments have similar total hip BMD in the target population of women with PMO regardless of treatment discontinuation or changes in concomitant/background medications (or interventions) or AEs (affecting bone)?	4.0 Treatment Policy Estimand	BMD Total hip percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	A treatment policy strategy for all IEs impacting secondary efficacy endpoint (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have similar Total hip BMD in the target population of women with PMO who take treatment as prescribed and only take permitted concomitant medications?	4.1 Trial Product Estimand	BMD Total hip percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as administered	Women with PMO in the PP Analysis Set	A treatment policy strategy for all IEs impacting secondary efficacy endpoint (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have similar total hip BMD in the target population of women with PMO had they continued treatment, had any changes in concomitant medications or interventions and had no AEs affecting bone?	4.2 Hypothetical Estimand	BMD Total hip percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	Hypothetical continuing per protocol strategy: 1. Treatment discontinuation[1] 2. Changes in concomitant medication or interventions 3. AEs affecting bone	Mean difference between the 2 treatment arms
Do the two treatments have similar Pharmacodynamics in the target population of women with PMO regardless of changes in concomitant medications or AEs?	5.0 Treatment Policy Estimand	Serum CTX percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	A treatment policy strategy for all IEs impacting secondary bone marker endpoint (all observed data will be used)	Mean difference between the 2 treatment arms
Do the two treatments have similar pharmacodynamics in the target population of women with PMO who take treatment as prescribed and only take permitted concomitant medications?	5.1 Trial Product Estimand	Serum CTX percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as administered	Women with PMO in the PD analysis set	A treatment policy strategy for all IEs impacting secondary bone marker endpoint (all observed data will be used).	Mean difference between the 2 treatment arms

Clinical Question of Interest	Estimand	Endpoint	Treatment	Population	Potential intercurrent events/strategy to address	Population level summary
Do the two treatments have similar pharmacodynamics in the target population of women with PMO had they continued treatment, had any changes in concomitant medications or interventions and had no AEs affecting bone?	5.2 Hypothetical Estimand	Serum CTX percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	Hypothetical continuing per protocol strategy: 1. Treatment discontinuation[1] 2. Changes in concomitant medication or interventions 3. AEs affecting bone	Mean difference between the 2 treatment arms
Do the two treatments have similar pharmacodynamics in the target population of women with PMO regardless of changes in concomitant medications or AEs?	6.0 Treatment Policy Estimand	P1NP percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	A treatment policy strategy for IEs impacting secondary bone marker endpoint (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have similar pharmacodynamics in the target population of women with PMO who take treatment as prescribed and only take permitted concomitant medications?	6.1 Trial Product Estimand	P1NP change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as administered	Women with PMO in the PD analysis set	A treatment policy strategy for IEs impacting secondary bone marker endpoint (all observed data will be used).	Mean difference between the 2 treatment arms
Do the two treatments have similar pharmacodynamics in the target population of women with PMO had they continued treatment, had any changes in concomitant medications or interventions and had no AEs affecting bone?	6.2 Hypothetical Estimand	P1NP percent change from baseline at Week 52	FKS518 or US-Prolia, 60 mg every 26 weeks, as prescribed	Women with PMO in the ITT Analysis Set	Hypothetical continuing per protocol strategy: 1. Treatment discontinuation[1] 2. Changes in concomitant medication or interventions 3. AEs affecting bone	Mean difference between the 2 treatment arms

The percent change from baseline at Week 52 in BMD at femoral neck and total hip by DXA was summarised descriptively over time and analysed using an ANCOVA with treatment, age (< 65 years; ≥ 65 years) and prior bisphosphonate therapy (Yes/No) as fixed effects and baseline BMD at femoral neck and total hip by DXA from the core treatment period as a covariate, respectively. The difference between treatments was estimated by the least squares mean difference between FKS518 and US-Prolia, with its 95% CI. Missing data were handled using the same imputation method used for estimand 1.0. No sensitivity analyses were planned (estimand 3.0, 4.0).

For analyses in relation to estimands 3.1 and 4.1, the same ANCOVA analysis used for the estimands 3.0 and 4.0 was performed. All data available were included in the analysis and MAR was assumed. No imputation was performed.

For analyses in relation to estimands 3.1 and 4.1, A similar hypothetical imputation used for the estimand 1.0 for EMA was applied. The same ANCOVA analysis used for the estimands 3.0 and 4.0 was performed.

For analyses in relation to estimands 5.0 and 6.0, the percent change from baseline at Week 52 in CTX and P1NP was analysed using an ANCOVA with treatment, age, and prior bisphosphonate therapy as fixed effects, and baseline CTX and P1NP as covariates, respectively. The difference between treatments was estimated by the least squares mean difference between FKS518 and US-Prolia, with its 95% CI. Missing data were handled using the same imputation method used for estimand 2.0.

For analyses in relation to estimands 5.1 and 6.1, the same ANCOVA analysis used for the estimands 5.0 and 6.0 was performed. All data available were included in the analysis and MAR was assumed. No imputation was applied.

For analyses in relation to estimands 5.2 and 6.2, a similar hypothetical imputation used for the estimand 1.0 for EMA was applied. The same ANCOVA analysis used for estimands 5.0 and 6.0 was performed.

No imputation of missing data was performed on the other efficacy analyses: Percent change from baseline in LS-BMD by DXA at Week 78/End of Study, Percent change from baseline in BMD at femoral

neck by DXA at Week 78/End of Study, and Percent change from baseline in BMD at total hip by DXA at Week 78/End of Study.

In order to test the long-term effect on efficacy, the percent change from baseline in LS-BMD and percent change from baseline in BMD at femoral neck and for total hip by DXA at Week 78 were summarised descriptively over time and analysed using a mixed-effect repeated measures model with treatment, visit, treatment-by-visit interaction, age, and prior bisphosphonate therapy included as factors and baseline BMD from the core treatment period as a covariate, respectively. The mixed models were performed over the Overall Period, utilizing the Overall ITT and Overall PP Analysis Sets. All 3 treatment groups were included in the model: FKS518 – FKS518 patients, Prolia – Prolia patients, and Prolia to FKS518 (FKS518/Prolia) patients. The 95% CI of the least squares means was provided for each time point. Least squares means and 95% CIs of differences resulting from the 3 pairwise treatment comparisons were presented.

- **Sample size**

A sample size of 526 randomised subjects (263 subjects per arm) was chosen to provide approximately 446 subjects (223 subjects per arm) in the Per Protocol (PP) Analysis Set at Week 52, assuming a 15% drop-out rate. This sample size was planned to provide 90% power to demonstrate equivalence between treatments for the primary endpoint LS-BMD, with equivalence margins of [-1.45%, 1.45%] and a Type I error of 2.5%, assuming a 0.2% difference between the 2 treatment groups and a common standard deviation (SD) of 4%. Power calculation revealed that a total of 446 subjects will provide 93.7% power assuming no difference between the 2 treatment groups.

For the co-primary endpoint AUEC(0-W26) CTX with defined equivalence margins of [0.89, 1.12], assuming that the reference population, and test population are identical, an ANCOVA of the natural logarithm (log) transformed AUEC controlling for the natural log of the baseline serum CTX, demonstrated that a sample size of n=223 per group would suffice to guarantee > 99% power to show equivalence between FKS518 and US-Prolia.

Overall, a total of 446 subjects was hence assumed to provide > 89% power to demonstrate equivalence between treatments for both co-primary endpoints under the conservative assumption of independence between endpoints.

- **Randomisation and blinding (masking)**

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

At the Week 52 Visit, subjects who enter the transition period and were initially randomised to the US-Prolia group were planned to be re-randomised in a 1:1 ratio to receive either FKS518 or US-Prolia. Subjects who were initially randomised to the FKS518 group were planned to remain on the same treatment with FKS518 for the Week 52 administration.

Subjects who discontinued study drug just before or at Week 52 were not to be re-randomised and would discontinue the study after Week 52. Re-randomisation was not to impact the double-blind nature of the study as blinding was planned to be kept. The same stratification factors were planned be used for the randomisation and re-randomisation.

The study was planned as double-blinded trial. Each IP (FKS518 and US-Prolia) PFS was to be blinded. The PFSs were to be identical in appearance prior to delivery to clinical sites. Randomisation information was to be kept strictly confidential, accessible only to authorized staff, until the time of pre-planned unblinding.

- **Statistical methods**

The study analysis sets were defined as follows:

The **Enrolled Analysis Set** was to include all subjects who signed an informed consent form and will be used to report disposition and screening failures.

The **ITT Analysis Set** was to include all randomised subjects. Subjects will be analysed according to their randomised treatment.

In the transition period (TP), the **TP-ITT Analysis Set** was to include all subjects who entered the TP (re-randomised). Subjects were to be analysed according to their randomised treatment group. For subjects initially randomised to US-Prolia, the TP-ITT Analysis Set was planned to include both their initial and re-randomisation assignments (either continue with US-Prolia or transition to FKS518).

The **PP Analysis Set** was to include all randomised subjects treated at both Day1 and Week 26 who have a valid LS-BMD assessment (the adjusted corrected average LS-BMD assessment) for the analysis week 52 and who do not have a clinically important protocol deviation up to the time of the week 52 LS-BMD assessment that could affect it (e.g., use of prohibited medications during the study).

The **TP-PP Analysis Set** was to include all subjects randomised and treated in the TP who do not have any clinically important protocol deviation impacting Week 78 (from week 52 to Week 78 visit) and who have a Week 78 Visit and a valid LS-BMD assessment (the adjusted corrected average LS-BMD assessment at week 78). Some clinically important protocol deviations occurring in the core period may also lead to exclusion from the TP-PP, as specified in the protocol deviation guidance.

Subjects were to be analysed according to their randomised and received treatment both in the core treatment period and the TP given that the administration of a treatment other than the one to which the subject was randomised constituted a clinically important protocol deviation.

The **Safety Analysis Set (SAF)** was to include all subjects who received at least 1 dose of IP and were to be analysed according to the actual treatment received. This analysis set was planned to be used for summaries of safety and immunogenicity data for the Core and Overall treatment periods.

The **TP-SAF Set** was to include all subjects who receive at least 1 dose of IP during the course of the TP. Subjects were planned to be analysed according to the actual treatment they received.

The **PD Analysis Set** was to include all subjects who received at least 1 dose of IP, have a quantifiable baseline PD marker concentration (CTX or P1NP) and with enough PD concentrations not impacted by a clinically important protocol deviation to calculate at least one of PD parameters (%CfB CTX at week 52 or %CfB P1NP at week 52 or AUEC(0-26) CTX). Subjects were planned to be analysed according to the actual treatment received.

The **PK Analysis Set** was to include all subjects who receive at least 1 dose of IP, with enough assessments to calculate reliable estimates of at least 1 PK parameter and without a clinically important protocol deviation affecting PK assessments. Subjects were planned to be analysed according to the actual treatment received.

The **TP-PK Analysis Set** included all subjects who have at least 1 measurement of any concentration during the TP and without any clinically important protocol deviation impacting PK from week 52 until (and including) Week 78.

Statistical analysis methods/models in relation to primary and secondary estimands for efficacy- and PD- endpoints are described above in the corresponding estimands-sections.

Standard descriptive statistical methodology was used to analyse and display PK and PD-data over time. Furthermore, standard statistical methodology was used to summarise and analyse safety and immunogenicity data.

Changes from protocol-specified analyses were as follows:

Clarifications to the planned analyses between the final protocol and the final analyses defined in Section 6.1 of the SAP version 3.0 approved before study unblinding (Appendix 16.1.9) are described below:

For the primary endpoint LS-BMD at Week 52, the protocol specified that the difference between treatments would be estimated by the least squares mean difference between FKS518 and US-Prolia, with its 95% CI and compared to the predefined equivalence intervals. The SAP further defined the exact tests and comparisons performed for EMA and FDA, including the two 1-sided tests (TOST procedure) at 5% alpha level.

For the co-primary endpoint AUEC(0-W26), the protocol specified that the natural logarithm (log) AUEC(0-W26) of serum CTX would be analysed on the PD Analysis Set using an ANCOVA with treatment, age strata, and prior bisphosphonate therapy as fixed effects, and the natural log of baseline serum CTX concentration as a covariate. In the SAP, it was clarified that the analysis of the co-primary endpoint would also be performed on the ITT Analysis Set (refer to Section 9.7.1.1.3 or further details).

Additional estimands (hypothetical estimands 1.2 and 2.2) were added to those already specified in the protocol to address the requirements of ICH E9 (R1).

In response to both EMA and FDA scientific advice, the delta-adjusted sensitivity analyses were extended to tipping-point analyses for the primary and co-primary efficacy endpoints. A hypothetical approach was proposed for the secondary endpoint estimands. Additional sensitivity analyses were proposed, which included adding continuous BMI as a factor in the primary model and another sensitivity analysis that excluded COVID-19 affected patients from the analysis.

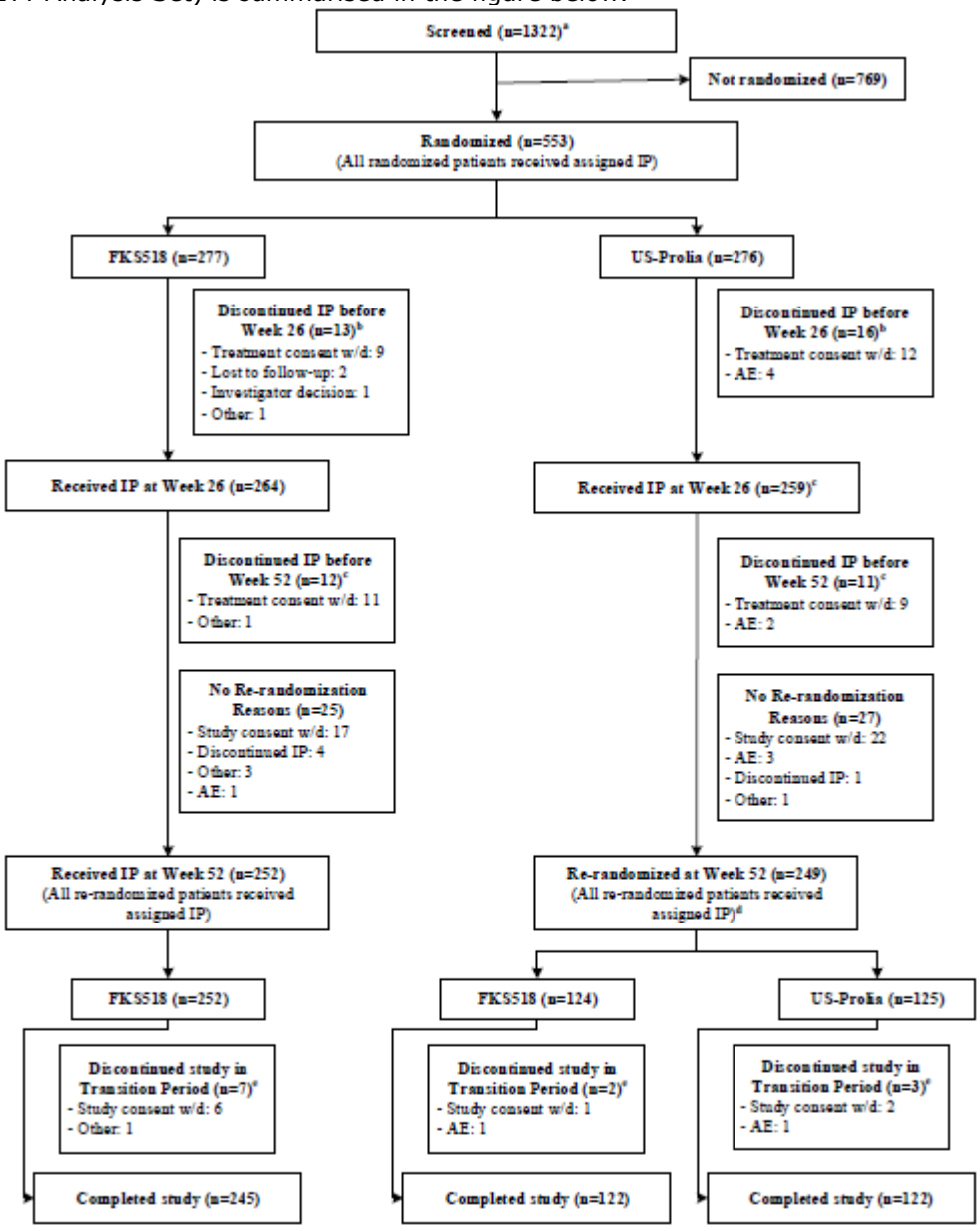
As pre-specified in the SAP, since there were no missing data for both PP and PD Analysis Sets, the related sensitivity analyses for estimands 1.1 (no missing LS-BMD values) and 2.1 (no missing AUEC[0-W26] values) were not performed.

As noted in the SAP, as there were < 10% of ADA-negative patients, subgroup analyses by ADA status were not produced.

Results

- **Participant flow**

Patient disposition for the core treatment period (ITT Analysis Set) and for the transition period (TP-ITT Analysis Set) is summarised in the figure below.



Source: Tables 14.1.1.1.1, 14.1.1.3.1, and 14.1.1.3.2.
AE = adverse event, CRF = case report form; IP = investigational product; w/d = withdrawal.
[a] Includes all patients who provided informed consent.
[b] Discontinuation includes all patients who only received Day 1 treatment administration.
[c] Patients discontinued study treatment on or after Week 26 and before Week 52.
[d] One patient had not received the Week 26 injection but was re-randomized and received the Week 52 injection.
[e] Patients discontinued study within the Transition Period, after re-randomization.

Note: A patient could have had more than 1 reason for discontinuation. Reasons for IP discontinuation are based on end-of-treatment CRF page and reasons for no re-randomization (i.e., study discontinuation) are based on re-randomization - Transition Period CRF page.

Figure 15. Patient disposition

Protocol deviations

Important protocol deviations are summarised for the core treatment period (ITT Analysis Set) in the table below.

Table 20. Important protocol deviations- Core treatment period (ITT Analysis Set)

Category Deviation [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Important Protocol Deviations	159 (57.4)	160 (58.0)	319 (57.7)
LABORATORY ASSESSMENT CRITERIA	94 (33.9)	86 (31.2)	180 (32.5)
VISIT SCHEDULE CRITERIA	54 (19.5)	56 (20.3)	110 (19.9)
STUDY PROCEDURES CRITERIA	37 (13.4)	39 (14.1)	76 (13.7)
ELIGIBILITY AND ENTRY CRITERIA	17 (6.1)	15 (5.4)	32 (5.8)
INFORMED CONSENT	10 (3.6)	14 (5.1)	24 (4.3)
CONCOMITANT MEDICATION CRITERIA	11 (4.0)	11 (4.0)	22 (4.0)
IP COMPLIANCE	12 (4.3)	8 (2.9)	20 (3.6)
RA OR CEC APPROVAL CRITERIA	6 (2.2)	7 (2.5)	13 (2.4)
SERIOUS ADVERSE EVENTS CRITERIA /AESI	6 (2.2)	6 (2.2)	12 (2.2)
Important Protocol Deviations Leading to Exclusion from PP Analysis Set	31 (11.2)	23 (8.3)	54 (9.8)
STUDY PROCEDURES CRITERIA	15 (5.4)	13 (4.7)	28 (5.1)
VISIT SCHEDULE CRITERIA	11 (4.0)	9 (3.3)	20 (3.6)
ELIGIBILITY AND ENTRY CRITERIA	3 (1.1)	2 (0.7)	5 (0.9)
IP COMPLIANCE	4 (1.4)	1 (0.4)	5 (0.9)
CONCOMITANT MEDICATION CRITERIA	2 (0.7)	1 (0.4)	3 (0.5)
Important Protocol Deviations Leading to Exclusion from PK Analysis Set	1 (0.4)	1 (0.4)	2 (0.4)
ELIGIBILITY AND ENTRY CRITERIA	1 (0.4)	1 (0.4)	2 (0.4)
Important Protocol Deviations Leading to Exclusion from PD Analysis Set	13 (4.7)	12 (4.3)	25 (4.5)
STUDY PROCEDURES CRITERIA	8 (2.9)	10 (3.6)	18 (3.3)
ELIGIBILITY AND ENTRY CRITERIA	3 (1.1)	2 (0.7)	5 (0.9)
CONCOMITANT MEDICATION CRITERIA	2 (0.7)	1 (0.4)	3 (0.5)

Source: Table 14.1.1.4.1.
AESI = Adverse Event of Special Interest; CEC = Central Ethics Committee; IP = Investigational Product; ITT = Intention-to-Treat; PD = Pharmacodynamic; PK = Pharmacokinetic; PP = Per-Protocol; RA = Regulatory Authority.
Note: For each category and deviation, patients were included only once, even if they experienced multiple events in a category or deviation.
Note: Percentages were based on all patients in the Intention-To-Treat Analysis Set.
Note: The protocol deviations considered for the definition of the Per-Protocol Analysis Set included deviations that occurred prior to randomization in the Core Treatment Period.

- **Recruitment**

First patients signed informed consent form: 16 Jun 2021

Study completion date: 07 Aug 2023 (last patient completed last visit assessments)

Database lock: 10 Nov 2023

Final SAP version 3.0: 20 Oct 2023

Report Version and Date: Version 1.0, 17 Jan 2024

- **Conduct of the study**

Changes in the conduct of the study that were implemented by protocol amendments are outlined below:

Protocol Version 2.0, dated 08 Mar 2021 (Protocol Amendment 1, substantial):

The planned number of sites was increased from approximately 50 to approximately 75 sites, which could include other regions apart of Europe.

A new exclusion criterion (Exclusion Criterion #31) was added to exclude patients who had received a COVID-19 vaccine within 4 weeks before randomisation or if COVID-19 vaccination was ongoing at the time of screening. COVID-19 vaccination was allowed during study participation, but without being administered within 1 week before and after the IP administrations to ensure distinction between the adverse reactions caused by vaccination and the study drug.

Assessment of PD biomarkers at Week 4 and Week 8 was added to elucidate early responses and their maintenance up to the first 3 months after initiation of dosing.

The coagulation panel was removed from the laboratory safety endpoints.

Protocol Version 3.0, dated 21 Jul 2021 (Protocol Amendment 2, non-substantial) and Protocol Version 4.0, dated 27 Jul 2021 (Protocol Amendment 3, non-substantial):

To participate in this study, COVID-19 eligibility review for all patients had to be made during the screening period, before randomisation. However, this check was noted only at the Baseline Visit in the Schedule of Assessments, and not at screening. This protocol amendment was issued to make this correction, by adding a check for eligibility criteria at the Screening Visit.

Wording was modified for clarification of when abnormal laboratory findings and other abnormal investigational findings had to be reported as AEs, description of the unblinding process was corrected, and procedures for DXA scans of the lumbar spine to be performed in duplicate, which was already noted in the Schedule of Assessments, but not in the corresponding section of the protocol body.

After approval of Protocol Amendment 2 dated 21 Jul 2021, it was noted that the wording of the explanatory footnote that was added regarding the COVID-19 eligibility check needed to be corrected for accuracy purposes. Since Protocol Version 3.0 had already been approved, a new Protocol Version 4.0 was produced to include this correction. Since Protocol Version 3.0 had not been implemented or submitted to the sites or authorities before preparation of Protocol Amendment 4, both versions were submitted and implemented at the same time, which was explained in a Note to File dated 28 Jul 2021.

Protocol Version 5.0, dated 23 Sep 2021 (Protocol Amendment 4, substantial):

AUEC(0-W26) of serum CTX was added as a co-primary endpoint for registration purposes in the EU and the EEA only, following EMA recommendation. This approach implied a change in the definition of the study objectives, where PD was no longer defined as a key secondary objective, and was instead considered a secondary objective, or a co-primary objective for the EMA submission (while remaining a secondary objective for FDA). Percent change in serum CTX was then regarded as a secondary endpoint for both agencies.

Exclusion Criterion #16, referring to the eligibility of patients with medical conditions that could have interfered with the study conduct, interpretation of study data, and/or otherwise could have put the subject at an unacceptable risk, was updated to clarify that patients with rheumatoid arthritis or other medically relevant autoimmune conditions were not eligible for the study. This exclusion was due to the potential risk of exacerbation of preexisting conditions during the long study duration (78 weeks). In addition, the potential usage of protocol prohibited medication in case of a flare could have resulted in protocol deviation and lower compliance.

Footnotes in the Schedules of Assessments were moved and reworded to clarify when a predose sampling was required.

A ±7-day window was added for the DXA scan to be performed at Week 52 (Day 365) and Week 78 (Day 547).

Wording was added to clarify that: when 2 blood samples were required, the second sample did not need to be in a fasting state; if the site was asked to re-acquire a DXA scan after analysis by the

central imaging vendor, this was also in duplicate; suitable ancillary care in accordance with local practices was provided to patients with unresolved AE, unless the patients was lost to follow-up: continuous AEs had to be reported as a single AE with severity changes: the highest severity was to be chosen to document the single AE at the end.

Wording was modified for the recording of medical history and previous surgery before screening, which was to be recorded in the eCRF only for randomised patients.

Wording was modified to clarify actual meaning of "enrolled" patients regarding safety reporting period, so the safety reporting period began when the patient was screened (ICF signature); eCRF collection of serious and nonserious AEs was required for randomised patients, but only SAEs for screening failures.

Wording was modified in the description of deviation from study protocol for accuracy.

Wording was simplified in the description of the planned handling of missing values.

Wording was removed regarding the requirement of having a list of laboratory normal ranges before shipment of IP (central laboratory was used for this study).

The description of the laboratory performing determination of bone biomarkers was changed, as the P1NP analysis was to be conducted at the central laboratory.

Wording was added to add a minimum of 25-year retention of essential documents after the end of the clinical study in line with the requirements set by EU Regulation 536/2014.

Protocol Version 6.0, dated 17 Jan 2023 (Protocol Amendment 5, substantial):

A Coordinating Investigator was appointed for this study

One of the changes included in the previous Protocol Amendment 4, to clarify the requirement for fasting state, had not been correctly implemented for the Week 52 samples, and was corrected in the current protocol amendment.

Similarly, one of the changes included in the previous Protocol Amendment 4, allowing the DXA to be performed within ±7 days of the Week 52 and Week 78 study visits, was not stated in all relevant sections of the protocol and this was corrected in the current protocol amendment.

The names of the Sponsor Signatories were updated.

- **Baseline data**

Demographic characteristics for the core treatment period are summarised in the table below for the ITT Analysis Set.

Table 21. Demographic characteristics – Core treatment period (ITT Analysis Set)

Characteristic	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Sex [n (%)]			
Female	277 (100)	276 (100)	553 (100)
Race [n (%)]			
White	277 (100)	276 (100)	553 (100)
Age (years)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	65.2 (6.44)	65.8 (6.47)	65.5 (6.46)
Median	65.0	65.0	65.0
Min, Max	55, 85	55, 84	55, 85
Age Group [n (%)]			
< 65 years	128 (46.2)	126 (45.7)	254 (45.9)
≥ 65 years	149 (53.8)	150 (54.3)	299 (54.1)
Prior Bisphosphonates Therapy [n (%)]			
Yes	32 (11.6)	34 (12.3)	66 (11.9)
No	245 (88.4)	242 (87.7)	487 (88.1)
Age Group by IRT [n (%)] [a]			
< 65 years	128 (46.2)	126 (45.7)	254 (45.9)
≥ 65 years	149 (53.8)	150 (54.3)	299 (54.1)
Prior Bisphosphonates Therapy by IRT [n (%)] [a]			
Yes	29 (10.5)	30 (10.9)	59 (10.7)
No	248 (89.5)	246 (89.1)	494 (89.3)
Country			
Bulgaria	47 (17.0)	34 (12.3)	81 (14.6)
Czechia	26 (9.4)	24 (8.7)	50 (9.0)
Estonia	11 (4.0)	14 (5.1)	25 (4.5)
Georgia	36 (13.0)	36 (13.0)	72 (13.0)
Hungary	20 (7.2)	25 (9.1)	45 (8.1)
Poland	137 (49.5)	143 (51.8)	280 (50.6)
Baseline Weight (kg)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	63.5 (9.78)	62.7 (8.83)	63.1 (9.32)
Median	62.7	61.5	62.4
Min, Max	43, 96	43, 89	43, 96
Baseline Height (cm)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	159.4 (5.76)	159.6 (6.21)	159.5 (5.98)
Median	159.0	160.0	159.7
Min, Max	144, 178	144, 180	144, 180
Baseline BMI (kg/m^2) [b]			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	24.944 (3.4914)	24.622 (3.3174)	24.783 (3.4064)
Median	24.570	24.090	24.280
Min, Max	18.05, 35.81	18.09, 33.27	18.05, 35.81

Source: Table 14.1.2.1.1.
BMI = Body Mass Index; CRF = Case Report Form; IRT = Interactive Response Technology; ITT = Intention-to-Treat; std = Standard Deviation; Max = Maximum; Min = Minimum.
a. These categories are based on randomization information. See Section 9.4.2.1 for discrepancies between IRT and CRF in age and prior bisphosphonates data.
b. BMI was calculated in CRF.
Note: Core Treatment Period baseline was defined as the last nonmissing assessment prior to randomization and the first dose of study drug.

During the study, minor discrepancies were noted between the information about prior bisphosphonate therapy recorded at randomisation in the IRT system and that recorded in the eCRF. Any noted discrepancy was queried and solved as follows: in the case the IRT information was the correct one, the eCRF was updated with the correct information. If the IRT information was incorrect but information in the eCRF was correct, a protocol deviation was reported with no modifications or updates to the IRT information. This resulted in the identification of 17 mis-stratified patients, all reported as important protocol deviation. Sensitivity analyses were included to account for the mis-stratifications. Minor discrepancies were also noted in the patients' age at screening between the IRT and the eCRF data; this resulted in mis-stratification of only 1 patient (in the FKS518 group) and was reported as an important protocol deviation and documented in a memo to the Trial Master File (available upon request). The IRT (and reporting database) was updated with the correct age, but the stratification was not to be updated retrospectively.

Osteoporosis history and reproductive system findings for the core treatment period are summarised for the ITT Analysis Set in the table below.

Table 22. Osteoporosis history and reproductive system findings – Core treatment period (ITT Analysis Set)

Characteristic	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
History of Fracture [n (%)]			
Yes	74 (26.7)	78 (28.3)	152 (27.5)
No	202 (72.9)	198 (71.7)	400 (72.3)
Unknown	1 (0.4)	0	1 (0.2)
Missing	0	0	0
Family History of Hip Fracture [n (%)]			
Yes	29 (10.5)	26 (9.4)	55 (9.9)
No	243 (87.7)	245 (88.8)	488 (88.2)
Unknown	5 (1.8)	5 (1.8)	10 (1.8)
Missing	0	0	0
Low Dietary Calcium Intake [n (%)]			
Yes	162 (58.5)	164 (59.4)	326 (59.0)
No	107 (38.6)	106 (38.4)	213 (38.5)
Unknown	8 (2.9)	6 (2.2)	14 (2.5)
Missing	0	0	0
Sedentary Lifestyle [n (%)]			
Yes	65 (23.5)	77 (27.9)	142 (25.7)
No	205 (74.0)	193 (69.9)	398 (72.0)
Unknown	7 (2.5)	6 (2.2)	13 (2.4)
Missing	0	0	0
Time Since Diagnosis[a] (years)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	2.5 (3.91)	2.9 (4.82)	2.7 (4.39)
Median	0.5	0.6	0.6
Min, Max	0, 21	0, 31	0, 31
Menarche Age (years)			
n (missing)	276 (1)	276 (0)	552 (1)
Mean (std)	13.8 (1.44)	13.7 (1.52)	13.8 (1.48)
Median	14.0	14.0	14.0
Min, Max	10, 19	9, 18	9, 19
Menopause Status [n (%)]			
Postmenopause	277 (100)	276 (100)	553 (100)
Missing	0	0	0
Menopause Age (years)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	49.4 (4.76)	48.6 (5.14)	49.0 (4.97)
Median	50.0	50.0	50.0
Min, Max	32, 62	28, 61	28, 62
Total Number of Pregnancies			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	2.3 (1.51)	2.2 (1.50)	2.3 (1.50)
Median	2.0	2.0	2.0
Min, Max	0, 12	0, 13	0, 13
Nulliparous Status [n (%)]			
Yes	21 (7.6)	26 (9.4)	47 (8.5)
No	256 (92.4)	250 (90.6)	506 (91.5)

Source: Table 14.1.2.2.1
ITT = Intention-to-Treat; Max = Maximum; Min = Minimum; std = Standard deviation.
a. Time Since Diagnosis was calculated as (date of informed consent – osteoporosis diagnosis date + 1)/365.25.

DXA, ADA, and NAb baseline characteristics for the core treatment period are summarised for the ITT Analysis Set in the table below.

Table 23. DXA, ADA and Nab baseline characteristics – Core treatment period (ITT Analysis Set)

Characteristic	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
LS-BMD by DXA (g/cm^2) (Adjusted Corrected Average)*			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	0.7872 (0.06381)	0.7929 (0.05962)	0.7901 (0.06176)
Median	0.7915	0.8033	0.7945
Min, Max	0.618, 0.915	0.624, 0.914	0.618, 0.915
LS-BMD T-score by DXA (Adjusted Corrected Average)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	-3.0151 (0.40586)	-3.0123 (0.39464)	-3.0137 (0.39994)
Median	-2.9550	-2.9550	-2.9550
Min, Max	-4.025, -2.210	-4.335, -2.185	-4.335, -2.185
BMD at Femoral Neck by DXA (Corrected) (g/cm^2)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	0.7053 (0.09450)	0.7217 (0.09434)	0.7135 (0.09469)
Median	0.7060	0.7120	0.7100
Min, Max	0.443, 1.008	0.462, 1.021	0.443, 1.021
BMD at Total Hip by DXA (Corrected) (g/cm^2)			
n (missing)	277 (0)	276 (0)	553 (0)
Mean (std)	0.7726 (0.09695)	0.7841 (0.08958)	0.7783 (0.09344)
Median	0.7730	0.7830	0.7800
Min, Max	0.488, 1.026	0.507, 1.042	0.488, 1.042
ADA [n (%)]			
Positive	1 (0.4)	0	1 (0.2)
Negative	275 (99.3)	276 (100)	551 (99.6)
Missing	1 (0.4)	0	1 (0.2)
ADA Titer[a]			
n (missing)	1 (276)	0 (276)	1 (552)
Mean (std)	50.0		50.0
Median	50.0		50.0
Min, Max	50, 50		50, 50
NAb [n (%)]			
Positive	0	0	0
Negative	276 (99.6)	276 (100)	552 (99.8)
Missing	1 (0.4)	0	1 (0.2)

Source: Table 14.1.2.3.1
ADA = Antidrug Antibody; BMD = Bone Mineral Density; DXA = Dual Energy X-ray Absorptiometry; ITT = Intention-to-Treat; LS-BMD = Lumbar Spine Bone Mineral Density; Max = Maximum; Min = Minimum; NAb = Neutralizing Antibody; std = Standard deviation.
a. The titer was the reciprocal of total sample dilution factor, including the assay minimum required dilution.
DXA scans of the lumbar spine were performed in duplicate. Lumbar spine scans include L1 through L4. LS-BMD is the average of BMD lumbar spine assessments from duplicate DXA scans.
* Baseline of primary LS-BMD endpoint.
The Core baseline was defined as the last non-missing assessment taken prior to randomization and hence prior to the first dose of study drug.

Prior and Concomitant Therapy

Prior medications had been taken by 80.5% of patients in the ITT Analysis Set and were balanced between both treatment groups. COVID-19 vaccines were the most commonly reported prior medications and were administered to 376 (68.0%) patients in the ITT Analysis Set, with no notable differences between the treatment groups (67.9% and 68.1% of patients in the FKS518 and US-Prolia groups, respectively). Other most commonly reported prior medications by ATC classification Level 2 term were those generally taken for the disease under study, including mineral supplements (20.3% of patients overall), vitamins (18.8% of patients), and drugs for treatment of bone diseases (12.1% of patients).

Prior medications for PMO had been taken by 35.1% of patients in the ITT Analysis Set and were balanced between both treatment groups (36.1% and 34.1% of patients in the FKS518 and US-Prolia groups, respectively). The most commonly reported prior medications for PMO by ATC classification Level 4 term were vitamin D and analogues (17.4% of patients), followed by bisphosphonates and

calcium (each taken by 11.0% of patients), and calcium combinations with vitamin D and/or other drugs (9.2% of patients). Among the bisphosphonates, the most commonly used one was ibandronic acid (7.8% of patients), followed by risedronic acid (2.4%) and alendronic acid (2.2% of patients).

The concomitant medications by ATC classification Level 4 term taken by ≥ 5% of patients in either treatment group during the core treatment period are summarised in the table below.

Table 24. Concomitant medications by ATC classification level 4 term taken by ≥ 5% of patients in either treatment group during the core treatment period (ITT Analysis Set)

Anatomical Therapeutic Chemical Classification [Level 4] [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Any Concomitant Medications	277 (100)	276 (100)	553 (100)
VITAMIN D AND ANALOGUES	223 (80.5)	227 (82.2)	450 (81.4)
CALCIUM	183 (66.1)	165 (59.8)	348 (62.9)
CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	100 (36.1)	113 (40.9)	213 (38.5)
HMG COA REDUCTASE INHIBITORS	72 (26.0)	73 (26.4)	145 (26.2)
OTHER VIRAL VACCINES (COVID-19)	72 (26.0)	62 (22.5)	134 (24.2)
BETA BLOCKING AGENTS, SELECTIVE	58 (20.9)	56 (20.3)	114 (20.6)
ANILIDES	56 (20.2)	53 (19.2)	109 (19.7)
THYROID HORMONES	50 (18.1)	46 (16.7)	96 (17.4)
ACE INHIBITORS, PLAIN	46 (16.6)	43 (15.6)	89 (16.1)
PROTON PUMP INHIBITORS	34 (12.3)	46 (16.7)	80 (14.5)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS), PLAIN	34 (12.3)	24 (8.7)	58 (10.5)
PROPIONIC ACID DERIVATIVES	20 (7.2)	27 (9.8)	47 (8.5)
DIHYDROPYRIDINE DERIVATIVES	26 (9.4)	19 (6.9)	45 (8.1)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	23 (8.3)	21 (7.6)	44 (8.0)
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	17 (6.1)	21 (7.6)	38 (6.9)
BIOFLAVONOIDS	20 (7.2)	15 (5.4)	35 (6.3)
MACROLIDES	14 (5.1)	20 (7.2)	34 (6.1)
OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	19 (6.9)	14 (5.1)	33 (6.0)
ASCORBIC ACID (VITAMIN C), PLAIN	14 (5.1)	15 (5.4)	29 (5.2)
MUCOLYTICS	11 (4.0)	18 (6.5)	29 (5.2)
SULFONAMIDES, PLAIN	16 (5.8)	12 (4.3)	28 (5.1)
NITROFURAN DERIVATIVES	15 (5.4)	12 (4.3)	27 (4.9)
INFLUENZA VACCINES	13 (4.7)	14 (5.1)	27 (4.9)
FLUOROQUINOLONES	12 (4.3)	15 (5.4)	27 (4.9)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	10 (3.6)	14 (5.1)	24 (4.3)
MAGNESIUM	6 (2.2)	16 (5.8)	22 (4.0)

Source: Table 14.1.5.1.
ACE = Angiotensin-converting Enzyme; ATC = Anatomical Therapeutic Chemical; COVID-19 = Coronavirus Disease 2019; HMG CoA = Hydroxymethylglutaryl Coenzyme A; IP = Investigational Product; ITT = Intention-to-Treat.
Note: Concomitant medications were those being taken on or after the first administration of IP on Day 1 up to Early Termination prior to Week 52/Prior to Week 52 dosing or started prior to first dose and was ongoing in the Core Treatment Period. Medications are coded using WHO Drug Dictionary version 2021 MAR.
Note: If a medication date was missing or partially missing and it could not have been determined whether the medication was prior or concomitant, it was considered as concomitant. For further details, see imputation methods as described in the Statistical Analysis Plan (Appendix 16.1.9).
Note: Patients reporting more than 1 drug belonging to the same level are counted once within that level.

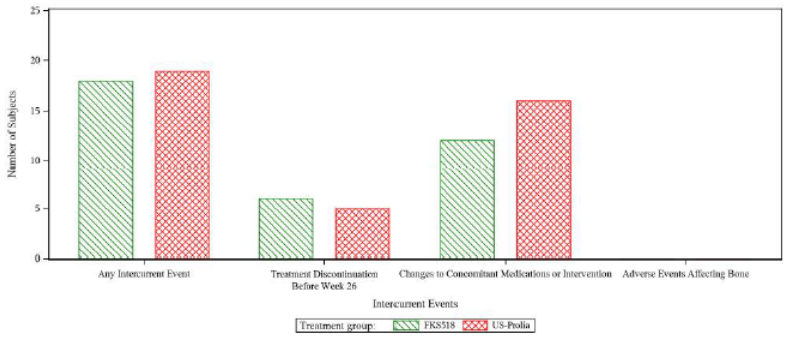
- **Numbers analysed**

Table 25. Patient Analysis Sets – Core treatment period (all enrolled patients)

Analysis Set Reason for Exclusion	FKS518	US-Prolia	Total
Enrolled Analysis Set [n]			1322
Not Randomized [n (%)]			769 (58.2)
Reason not Randomized			
Adverse Event			0
Trial Screen Failure			694 (52.5)
Death			0
Withdrawal of Consent from Study			68 (5.1)
COVID-19			0
Other			7 (0.5)
Randomized: ITT Analysis Set [n (%)]	277	276	553 (41.8)
Safety Analysis Set [n (%)]	277 (100)	276 (100)	553 (100)
Reason for Exclusion from Safety Analysis Set			
Randomized but Not Treated	0	0	0
Per-Protocol Analysis Set [n (%)]	231 (83.4)	237 (85.9)	468 (84.6)
Reason for Exclusion from PP Analysis Set			
Participant had Clinically Important Protocol Deviation	31 (11.2)	23 (8.3)	54 (9.8)
Participant had no Treatment at Baseline and/or Week 26	13 (4.7)	17 (6.2)	30 (5.4)
Participant did not have Week 52 Assessment Data	22 (7.9)	24 (8.7)	46 (8.3)
Pharmacokinetic Analysis Set (PK) [n (%)]	269 (97.1)	261 (94.6)	530 (95.8)
Reason for Exclusion from PK Analysis Set			
Participant had no PK assessments completed	8 (2.9)	15 (5.4)	23 (4.2)
Participant had Clinically Important Protocol Deviation	1 (0.4)	1 (0.4)	2 (0.4)
Pharmacodynamic Analysis Set (PD) [n (%)]	253 (91.3)	250 (90.6)	503 (91.0)
Reason for Exclusion from PD Analysis Set			
Participant had no PD assessments completed	11 (4.0)	16 (5.8)	27 (4.9)
Participant had Clinically Important Protocol Deviation	13 (4.7)	12 (4.3)	25 (4.5)
Participant had no Bone Biomarker at Baseline	0	0	0

Source: Table 14.1.1.1.1.
ITT = Intention-to-Treat; PD = Pharmacodynamic; PK = Pharmacokinetic; PP = Per Protocol.
Definitions of the analysis sets are provided in Section 9.7.2.
Note: Patients could have had more than 1 reason for exclusion from the Analysis Set. Percentages are based on all randomized patients with the exception of "Not Randomized" and "Randomized" patients which are based on the number of enrolled patients.

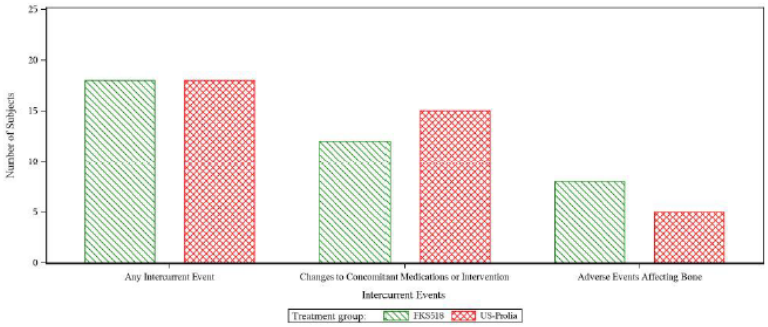
A summary of intercurrent events (IEs) for the primary endpoint (LS-BMD at Week 52) is presented by treatment group for the ITT Analysis in the figure below.



Source: Figure 14.1.1.5.
ITT = Intention-to-Treat; LS-BMD = Lumbar Spine Bone Mineral Density.
Note: For each category of intercurrent events, patients were included only once even if they had more than 1 event within that category.

Figure 16. Intercurrent events of LS-BMD in the core treatment period (ITT Analysis Set)

A summary of IEs for the co-primary endpoint for the EMA only (AUEC[0-W26] of serum CTX) is presented by treatment group for the ITT Analysis Set in the figure below.



Source: Figure 14.1.2.4.
AUEC = Area Under the Effect Curve; CTX = C-terminal cross-linking telopeptide of Type 1 collagen; ITT = Intention-to-Treat.
Note: For each category of intercurrent events, patients are included only once even if they had more than 1 event within that category.

Figure 17. Intercurrent events of AUEC of serum CTX up to Week 26 (ITT Analysis Set)

- **Outcomes and estimation**

Of note, the results of the co-primary PD endpoint "mean AUEC of serum CTX up to week 26" are depicted in section 2.6.2.2 Pharmacodynamics.

estimand 1.2: Hypothetical estimand (co-primary estimand)

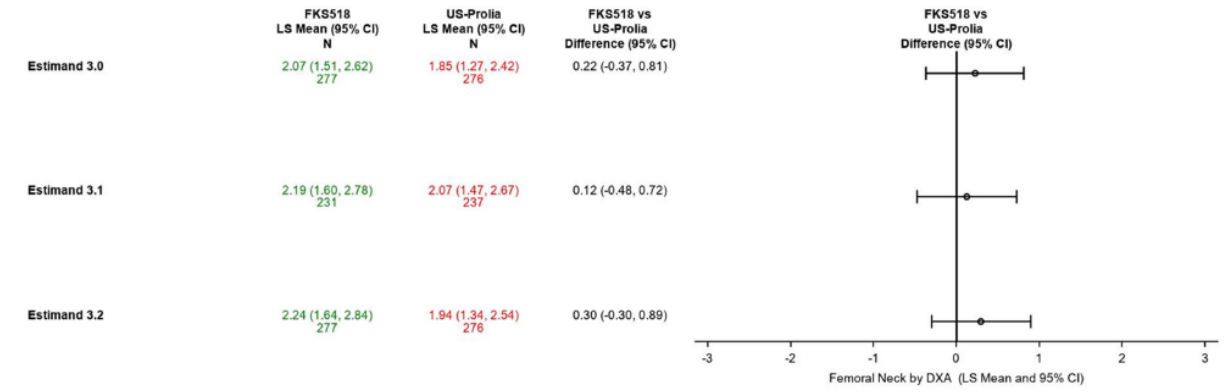
The analysis of the primary endpoint estimand 1.2 is summarised in the ITT Analysis Set in the table below. The comparison was made as per a hypothetical strategy, where measurements were projected as a per-protocol scenario as if the patient had followed the protocol and had no IEs.

Table 26. Analysis of percent change from baseline in LS-BMD (g/cm^2) by DXA at Week 52- Estimand 1.2 (ITT Analysis Set)

Variable Statistic	FKS518 (N=277)	US-Prolia (N=276)	Difference FKS518 - US-Prolia
Percent Change from Baseline to Week 52[a]			
LS Mean (SE)[a]	5.74 (0.315)	5.07 (0.321)	
95% Confidence Interval	(5.12, 6.35)	(4.44, 5.70)	
90% Confidence Interval	(5.22, 6.25)	(4.54, 5.60)	
Number of Imputed Values [n (%)]	36 (13.0)	39 (14.1)	
Difference in Percent Change from Baseline[a]			
Difference in LS Mean (SE)			0.66 (0.317)
95% Confidence Interval[b]			(0.04, 1.29)**
90% Confidence Interval[b]			(0.14, 1.19)**

Source: Table 14.2.1.2.3.
AE = Adverse Event; DXA = Dual Energy X-ray Absorptiometry; EMA = European Medicines Agency; IE = Intercurrent Event; IRT = Interactive Response Technology; ITT = Intention-to-Treat; LS = Least Squares; LS-BMD = Lumbar Spine Bone Mineral Density; SE = Standard Error.
** Indicates that equivalent efficacy was achieved.
a. LS means, SEs, and confidence intervals are from an ANCOVA model on the percent change from baseline in LS-BMD by DXA with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline LS-BMD measurement. Fixed effects as entered in IRT.
b. For the FDA: FKS518 was considered equivalent to US-Prolia if the 90% Confidence Interval laid entirely within the equivalence interval of [-1.45%; 1.45%]. For EMA: FKS518 was considered equivalent to US-Prolia if the 95% Confidence Interval laid entirely within the equivalence interval of [-1.45%; 1.45%].
Note: Estimand 1.2: Assessments impacted by IEs were imputed as per hypothetical strategy, where assessments at Week 52 impacted by: treatment discontinuation prior to Week 52 (did not take injection at Week 26), modification in concomitant medications and interventions, bone-affecting AEs were imputed using data from patients with similar baseline characteristics (within the same treatment group) who had no IEs.
Note: Censored and missing LS-BMD Week 52 data were imputed from the pool of patients with similar baseline profile, for whom LS-BMD Week 52 data were available and for whom an IE had not occurred.

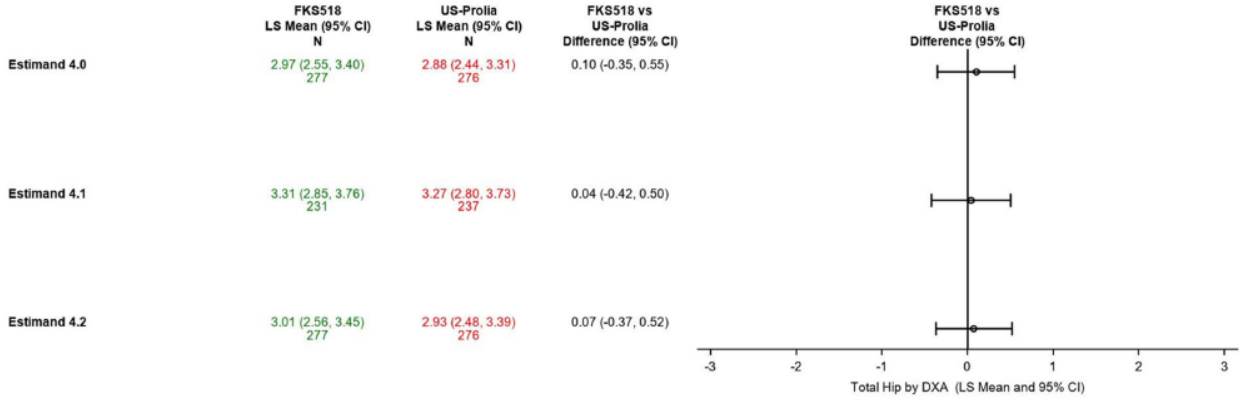
A forest plot for the percent change from baseline in femoral neck BMD at Week 52 is presented for estimand 3.0, estimand 3.1, and estimand 3.2 in the figure below.



Source: Figure 14.2.3.1.1.
BMD = Bone Mineral Density; CI = Confidence Interval; DXA = Dual Energy X-ray Absorptiometry; IRT = Interactive Response Technology; LS = Least Squares.
Note: LS means, standard errors, and CIs were from an ANCOVA model on the percent change from baseline in BMD by DXA with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline BMD measurement. Fixed effects as entered in IRT.

Figure 18. Bone mineral density at femoral neck by DXA percent change from baseline at Week 52 – Estimands 3.0,3.1 and 3.2 – Forest plot

A forest plot for the percent change from baseline in total hip BMD at Week 52 is presented for estimand 4.0, estimand 4.1, and estimand 4.2 in the figure below.



Source: Figure 14.2.3.1.2.
BMD = Bone Mineral Density; CI = Confidence Interval; DXA = Dual Energy X-ray Absorptiometry; IRT = Interactive Response Technology; LS = Least Squares.
Note: LS means, standard errors, and CIs were from an ANCOVA model on the percent change from baseline in BMD by DXA with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline BMD measurement. Fixed effects as entered in IRT.

Figure 19. Bone mineral density at total hop by DXA percent change from baseline at Week 52 – Estimands 4.0,4.1 and 4.2 – Forest Plot

A repeated measures analysis of the percent change from baseline in BMD at LS/femoral neck/total hip at Week 78/End of Study for the Overall Period is presented in the Overall ITT Analysis Set in the table below.

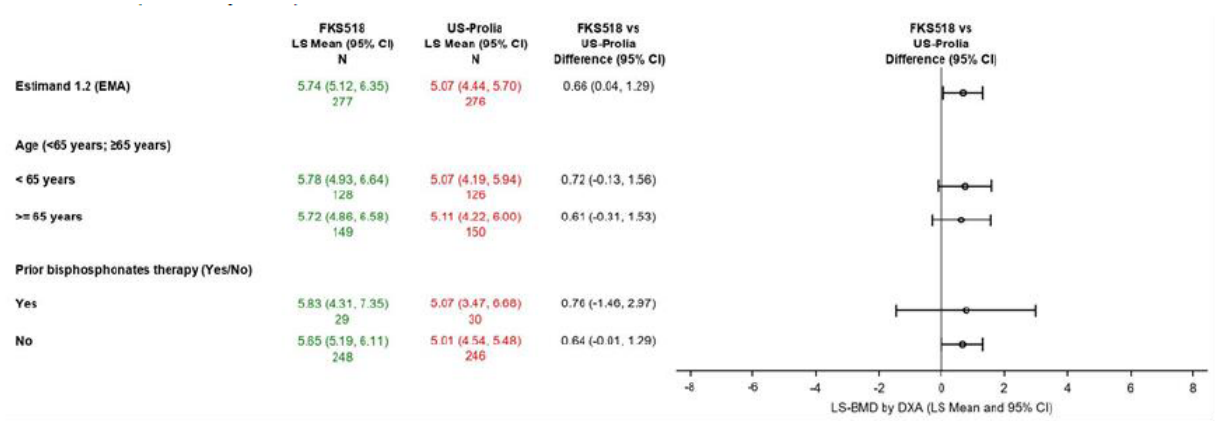
Table 27. Repeated measure analysis of percent change from baseline in BMD (g/cm²) by DXA at Week 78/ End of Study- Overall Period (Overall ITT Analysis Set)

Variable Statistic	FKS518 (N=252)	US-Prolia (N=125)	US-Prolia/ FKS518 (N=124)
Lumbar Spine			
Percent Change from Baseline at Week 78/End of Study			
LS Mean (SE)[a]	7.10 (0.320)	5.89 (0.408)	6.73 (0.414)
95% Confidence Interval[a]	(6.47, 7.73)	(5.09, 6.69)	(5.91, 7.54)
Difference in Percent Change from Baseline at Week 78/End of Study[a]			
FKS518 vs US-Prolia			
LS Mean Difference (SE)	1.21 (0.438)		
95% Confidence Interval[a]	(0.35, 2.07)		
FKS518 vs US-Prolia/FKS518			
LS Mean Difference (SE)	0.38 (0.439)		
95% Confidence Interval[a]	(-0.49, 1.24)		
US-Prolia/FKS518 vs US-Prolia			
LS Mean Difference (SE)			0.84 (0.506)
95% Confidence Interval[a]			(-0.16, 1.83)
Femoral Neck			
Percent Change from Baseline at Week 78/End of Study			
LS Mean (SE)[a]	2.79 (0.286)	2.28 (0.364)	3.37 (0.368)
95% Confidence Interval[a]	(2.23, 3.36)	(1.57, 3.00)	(2.65, 4.09)
Difference in Percent Change from Baseline at Week 78/End of Study[a]			
FKS518 vs US-Prolia			
LS Mean Difference (SE)	0.51 (0.387)		
95% Confidence Interval[a]	(-0.25, 1.27)		
FKS518 vs US-Prolia/FKS518			
LS Mean Difference (SE)	-0.58 (0.386)		
95% Confidence Interval[a]	(-1.33, 0.18)		
US-Prolia/FKS518 vs US-Prolia			
LS Mean Difference (SE)			1.09 (0.447)
95% Confidence Interval[a]			(0.21, 1.96)
Total Hip			
Percent Change from Baseline at Week 78/End of Study			
LS Mean (SE)[a]	4.09 (0.228)	3.51 (0.292)	4.19 (0.294)
95% Confidence Interval[a]	(3.64, 4.53)	(2.94, 4.09)	(3.62, 4.77)
Difference in Percent Change from Baseline at Week 78/End of Study[a]			
FKS518 vs US-Prolia			
LS Mean Difference (SE)	0.57 (0.311)		
95% Confidence Interval[a]	(-0.04, 1.18)		
FKS518 vs US-Prolia/FKS518			
LS Mean Difference (SE)	-0.11 (0.310)		
95% Confidence Interval[a]	(-0.72, 0.50)		
US-Prolia/FKS518 vs US-Prolia			
LS Mean Difference (SE)			0.68 (0.359)
95% Confidence Interval[a]			(-0.03, 1.39)

Source: Table 14.2.5.1.1, Table 14.2.5.2.1, Table 14.2.5.2.2.
BMD = Bone Mineral Density; DXA = Dual Energy X-ray Absorptiometry; IRT = Interactive Response Technology; ITT = Intention-to-Treat; LS = Least Squares; SE = Standard Error.
a. LS means, SEs, and confidence intervals were from a repeated measures model on the response variable percent change from baseline in BMD by DXA with fixed factors for treatment, visit, visit*treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline BMD measurement from the Core Treatment Period. Fixed effects as recorded on IRT. An unstructured covariance matrix was used to account for within-patient variability.
Note: Baseline values from the Core Treatment Period.

- **Ancillary analyses**

Forest plots for the analysis of the primary endpoint estimand 1.2 by the subgroups age (< 65 years; ≥ 65 years) and prior bisphosphonate therapy (Yes/No) are displayed in the figure below.



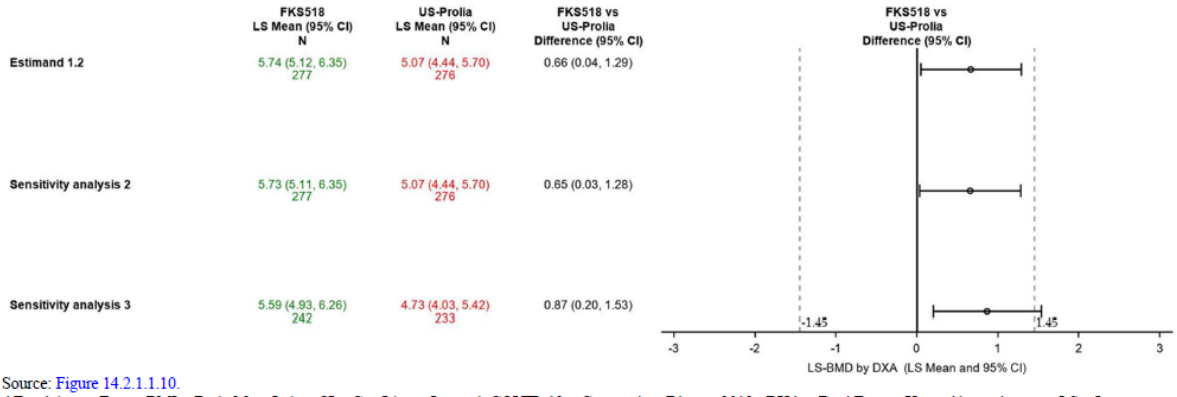
Source: Figure 14.2.1.1.12.
CI = Confidence Interval; DXA = Dual Energy X-ray Absorptiometry; IE = Intercurrent Event; ITT = Intention-to-Treat; LS = Least Squares; LS-BMD = Lumbar Spine Bone Mineral Density; NAb = Neutralizing Antibody.
Note: LS means, standard errors and CIs are from an ANCOVA model on the percent change from baseline in LS-BMD by DXA with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no) and a covariate for baseline LS-BMD measurement. Fixed effects as entered in IRT.
Note: DXA scans of the lumbar spine were performed in duplicate. Lumbar spine scans include L1 through L4. LS-BMD is the average of corrected BMD lumbar duplicate DXA scans.
Note: Estimand 1.2: Assessments impacted by IEs were imputed as per hypothetical strategy, where assessments at Week 52 impacted by: treatment discontinuation prior to Week 52 (did not take injection at Week 26), modification in concomitant medications and interventions, bone-affecting AE|were imputed using data from patients with similar baseline characteristics (within the same treatment group) who had no IEs.

Figure 20. LS-BMD by DXA percent change from baseline at Week 52 by subgroups- Estimand 1.2 (EMA) – Forest plot (ITT Analysis Set)

Sensitivity analyses for estimand 1.2 (hypothetical estimand)

The tipping point was observed in extreme scenarios where shifts ≥ 70% in the US-Prolia group were applied with a shift between 0% and 40% in the FKS518 group.

The sensitivity analysis for estimand 1.2 including baseline BMI as covariate is presented for the ITT Analysis Set in the figure below. With BMI as covariate in the analysis, the 95% CI for the difference between groups in the percent change from baseline in LS-BMD at Week 52 was similar to that described for the main analysis of estimand 1.2, indicating no impact of BMI on the results.



Source: Figure 14.2.1.1.10.
AE = Adverse Event; BMI = Body Mass Index; CI = Confidence Interval; COVID-19 = Coronavirus Disease 2019; DXA = Dual Energy X-ray Absorptiometry; LS = Least Squares; LS-BMD = Lumbar Spine Bone Mineral Density.
Note: LS means, standard errors and confidence intervals are from an ANCOVA model on the percent change from baseline in LS-BMD by DXA with fixed effects for treatment, age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no) and a covariate for baseline LS-BMD measurement. Fixed effects as entered in IRT.
Note: For the EMA: FKS518 was considered equivalent to US-Prolia if the 95% Confidence Interval of the treatment difference laid entirely within the equivalence interval of [-1.45%; 1.45%].
Note: DXA scans of the lumbar spine were performed in duplicate. Lumbar spine scans include L1 through L4. LS-BMD is the average of corrected BMD lumbar duplicate DXA scans.
Note: Estimand 1.2: Assessments impacted by intercurrent events were imputed as per hypothetical strategy, where assessments at Week 52 impacted by: treatment discontinuation prior to Week 52 (did not take injection at Week 26), modification in concomitant medications and interventions, bone-affecting AE were imputed using data from patients with similar baseline characteristics (within the same treatment group) who had no IEs.
Note: Sensitivity Analysis 2: Analysis of Estimand 1.2 including baseline BMI as covariate
Sensitivity Analysis 3: Analysis of Estimand 1.2 excluding patients affected by COVID-19.

Figure 21. LS-BMD by DXA percent change from baseline at Week 52 – Sensitivity analysis of estimand 1.2 (EMA) – Forest plot (ITT Analysis Set)

The sensitivity analysis for estimand 1.2 excluding patients who reported a COVID-19 infection by the time of the Week 52 LS-BMD assessment is presented for the ITT Analysis Set in the figure above. Excluding patients who had reported COVID-19 infection, the 95% CI for the difference between the groups in the percent change from baseline in LS-BMD at Week 52 was similar to that described for the main analysis of estimand 1.2, indicating no impact of COVID-19 on the study results.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 28. Summary of efficacy for trial FKS518-002

Title: A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)		
Study identifier	EudraCT Number: 2020-004422-31 PIND Number: 145897 ClinicalTrials.gov Number: NCT04934072	
Design	This was a double-blind, randomised, multicentre, 2-arm, multiple-dose, parallel-group study with a transition period, to compare the efficacy, safety, tolerability, and immunogenicity of the proposed biosimilar denosumab FKS518 with US-Prolia (denosumab) in ambulatory women with Postmenopausal Osteoporosis (PMO). Bone biomarkers (PD) and PK were also assessed. The study included a Screening Period of maximum 4 weeks (28 days) prior to first drug administration, a double-blind core treatment period up to Week 52, and a double-blind single transition period from Week 52 up to Week 78, with administration of the study drug on Day 1, Week 26 (Month 6), and Week 52 (Month 12). Total study duration was up to 82 weeks (including up to 4 weeks of screening).	
	Duration of main phase:	52 weeks (also referred as Core Treatment

			Period) Duration of Run-in phase: 4 weeks (also referred as Screening Period) Duration of Extension phase: 26 weeks (also referred as transition period)
Hypothesis	Equivalence		
Treatments groups	FKS518		Denosumab biosimilar candidate, 60 mg every 26 weeks (6 months) administered subcutaneously by single-use prefilled syringe (PFS) for a duration of maximum 78 weeks. Number of randomised patients: n=277 in main phase, n= 252 in Extension phase.
	US-Prolia		US-Prolia (denosumab) 60 mg every 26 weeks (6 months) administered subcutaneously by single-use PFS for a duration of maximum 78 weeks. Number of randomised patients: n=276 in main phase, n= 125 in Extension phase.
	US-Prolia/ FKS518		US-Prolia, 60 mg at Day 1 and Week 26 administered subcutaneously by single-use PFS in main Phase, followed by FKS518, 60 mg administered subcutaneously by single-use PFS at week 52 in Extension phase. Number of randomised patients: n=124 in Extension phase.
Endpoints and definitions	Primary endpoint	Percent change from baseline in LS-BMD at Week 52	Percent change from baseline in lumbar spine bone mineral density (LS-BMD) by dual energy X-ray absorptiometry (DXA) at Week 52.
	Co-Primary endpoint	AUEC of CTX up to week 26	Area under the effect curve (AUEC) of serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) up to Week 26 (ng*h/L).
	Secondary endpoint	Percent change from baseline in femoral neck BMD at Week 52	Percent change from baseline in BMD at femoral neck by DXA at Week 52.
	Secondary endpoint	Percent change from baseline in total hip BMD at Week 52	Percent change from baseline in BMD at total hip by DXA at Week 52.
	Secondary endpoint	Percent change from baseline in Serum CTX at Week 52	Percent change from baseline in serum CTX at Week 52.
	Secondary endpoint	Percent change from baseline in Serum P1NP at Week 52	Percent change from baseline in serum procollagen type 1 N-terminal propeptide (P1NP) at Week 52.
Database lock	10Nov2023		
Results and Analysis			

Analysis description	**Primary Analysis of the primary estimand: Percent change from baseline in LS-BMD at Week 52 (pre-specified)**		
Analysis population and time point description	ITT Analysis Set: includes all randomised patients Timepoint: Week 52		
Descriptive statistics and estimate variability	Treatment group	FKS518	US-Prolia
	Number of subjects	277	276
	Percent change from baseline in LS-BMD at Week 52 Least Square Means	5.74	5.07
	Standard Error (SE)	0.315	0.321
	95% Confidence Internal	(5.12, 6.35)	(4.44, 5.70)
Effect estimate per comparison	Primary endpoint	Comparison groups	Difference FKS518 - US-Prolia
		Difference in LS Mean (SE)	0.66 (0.317)
		95% Confidence Interval	(0.04, 1.29)
		P-value	N/A
Notes	FKS518 was considered equivalent to US-Prolia if the 95% Confidence Interval for the treatment difference was included in the pre-defined equivalence interval of [-1.45%; 1.45%]. Least Square (LS) means, standard errors (SE), and confidence intervals are obtained from an Analysis of Covariance (ANCOVA) model on the percent change from baseline in LS-BMD with fixed effects for treatment (FKS518, US-Prolia), age (<65 years; ≥65 years), prior bisphosphonates therapy (yes/no), and a covariate for baseline LS-BMD measurement. LS-BMD assessments were censored when affected by intercurrent events (IEs). Censored and missing LS-BMD Week 52 assessments were imputed by means of multiple imputation applying a hypothetical strategy. They were projected as a per-protocol scenario as if all patients had followed the protocol without occurrence of IEs. There was a total of 36 (13.0%) imputed data in FKS518 arm versus 39 (14.1%) in US-Prolia arm.		
Analysis description	**Primary analysis of the co-primary estimand: Area under the effect curve (AUEC) of serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) up to Week 26 (ng*h/L) (pre-specified)**		
Analysis population and time point description	ITT Analysis Set: includes all randomised patients Timepoint: Week 26		
Descriptive statistics and estimate variability	Treatment group	FKS518	US-Prolia
	Number of subjects	277	276
	AUEC of CTX up to week 26 Geometric Least Square Means	1895	1875
	95% Confidence Internal	(1849, 1941)	(1828, 1923)
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	Ratio of FKS518 versus US-Prolia

		Geometric LS Means Ratio	1.01
		95% Confidence Interval	(0.99, 1.04)
		P-value	N/A
Notes	FKS518 was considered equivalent to US-Prolia on AUEC of CTX up to week 26 if the 95% confidence interval for the ratio of means laid entirely within the equivalence interval of [0.89; 1.12]. Least Square (LS) means, ratio of LS means, and confidence intervals were obtained from an ANCOVA model on the natural log transformed AUEC of 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. CTX assessments were censored for the duration of the IEs. Comparison was made as per hypothetical strategy. An imputation model using a multiple imputation approach was used to impute missing/censored AUEC of CTX as if the patient had continued to follow the protocol and did not have an IE. There was a total of 27 (9.7%) imputed data in FKS518 arm versus 31 (11.2%) in US-Prolia arm.		
Analysis description	**Analysis of the secondary endpoint estimand: Percent change from baseline in femoral neck BMD at Week 52 (pre-specified)**		
Analysis population and time point description	ITT Analysis Set: includes all randomised patients Timepoint: Week 52		
Descriptive statistics and estimate variability	Treatment group	FKS518	US-Prolia
	Number of subjects	277	276
	Percent change from baseline in femoral neck BMD at Week 52 Least Square Means	2.24	1.94
	Standard Error (SE)	0.306	0.306
	95% Confidence Internal	(1.64, 2.84)	(1.34, 2.54)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference FKS518 - US-Prolia
		Difference in LS Mean (SE)	0.30 (0.306)
		95% Confidence Interval	(-0.30, 0.89)
		P-value	N/A
Notes	LS means, standard errors and confidence intervals were obtained from an ANCOVA model on the percent change from baseline in BMD at Femoral Neck with fixed effects for treatment, age (<65 years; >=65 years), prior bisphosphonates therapy (yes; no) and a covariate for baseline BMD at Femoral Neck. Femoral neck BMD assessments were censored when affected by intercurrent events (IEs). Censored and missing femoral neck BMD assessments were imputed by means of multiple imputation applying a hypothetical strategy, where assessments were projected as a per-protocol scenario as if all patients had followed the protocol without occurrence of IEs. There was a total of 34 (12.3%) imputed data in FKS518 arm versus 38 (13.8%) in US-Prolia arm.		

Analysis description	**Analysis of the secondary endpoint estimand: Percent change from baseline in total hip BMD at Week 52 (pre-specified)**		
Analysis population and time point description	ITT Analysis Set: includes all randomised patients Timepoint: Week 52		
Descriptive statistics and estimate variability	Treatment group	FKS518	US-Prolia
	Number of subjects	277	276
	Percent change from baseline in total hip BMD at Week 52 Least Square Means	3.01	2.93
	Standard Error (SE)	0.226	0.231
	95% Confidence Internal	(2.56, 3.45)	(2.48, 3.39)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference FKS518 - US-Prolia
		Difference in LS Mean (SE)	0.07 (0.227)
		95% Confidence Interval	(-0.37, 0.52)
		P-value	N/A
Notes	LS means, standard errors and confidence intervals were obtained from an ANCOVA model on the percent change from baseline in BMD at total hip with fixed effects for treatment, age (<65 years; >=65 years), prior bisphosphonates therapy (yes; no) and a covariate for baseline BMD at total hip. Total hip BMD assessments were censored when affected by intercurrent events (IEs). Censored and missing total hip BMD assessments were imputed by means of multiple imputation applying a hypothetical strategy, where assessments were projected as a per-protocol scenario as if all patients had followed the protocol without occurrence of IEs. There was a total of 34 (12.3%) imputed data in FKS518 arm versus 38 (13.8%) in US-Prolia arm.		
Analysis description	**Analysis of the secondary endpoint estimand: Percent change from baseline in Serum CTX at Week 52 (pre-specified)**		
Analysis population and time point description	ITT Analysis Set: includes all randomised patients Timepoint: Week 52		
Descriptive statistics and estimate variability	Treatment group	FKS518	US-Prolia
	Number of subjects	277	276
	Percent change from baseline in Serum CTX at Week 52 Least Square Means	-72.26	-66.55
	Standard Error (SE)	3.767	3.778
	95% Confidence Internal	(-79.65, -64.88)	(-73.96, -59.15)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference FKS518 - US-Prolia
		Difference in LS Mean (SE)	-5.71 (3.874)

		95% Confidence Interval	(-13.30, 1.89)
		P-value	N/A
Notes	LS means, standard errors and confidence intervals are from an ANCOVA model on the percent change from baseline in CTX at week 52 with fixed effects for treatment, age (<65 years; >=65 years), prior bisphosphonates therapy (yes; no) and a covariate for baseline CTX measurement from the core treatment period. Serum CTX assessments were censored when affected by intercurrent events (IEs). Censored and missing serum CTX assessments were imputed by means of multiple imputation applying a hypothetical strategy, where the assessments were projected as a per-protocol scenario as if all patients had followed the protocol without occurrence of IEs. There was a total of 51 (18.4%) imputed data in FKS518 arm versus 60 (21.7%) in US-Prolia arm.		
Analysis description	**Analysis of the secondary estimand: Percent change from baseline in Serum P1NP at Week 52 (pre-specified)**		
Analysis population and time point description	ITT Analysis Set: includes all randomised patients Timepoint: Week 52		
Descriptive statistics and estimate variability	Treatment group	FKS518	US-Prolia
	Number of subjects	277	276
	Percent change from baseline in Serum P1NP at Week 52 Least Square Means	-65.26	-65.78
	Standard Error (SE)	3.126	3.054
	95% Confidence Internal	(-71.38, -59.13)	(-71.76, -59.79)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference FKS518 - US-Prolia
		Difference in LS Mean (SE)	0.52 (3.276)
		95% Confidence Interval	(-5.90, 6.94)
		P-value	N/A
Notes	LS means, standard errors and confidence intervals were obtained from an ANCOVA model on the percent change from baseline in P1NP at week 52 with fixed effects for treatment, age (<65 years; >=65 years), prior bisphosphonates therapy (yes; no) and a covariate for baseline P1NP measurement from the core treatment period. Serum P1NP assessments were censored when affected by intercurrent events (IEs). Censored and missing serum P1NP assessments were imputed by means of multiple imputation applying a hypothetical strategy, projected as a per-protocol scenario as if all patients had followed the protocol without occurrence of IEs. There was a total of 51 (18.4%) imputed data in FKS518 arm versus 60 (21.7%) in US-Prolia arm.		

2.6.5.3. Clinical studies in special populations

Not applicable

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study(ies)

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme to demonstrate biosimilarity regarding efficacy is based on study FKS518-002. Study FKS518-002 was a randomised, double-blind, multicentre phase III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of FKS518 and US-authorized Prolia. The study was conducted in 64 investigative sites across six countries (Bulgaria, Czech Republic, Estonia, Georgia, Hungary and Poland). Subjects were randomised in a 1:1 ratio for the core treatment period (52 weeks). In the transition period (week 52-78) subjects receiving US-Prolia were re-randomised to receive either FKS518 or US-Prolia. The subjects received in total three s.c. doses of FKS518 or US-Prolia on day 1, month 6 and month 12. Overall, the design of study FKS518-002 is acceptable and is generally in agreement with previous scientific advice received from EMA (EMEA/H/SA/4510/1/2020/III, EMA/SA/0000061878 and EMA/SA/0000095042). Specific design aspects will be discussed below.

The study was conducted in the PMO indication. For all indications of Prolia/Xgeva, the mechanism of action of denosumab is identical, i.e. binding to RANK-L and thus preventing activation of its receptor RANK. The desired pharmacological action of denosumab occurs invariably in the bony tissue, through prevention of generalised bone resorption in primary or secondary osteoporosis, or local bone resorption and destruction around bone metastases. Because of the same mechanism of action, it is agreed that the efficacy results can be extrapolated to all indications.

For study FKS518-002 a population consisting of postmenopausal women with osteoporosis was selected. The main inclusion criteria were "women with confirmed postmenopausal status", "age between 55 to 85 years", "body mass index between 18 to 32 kg/m2". These inclusion criteria are regarded adequate for the intended purpose. A further inclusion criterion was "absolute BMD consistent with T-score of ≤-2.5 and ≥-4.0 at the lumbar spine as measured by DXA". The inclusion of postmenopausal women with a T-score of ≤-2.5 and ≥-4.0 is in line with state of art definition of the WHO and therefore acceptable by the CHMP. Furthermore, patients had to give written informed consent before any study-related activities were performed. This is regarded a prerequisite and therefore endorsed. The exclusion criteria were chosen to recruit a population of PMO patients without previous exposure to denosumab or ongoing use of any osteoporosis treatment. The washout periods for previous osteoporosis treatments are also adequately reflected. Overall, the inclusion and exclusion criteria are considered appropriate for recruitment of a population consisting of postmenopausal women with a diagnosis of osteoporosis. In addition, it is agreed that the chosen study population is appropriate to conduct a biosimilar study with denosumab as it is regarded a sensitive population to identify, or exclude, differences between the test and the reference product, if existent.

Patients were randomised in a 1:1 ratio to one of the two treatment groups FKS518 or US-sourced Prolia. In the CHMP scientific advice procedures (EMEA/H/SA/4510/1/2020/III and EMA/SA/0000095042), the applicant was recommended to stratify for age, body weight, previous osteoporosis treatments and geographical area. However, the applicant did not follow this advice regarding stratification factors completely and only stratified by age (< 65 years; ≥ 65 years) and prior bisphosphonate therapy (yes/no). Nevertheless, as the baseline data show that a very homogenous population with balanced characteristics between the groups has been recruited, this is considered acceptable. For the transition period, patients in the US-Prolia group were re-randomised in a 1:1 ratio to further receive US-Prolia or switch to FKS518 after month 12. Subjects in the initial FKS518 group continued their initial treatment. The stratification factors for the re-randomisation were the same as for the initial randomisation. Overall, the process of randomisation was adequately described and is considered acceptable by the CHMP. A subject randomisation list was also provided, which is endorsed.

Study FKS518-002 was a double-blind study with patients, investigators, sponsor, CRO and the bioanalytical laboratories being blinded throughout the study. In order to ensure blinding, the FKS518 and US-Prolia PFS were blinded and were identical in appearance prior to delivery to clinical site. According to the applicant, no unblinding occurred during the study. The process of blinding was adequately described and is considered acceptable by the CHMP.

The participants from study FKS518-002 each received three subcutaneous doses of study drug (FKS518 or US-sourced Prolia) at 6-month intervals. The route of administration is in line with the recommendations of the Prolia SmPC and is therefore acceptable. The chosen dose of 60 mg every 6 months is also according to the posology recommendations from the Prolia SmPC for the treatment of osteoporosis and is regarded adequate for the assessment of biosimilarity of the test and reference product. All enrolled subjects received calcium (1000 mg/day) and vitamin D (400 IU/day) supplementation during the study, which is endorsed. This is in line with the clinical efficacy and safety studies for the initial marketing authorization of the reference product, where women received 1g/day calcium and 400 IU/day vitamin D.

Several medications were prohibited during the study. These included strontium ranelate, fluoride, intravenous/oral bisphosphonates, teriparatide, calcitonin, cinacalcet, cathepsin K inhibitors, romosozumab, other osteoporotic agents, any investigational drugs and any medication with known influence on skeletal system. If a patient used prohibited medications during the study, the patient had to discontinue from the study drug. This is endorsed. Patients were allowed to receive COVID-19 vaccination during study participation, with a temporal distance of 1 week to the study drug administration in order to ensure distinction between adverse reactions caused by vaccination and the study drugs. This is considered acceptable.

Study FKS518-002 had two co-primary objectives. The primary objectives aimed at demonstrating equivalent efficacy and PD of FKS518 to US-Prolia in postmenopausal women with osteoporosis. This issue was also discussed in the CHMP scientific advice procedures (EMEA/H/SA/4510/1/2020/III, EMA/SA/0000061878 and EMA/SA/0000095042) where it was recommended to have two co-primary objectives. The co-primary endpoints of the study were the "Percent change from baseline in LS-BMD at Week 52" and the "AUEC(0-W26) of serum CTX". BMD is a quantitative predictor of osteoporotic fractures in postmenopausal women without a previous fracture. However, the causal link (surrogacy) between the marker and longer-term endpoints has not been unequivocally proven (GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PRIMARY OSTEOPOROSIS, CPMP/EWP/552/95 Rev. 2). After denosumab treatment, the changes in BMD are slow and modest, while the changes in sCTX are large and dynamic. Thus, sCTX might be more sensitive to compare test and reference product in terms of biosimilarity, however, the clinical relevance might be higher for BMD. Thus, the choice of these endpoints as co-primary endpoints for study FKS518-002 is considered appropriate for the assessment of biosimilarity of FKS518 and US-Prolia.

The equivalence margin for the primary endpoint "percent change from baseline in LS-BMD at Week 52" was derived from a meta-analysis of three historical studies with Prolia. According to the applicant, a margin of 1.45% retains at least 70% of the minimum treatment effect. Acceptability of equivalence margins has been discussed during the planning phase within CHMP scientific advice interaction. At that point in time, the applicant was asked to add a justification for the clinical (non-) relevance of the proposed LS-BMD margin. While such a justification was not found in the dossier, the actual magnitude of the estimated group difference in BMD change to baseline does not call for further margin justifications. The equivalence margin for the co-primary endpoint "AUEC(0-W26) of serum CTX" was based on a population PD model for CTX. This was already discussed in the CHMP scientific advice procedure EMA/SA/0000061878 in July 2021, where the PK/PD-model based approach was regarded reasonable and the proposed equivalence margin of [0.89; 1.12] for the PD-variable AUEC (0-week 26) of s-CTX was agreed to. Hence, overall, the chosen framework for PD/efficacy equivalence testing is acceptable.

The efficacy parameter BMD was assessed by DXA scans using Lunar or Hologic DXA system. For a particular patient, the same system had to be used throughout the study. The DXA scans were analysed by a central imaging vendor. The assessments were performed equally between treatment arms. This is regarded acceptable. Additionally, the applicant provided a well-structured schedule of activities, which is endorsed.

The applicant defined three primary estimands and a detailed description of all estimand attributes (endpoint, treatment, population, IEs/strategies to address IEs and population level summary) was provided. For the EMA, the hypothetical estimand was pre-specified as the primary estimand, while a treatment policy estimand and a trial product estimand were considered as supportive estimands. This has already been discussed in the CHMP scientific advice procedure EMA/SA/0000095042 in September 2022 and is principally acceptable. A detailed discussion on the hypothetical estimand is provided below.

The two co-primary endpoints of the study were the "Percent change from baseline in LS-BMD at Week 52" and the "AUEC(0-W26) of serum CTX", which are regarded acceptable. The treatment (FKS518 or US-Prolia, 60mg every 26 weeks) has already been discussed above and is also considered adequate. The population consisted of women with PMO in the ITT analysis set. This is also acceptable. For the primary endpoint "Percent change from baseline in LS-BMD at Week 52", the population level summary was the mean difference between the 2 treatment arms. For the primary endpoint "AUEC(0-W26) of serum CTX" the population level summary was the geometric mean ratio of the 2 treatment arms. This is regarded appropriate. There were different intercurrent events defined for the two co-primary endpoints. For both endpoints, changes in the concomitant medication and interventions were defined as an intercurrent event. Of note, the exact definition was different, as bone interventions only included lumbar spine surgery for the primary BMD endpoint, but also dental procedures for the s-CTX endpoint. The intercurrent event "AEs affecting bone" included vertebral fracture in the area of interest (L1-L4) and any other AE with bone involvement in the lumbar area for the BMD endpoint, but fractures and any other AE with bone involvement for the s-CTX endpoint. Additionally, treatment discontinuation due to any reason before week 26 was only defined as an intercurrent event for the BMD endpoint, as the s-CTX endpoint was only assessed until week 26 and treatment discontinuation at week 26 would not be of relevance for the evaluation of this endpoint. The strategy of defining different intercurrent events for the two co-primary endpoints is regarded reasonable. The intercurrent event definition is regarded acceptable by the CHMP. The strategy to handle defined IEs under hypothetical estimand assumptions was adequately prespecified and is generally in line with corresponding advice given prior to study initiation. Whilst the application of multiple imputation technique is generally endorsed for this purpose, planning documents (i.e. the SAP) lack some details, in particular concerning the selection of baseline variables which were used to define the set of patients with "similar baseline characteristics" having no IEs. In order to clarify, the applicant was asked to provide the list of baseline variables used as well as

the associated similarity criteria. In addition, the applicant was asked to confirm that this selection of variables and criteria has been prespecified prior to database lock. As requested, the applicant clarified which baseline covariate information was used for multiple imputation methods. Further information has been provided as regards details of technical implementation and programming. The applicant also confirmed that method implementation followed prespecified plans. Hence, there remain no concerns in relation to bias introduced through applied imputation techniques. The set of pre-defined sensitivity and supportive estimands allows a reasonable evaluation of the robustness of the outcome of primary equivalence testing.

The secondary objectives of study FKS518-002 include PD, safety, tolerability and immunogenicity aspects of FKS518 and the reference product. The other objectives of the study include the exploration of long-term efficacy, the evaluation of the effects on immunogenicity and safety of a single treatment transition and the description of PK parameters.

The secondary efficacy endpoints were the percent change from baseline in BMD at femoral neck and total hip at week 52. This is considered adequate to support the primary efficacy endpoint. Other efficacy endpoints were the percent change from baseline in LS-BMD/femoral neck BMD/total hip BMD at week 78. This is also acceptable.

The secondary PD endpoints consisted of percent change from baseline in serum CTX at week 52 and percent change from baseline in serum P1NP at week 52. The secondary PD endpoints are considered acceptable to support the demonstration of PD similarity of FKS518 and US-Prolia. The PD sampling time points are also regarded acceptable.

The safety, tolerability and immunogenicity endpoints are also regarded adequate to compare the test and the reference product.

The PK endpoints in this study were the denosumab concentrations and area under the concentration-time curve (AUC) tau and partial AUCs related to different phases of denosumab elimination. As the PK has been evaluated as a primary objective in study FKS518-001 in the sensitive population of healthy volunteers, the proposed PK evaluation in study FKS518-002 is regarded sufficient to support the PK similarity of the test and reference product. In addition, the PK sampling time points in study FKS518-002 are deemed acceptable to compare the PK characteristics of the test and reference product and further support the PK evaluation of study FKS518-001.

Similarly to the primary endpoints, the applicant also defined three estimands with their respective estimand attributes for the secondary endpoints "Percent change from baseline in bone mineral density (BMD) at femoral neck and total hip by DXA at Week 52" and "Percent change from baseline in serum CTX/P1NP at Week 52". One of the estimands followed a hypothetical strategy, which is in line with the recommendations from the CHMP scientific advice procedure EMA/SA/0000095042, where the applicant was strongly encouraged to additionally conduct secondary analyses in line with a hypothetical strategy. Thus, the assessment of the secondary endpoints also focusses on the hypothetical estimand. For the hypothetical estimand, which is regarded the most important in assessment of the biosimilarity of the test and reference product, the attributes endpoint, treatment and population have already been discussed in other sections of this discussion and are regarded acceptable by the CHMP. The population level summary for all endpoints is the mean difference between the 2 treatment arms and therefore acceptable. The intercurrent events definition was slightly different for the secondary efficacy and bone marker endpoints. While treatment discontinuation due to any reason before week 26 was an intercurrent event for all secondary endpoints, the bone intervention intercurrent event focused on the specific area of interest for the efficacy endpoints (femoral neck or hip fracture) and included all bone interventions for the bone marker endpoints. Similarly, the intercurrent event bone-affecting AE focused on femoral neck or hip fractures for the secondary efficacy endpoints but included all fractures for the bone marker endpoints. The strategy of defining different intercurrent events for the different secondary endpoints is

regarded reasonable. The intercurrent event definition is regarded acceptable. The spectrum of estimands pre-specified allows a thorough comparative evaluation of secondary efficacy endpoints.

While the definitions of analysis sets become clear from the descriptions provided, the necessity of such classical definitions somehow appears questionable, given the assumption that patient selection for efficacy analyses can be seen as a consequence of the various estimands' attributes defined. However, no concerns arise from the methodological perspective as regards the choice of analysis models (ANCOVA, MMRM) for the purpose of equivalence testing. Multiplicity issues were handled adequately and an interim analysis was nor foreseen.

From the trial planning perspective, sample size calculations are considered adequate. While power computations for LS-BMD could be reproduced during assessment, the simulation-based calculation for the co-primary AUEC CTX endpoint could not be assessed in detail. However, no methodological concerns arise in relation to sample size planning and power calculation.

Changes for the eventual statistical analyses as compared to the plans given in the trial protocol were well described and very likely not influenced by actual outcome data.

The data quality assurance measures put in place are considered adequate.

The protocol of the study was amended five times. In summary, the applicant provided a detailed overview of the protocol amendments and provided all relevant protocol versions. All protocol amendments happened prior to database lock and do not seem to be driven by data. The protocol amendments are regarded appropriate.

The study started on 16-Jun-2021 with the first subject signing informed consent and was completed on 07-Aug-2023 with the last patients last visit assessments. Of note, the date of the final SAP version 3.0 was dated on 20-Oct-2023. Thus, the SAP was finalized after the last subject last assessment. This is acceptable, as the database lock was on 10-Nov-2023 and therefore after the SAP finalization and prior to unblinding.

Overall, the participant flow is described in sufficient detail. Of the 1322 screened subjects, 553 subjects were randomised in a 1:1 ratio (277 in the FKS518 arm and 276 in the US-Prolia arm). Major reasons for not randomizing patients were screen failure and consent withdrawal. This is regarded acceptable. Of the 553 randomised subjects, most subjects received IP at week 26 (264 in the FKS518 arm and 259 in the US-Prolia arm) and entered the transition period (252 from the FKS518 arm and 249 from the US-Prolia arm). 25 subjects in the FKS518 arm and 27 subjects in the US-Prolia arm were not re-randomised at week 52. The main reasons were withdrawal of treatment consent (17 subjects in the FKS518 group; 22 subjects in the US-Prolia group), adverse events (1 subject in the FKS518 group; 3 subjects in the US-Prolia group) and discontinuation of IP (4 subjects in the FKS518 group; 1 subject in the US-Prolia group). Thus, the number of subjects completing the core treatment period was high. In addition, the number of subjects discontinuing the study and reasons for discontinuation were similar between the groups. Of the 501 subjects re-randomised for the transition period, 489 completed the transition period. The main reason for discontinuation during transition period was consent withdrawal (6 subject in the FKS518 group; 1 subject in the US-Prolia/FKS518 group and 2 subjects in the US-Prolia/US-Prolia group). Thus, the number of subjects completing the transition period was high.

The number of subjects with an important protocol deviation during the core treatment period was 159 in the FKS518 group and 160 in the US-Prolia group. Thus, the numbers were similar between the treatment groups. 31 subjects in the FKS518 group and 23 subjects in the US-Prolia treatment group were excluded from the per-protocol set due to important protocol deviations. Although the number is slightly different between the groups, no concern is raised as it seems to be due to an accumulation of small differences in all of the reasons for important protocol deviations leading to exclusion from PP analysis (study procedures criteria, visit schedule criteria, eligibility criteria, IP compliance and

concomitant medication criteria). One subject per group was excluded from the PK analysis set due to not meeting the eligibility criteria. The number of subjects excluded from the PD analysis set due to important protocol deviations was also balance between the groups (13 in the FKS518 group and 12 in the US-Prolia group). This is acceptable. The applicant also provided the number of important protocol deviations during the transition period. Also for this period, the number and reasons for protocol deviations was similar among the groups. This is acceptable.

Furthermore, the applicant provided an overview of the number of subjects per analysis set. The number of subjects randomised to the study was 553 and all of these subjects were included in the ITT analysis set. The safety analysis set also included all 553 randomised subjects. The PP set included 468 subjects (FKS518 group: 231 subjects; US-Prolia group: 237 subjects). The main reasons for exclusion from PP were clinically important protocol deviations, no treatment at baseline and/or week 26 or no week 52 assessment data. The reasons were balance between the groups. This is acknowledged. In the PK analysis set 25 subjects were excluded (FKS518 group: 9 subjects; US-Prolia group: 16 subjects). The main reasons for these exclusions were that PK assessments were not completed and clinically important protocol deviations. Although there is a slight imbalance of subjects excluded in both groups, no concern is raised, as the overall number of subjects in the PK analysis is high. In the pharmacodynamic analysis set, 52 subjects were excluded (FKS518 group: 24 subjects; US-Prolia group: 28 subjects). This was due to no PD assessments completed and clinically important protocol deviations. The applicant also provided the number of subjects per analysis set for the transition period. The number of subjects included in the respective sets was high and no concerns arise.

An overview of the intercurrent events for the primary and co-primary endpoint was also provided. As discussed above, the definition of intercurrent events was different for the two co-primary endpoints, which is reasonable. For the co-primary endpoint "Percent change from baseline in LS-BMD at Week 52", 18 subjects in the FKS518 group and 19 subjects in the US-Prolia group had any intercurrent event. The most common intercurrent events were changes in concomitant medication (12 subjects in the FKS518 group and 16 subjects in the US-Prolia group) and treatment discontinuation before week 26 (6 subjects in the FKS518 group and 5 subjects in the US-Prolia group). For the co-primary endpoint "AUEC(0-W26) of serum CTX", 18 subjects in both groups had any intercurrent event. The most common intercurrent events were changes in concomitant medication (12 subjects in the FKS518 group and 15 subjects in the US-Prolia group) and adverse events affecting bone (8 subjects in the FKS518 group and 5 subjects in the US-Prolia group). Thus, the occurrence of and reasons for intercurrent events was similar between the groups and no concern arises.

Overall, the demographic characteristics were well balanced between the FKS518 and US-Prolia group for the ITT analysis set. The mean age was 65.2 and 65.8 years, respectively. All of the subjects in the study were "White". In addition, the height, weight and BMI of the subjects was comparable between the groups. Thus, the demographics data show that a very homogeneous population of female subjects with a diagnosis of osteoporosis was recruited. Additionally, the demographic characteristics were also similar and balanced between the groups for the PP analysis set. Although the use of prior bisphosphonate therapy was also balanced between the groups, the information provided was discrepant depending on the source used. According to the baseline characteristics table, it seems as if this discrepancy concerns 7 patients. However, according to the applicant, there was a mis-stratification of 17 patients due to discrepant information on prior bisphosphonate use in the IRT system and the eCRF. A sensitivity analysis on the treatment policy estimand 1.0 of the primary efficacy endpoint was performed to account for the mis-stratification of 17 patients due to discrepant information about prior bisphosphonate therapy recorded at randomisation in the IRT system and that recorded in the eCRF. When eCRF information on prior bisphosphonate use was used in the analysis, the results were similar to the main analysis, indicating that mis-stratification did not impact the results relevantly. Thus,

although it is not totally clear how this discrepancy could have happened, it seems as if this mis-stratification does not impact the efficacy analysis. Therefore, no concern is raised.

The medical history and concurrent illnesses were comparable between the FKS518 and US-Prolia group. In addition, the prior and concomitant therapies and medications were balanced between the groups. This is acknowledged. The applicant also provided an overview of osteoporosis history and reproductive system findings. In total 27.5% of the patients had a history of fracture with similar frequencies between the groups. The family history of hip fracture was also balanced between the FKS518 and US-Prolia group. More than 50% of the subjects had low dietary calcium intake. The menarche age, menopause status, menopause age, total number of pregnancies and nulliparous status were comparable between the groups. The mean time since osteoporosis diagnosis was 2.5 years for the FKS518 group and 2.9 years for the US-Prolia group. Although there is a slight difference, no concern arises as other baseline/disease/medical history characteristics are well balanced between the groups.

The DXA baseline characteristics (LS-BMD, LS-BMD T-score, BMD at femoral neck and BMD at total hip) were balanced between the groups. However, the min/max values for the LS-BMD T-score were not in line with the inclusion criteria and the applicant was asked to clarify. The applicant clarified that the data presented in table 16 with LS-BMD T-score values outside the eligibility range (≤ -2.5 and ≥ -4.0) depict the baseline adjusted corrected average T-score, which have also been used for the efficacy analyses. However, for the evaluation of eligibility, the baseline adjusted average T-score has been used and in the newly presented table for this parameter, all patients were within the eligibility criteria. This is acknowledged. The applicant further outlined the difference between the adjusted and corrected values, which has already been provided in the CSR. No issues arise from these explanations. Additionally, further efficacy analyses were performed with the 28 patients (13 in the FKS518 group and 15 in the US-Prolia group) who appeared to be outside the eligibility criteria based on their corrected T-score. Their mean percent change from baseline to week 52 in LS-BMD was lower than for the ITT set. However, this was true for the FKS518 as well as the US-Prolia group. Additionally, an analysis excluding these patients had little impact on the conclusions drawn from the primary endpoint efficacy analysis.

3 patients in the FKS518 group and 5 patients in the US-Prolia group were ADA positive at baseline. No patients were NAb positive at baseline. The applicant was asked to provide a possible explanation for the ADA positive results at baseline. The applicant explained that the overall high positivity rate in study FKS518-002 was due to target interference. Therefore, the ADA assay was modified and ADA positive samples were re-analysed. As a consequence, updated CSRs and integrated summary of immunogenicity have been provided. With regards to the baseline levels, the applicant further explains that with the modified ADA assay and the updated immunogenicity results, only one patient had an ADA positive sample at baseline. Although a possible explanation was not provided by the applicant, no further issue is made due to the low number of ADA positives at baseline.

Efficacy data and additional analyses

For the hypothetical estimand, the percent change from baseline in LS-BMD at Week 52 was 5.74% for the FKS518 group and 5.07% for the US-Prolia group. The statistical analysis for the hypothetical estimand revealed that the difference between the FKS518 and the US-Prolia group was 0.66% with the corresponding 95% CI being 0.04% and 1.29%. Thus, the 95% CI was within the pre-specified and accepted equivalence range of [-1.45%, 1.45%] and the co-primary efficacy endpoint was met. Thus, the results of the co-primary efficacy endpoint analysis support biosimilarity of the test and reference product. In addition, for the supportive treatment policy and trial product estimand, the 95% CI was within the pre-specified and accepted equivalence range of [-1.45%, 1.45%], respectively. Thus, these results also support the co-primary hypothetical estimand results.

For the hypothetical estimand of the co-primary LS-BMD endpoint, subgroup analyses by age (< 65 years and ≥ 65 years) and prior bisphosphonate therapy (Yes/No) were provided. These are generally

consistent with the main co-primary efficacy endpoint analysis, although the 95% confidence intervals for most of the subgroup analysis were not contained within the pre-specified margin for the primary analysis. This might be due to the small number of subjects by subgroup. Overall, the predefined subgroup analyses support the conclusion of the co-primary efficacy analysis and no concerns arise from these subgroup analyses. Similarly, subgroup analyses were provided for the treatment policy estimand which also support the main analysis.

Furthermore, the applicant provided several sensitivity analyses for the co-primary hypothetical estimand of the LS-BMD endpoint with most of them supporting the primary efficacy analysis. Sensitivity analysis 1 was a tipping point analysis which indicates that a conclusion on non-equivalence might have only been possible under implausibly high shifts in imputed data. Thus, the tipping point analysis supports the robustness of the primary analysis. Sensitivity analysis 2 included baseline BMI as covariate. The results were similar to the primary analysis, indicating that baseline BMI does not impact the results. Sensitivity analysis 3 excluded patients who had reported a COVID-19 infection during the core treatment period. There were 35 patients excluded in the FKS518 group and 43 patients excluded in the US-Prolia group. The upper bound of the 95% CI for this analysis exceeds the pre-specified margin of [-1.45%, 1.45%]. However, this can be explained by the reduced number of patients used for this analysis.

The secondary efficacy endpoints also support the findings of the co-primary efficacy endpoint. For the hypothetical estimand, the percent change from baseline in bone mineral density at femoral neck at Week 52 was 2.24% for the FKS518 group and 1.94% for the US-Prolia group. The difference between the FKS518 and the US-Prolia group was 0.3% with the corresponding 95% CI being -0.3% and 0.89%. Thus, the percent change from baseline in BMD at the femoral neck was similar between the groups at week 52. Similar results were seen with the treatment policy estimand and the trial product estimand. Thus, the BMD results in the femoral neck support the results in the LS-BMD.

Similarly, the percent change from baseline in bone mineral density at total hip at Week 52 was 3.01% for the FKS518 group and 2.93% for the US-Prolia group under the hypothetical estimand. The difference between the FKS518 and the US-Prolia group was 0.07% with the corresponding 95% CI being -0.37% and 0.52%. Thus, the percent change from baseline in BMD at the total hip was similar between the groups at week 52. Similar results were seen with the treatment policy estimand and the trial product estimand. Thus, the BMD results at the total hip also support the results in the LS-BMD.

The percent change from baseline in BMD at LS/femoral neck/total hip at Week 78 was similar among the treatment groups. However, it has to be noted that there seems to be a consistent higher increase in BMD at LS/femoral neck/total hip when patients are switched from US-Prolia to FKS518 compared to patients staying on US-Prolia. Nevertheless, this increase does not give rise to any concern.

2.6.7. Conclusions on the clinical efficacy

In study FKS518-002, the co-primary efficacy analysis based on the percent change from baseline in LS-BMD at week 52 was met as the 95% CI of the difference between the FKS518 and the US-Prolia group was within the pre-specified and accepted equivalence criteria. This was further supported by secondary endpoint results and subgroup/sensitivity analyses. Thus, the provided efficacy data support the biosimilarity of FKS518 and US-Prolia.

2.6.8. Clinical safety

The clinical development programme to demonstrate biosimilarity regarding safety included two clinical studies (FKS518-001 and FKS518-002).

Safety and tolerability data included the recording of treatment-emergent adverse events (TEAEs), including SAEs, injection site reactions (ISRs), and adverse events of special interest (AESI). In addition, clinically significant abnormalities of laboratory (haematology, clinical chemistry, and urinalysis), vital sign measurements (blood pressure, respiratory rate, pulse rate, and temperature), abnormalities in 12 lead electrocardiogram (ECG) assessment, and physical examination were also recorded.

2.6.8.1. Patient exposure

Study FKS518-001

All participants that received at least one dose of IP were included in the Safety Analysis Set (SAS) and were analysed according to the actual treatment received (N = 213).

Study FKS518-002

All 553 randomised patients with PMO were administered at least 1 injection of either FKS518 or US-Prolia during the core treatment period.

The second injection at Week 26 was administered to 523 (94.6%) patients:

264 (95.3%) patients in the FKS518 group and 259 (93.8%) in the US-Prolia group. The most common reason for not receiving the second injection at Week 26 was withdrawal of consent from treatment (19 [3.4%] patients overall).

The third injection at Week 52 was administered to 501 patients: 252 patients in the FKS518 group, 124 in the US-Prolia/FKS518 group, and 125 in the US-Prolia group.

2.6.8.2. Adverse events

Study FKS518-001

Data are presented in Table 29 and Table 30.

Table 29. Summary of treatment emergent adverse events

	FKS518 (N = 107) n (%) E	US-Prolia (N = 106) n (%) E	Overall (N = 213) n (%) E
Number of subjects (%) with at least 1 TEAE and number of TEAEs	84 (78.5) 225	82 (77.4) 211	166 (77.9) 436
Subjects with Worst Grade of TEAE in each of the following categories:			
Mild TEAE	30 (28.0) 132	28 (26.4) 117	58 (27.2) 249
Moderate TEAE	50 (46.7) 88	50 (47.2) 88	100 (46.9) 176
Severe TEAE	3 (2.8) 4	4 (3.8) 6	7 (3.3) 10
Life-threatening TEAE	1 (0.9) 1	0 0	1 (0.5) 1
Death	0 0	0 0	0 0
Number of Subjects (%) with at least 1 study drug-related TEAE	0 0	0 0	0 0
Number of Subjects (%) with at least 1 injection site reaction	1 (0.9) 1	6 (5.7) 6	7 (3.3) 7
Number of Subjects (%) with at least 1 SAE	14 (13.1) 14	9 (8.5) 9	23 (10.8) 23
Number of Subjects (%) with at least 1 study drug-related SAE	0 0	0 0	0 0
Number of Subjects (%) with at least 1 AESI	1 (0.9) 1	0 0	1 (0.5) 1
Number of Subjects (%) with at least 1 TEAE leading to death	0 0	0 0	0 0
Number of Subjects (%) with at least 1 study drug-related TEAE leading to death	0 0	0 0	0 0
Number of Subjects (%) who discontinued study due to a TEAE	1 (0.9) 1	0 0	1 (0.5) 1

Source: Table 14.3.1.1
Abbreviations: AESI = adverse event of special interest; E = number of events; n = number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Adverse events were coded using MedDRA Version 24.0.
Subjects are counted only once under the category of their worst grade of TEAE, but all TEAEs are counted as per their actual grade.

Table 30. Summary of TEAE by SOC – Preferred term and by relationship to denosumab (Safety Analysis Set)

	FKS518 (N=107)		US-Prolia (N=106)		Overall (N=213)	
	Unrelated	Related	Unrelated	Related	Unrelated	Related
System Organ Class Preferred Term	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Number of subjects (%) with at least one TEAE and number of TEAEs	84 (78.5) 225	0	82 (77.4) 211	0	166 (77.9) 436	0
Blood and lymphatic system disorders	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Neutropenia	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Ear and labyrinth disorders	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Ear discomfort	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Endocrine disorders	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Hypothyroidism	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Eye disorders	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Lacrimation increased	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Gastrointestinal disorders	13 (12.1) 15	0	11 (10.4) 12	0	24 (11.3) 27	0
Diarrhoea	3 (2.8) 3	0	2 (1.9) 2	0	5 (2.3) 5	0
Toothache	4 (3.7) 6	0	1 (0.9) 1	0	5 (2.3) 7	0
Gastritis	1 (0.9) 1	0	2 (1.9) 3	0	3 (1.4) 4	0
Abdominal pain	2 (1.9) 2	0	0	0	2 (0.9) 2	0
Abdominal pain upper	0	0	2 (1.9) 2	0	2 (0.9) 2	0
Gastrointestinal disorders(Contd...)						
Vomiting	1 (0.9) 1	0	1 (0.9) 1	0	2 (0.9) 2	0
Abdominal pain lower	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Dental caries	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Dyspepsia	0	0	1 (0.9) 1	0	1 (0.5) 1	0
Gingival pain	1 (0.9) 1	0	0	0	1 (0.5) 1	0
Tooth disorder	1 (0.9) 1	0	0	0	1 (0.5) 1	0
General disorders and administration site conditions	3 (2.8) 3	0	3 (2.8) 3	0	6 (2.8) 6	0
Fatigue	1 (0.9) 1	0	1 (0.9) 1	0	2 (0.9) 2	0
Pyrexia	0	0	2 (1.9) 2	0	2 (0.9) 2	0
Influenza like illness	1 (0.9) 1	0	0	0	1 (0.5) 1	0
Oedema peripheral	1 (0.9) 1	0	0	0	1 (0.5) 1	0
Infections and infestations	54 (50.5) 88	0	66 (62.3) 90	0	120 (56.3) 178	0
Nasopharyngitis	38 (35.5) 52	0	47 (44.3) 61	0	85 (39.9) 113	0
COVID-19	10 (9.3) 10	0	9 (8.5) 9	0	19 (8.9) 19	0
Upper respiratory tract infection	8 (7.5) 9	0	2 (1.9) 2	0	10 (4.7) 11	0

Infections and infestations(Contd...)										
Rhinitis	3 (2.8)	3	0	4 (3.8)	4	0	7 (3.3)	7	0	
Oral herpes	2 (1.9)	2	0	4 (3.8)	4	0	6 (2.8)	6	0	
Gastroenteritis	2 (1.9)	2	0	1 (0.9)	1	0	3 (1.4)	3	0	
Asymptomatic COVID-19	2 (1.9)	2	0	0		0	2 (0.9)	2	0	
Bronchitis	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Herpes zoster	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Otitis externa	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Pharyngitis streptococcal	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Sinusitis	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Conjunctivitis	0		0	1 (0.9)	2	0	1 (0.5)	2	0	
Cystitis	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Gingivitis	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Influenza	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Periodontitis	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Urinary tract infection	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Injury, poisoning and procedural complications	15 (14.0)	20	0	13 (12.3)	16	0	28 (13.1)	36	0	
Contusion	3 (2.8)	3	0	2 (1.9)	2	0	5 (2.3)	5	0	
Tooth fracture	1 (0.9)	1	0	2 (1.9)	2	0	3 (1.4)	3	0	
Chest injury	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Fall	0		0	2 (1.9)	2	0	2 (0.9)	2	0	
Joint injury	0		0	2 (1.9)	2	0	2 (0.9)	2	0	
Limb injury	2 (1.9)	2	0	0		0	2 (0.9)	2	0	
Post vaccination syndrome	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Procedural pain	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Traumatic haematoma	2 (1.9)	2	0	0		0	2 (0.9)	2	0	
Accident	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Foot fracture	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Hand fracture	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Head injury	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Injury	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Injury, poisoning and procedural complications(Contd...)										
Ligament injury	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Ligament rupture	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Ligament sprain	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Muscle rupture	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Road traffic accident	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Skin abrasion	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Spinal column injury	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Thermal burn	0		0	1 (0.9)	2	0	1 (0.5)	2	0	
Investigations	1 (0.9)	3	0	3 (2.8)	4	0	4 (1.9)	7	0	
Aspartate aminotransferase increased	1 (0.9)	1	0	2 (1.9)	2	0	3 (1.4)	3	0	
Gamma-glutamyltransferase increased	1 (0.9)	1	0	2 (1.9)	2	0	3 (1.4)	3	0	
Alanine aminotransferase increased	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Metabolism and nutrition disorders	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Gout	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Musculoskeletal and connective tissue disorders	20 (18.7)	23	0	19 (17.9)	27	0	39 (18.3)	50	0	
Musculoskeletal and connective tissue disorders(Contd...)										
Back pain	10 (9.3)	10	0	6 (5.7)	11	0	16 (7.5)	21	0	
Pain in extremity	5 (4.7)	5	0	5 (4.7)	5	0	10 (4.7)	10	0	
Arthralgia	3 (2.8)	3	0	2 (1.9)	3	0	5 (2.3)	6	0	
Myalgia	1 (0.9)	1	0	3 (2.8)	3	0	4 (1.9)	4	0	
Musculoskeletal chest pain	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Musculoskeletal pain	1 (0.9)	1	0	1 (0.9)	1	0	2 (0.9)	2	0	
Spinal pain	0		0	2 (1.9)	2	0	2 (0.9)	2	0	
Limb discomfort	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Synovitis	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Tenosynovitis	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Bile duct adenocarcinoma	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Nervous system disorders	24 (22.4)	48	0	19 (17.9)	28	0	43 (20.2)	76	0	
Headache	24 (22.4)	48	0	15 (14.2)	22	0	39 (18.3)	70	0	
Syncope	0		0	3 (2.8)	3	0	3 (1.4)	3	0	
Nervous system disorders(Contd...)										
Dizziness	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Hypoaesthesia	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Paraesthesia	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Psychiatric disorders	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Suicide attempt	1 (0.9)	1	0	0		0	1 (0.5)	1	0	
Renal and urinary disorders	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Pollakiuria	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Reproductive system and breast disorders	0		0	2 (1.9)	3	0	2 (0.9)	3	0	
Dyspareunia	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Penile blister	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Penile pain	0		0	1 (0.9)	1	0	1 (0.5)	1	0	
Respiratory, thoracic and mediastinal disorders	12 (11.2)	13	0	14 (13.2)	15	0	26 (12.2)	28	0	
Oropharyngeal pain	5 (4.7)	5	0	6 (5.7)	6	0	11 (5.2)	11	0	
Rhinorrhoea	5 (4.7)	5	0	6 (5.7)	6	0	11 (5.2)	11	0	
Cough	3 (2.8)	3	0	2 (1.9)	2	0	5 (2.3)	5	0	

Respiratory, thoracic and mediastinal disorders (Contd...)									
Rhinitis allergic	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Skin and subcutaneous tissue disorders	4 (3.7)	5	0	1 (0.9)	2	0	5 (2.3)	7	0
Rash	2 (1.9)	2	0	0		0	2 (0.9)	2	0
Dermatitis contact	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Ecchymosis	1 (0.9)	1	0	0		0	1 (0.5)	1	0
Erythema	1 (0.9)	1	0	0		0	1 (0.5)	1	0
Papule	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Pruritus	1 (0.9)	1	0	0		0	1 (0.5)	1	0
Social circumstances	0		0	1 (0.9)	2	0	1 (0.5)	2	0
Alcohol use	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Inadequate diet	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Surgical and medical procedures	4 (3.7)	4	0	3 (2.8)	3	0	7 (3.3)	7	0
Tooth extraction	3 (2.8)	3	0	1 (0.9)	1	0	4 (1.9)	4	0
Endodontic procedure	1 (0.9)	1	0	0		0	1 (0.5)	1	0
Inguinal hernia repair	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Surgical and medical procedures (Contd...)									
Tooth repair	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Vascular disorders	0		0	1 (0.9)	1	0	1 (0.5)	1	0
Phlebitis	0		0	1 (0.9)	1	0	1 (0.5)	1	0

Abbreviations: E = Number of Events; n = Number of Subjects; TEAE = Treatment-Emergent Adverse Event.
Adverse events were coded using MedDRA version 24.0.
Subjects are counted only once under the category of their drug-related event over unrelated within each system organ class and preferred term.
Source: Listing 16.2.7.2.

None of the reported TEAE was considered by the Investigator to be related to the study drug.

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Data are presented in Table 31, Table 32, Table 33, Table 34, Table 35, Table 36 and Table 37.

Table 31. Overall summary of TEAEs – Core treatment period (Safety Analysis Set)

Adverse Event Category [n (%) m] Rate per 100 Patient Years (95% CI)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Any TEAE	185 (66.8) 583 217.391 (200.441- 235.773)	189 (68.5) 613 230.894 (213.321 - 249.916)	374 (67.6) 1196 224.108 (211.760 - 237.177)
Any TEAE Related to IP	25 (9.0) 50 18.644 (14.131 - 24.599)	31 (11.2) 44 16.573 (12.333 - 22.271)	56 (10.1) 94 17.614 (14.390 - 21.560)
Any Serious TEAE	43 (15.5) 46 17.153 (12.848 - 22.900)	50 (18.1) 54 20.340 (15.578 - 26.557)	93 (16.8) 100 18.738 (15.403 - 22.795)
Any Serious TEAE Related to IP	1 (0.4) 1 0.373 (0.053 - 2.647)	0	1 (0.2) 1 0.187 (0.026 - 1.330)
Any TEAE ≥ Grade 3	7 (2.5) 8 2.983 (1.492 - 5.965)	11 (4.0) 15 5.650 (3.406 - 9.372)	18 (3.3) 23 4.310 (2.864 - 6.486)
Any TEAE Related to IP ≥ Grade 3	0	0	0
Any TEAE ≥ Grade 4	0	1 (0.4) 1 0.377 (0.053 - 2.674)	1 (0.2) 1 0.187 (0.026 - 1.330)
Any TEAE Related to IP ≥ Grade 4	0	0	0
Any TEAE of Special Interest	0	7 (2.5) 11 4.143 (2.295 - 7.482)	7 (1.3) 11 2.061 (1.141 - 3.722)
Any TEAE of Special Interest Related to IP	0	0	0
Any TEAE Leading to Withdrawal of IP	0	6 (2.2) 10 3.767 (2.027 - 7.001)	6 (1.1) 10 1.874 (1.008 - 3.483)
Any TEAE Related to IP Leading to Withdrawal of IP	0	0	0
Any TEAE Leading to Interruption of IP	3 (1.1) 3 1.119 (0.361 - 3.469)	1 (0.4) 1 0.377 (0.053 - 2.674)	4 (0.7) 4 0.750 (0.281 - 1.997)
Any TEAE Related to IP Leading to Interruption of IP	1 (0.4) 1 0.373 (0.053 - 2.647)	0	1 (0.2) 1 0.187 (0.026 - 1.330)
Any TEAE Leading to Discontinuation of Study	0	7 (2.5) 11 4.143 (2.295 - 7.482)	7 (1.3) 11 2.061 (1.141 - 3.722)
Any TEAE Related to IP Leading to Discontinuation of Study	0	0	0
Any TEAE Leading to Death	0	0	0
Any TEAE Related to IP Leading to Death	0	0	0
Any Serious Injection Site Reaction	0	0	0
Any Injection Site Reaction Leading to Interruption or Discontinuation of IP	0	0	0
Any TEAE Involving Fracture	3 (1.1) 3 1.119 (0.361 - 3.469)	9 (3.3) 10 3.767 (2.027 - 7.001)	12 (2.2) 13 2.436 (1.414 - 4.195)
Any TEAE Fracture Involving Spine	1 (0.4) 1 0.373 (0.053 - 2.647)	0	1 (0.2) 1 0.187 (0.026 - 1.330)
Any TEAE Fracture Involving Femur and Hip	0	1 (0.4) 2 0.753 (0.188 - 3.012)	1 (0.2) 2 0.375 (0.094 - 1.499)

Source: Table 14.3.2.1.1.
AE = Adverse Event; CI = Confidence Interval; IP = Investigational Product; m = Number of events; n = Number of patients; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = Serious Adverse Event; SE = Standard Error; TEAE = Treatment-Emergent Adverse Event.
Note: For each category, patients were included only once, even if they experienced multiple events in that category. Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit.
Note: Incidence per 100 patient years was calculated by dividing the number of events multiplied by 365.25, and then by 100, by the sum of the days on study for all patients in the Core Treatment Period.
Note: TEAEs of Special Interest were drug-related hypersensitivity/allergic reactions (NCI-CTCAE Grade ≥ 3 or reported as SAEs) and AEs leading to IP discontinuation or study withdrawal during the Core Treatment Period.
Note: The 95% CI was calculated as: LnRate= log(Rate), and SE of LnRate=1/sqrt(number of events); 95% CI Rate = exp(LnRate +/- 1.96*SE).
Note: If any TEAE was missing the relatedness information, that AE was considered as related to the study drug.

Table 32. Overall summary of TEAEs – Transition treatment period (TP – Safety Analysis Set)

Adverse Event Category [n (%) m] Rate per 100 Patient Years (95% CI)]	FKS518 (N=252)	US-Prolia/FKS518 (N=124)	US-Prolia (N=125)	Total (N=501)
Any TEAE	106 (42.1) 200 159.707 (139.038 - 183.449)	58 (46.8) 113 183.976 (152.998 - 221.227)	47 (37.6) 91 145.869 (118.777 - 179.141)	211 (42.1) 404 162.226 (147.154 - 178.843)
Any TEAE Related to IP	4 (1.6) 6 4.791 (2.152 - 10.665)	3 (2.4) 3 4.884 (1.575 - 15.145)	3 (2.4) 4 6.412 (2.406 - 17.084)	10 (2.0) 13 5.220 (3.031 - 8.990)
Any Serious TEAE	8 (3.2) 8 6.388 (3.195 - 12.774)	6 (4.8) 6 9.769 (4.389 - 21.744)	6 (4.8) 6 9.618 (4.321 - 21.408)	20 (4.0) 20 8.031 (5.181 - 12.448)
Any Serious TEAE Related to IP	0	0	0	0
Any TEAE ≥ Grade 3	4 (1.6) 4 3.194 (1.199 - 8.511)	4 (3.2) 5 8.141 (3.388 - 19.558)	3 (2.4) 3 4.809 (1.551 - 14.911)	11 (2.2) 12 4.819 (2.737 - 8.485)
Any TEAE Related to IP ≥ Grade 3	0	0	0	0
Any TEAE ≥ Grade 4	0	0	0	0
Any TEAE Related to IP ≥ Grade 4	0	0	0	0
Any TEAE of Special Interest	0	1 (0.8) 1 1.628 (0.229 - 11.558)	0	1 (0.2) 1 0.402 (0.057 - 2.851)
Any TEAE of Special Interest Related to IP	0	0	0	0
Any TEAE Leading to Withdrawal of IP	0	0	0	0
Any TEAE Related to IP Leading to Withdrawal of IP	0	0	0	0
Any TEAE Leading to Interruption of IP	0	0	0	0
Any TEAE Related to IP Leading to Interruption of IP	0	0	0	0
Any TEAE Leading to Discontinuation of Study	0	1 (0.8) 1 1.628 (0.229 - 11.558)	0	1 (0.2) 1 0.402 (0.057 - 2.851)
Any TEAE Related to IP Leading to Discontinuation of Study	0	0	0	0
Any TEAE Leading to Death	0	0	0	0
Any TEAE Related to IP Leading to Death	0	0	0	0
Any Serious Injection Site Reaction	0	0	0	0
Any Injection Site Reaction Leading to Interruption or Discontinuation of IP	0	0	0	0
Any TEAE Involving Fracture	2 (0.8) 2 1.597 (0.399 - 6.386)	1 (0.8) 1 1.628 (0.229 - 11.558)	2 (1.6) 3 4.809 (1.551 - 14.911)	5 (1.0) 6 2.409 (1.082 - 5.363)
Any TEAE Fracture Involving Spine	1 (0.4) 1 0.799 (0.112 - 5.669)	0	0	1 (0.2) 1 0.402 (0.057 - 2.851)
Any TEAE Fracture Involving Femur and Hip	0	0	0	0

Source: Table 14.3.2.1.2.
AE = Adverse Event; CI = Confidence Interval; IP = Investigational Product; m = Number of events; n = Number of patients; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = Serious Adverse Event; SE = Standard Error; TEAE = Treatment-Emergent Adverse Event; TP = Transition Period.
Note: For each category, patients were included only once, even if they experienced multiple events in that category.
Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit.
Note: Incidence per 100 patient years was calculated by dividing the number of events multiplied by 365.25, and then by 100, by the sum of the days on study for all patients in the Transition Period.
Note: TEAEs of Special Interest were drug-related hypersensitivity/allergic reactions (NCI-CTCAE Grade ≥ 3 or reported as SAEs) and AEs leading to IP discontinuation or study withdrawal during the Transition Period.
Note: The 95% CI was calculated as: LnRate= log(Rate), and SE of LnRate=1/sqrt(number of events); 95% CI Rate = exp(LnRate +/- 1.96*SE).
Note: If any TEAE was missing the relatedness information, that AE was considered as related to the study drug.

Table 33. TEAE in≥ 5% of patients in either treatment group by SOC and PT – Core treatment period (Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Number of Patients with Any TEAE	185 (66.8)	189 (68.5)	374 (67.6)
Infections and infestations	118 (42.6)	131 (47.5)	249 (45.0)
COVID-19	32 (11.6)	41 (14.9)	73 (13.2)
Nasopharyngitis	26 (9.4)	33 (12.0)	59 (10.7)
Upper respiratory tract infection	23 (8.3)	30 (10.9)	53 (9.6)
Urinary tract infection	18 (6.5)	23 (8.3)	41 (7.4)
Nervous system disorders	24 (8.7)	34 (12.3)	58 (10.5)
Headache	13 (4.7)	14 (5.1)	27 (4.9)

Source: Table 14.3.2.2.1.1.
AE = Adverse Event; COVID-19 = Coronavirus Disease 2019; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-Emergent Adverse Event.
Note: AEs were coded using MedDRA version 24.0. For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that system organ class or preferred term.
Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Core Treatment Period.

Table 34. TEAE in≥ 5% of patients in either treatment group by SOC and PT – Transition Treatment Period (TP – Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=252)	US-Prolia/ FKS518 (N=124)	US-Prolia (N=125)	Total (N=501)
Number of Patients with Any TEAE	106 (42.1)	58 (46.8)	47 (37.6)	211 (42.1)
Infections and infestations	62 (24.6)	38 (30.6)	24 (19.2)	124 (24.8)
Nasopharyngitis	11 (4.4)	17 (13.7)	8 (6.4)	36 (7.2)
Upper respiratory tract infection	12 (4.8)	8 (6.5)	7 (5.6)	27 (5.4)

Source: Table 14.3.2.2.1.2.
AE = Adverse Event; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-Emergent Adverse Event; TP = Transition Period.
Note: AEs were coded using MedDRA version 24.0. For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that system organ class or preferred term.
Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Transition Period.

Table 35. TEAEs by SOC and PT involving a fracture – Core treatment period (Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Number of Subjects with Any TEAE involving Fracture	3 (1.1)	9 (3.3)	12 (2.2)
Injury, poisoning and procedural complications	3 (1.1)	9 (3.3)	12 (2.2)
Tooth fracture	0	4 (1.4)	4 (0.7)
Radius fracture	1 (0.4)	1 (0.4)	2 (0.4)
Femur fracture	0	1 (0.4)	1 (0.2)
Foot fracture	0	1 (0.4)	1 (0.2)
Fractured sacrum	1 (0.4)	0	1 (0.2)
Humerus fracture	0	1 (0.4)	1 (0.2)
Patella fracture	1 (0.4)	0	1 (0.2)
Tibia fracture	0	1 (0.4)	1 (0.2)

IP = Investigational Product; TEAE = Treatment-Emergent Adverse Event.
Note: Adverse events were coded using MedDRA version 24.0. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term. Treatment-emergence is defined as AEs that begin or increase in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit.
Note: The preferred terms used to search for TEAEs involving a fracture are listed in SAP Section 16.8.

Source: Listing 16.2.7.1, Dataset: ADAE, Program: t-ae-bysoc-pt-fracture-core.sas, Output: T-14-03-02-02-19-03-01-bysoc-pt-fracture-core.rtf, Generated on: 2023-12-19T15:31
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Table 36. TEAEs by SOC and PT involving a fracture – Transition Treatment Period (TP-Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=252)	US-Prolia/ FKS518 (N=124)	US-Prolia (N=125)	Total (N=501)
Number of Subjects with Any TEAE involving Fracture	2 (0.8)	1 (0.8)	2 (1.6)	5 (1.0)
Injury, poisoning and procedural complications	2 (0.8)	1 (0.8)	2 (1.6)	5 (1.0)
Clavicle fracture	0	0	1 (0.8)	1 (0.2)
Foot fracture	0	0	1 (0.8)	1 (0.2)
Forearm fracture	1 (0.4)	0	0	1 (0.2)
Lumbar vertebral fracture	1 (0.4)	0	0	1 (0.2)
Rib fracture	0	0	1 (0.8)	1 (0.2)
Tooth fracture	0	1 (0.8)	0	1 (0.2)

IP = Investigational Product; TEAE = Treatment-Emergent Adverse Event; TP = Transition Period.
Note: Adverse events were coded using MedDRA version 24.0. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term. Treatment-emergence is defined as AEs that begin or increase in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit.
Note: The preferred terms used to search for TEAEs involving a fracture are listed in SAP Section 16.8.

Source: Listing 16.2.7.1, Dataset: ADAE, Program: t-ae-bysoc-pt-fracture-trans.sas, Output: T-14-03-02-02-19-03-02-bysoc-pt-fracture-trans.rtf, Generated on: 2023-12-19T15:31
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Table 37. Treatment-Related TEAE in ≥ 1% of patients in any treatment group by PT during the Core treatment period (Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Number of Patients with Any TEAE Related to IP	25 (9.0)	31 (11.2)	56 (10.1)
Musculoskeletal and connective tissue disorders	10 (3.6)	11 (4.0)	21 (3.8)
Arthralgia	4 (1.4)	4 (1.4)	8 (1.4)
Pain in extremity	3 (1.1)	0	3 (0.5)
Infections and infestations	9 (3.2)	10 (3.6)	19 (3.4)
Upper respiratory tract infection	2 (0.7)	3 (1.1)	5 (0.9)
Nasopharyngitis	0	3 (1.1)	3 (0.5)
Skin and subcutaneous tissue disorders	4 (1.4)	3 (1.1)	7 (1.3)
Alopecia	2 (0.7)	3 (1.1)	5 (0.9)

Source: Table 14.3.2.2.2.1.
AE = Adverse Event; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-Emergent Adverse Event.
Note: AEs were coded using MedDRA version 24.0. Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit.
Note: Relatedness was assessed by the Investigator. Missing relatedness was imputed as 'Related'.
Note: For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that category.

2.6.8.3. Serious adverse event/deaths/other significant events

Study FKS518-001

No deaths were reported during the study in healthy subjects.

During the study, 23 SAEs were reported in 23 subjects in the Safety Analysis Set.

The most commonly reported SAE was COVID-19 in both groups (symptomatic COVID-19 in 19 subjects and asymptomatic COVID-19 in 2 subjects); none of the other SAEs were reported for more than 1 subject. There were no discernable patterns in terms of the nature, frequency, or other characteristics of the SAEs that would suggest a difference between the FKS518 and US-Prolia groups.

During the screening period, 1 pretreatment SAE of symptomatic COVID-19 was reported in a screen failure subject, who was not randomised and dosed. Therefore, this subject was not included in the

Safety Analysis Set. No pre-treatment SAEs were reported during the screening period for the randomised subjects.

For the purpose of this study, and to facilitate monitoring of the course of events, confirmed COVID-19 cases were defined as serious using the category 'otherwise medically important' in the study protocol and consequently classified and managed as SAEs. All COVID-19 cases were categorized as Grade 1 to Grade 2 in severity. None of these COVID-19 cases led to hospitalisation or death.

A summary of the 2 non-COVID-19 SAEs reported during the study is provided below:

• One subject (FKS518 group) experienced Grade 3 bile duct adenocarcinoma on Study Day 115, which was considered an SAE for being medically important. No clinical symptoms were reported, but liver laboratory tests and enlarged liver on palpation during the physical examination led to suspicion, an abdominal ultrasound showed a liver tumor, and the pathology examination confirmed the bile duct adenocarcinoma.

• One Subject (FKS518 group) experienced a Grade 4 suicide attempt on Study Day 68, which was considered an SAE for being life threatening and resulting in hospitalisation. The subject was hospitalised from Study Day 69 to Study Day 125. On Study Day 127, during an ambulatory visit, the subject provided the discharge documentation from psychiatric hospitalisation with the diagnosis of paranoid schizophrenia and instructions to take antipsychotic drugs, although the subject did not take them. The study site clarified that prior to this visit, the subject had not informed them about this disorder, despite having been asked to present full medical and treatment history. The subject did not provide any information about alcohol abuse or brain injury prior to the psychiatric episode. On the screening visit, the subject did not mention the diagnosis and denied any psychiatric disorder. The subject did not take antipsychotic drugs while entering and during the study until the suicide attempt. None of the SAEs was considered related to the IP.

Adverse event of special interest (AESI) was defined as: Hypersensitivity/allergic reactions (common terminology criteria for adverse events [CTCAE] Grade ≥ 3 or reported as serious events), and adverse events (AEs) leading to study withdrawal.

Data are presented in Table 38.

Table 38. Hypersensitivity SMQ TEAES by SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	FKS518 (N=107) n (%) E	US-Prolia (N=106) n (%) E	Overall (N=213) n (%) E
Number of subjects (%) with at least one Hypersensitivity SMQ TEAE and number of Hypersensitivity SMQ TEAEs	3 (2.8) 4	3 (2.8) 4	6 (2.8) 8
Infections and infestations	0	1 (0.9) 2	1 (0.5) 2
Conjunctivitis	0	1 (0.9) 2	1 (0.5) 2
Respiratory, thoracic and mediastinal disorders	0	1 (0.9) 1	1 (0.5) 1
Rhinitis allergic	0	1 (0.9) 1	1 (0.5) 1
Skin and subcutaneous tissue disorders	3 (2.8) 4	1 (0.9) 1	4 (1.9) 5
Rash	2 (1.9) 2	0	2 (0.9) 2
Dermatitis contact	0	1 (0.9) 1	1 (0.5) 1
Erythema	1 (0.9) 1	0	1 (0.5) 1
Pruritus	1 (0.9) 1	0	1 (0.5) 1

Abbreviations: E = Number of Events; n = Number of Subjects; SMQ = Standardised MedDRA Queries; TEAE = Treatment-Emergent Adverse Event.
Adverse events were coded using MedDRA version 24.0.
A subject can experience multiple occurrences of an adverse event, but will only be counted once per system organ class and preferred term for each treatment.
The SMQs for Hypersensitivity reactions include both the 'narrow' terms and the additional 'broad' terms.
Source: Listing 16.2.7.2

No episodes of anaphylactic reactions were reported during the study.

One AESI (AE leading to study withdrawal) was reported during the study: a serious TEAE of bile duct adenocarcinoma. See 2.6.8.9.

Study FKS518-002

No deaths were reported during this study.

Serious TEAEs by SOC and PT are summarised for the core treatment period (Safety Analysis Set) in the table below.

Data are presented in Table 39 and Table 40.

Table 39. Serious TEAEs by SOC and PT – Core treatment period (Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Number of Patients with Any SAE	43 (15.5)	50 (18.1)	93 (16.8)
Infections and infestations	35 (12.6)	43 (15.6)	78 (14.1)
COVID-19	32 (11.6)	41 (14.9)	73 (13.2)
Asymptomatic COVID-19	3 (1.1)	1 (0.4)	4 (0.7)
COVID-19 pneumonia	1 (0.4)	1 (0.4)	2 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7)	7 (2.5)	9 (1.6)
Bladder neoplasm	0	1 (0.4)	1 (0.2)
Bladder transitional cell carcinoma	1 (0.4)	0	1 (0.2)
Glioblastoma	0	1 (0.4)	1 (0.2)
Lung adenocarcinoma	0	1 (0.4)	1 (0.2)
Metastases to lymph nodes	0	1 (0.4)	1 (0.2)
Nasopharyngeal cancer	0	1 (0.4)	1 (0.2)
Neuroendocrine tumour of the lung metastatic	0	1 (0.4)	1 (0.2)
Oral papilloma	0	1 (0.4)	1 (0.2)
Ovarian cancer	0	1 (0.4)	1 (0.2)
Squamous cell carcinoma	1 (0.4)	0	1 (0.2)
Nervous system disorders	2 (0.7)	1 (0.4)	3 (0.5)
Balance disorder	1 (0.4)	1 (0.4)	2 (0.4)
Loss of consciousness	1 (0.4)	0	1 (0.2)
Reproductive system and breast disorders	2 (0.7)	0	2 (0.4)
Hydrometra	1 (0.4)	0	1 (0.2)
Rectocele	1 (0.4)	0	1 (0.2)
Ear and labyrinth disorders	1 (0.4)	0	1 (0.2)
Vestibular disorder	1 (0.4)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.4)	0	1 (0.2)
Foot deformity	1 (0.4)	0	1 (0.2)
Product issues	0	1 (0.4)	1 (0.2)
Device dislocation	0	1 (0.4)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0	1 (0.2)
Asthma	1 (0.4)	0	1 (0.2)
Vascular disorders	1 (0.4)	0	1 (0.2)
Hypertension	1 (0.4)	0	1 (0.2)

Source: Table 14.3.2.2.15.1.
AE = Adverse Event; COVID-19 = Coronavirus Disease 2019; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; SAE = Serious adverse event.
Note: AEs were coded using MedDRA version 24.0. For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that system organ class or preferred term.
Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Core Treatment Period.

Serious TEAEs by SOC and PT are summarised for the transition period (TP-Safety Analysis Set) in the table below.

Table 40. Serious TEAEs by SOC and PT – Transition treatment period (TP – Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=252)	US-Prolia/ FKS518 (N=124)	US-Prolia (N=125)	Total (N=501)
Number of Patients with Any SAE	8 (3.2)	6 (4.8)	6 (4.8)	20 (4.0)
Infections and infestations	6 (2.4)	4 (3.2)	3 (2.4)	13 (2.6)
COVID-19	6 (2.4)	4 (3.2)	3 (2.4)	13 (2.6)
Nervous system disorders	0	0	2 (1.6)	2 (0.4)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.8)	1 (0.2)
Dizziness	0	0	1 (0.8)	1 (0.2)
Blood and lymphatic system disorders	1 (0.4)	0	0	1 (0.2)
Thrombocytosis	1 (0.4)	0	0	1 (0.2)
Cardiac disorders	1 (0.4)	0	0	1 (0.2)
Angina pectoris	1 (0.4)	0	0	1 (0.2)
Gastrointestinal disorders	0	1 (0.8)	0	1 (0.2)
Pancreatitis acute	0	1 (0.8)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0	0	1 (0.8)	1 (0.2)
Spinal osteoarthritis	0	0	1 (0.8)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.8)	0	1 (0.2)
Bladder cancer recurrent	0	1 (0.8)	0	1 (0.2)

Source: Table 14.3.2.2.15.2.
AE = Adverse Event; COVID-19 = Coronavirus Disease 2019; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; SAE = Serious adverse event; TP = Transition Period.
Note: AEs were coded using MedDRA version 24.0. For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that system organ class or preferred term.
Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Transition Period.

Adverse Events of Special Interest

As no IP-related hypersensitivity/allergic reactions were reported during the study that were CTCAE Grade ≥ 3 or were reported as SAEs, all AESIs during the study consisted of AEs leading to IP discontinuation or study withdrawal. See 2.6.8.9.

During the study, few patients had at least 1 SMQ hypersensitivity TEAE: 29 and 17 patients in the FKS518 and US-Prolia groups, respectively, during the core treatment period and 3, 8, and 4 patients in the FKS518, US-Prolia/FKS518, and US-Prolia groups, respectively, during the transition period. The incidence and distribution of SMQ hypersensitivity TEAEs across SOCs and PTs was not notably different among the treatment groups. None of the hypersensitivity TEAEs were severe, serious, or IP-related, and therefore, no episodes of hypersensitivity reactions qualified as AESIs during the study.

2.6.8.4. Laboratory findings

Study FKS518-001

Hematology

There were no clinically meaningful differences across treatments in the proportions of subjects with the worst on-treatment haematology values in each CTCAE category (i.e., Grade 0 to Grade 2 or 3). The only haematology parameter that was reported as a Grade ≥ 3 AE during the study was 1 case of Grade 3 neutropenia (in the US-Prolia group).

Clinical Chemistry

During the study, Grade 3 or 4 creatine kinase values were observed in 14 subjects in the FKS518 group and 12 subjects in the US-Prolia group, but these high values were queried and resulted being due to subject's exercise and not clinically significant, with no differences observed between the treatment groups regarding this observation. Grade 3 low phosphate values were observed at some

time points during the study in 4 subjects in the FKS518 group and 2 subjects in the US-Prolia group, none of which was assessed as clinically significant. Moreover, no Grade ≥ 2 calcium values were observed during the study.

During the study, the following biochemistry parameters were reported as Grade ≥ 3 AEs: increased AST (US-Prolia group) in one patient; increased GGT (US-Prolia group) in one patient who also had Grade 3 AEs of alcohol use and inadequate diet, increased GGT (US-Prolia group) in one patient who also had Grade 2 increased AST. In addition, one patient who was discontinued early from the study due to the SAE of bile duct adenocarcinoma, had Grade 3 high AST and Grade 3 high GGT values.

Urinalysis

There were no clinically meaningful differences across treatments in the proportions of subjects with the worst on-treatment urinalysis in each CTCAE category.

Local Tolerability

No subject was withdrawn from the study as a result of poor local tolerability in either treatment. The proportion of subjects reporting at least 1 ISR was low in both treatment groups, although numerically higher in the US-Prolia group (6 [5.7%] subjects) than in the FKS518 group (1 [0.9%] subject). All the ISRs consisted of injection site bruising and were graded as of mild (CTCAE Grade 1) severity.

For each of these subjects, only 1 ISR was reported. None of the subjects received an ancillary intervention for the ISR. ISRs were considered to be unrelated to the IP in 3 subjects in the US-Prolia group, and the remaining 4 ISRs (1 in the FKS518 group and 3 in the US-Prolia group) were considered to be related to the IP.

The ISR in the FKS518 group occurred 24 hours after injection; in the US-Prolia group, the median time from injection to the ISR was 48 hours, ranging from 2 to 179 hours.

Vital Signs

Vital signs at baseline and during the further course of the study in terms of group descriptive statistics and outliers were similar across treatments. The mean changes with time from baseline did not show a noteworthy pattern between the treatment groups.

Electrocardiograms

Several abnormal ECG results were reported but considered not clinically significant ~~(Listing 16.2.9.2).~~ There was no noteworthy imbalance in this regard between the treatment groups. Several ECG interpretations shifted from the baseline interpretation, but these did not show a noteworthy pattern between the treatment groups.

Study FKS518-002

Laboratory values over time

Clinically significant laboratory abnormalities with an onset after the initial exposure to IP were reported as TEAEs.

Hematology

There were no clinically meaningful differences in mean or median haematology values between the treatment groups for the core treatment period, transition period or overall period.

Clinical Chemistry

The majority of patients (> 90%) generally had normal values throughout the study for most clinical chemistry parameters, and there were no clinically meaningful differences among treatment groups in

the numbers of patients with shifts from normal at baseline to abnormal at any time during the study, notwithstanding clinically not meaningful numerical differences at isolated time points.

Urinalysis

No notable differences in the results of categorical urinalysis parameters were observed across the treatment groups for the core treatment period, the transition period, or the overall period.

Vital signs

Vital sign assessments at baseline and during the core treatment period in terms of group descriptive statistics and outliers were comparable between treatment groups. The mean changes over time from baseline did not show any noteworthy differences between treatment groups during the core treatment period. Consistent findings were observed for the Overall Period. In the transition period, any changes from the transition period baseline were small and appeared in similar proportions of patients who transitioned from US-Prolia to FKS518 compared to those who continued on their initially assigned IP. During the core treatment period, there were no clinically meaningful differences between the treatment groups in the proportions of patients with shifts in systolic and diastolic blood pressure, heart rate, respiration rate, or temperature values. Similar findings were noted for the transition period and the overall period.

Electrocardiograms

Overall, as expected for the study population, several abnormal ECG results were reported during the study; however, these were considered clinically significant only in 2 patients in the FKS518 group and 2 patients in the US-Prolia.

Physical Examinations

Any clinically important physical examination findings were reported as TEAEs.

Injection Site Reactions

Low proportions of patients reported at least 1 ISR during the study, with no notable differences among the treatment groups. During the core treatment period (first and second injections), 2 ISRs were reported for 1 (0.4%) patient in the FKS518 group (Itching and Pain) and 3 ISRs for 2 (0.7%) patients in the US-Prolia group (Swelling, Bruising, and Pain). After the third injection (transition period), 1 ISR was reported for 1 (0.4%) patient in the FKS518 group (Bruising), 1 ISR was reported for 1 (0.8%) patient in the US-Prolia group (Erythema), and no ISRs were reported in the US-Prolia/FKS518 group. In the Overall Period, focusing on the FKS518 versus US-Prolia groups, 3 ISRs were reported for 2 (0.7%) patients in the FKS518 group (Itching, Bruising, and Pain) and 2 ISRs for 2 (1.3%) patients in the US-Prolia group (Bruising and Erythema). Except a Grade 2 ISR of Itching on Study Day 2 experienced by a patient in the FKS518 group, all other reported ISRs during the study were Grade 1. All ISRs were considered related to the IP during the study. No serious ISR or ISR leading to interruption or discontinuation of IP was reported during the study.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Not applicable

2.6.8.7. Immunological events

ADA Assay

The applicant has adopted an electrochemiluminescence immunoassay (ECLIA) bridging assay to screen, confirm and quantify denosumab specific antibodies in human serum matrix. The adopted three-tiered approach for determination of ADAs was well described and developed and is considered state of the art. Furthermore, the applicant presented an electrochemiluminescence assay for the detection of neutralising ADA's in human serum. The assay for ADA detection was developed and validated by the same third-party laboratory, and information about validation and QC was provided by the applicant.

During review, the applicant explained that the overall high positivity rate in study FKS518-002 was due to target interference. Therefore, the ADA assay was modified and it could be confirmed that the occurrence of interference was accounted by the soluble form of the receptor activator of nuclear factor kappa-B ligand (sRANKL), the target for denosumab, in the ADA assay. Consequently, a partial validation of the modified ADA method was performed. In addition, the impact of endogenous RANKL interference on the NAb-assay was investigated. Results indicate that the method format did not present false positives in the presence of up to 313 ng/mL RANKL.

Study FKS518-001

All samples from the FKS518-001 study were ADA negative. No treatment-emergent adverse event (TEAE) fulfilling the protocol-defined adverse event of special interest (AESI) criterion of hypersensitivity reaction (Grade ≥ 3 or reported as serious events) were reported during the study.

Study FKS518-002

Data are presented in Table 41, Table 42 and Table 43.

Table 41. ADA and NAb incidence and ADA titre by time point – Core treatment period (Safety Analysis Set)

	ADA Incidence % (n/N+)		ADA Titer Median		ADA Titer Geometric Mean (Min, Max)		NAb Incidence % (n/N+)	
Time Point	FKS518 (N=277)	US-Prolia (N=276)	FKS518 (N=277)	US-Prolia (N=276)	FKS518 (N=277)	US-Prolia (N=276)	FKS518 (N=277)	US-Prolia (N=276)
Overall	1.1 (3/274)	2.2 (6/276)					0.4 (1/274)	0.4 (1/276)
Baseline	0.4 (1/276)	0	50.0		50.0 (50,50)		0	0
Week 2	0	0					0	0
Week 4	0	0					0	0
Week 8	0	0.4 (1/265)		50.0		50.0 (50,50)	0	0
Week 12	0.7 (2/268)	1.1 (3/265)	50.0	50.0	50.0 (50,50)	50.0 (50,50)	0.4 (1/268)	0.4 (1/265)
Week 26	0	0					0	0
Week 32	0	0					0	0
Week 40	0.4 (1/252)	0	50.0		50.0 (50,50)		0	0
Week 52	0	0.8 (2/252)		50.0		50.0 (50,50)	0	0

Source: Table 14.2.4.1.1.
ADA = Antidrug Antibody; Max = Maximum; Min = Minimum; MRD = Minimum Required Dilution; n = Number of patients with positive status; N = Number of patients in the Safety Analysis Set; N* = Number of patients with an ADA valid result; NAb = Neutralizing Antibody.
Note: The titer value was defined as the reciprocal of total sample dilution factor, including the assay MRD.
Note: If the titer of a confirmed ADA positive sample could not be determined the titer is set at the assay MRD (50).
Note: Overall was determined across all time points except Baseline (predose).
Note: ADA status was defined as positive for the study period if the patient had at least 1 positive postdose result in the ADA confirmatory assay any time during this period. NAb status was defined as positive for the study period if the patient had at least 1 positive postdose result in the NAb assay any time during this period. Otherwise, the status was defined as negative.

Table 42 ADA and NAb incidence and ADA titre by time point – Transition period (TP-Safety Analysis Set)

Time Point	ADA Incidence % (n/N*) FKS518 (N=252)	US-Prolia /FKS518 (N=124)	US-Prolia (N=125)	ADA Titer Median FKS518 (N=252)	US-Prolia /FKS518 (N=124)	US-Prolia (N=125)
Overall	0.8 (2/247)	0.8 (1/124)	1.6 (2/124)			
Transition Baseline	0	0	1.6 (2/125)			50.0
Week 64	0.8 (2/240)	0.8 (1/122)	0.8 (1/122)	50.0	50.0	50.0
Week 78	0	0	0.8 (1/122)			50.0

Time Point	ADA Titer Geometric Mean (Min, Max) FKS518 (N=252)	US-Prolia /FKS518 (N=124)	US-Prolia (N=125)	NAb Incidence % (n/N*) FKS518 (N=252)	US-Prolia /FKS518 (N=124)	US-Prolia (N=125)
Overall				0.4 (1/247)	0.8 (1/124)	0.8 (1/124)
Transition Baseline			50.0 (50,50)	0	0	0
Week 64	50.0 (50,50)	50.0 (50,50)	50.0 (50,50)	0.4 (1/240)	0.8 (1/122)	0.8 (1/122)
Week 78			50.0 (50,50)	0	0	0

Source: Table 14.2.4.1.2.
ADA = Antidrug Antibody; Max = Maximum; Min = Minimum; MRD = Minimum Required Dilution; n = Number of patients with Positive Status; N* = Number of patients with an ADA valid result; N = Number of patients in the TP-Safety Analysis Set; NAb = Neutralizing Antibody; TP = Transition Period;
Note: The titer value was defined as the reciprocal of total sample dilution factor, including the assay MRD.
Note: If the titer of a confirmed ADA positive sample could not have been determined the titer was set at the assay MRD (50).
Note: Overall was determined across all time points except Baseline (predose).
Note: ADA status was defined as positive for the study period if the patient had at least 1 positive postdose result in the ADA confirmatory assay any time during this period. NAb status was defined as positive for the study period if the patient had at least 1 positive postdose result in the NAb assay any time during this period. Otherwise, the status was defined as negative.

Table 43. Incidence of TEAEs by ADA and NAb status – Core treatment period (Safety Analysis Set)

	ADA/NAb Status	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
ADA Status				
Subgroups, n1	Positive	3	6	9
	Negative	271	270	541
Any TEAE, n (%)	Positive	2 (66.7)	5 (83.3)	7 (77.8)
	Negative	182 (67.2)	184 (68.1)	366 (67.7)
NAb Status				
Subgroups, n1	Positive	1	1	2
	Negative	273	275	548
Any TEAE, n (%)	Positive	1 (100)	1 (100)	2 (100)
	Negative	183 (67.0)	188 (68.4)	371 (67.7)

Source: Table 14.3.2.2.10.1 and Table 14.3.2.2.11.1.
ADA = Antidrug Antibody; AE = Adverse Event; IP = Investigational Product; NAb = Neutralizing Antibody; TEAE = Treatment-Emergent Adverse Event.
n1 = number of patients in each subgroup. This was the denominator of the percentages of patients with AEs.
Note: Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Core Treatment Period.
ADA Positive = Patients with at least 1 confirmed postbaseline positive ADA result.
ADA Negative = Patients who were negative in the screening assay + patients who were positive in the screening assay but negative in the confirmatory assay.
NAb Positive = Patients with at least 1 confirmed postbaseline positive NAb result. Otherwise, the NAb status was considered negative.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable

2.6.8.9. Discontinuation due to adverse events

Study FKS518-001

During Study FKS518-001, 1 subject in the Safety Analysis Set was discontinued early from the study due to a serious TEAEs of bile duct adenocarcinoma. There were no dose modifications due to AEs during the study.

Study FKS518-002

Data are presented in Table 44 and Table 45.

Table 44. TEAEs leading to discontinuation of IP by SOC and PT – Core treatment period (Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Number of Patients with Any TEAE Leading to Withdrawal of IP	0	6 (2.2)	6 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (1.1)	3 (0.5)
Glioblastoma	0	1 (0.4)	1 (0.2)
Metastases to lymph nodes	0	1 (0.4)	1 (0.2)
Nasopharyngeal cancer	0	1 (0.4)	1 (0.2)
Ovarian cancer	0	1 (0.4)	1 (0.2)
Cardiac disorders	0	1 (0.4)	1 (0.2)
Arrhythmia	0	1 (0.4)	1 (0.2)
Gastrointestinal disorders	0	1 (0.4)	1 (0.2)
Periodontal disease	0	1 (0.4)	1 (0.2)
Infections and infestations	0	1 (0.4)	1 (0.2)
Pulpitis dental	0	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.4)	1 (0.2)
Arthralgia	0	1 (0.4)	1 (0.2)
Spinal osteoarthritis	0	1 (0.4)	1 (0.2)
Nervous system disorders	0	1 (0.4)	1 (0.2)
Intercostal neuralgia	0	1 (0.4)	1 (0.2)

Source: Table 14.3.2.2.5.1.
AE = Adverse Event; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-Emergent Adverse Event.
Note: AEs were coded using MedDRA version 24.0. For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that system organ class or preferred term. Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Core Treatment Period.

Table 45. TEAEs leading to discontinuation of study by SOC and PT – Core treatment period (Safety Analysis Set)

System Organ Class Preferred Term [n (%)]	FKS518 (N=277)	US-Prolia (N=276)	Total (N=553)
Number of Patients with Any TEAE Leading to Discontinuation of Study	0	7 (2.5)	7 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (1.4)	4 (0.7)
Glioblastoma	0	1 (0.4)	1 (0.2)
Lung adenocarcinoma	0	1 (0.4)	1 (0.2)
Metastases to lymph nodes	0	1 (0.4)	1 (0.2)
Nasopharyngeal cancer	0	1 (0.4)	1 (0.2)
Ovarian cancer	0	1 (0.4)	1 (0.2)
Cardiac disorders	0	1 (0.4)	1 (0.2)
Arrhythmia	0	1 (0.4)	1 (0.2)
Gastrointestinal disorders	0	1 (0.4)	1 (0.2)
Periodontal disease	0	1 (0.4)	1 (0.2)
Infections and infestations	0	1 (0.4)	1 (0.2)
Pulpitis dental	0	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.4)	1 (0.2)
Arthralgia	0	1 (0.4)	1 (0.2)
Spinal osteoarthritis	0	1 (0.4)	1 (0.2)
Nervous system disorders	0	1 (0.4)	1 (0.2)
Intercostal neuralgia	0	1 (0.4)	1 (0.2)

Source: Table 14.3.2.2.6.1.
AE = Adverse Event; IP = Investigational Product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-Emergent Adverse Event.
Note: AEs were coded using MedDRA version 24.0. For each system organ class and preferred term, patients were included only once, even if they experienced multiple events in that system organ class or preferred term. Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP up to the Early Termination/End of Study Visit in the Core Treatment Period.

2.6.8.10. Post marketing experience

Not applicable

2.6.9. Discussion on clinical safety

Comparability of safety of FKS518 with the reference product US-Prolia was investigated in two clinical studies.

- **Study FKS518-001 (comparative PK study)**: pivotal, two-arm, parallel group, single dose study comparing FKS518 with US-Prolia in healthy male subjects.
- **Study FKS518-002 (comparative efficacy and safety study)**: pivotal, two-arm parallel-group study to demonstrate equivalent efficacy and PD of the proposed denosumab biosimilar FKS518 to US-Prolia in female patients with PMO.

No clinical studies were conducted with Xgeva as comparator. Since analytical similarity of FKS518 has been demonstrated in a 3-way analytical similarity assessment using EU-licensed as well as US-licensed Prolia and Xgeva, the results obtained in studies with US-Prolia as comparator can be extrapolated to similarity of FKS518 with EU-Prolia and Xgeva.

Additionally, the mechanism of action of denosumab is identical for all indications of Prolia/Xgeva. Therefore, safety and immunogenicity results can be extrapolated from patients with PMO to all indications. This extrapolation is further supported by the known safety and immunogenicity profile of denosumab as summarised in the product information for Prolia/Xgeva which is comparable across the approved indications and patient populations.

The safety data are discussed separately for each study as they were conducted in different populations (healthy male subjects and female subjects with PMO, respectively).

Study FKS518-001

Safety assessments were performed after administration of a single s.c. injection of 60 mg FKS518 and US-Prolia in healthy male volunteers. The safety endpoints consisted of AEs, physical examination findings, vital signs, a 12-lead electrocardiogram tracing, laboratory tests (clinical chemistry, haematology, and urinalysis) and local tolerability. Assessments were made at regular intervals.

The overall design of the clinical study is considered adequate for a comprehensive safety and immunogenicity assessment of FKS518 vs. US-Prolia. The safety assessments were designed to capture the known safety issues listed in the Prolia and Xgeva labels and are considered appropriate. The number of healthy male subjects who received a single dose of study drug was 213 (107 subjects in the FKS518 group and 106 subjects in the US-Prolia group). The available safety data and extent of exposure are considered adequate to assess the safety of FKS518 in comparison to US-Prolia.

A total of 166/213 (77.9%) subjects reported at least 1 TEAE. The number and proportion of subjects reporting at least 1 TEAE, as well as the number of reported events were similar in the FKS518 (225 TEAEs in 84 [78.5%] subjects) and the US-Prolia (211 TEAEs in 82 [77.4%] subjects) groups. There were no meaningful differences in the type, frequency, severity, or resolution of TEAEs across treatments. Most TEAEs were mild (58 subjects [27.2%]) or moderate (100 subjects [46.9%]). For 7 subjects (3.3%), at least one severe TEAE was reported, with no notable imbalances between treatment groups (2.8% in the FKS518 study arm and 3.8% in the US-Prolia study arm). Furthermore, 23 SAEs were reported by 23 subjects (10.8%) during the study. Most SAEs (21/23) were symptomatic or asymptomatic COVID-19 events. The other 2 SAEs were one event of bile duct adenocarcinoma on Day 115 (classified as an AESI) and one suicide attempt on Day 68, which was the one life-threatening event. The latter subject had a diagnosis of paranoid schizophrenia but did not provide any information at screening visit. The subject did not take antipsychotic drugs while entering and during the study until the suicide attempt. None of the TEAEs or SAEs was considered to be related to study drug, which is acknowledged. Furthermore, no deaths were reported during the study. TEAEs leading to study discontinuation were only reported for the study subject from the FKS518 treatment arm who had bile duct adenocarcinoma, which was unrelated to FKS518.

The most commonly reported SOC in both treatments arms belong to the group of Infections and infestations (50.5% of subjects in the FKS518 group and 62.3% of subjects in the US-Prolia group), followed by Nervous system disorders (22.4% and 17.9%, respectively), and Musculoskeletal and connective tissue disorders (18.7% and 17.9%, respectively). Nasopharyngitis was the most commonly reported TEAE (35.5% FKS518 group vs 44.3% US-Prolia), followed by headache (22.4% FKS518 vs 14.2% US-Prolia group). Contrarily to nasopharyngitis events, upper respiratory tract infections had the opposite incidence pattern to nasopharyngitis (7.5% FKS518 group vs 1.9% US-Prolia group). These nominal imbalances are likely to be due to chance, especially since the cases of nasopharyngitis and upper respiratory tract infections fit into the same medical concept. The TEAEs were mild to moderate in severity and resolved consequently. Overall, merely insignificant differences were found between FKS518 and US-Prolia regarding AEs.

Hypersensitivity/allergic reactions and AEs leading to study withdrawal were defined as AESI. Hypocalcaemia, skin infection, osteonecrosis of the jaw (ONJ), atypical femoral fracture, and injection site reaction are known adverse reactions from Prolia (Prolia SmPC) and should normally be included as AESI. As no events of this type were reported in the subjects, this is not of concern.

In study FKS518-001, hypersensitivity TEAEs were reported for 3 subjects in each treatment group but none of these TEAEs was severe, serious, or was considered as drug-related. Furthermore, no events

of anaphylactic reactions were reported. In general, there was no notable difference in serious TEAEs or AESIs between the treatment groups. This is acknowledged.

The proportion of subjects reporting at least one ISR was low in both treatment groups (6 [5.7%] subjects in the US-Prolia group and 1 [0.9%] subject in the FKS518 group). All ISRs were injection site bruises classified as mild and no one received additional intervention for ISR. Thus, no subject was withdrawn from the study due to poor local tolerability.

There were no remarkable findings on vital signs, laboratory analyses, physical examination or ECG results.

Following analysis in the ADA specificity tier, the immunogenicity results originally presented, which had previously been classified as ADA positive (96.2% FKS518 vs 97.1% US-Prolia), proved to be negative. Sensitivity analyses for the PK or PD parameters are therefore no longer shown. No TEAEs classified as drug-related hypersensitivity/allergic reactions were reported.

Study FKS518-002

In study FKS518-002, the safety evaluation included the analysis of AEs, physical examination findings, vital signs, a 12-lead electrocardiogram tracing, laboratory tests (clinical chemistry, haematology, and urinalysis) and local tolerability. The assessments were performed at regular intervals throughout the study period. Overall, the collection of safety data in study FKS518-002 is considered sufficiently reliable.

All randomised subjects received the first injection of either FKS518 or US-Prolia. The second injection was given to 94.6% of the patients with similar frequencies between the groups (95.3% of the patients in the FKS518 group and 93.8% of the patients in the US-Prolia group). The third injection was administered to 501 patients, with balanced frequencies among the groups. Thus, the number of patients exposed to the test and reference product is considered sufficient for conclusions to be drawn regarding comparability of safety. The follow-up time is also acceptable for the evaluation of safety in the biosimilar setting.

In the core treatment period of study FKS518-002, the number of patients experiencing any TEAE was similar between the groups (185 subjects in the FKS518 group and 189 subjects in the US-Prolia group). No TEAE led to death. The proportion of patients experiencing any TEAE related to IP was also similar between the groups (9% in the FKS518 group and 11.2% in the US-Prolia group). Serious TEAEs were also balanced between the groups with 15.5% in the FKS518 group and 18.1% in the US-Prolia group. Only one serious TEAE was related to IP (FKS518 group). The proportion of patients experiencing TEAE ≥ Grade 3 was low and balanced between groups (2.5% and 4.0%, respectively). Only one patient in the US-Prolia group experienced a TEAE ≥ Grade 4. In summary, for the core treatment period, there were no significant differences between the FKS518 and US-Prolia group regarding the number of TEAEs and seriousness of TEAEs. In the transition period, there was a balanced distribution of TEAEs among the FKS518 group, US-Prolia/FKS518 group and US-Prolia group.

In the core treatment period, the incidence of TEAEs by SOC was similar between the groups. The most frequent TEAE by SOC were infections and infestations (42.6% in the FKS518 group and 47.5% in the US-Prolia group). The most frequently reported TEAES by PT were COVID-19, nasopharyngitis, upper respiratory tract infection and urinary tract infection. All TEAEs by PT were of similar frequency between the FKS518 and US-Prolia group. Nervous system disorders were also balanced between the groups (8.7% in the FKS518 group and 12.3% in the US-Prolia group). The applicant also provided the non-serious TEAEs experienced by ≥ 1% of patients in either treatment group by PT. There were also no imbalances found between the groups. For the transition period, the most frequently reported TEAE were also infections and infestations. There were slightly higher frequencies in the US-Prolia/FKS518 group (30.6%) compared to the FKS518 group (24.6%) and US-Prolia group (19.2%). The most

frequently reported TEAES by PT in the transition period were nasopharyngitis (4.4% in the FKS518 group, 13.7% in the in the US-Prolia/FKS518 group and 6.4% in the US-Prolia group), followed by upper respiratory tract infection (4.8% in the FKS518 group, 6.5% in the in the US-Prolia/FKS518 group and 5.6% in the US-Prolia group). In summary, for the core treatment period, there were no significant differences between the FKS518 and US-Prolia group regarding the number of TEAEs by PT or SOC. For the transition period there were slightly higher frequencies of infections and infestations in the US-Prolia/FKS518 group. However, as the frequencies were balanced during the core treatment period and there was only a slight difference in the transition period, no concern arises.

The initially presented ADA results show that in the core treatment period of study FKS518-002, the overall ADA incidence was 94.2% for the FKS518 group and 94.9% for the US-Prolia group. The overall NAb incidence was 39.4% in the FKS518 group and 43.8% in the US-Prolia group. The ADA/NAb incidence by timepoint was also similar between the groups. Mean and median ADA titre was also comparable between the groups at each timepoint. Thus, the overall incidence of ADA and NAb-positive subjects was high but similar for both groups in this study. For the transition period, the ADA incidence was also similar among the groups (89.1% for the FKS518 group; 91.1% for the US-Prolia/FKS518 group and 86.3% for the US-Prolia group). The same holds true for the NAb incidence (28.3% for the FKS518 group; 29.8% for the US-Prolia/FKS518 group and 29.0% for the US-Prolia group). ADA titres were also similar among the groups in the transition period. Thus, the switch from US-Prolia to FKS518 does not seem to induce an alteration in the immunological response.

Overall, the initially presented results for both ADA and nAb incidence indicated that the rates are much higher than has been reported in other studies with denosumab, i.e. < 1% and 0% ADA and nAb, respectively. During the procedure, the applicant explained that the overall high positivity rate in study FKS518-002 was due to target interference. Therefore, the ADA assay was modified and ADA positive samples were re-analysed. As a consequence, updated CSRs and integrated summary of immunogenicity have been provided. The updated immunogenicity results show that the ADA incidence was much lower than initially presented. During the core treatment period, only 1.1% in the FKS518 group and 2.2% in the US-Prolia group were ADA positive (initially 94.2% in the FKS518 group and 94.9% in the US-Prolia group were ADA positive). Similarly low numbers which were balanced among treatment groups were observed during the transition period. The number of NAb positive subjects was also low and balanced between the groups. The wording of the immunogenicity section in the SmPC is considered appropriate.

In the core treatment period, the number of subjects with any TEAE involving fracture was 3 for the FKS518 group and 9 for the US-Prolia group. 4 of the 9 subjects in the US-Prolia group had a tooth fracture, while there was no tooth fracture in the FKS518 group. In the transition period, the number of subjects with any TEAE involving fracture was 2 in the FKS518 group, 1 in the US-Prolia/FKS518 group and 2 in the US-Prolia group. There were 2 patients experiencing a TEAE of fracture involving the spine during the study. One patient in the core treatment period had a fractured sacrum and one patient in the transition period had a lumbar vertebral fracture. The dissimilarity in fractures between the treatment groups is considered concerning, as this outcome might be considered as clinically relevant. The applicant was asked to provide narratives for all fractures, report whether these were pathological or non-pathological fractures, and discuss the implications on clinical relevance. Overall, 16 patients experienced 19 fractures during the study. The applicant further divided the fractures into osteoporotic and non-osteoporotic (either due to investigator considerations or due to location of the fracture and the circumstances). This resulted in 8 patients with likely osteoporotic fractures (5 patients in the FKS518 group and 3 patients in the US-Prolia group). The CHMP agreed, that the overall number of patients experiencing fractures was low during the study. Further, the osteoporotic fractures seem to have been balanced between treatment groups. Therefore, the imbalance in fracture frequencies between treatment groups in the core treatment period (3 patients in the FKS518 group

and 9 patients in the US-Prolia group) could be explained by the 4 patients with tooth fractures in the US-Prolia group and might be a chance finding.

In study FKS518-002, the proportion of patients experiencing serious TEAEs was high but similar between the groups in the core treatment period (15.5% in the FKS518 group and 18.1% in the US-Prolia group). The most common serious TEAE by preferred term was COVID-19 for both groups (12.6% in the FKS518 group and 15.6% in the US-Prolia group). The applicant clarified that due to the COVID-19 pandemic and limited knowledge on this new disease at the start of this study, COVID-19 infections were classified and managed as SAE. This is acceptable and explains the high number of serious TEAEs in the study. Apart from COVID-19, proportion of patients experiencing a serious TEAE was low and balanced between the groups. For the transition period, the proportion of patients with serious TEAEs was also similar among the groups with COVID-19 being the most common serious TEAE.

The applicant provided the narratives for all serious TEAEs, which is acknowledged. According to the discretion of the investigator, only 1 serious TEAE was related to the IP in the core treatment period, which was a COVID-19 infection in the FKS518 group. On 2022, the patient experienced an upper respiratory tract infection and was diagnosed with COVID-19. The patient received oral azithromycin and respiratory budesonide for the event. On 2022, patient's upper respiratory tract infection was resolved. Although there was a delay between last dose administered and COVID-19 infection (patient received the denosumab doses on 2021, on 2022 and on 2022), the investigator considered the event possibly related to the IP, as infections are a common complication described for Prolia. This is comprehensible.

In study FKS518-002, AESIs were defined as IP-related hypersensitivity/allergic reactions (CTCAE Grade ≥ 3 or reported as SAEs) and AEs leading to IP discontinuation or study withdrawal. All AESIs consisted of AEs leading to IP discontinuation or study withdrawal. Overall, there were 6 patients in the US-Prolia group and none in the FKS518 group who discontinued IP due to a TEAE. In the core treatment period, there were 7 patients discontinuing the study due to a TEAE. All of these patients were in the US-Prolia group. In the transition period, one patient in the US-Prolia/FKS518 group discontinued the study due to a TEAE. Although there is a slight imbalance in the number of patients discontinuing IP/treatment due to a TEAE in the core treatment period between the groups, no concern arises as the proportion is overall low and still similar between the groups. Of note, other adverse reactions that were described for Prolia, such as hypocalcaemia, osteonecrosis of the jaw and atypical femoral fractures, could have also been defined as potential AESIs, but were lacking in this definition. However, no concern arises as these events were evaluated as TEAEs and in the clinical chemistry. In the core treatment period, hypocalcaemia was reported as TEAE in only one patient in the FKS518 group and none in the US-Prolia group. Furthermore, in the clinical chemistry summary, the number of subjects with hypocalcaemia Grade 1 or 2 by timepoint was low and balanced between the groups. Most of the subjects had no hypocalcaemia. Furthermore, no events of osteonecrosis of jaw were reported during the study. Femoral fractures were already described above.

The Summary of Clinical safety reports three patients with treatment related hypersensitivity reactions; two in the FKS518 (pruritus and swelling of eyelid in one and injection related flu like symptoms in the other) and one in the Prolia group (allergic conjunctivitis) during the core treatment period and two reports of treatment related hypersensitivity during the transition period, rash in Prolia/FKS518 group and erythema in the Prolia group.

The applicant also provided an overview of the "Analysis of Hypersensitivity and Anaphylactic Reactions Using Standardized MedDRA Queries (SMQs)". Hypersensitivity reactions were more commonly reported in the FKS518 group during the core treatment period of 52 weeks; 11.2% (29 patients) vs 6.5% (17 patients) in the FKS518 and US-Prolia group reported at least 1 SMQ hypersensitivity TEAE.

None were serious and no anaphylactic reaction was reported. None qualified as an AESI. The frequency in the FKS518 group is substantially higher than in the US-Prolia group. The applicant was asked to provide a possible explanation and clarify why this observation is not reflected in the treatment-related hypersensitivity numbers for the core treatment period, where hypersensitivity was only reported for 2 patients in the FKS518 group and 1 patient in the US-Prolia group. The applicant confirmed that there were only three treatment-related hypersensitivity reactions in the core treatment period (2 patients in the FKS518 group and 1 patient in the US-Prolia group). This is acknowledged. Additionally, the applicant explained that the particular hypersensitivity or anaphylaxis SMQ TEAEs were mild to moderate with no or inconsequential concomitant medications recorded for them and none of them led to treatment or study discontinuation. This is endorsed. Due to the low frequency of the specific TEAEs and their unrelatedness to treatment, the issue is not further pursued.

The applicant provided haematology/clinical chemistry and urinalysis results by timepoint for the core and transition treatment period of study FKS518-002. There were no trends in clinically meaningful differences among treatment groups for any laboratory parameter in study FKS518-002. Laboratory measurement results raise no concerns.

The applicant further provided vital signs descriptive statistics for the core treatment period and the transition period. There were no trends in clinically meaningful differences among treatment groups for vital signs in study FKS518-002. In addition, ECG results did not show relevant differences between the groups. Injection site reactions in the core treatment period were reported by 1 patient in the FKS518 group and 2 patients in the US-Prolia group. Similarly low number of injection site reactions were reported in the transition period.

2.6.10. Conclusions on the clinical safety

Throughout the two clinical trials, the safety observations made were consistent with the established safety profile of the reference product Prolia.

The submitted safety data were considered supportive of biosimilarity.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 46. Summary of safety concerns

• Important identified risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation
• Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
• Missing information	• None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 47. summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: **Hypocalcaemia**	**Routine risk minimisation measures:** • SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Hypocalcaemia **Additional pharmacovigilance activities:** • None
Important identified risk: **Skin infection leading to hospitalisation**	**Routine risk minimisation measures:** • SmPC: Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Infection **Additional pharmacovigilance activities:** • None
Important identified risk: **Osteonecrosis of the jaw**	**Routine risk minimisation measures:** • SmPC: Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Osteonecrosis of the jaw **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Patient Reminder Card	
Important identified risk: **Hypersensitivity reactions**	**Routine risk minimisation measures:** • SmPC: Section 4.3, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire - Hypersensitivity **Additional pharmacovigilance activities:** • None
Important identified risk: **Atypical femoral fracture**	**Routine risk minimisation measures:** • SmPC: Section 4.4, Section 4.8 • PIL: Section 2, Section 4 **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – AFF **Additional pharmacovigilance activities:** • None
Important identified risk: **Hypercalcaemia in paediatric patient receiving denosumab and after treatment discontinuation**	**Routine risk minimisation measures:** • SmPC: Section 4.2, Section 4.4, Section 4.8 • PIL: Section 2 **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Important potential risk: **Fracture healing complications**	**Routine risk minimisation measures:** • SmPC: Section 5.3 **Routine risk minimisation activities recommending specific clinical measures to address the risk**:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – Fracture healing complications

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• None **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Additional pharmacovigilance activities:** • None
Important potential risk: **Infection**	**Routine risk minimisation measures:** • SmPC: Section 4.8 • PIL: Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • None **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – Infection **Additional pharmacovigilance activities:** • None
Important potential risk: **Cardiovascular events**	**Routine risk minimisation measures:** • None **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: **Malignancy**	**Routine risk minimisation measures:** • None **Other risk minimisation measures** • Legal status: prescription only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire – Malignancy **Additional pharmacovigilance activities:** • None
Missing information **None**	-	-

2.7.4. Conclusion

The CHMP considers that the risk management plan version 2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Conexxence (FKS518) was developed as a biosimilar product to Prolia (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation (Prolia: 60 mg/mL PFS). Prolia is indicated for:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

For this MAA, the applicant intends to claim all of the indications of the reference product.

Summary of Quality data

The applicant performed a comprehensive analytical biosimilarity exercise to compare FKS518 60 mg-PFS batches (including the clinical batch) and FKS518 120 mg-Vial batches to the reference medicinal product EU-Prolia and EU-Xgeva, respectively. US-licensed Prolia/Xgeva batches has been included in the biosimilarity exercise, as well.

The number of FKS518 batches (vial and PFS) and EU-Prolia/Xgeva included in the similarity assessment is considered sufficient. The use of frozen reference product batches is properly justified.

A range of state-of-the-art, orthogonal techniques were used to compare the physicochemical properties including the primary structure and post-translational modifications, higher order structure, purity and impurities, product variants and purity and impurities and biological activity. Fab-dependent binding and biological activity of denosumab were evaluated by measuring the ability of denosumab to inhibit the sRANKL-induced IkB degradation, the binding affinity to soluble RANKL (sRANKL) and transmembrane RANKL (tmRANKL) and the ability of denosumab to inhibit osteoclastogenesis in a cell-based bioassay. The therapeutic efficacy of denosumab is based on the ability to block the receptor activator of nuclear factor kappa-B ligand (RANKL) from binding the receptor activator of nuclear factor-kappa B (RANK) and Fc-dependent effector activities are not part of the mode of action (MoA) of denosumab, and no or very low binding to FcγRI and FcγRIII, and minimal Fc effector activities are expected for a monoclonal antibody (mAb) of the IgG2 subclass. Nevertheless, to ensure that the products are comparable, head-to-head testing of FKS518, reference product (RP) and reference medicinal product (RMP) batches was performed to evaluate Fc effector activities: FcγRI binding, FcγRIIIa (V158 & F158) binding, FcγRIIIb binding, C1q binding, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Comparative forced degradation studies were performed to compare the degradation profiles. The methodology applied is considered appropriate and suitable to detect minor differences between FKS518 and the reference products Prolia/Xgeva.

A stepwise approach was applied to evaluate similarity of the analytical data, based on a criticality assessment of quality attributes. Quality Ranges were applied for attributes of moderate to very high criticality and descriptive assessment was applied to the other physicochemical attributes and

functional activities not related to the MoA. The full data range for each batch is provided in tabular form, including the mean and standard deviation, and in graphical form to show distribution for each parameter, and comparison to the reference products. Chromatographs, spectra, electropherograms etc. are provided for the individual batches, when applicable.

The results provided show that for all quality attributes tested, FKS518 PFS/Vial was demonstrated to be analytically similar to EU-approved Prolia/Xgeva. Minor differences were properly discussed, justified, and are not expected to have an impact on the clinical performance of FKS518.

Summary of Clinical data

FKS518 is a biosimilar product for Amgen denosumab, intended to be marketed with two different brand names, Conexxence and Bomyntra, similarly to the innovator (EU-Prolia, EU-XGEVA) containing the same active substance, but with separate indications, strengths and presentations. In the current clinical development, the applicant has used only US-licenced Prolia as a control treatment.

The clinical development programme of FKS518 included two clinical studies to demonstrate similarity in PK, PD, efficacy, safety and immunogenicity of FKS518 and the reference product.

Study FKS518-001 was a double-blind, randomised, 2-arm, single-dose, parallel-group study to demonstrate pharmacokinetic (PK) equivalence and to compare pharmacodynamics (PD), safety, tolerability, and immunogenicity of FKS518 with US-Prolia in healthy male subjects. The study was conducted at one investigational site in Poland. Subjects were randomised in a 1:1 ratio to one of the treatments groups and stratified by body weight (≥ 50 kg to ≤ 70 kg versus > 70 kg to ≤ 110 kg). The study had a duration of up to 44 weeks, including a screening period of up to 4 weeks prior to IP administration on Day 1 and a follow-up period of 40 weeks. The EOS visit was at Day 274. Overall, the design of study FKS518-001 is acceptable and is generally in agreement with previous scientific advice received from EMA (EMEA/H/SA/4510/1/2020/III).

Study FKS518-002 was a randomised, double-blind, multicentre, 2-arm, multiple-dose, parallel-group, phase III study in postmenopausal women with osteoporosis to compare the efficacy, safety, tolerability, immunogenicity, pharmacodynamics and pharmacokinetics of FKS518 and US-authorized Prolia. The study was conducted in 64 investigative sites across six countries (Bulgaria, Czech Republic, Estonia, Georgia, Hungary and Poland). Subjects were randomised in a 1:1 ratio for the core treatment period (52 weeks). In the transition period (week 52-78) subjects receiving US-Prolia were re-randomised to receive either FKS518 or US-Prolia. The subjects received in total three s.c. doses of FKS518 or US-Prolia on day 1, month 6 and month 12. Overall, the design of study FKS518-002 is acceptable and is generally in agreement with previous scientific advice received from EMA (EMEA/H/SA/4510/1/2020/III, EMA/SA/0000061878 and EMA/SA/0000095042).

3.2. Results supporting biosimilarity

Quality

Analytical similarity between FKS518 and the reference product EU-Prolia/Xgeva has been demonstrated for all quality attributes including those related to the MoA. Minor differences observed have been properly discussed and finally considered to not have impact on the clinical performance of the product. Additional characterisation studies have been performed on size and charge variant fractions. FKS518 and the reference product EU-Prolia/Xgeva have comparable degradation profiles and kinetics further supporting biosimilarity.

Clinical

PK/PD

Study FKS518-001

Biosimilarity in PK of FKS518 and US-Prolia was shown in healthy male subjects. The ratio (FKS518/US-Prolia) of the geometric LS mean for C_{max} was 104.79% with the corresponding 90% CI being (97.04% and 113.15%). The ratio of the geometric mean for $AUC_{0\text{-last}}$ was 112.29% with the 90% CI being (104.17% and 121.04%). The ratio of the geometric mean for $AUC_{0\text{-inf}}$ was 112.65% with the corresponding 90% CI being (104.27% and 121.70%). Thus, all primary PK endpoints were met as all results were within the pre-defined equivalence margin of 0.80 and 1.25.

Additional sensitivity analyses support a conclusion on PK equivalence between FKS518 and Prolia.

The 90% CIs for the GLSMs of the ratio FKS518/ US-Prolia for the three primary PK parameters were fully contained within the predefined bioequivalece limits for both analysis methods even if the affected time points were set to missing or if the full subject profiles were excluded.

The means of the secondary PK parameters (i.e., tmax, $t_{1/2}$, Vz/F, CL/F, and median $pAUC_{0\text{-}19W}$) were comparable between the treatments supporting the PK similarity.

The mean denosumab serum concentration time-profiles within the PK-analysis set were overall comparable between FKS518 and US-Prolia groups.

Sensitivity analysis of PK parameters by body weight category were generally comparable.

The evidence for the PD equivalence stems from study FKS518-002, while the PD results in study FKS518-001 are considered in support of these primary results. Overall, the secondary PD endpoints from study FKS518-001, AUEC over the study period of s-CTX and P1NP were comparable between FKS518 and US-Prolia.

The overall shape of the %CfB-time profiles of s-CTX and P1NP was similar between the FKS518 and US-Prolia groups.

The median percent change from baseline of s-CTX and P1NP at each study visit showed practically overlapping curves for the s-CTX parameter throughout the 40-week treatment period and up to the W17 visit for the P1NP parameter. The P1NP concentration returned to its initial value more quickly in the US-Prolia group. However, terminal elimination phase is considered to be less sensitive for biosimilarity as the measurement errors and variability increases.

The secondary PD parameters of s-CTX and P1NP including %CfBmax, AUEC0-W26, AUEC0-W40 for %CfB and Net AUEC0-W40 for %CfB were comparable between FKS518 and US-Prolia treatment arms.

Plots of arithmetic mean denosumab concentrations and CTX/ P1NP %CfB values were evaluated as exploratory endpoints. An exposure-response relationship was recognizable for both PD markers.

Study FKS518-002

The mean denosumab concentration-time profiles for the whole study period were similar for the treatment groups, supporting pharmacokinetic similarity of the test and reference product.

Several PK parameters were calculated for the first IP dose in study FKS518-002 (AUCtau, AUC0-W16, AUC0-W20 and AUC16-W26). There was an approximately 10% higher exposure in the evaluated PK parameters in the FKS518 group. Nevertheless, the PK parameters were similar between the groups and support the PK similarity of the test and reference product in the osteoporosis patients.

Biosimilarity in pharmacodynamics was also demonstrated in osteoporosis patients in study FKS518-002. The co-primary PD endpoint "AUEC(0-W26) of serum CTX" was met. The point estimate of the geometric LS means ratio (FKS518/US-Prolia) for AUEC was 1.01 with the corresponding 95% CI being (0.99; 1.04). Thus, the 95% CI was within the pre-specified and accepted equivalence range of [0.89,

1.12]. The primary analysis on the hypothetical estimand was further supported by analyses on the treatment policy estimand and the trial product estimand. Additionally, several sensitivity and subgroup analyses support the robustness of the results of the co-primary analysis.

PD similarity was further demonstrated by similar percent change from baseline in serum CTX/P1NP at Week 52 and comparable serum CTX/P1NP concentration-time profiles for the FKS518 and US-Prolia group.

Efficacy

Study FKS518-002

The biosimilarity of FKS518 and US-Prolia in terms of efficacy was demonstrated in osteoporosis patients. The percent change from baseline in LS-BMD at Week 52 was the co-primary efficacy endpoint in this study. The statistical analysis on the hypothetical estimand revealed that the difference between the FKS518 and the US-Prolia group was 0.66% with the corresponding 95% CI being 0.04% and 1.29%. Thus, the 95% CI was within the pre-specified and accepted equivalence range of [-1.45%, 1.45%] and the co-primary efficacy endpoint was met. The primary analysis on the hypothetical estimand was further supported by analyses on the treatment policy estimand and the trial product estimand. Additionally, several sensitivity and subgroup analyses support the robustness of the results of the co-primary analysis.

Similarity in efficacy was further supported by the secondary efficacy endpoints. The percent change from baseline in bone mineral density at femoral neck at Week 52 was comparable between the groups. Similarly, the percent change from baseline in bone mineral density at total hip at Week 52 was also comparable between the groups. Additionally, the percent change from baseline in BMD at LS/femoral neck/total hip at Week 78 was similar among the treatment groups.

Safety

In terms of safety, the biosimilarity of FKS518 and US-Prolia was demonstrated in two clinical trials, one in healthy male volunteers and one in female patients with PMO. The safety findings observed in the clinical studies FKS518-001 and FKS518-002 were in line with the Prolia SmPC. No new or unexpected safety issues arose during the course of the studies.

In study FKS518-001, the test and reference product showed a comparable safety profile. The incidence of TEAEs was similar between the treatment groups and most TEAEs were of mild or moderate severity. There were no relevant changes in vital signs or laboratory data.

In the core treatment period of study FKS518-002, FKS518 and US-Prolia showed similar incidences of TEAEs, most of which were mild in severity and not considered related to study drug. No deaths were reported during the study. The incidences of SAEs and AESIs were comparable between the treatment groups. There were no relevant changes in vital signs or laboratory data between the groups. For the transition period, there was also a balanced distribution of TEAEs among the FKS518 group, US-Prolia/FKS518 group and US-Prolia group.

Immunogenicity

In study FKS518-001, all samples from the FKS518-001 study were ADA negative.

In the core treatment period of study FKS518-002, the overall ADA incidence was comparable between the FKS518 and US-Prolia group. Similarly, the overall NAb incidence was similar between the groups. The same held true for the transition period. The presence of ADA or NAb did not have a clinical impact on PK, PD, efficacy or safety parameters.

3.3. Uncertainties and limitations about biosimilarity

Clinical

For study FKS518-001, in 12 of 208 individual PK curves, a pronounced drop in concentration was observed at time point 264h or 336h.

Re-measurement of the affected denosumab serum concentration-time curves show a lack of reproducibility of few datapoints, this data discrepancy is indicative for an (analytical) measurement error in the first place. The exact reason for this remains unknown. This is further discussed below.

The upper bounds of the 90% CI of AUC0-inf and AUC0-last were close to 125% and unity was not included [112.29% (104.17% and 121.04%), and 112.65% (104.27% and 121,70%), respectively], suggesting significant higher exposure with FKS518 compared to US-Prolia.

3.4. Discussion on biosimilarity

Quality

Similarity between FKS518 PFS/Vial and EU-approved Prolia/Xgeva has been demonstrated for most of the quality attributes in a comprehensive analytical similarity exercise. Minor differences have been properly evaluated and justified and are not expected to impact clinical performance of the product in the targeted indications.

Clinical

In *study FKS518-001* conducted in healthy male volunteers, PK similarity was formally demonstrated between FKS518 and US-Prolia as the 90% CIs for the GLSM of the ratio test/reference for the primary PK parameters (AUC0-inf, AUC0-last, and Cmax) were fully contained within the predefined bioequivalence limits of [80.00% to 125.00%]. Furthermore, no notable treatment differences were observed in the secondary PK parameters tmax, t1/2, Vz/F, CL/F and pAUC0-19W.

It is however noted that the upper bounds of the 90% CI of AUC0-inf and AUC0-last were close to 125% and unity was not included, signalling higher exposure with FKS518 compared to US-Prolia. Validity of PK raw data was questioned with the preliminary assessment round considering that in some of the subjects' individual serum concentration profiles, a sudden drop in concentration was observed at time point 264h or 336h. A review of individual PK curves revealed that a similar pronounced drop can be seen for at least 12 more subjects. In addition, there are several PK curves that show a less pronounced drop at the same time point. All of those drops recovered at the next evaluation time point.

In a root cause analysis, no experimental errors related to clinical conduct or sample analysis were found for the observed PK fluctuations. Re-analysis of the 12 affected profiles revealed a data discrepancy as most of the formerly observed short-term fluctuations were not reproducible. This is indicative for an (analytical) measurement error in the first place. The likelihood to discover the exact reasons for the originally observed large short-term fluctuations is considered low at this stage. Given the totality of information generated on this issue, it is considered unlikely that additional elaboration/investigation would result in an outcome that eventually jeopardises the conclusion of PK-equivalence between the biosimilar candidate and the originator product. PK equivalence can be assessed and concluded based on the available data.

Moreover, the results of additional sensitivity analyses, addressing the impact of the short-term fluctuations, further support the assumption that the remaining uncertainty in relation to the

conclusion on PK-equivalence is sufficiently low. The totality of PK data supports a conclusion on PK-equivalence.

PK data from *study FKS518-002* conducted in female osteoporosis patients further support PK similarity of the test and reference product. The mean denosumab concentration-time profiles for the whole study period were similar for the treatment groups. Additionally, although there was an approximately 10% higher exposure in the PK parameters calculated for the first IP dose (AUCtau, AUC0-W16, AUC0-W20 and AUC16-W26) in study FKS518-002, the exposure was overall similar between the treatment groups, supporting the PK similarity of the test and reference product in the osteoporosis patients.

PD similarity is supported by both clinical studies, and is specifically demonstrated in study *FKS518-002*. In *study FKS518-001*, the secondary PD endpoints AUEC(0-W40) for CTX and P1NP were similar between the two treatment groups. Similar results could be observed when following Treatment Policy (Randomized Analysis Set) or Trial Product (PD Analysis Set) estimand analysis strategies.
Following s.c. administration of 60 mg denosumab, similar median percent change from baseline in s-CTX over the study duration and up to week 17 for the P1NP parameter was demonstrated. The curves depicting %CfB at each study visits for P1NP separate at the terminal elimination phase starting from W17 visit up to the EOS visit. The P1NP concentration returned to its initial value more quickly in the US-Prolia group. However, terminal elimination phase is considered to be less sensitive for biosimilarity as the measurement errors and variability increases, and hence this is not pursued further.
Similar results for the maximal %CfB, AUEC0-W26, AUEC0-W40 for %CfB and Net AUEC0-W40 for %CfB for serum CTX and maximal %CfB, AUEC0-W40 for %CfB and Net AUEC0-W40 for %CfB for P1NP were also observed between FKS518 and US-Prolia in healthy male subjects.

In *study FKS518-002*, biosimilarity in pharmacodynamics was demonstrated in female osteoporosis patients. The co-primary PD endpoint "AUEC(0-W26) of serum CTX" was met as the geometric LS means ratio (FKS518/US-Prolia) for AUEC with the corresponding 95% CI was within the pre-specified and accepted acceptance range of 0.89 to 1.12. This was true for the primary analysis on the hypothetical estimand, as well as supportive analyses on the treatment policy estimand and trial product estimand. PD similarity was further demonstrated by similar percent change from baseline in serum CTX/P1NP at Week 52 and comparable serum CTX/P1NP concentration-time profiles for the FKS518 and US-Prolia group.

Similarity regarding efficacy was shown in *study FKS518-002*. The co-primary efficacy analysis on the percent change from baseline in LS-BMD at Week 52 was met, as the difference between the FSK518 and the US-Prolia group with the corresponding 95% CI was within the pre-specified and accepted acceptance range [-1.45%, 1.45%]. The statistical analysis on the hypothetical estimand revealed that the difference between the FKS518 and the US-Prolia group was 0.66% with the corresponding 95% CI being 0.04% and 1.29%. The primary analysis was further supported by analyses on the treatment policy estimand and the trial product estimand. Efficacy analyses of the bone mineral density at femoral neck and total hip at Week 52 further support the similarity in efficacy between the test and reference product.

Based on the provided safety data of *both clinical studies FKS518-001* and *FKS518-002*, no unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the reference products. However, there were more fractures observed in the US-Prolia group during the core treatment period of study FKS518-002. This was of concern, as this might be a clinically relevant finding and pointing towards lower efficacy in the US-Prolia study group. The applicant explained that the osteoporotic fractures were balanced between treatment groups. Therefore, the imbalance in fracture frequencies between treatment groups in the

core treatment period (3 patients in the FKS518 group and 9 patients in the US-Prolia group) could be explained by the 4 patients with tooth fractures in the US-Prolia group and might be a chance finding.

The immunogenicity profiles of FKS518 and US-Prolia were comparable in healthy male subjects as well as in female patients with PMO.

3.5. Extrapolation of safety and efficacy

FKS518 was developed as a biosimilar product to Prolia/Xgeva. The mechanism of action is identical to the reference products. The monoclonal antibody denosumab targets and binds to RANKL, thus preventing interaction of RANKL with RANK. Block of interaction of RANKL with RANK leads to reduced osteoclast formation and function. Thus, bone resorption and cancer induced bone destruction is decreased.

The mechanism of action is identical across all indications, i.e. binding to RANKL and thus preventing activation of its receptor RANK. The desired pharmacological action of denosumab occurs invariably in the bony tissue, through prevention of generalised bone resorption in primary or secondary osteoporosis, or local bone resorption and destruction around bone metastases. Thus, based on the same mechanism of action, extrapolation to all indications might be allowed.

The extrapolation is further supported by the fact that the known PK, safety and immunogenicity profile of denosumab as summarised in the product information for Prolia/Xgeva is comparable across the approved indications and patient populations.

Furthermore, the clinical data were derived from healthy male volunteers and female osteoporosis patients. These are regarded sensitive populations in terms of evaluating biosimilarity of FKS518 and the reference product.

Based on the above, the safety and efficacy profile of FKS518 as assessed in the PMO indication can be extrapolated to all indications applied for FKS518, provided that a positive benefit/risk can be concluded.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Conexxence is considered biosimilar to Prolia. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Conexxence is favourable in the following indication(s):

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.