



Clinical trial results:

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)

Summary

EudraCT number	2020-004422-31
Trial protocol	HU BG EE CZ
Global end of trial date	07 August 2023

Results information

Result version number	v1 (current)
This version publication date	22 August 2024
First version publication date	22 August 2024

Trial information

Trial identification

Sponsor protocol code	FKS518-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04934072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi SwissBioSim GmbH (FKSBS)
Sponsor organisation address	Terre Bonne Business Park, Route de Crassier 23 – Bâtiment A3, Switzerland, CH – 1262 Eysins
Public contact	Clinical Development, Fresenius Kabi SwissBioSim GmbH, +41 793075735, medinfo_biosim@fresenius-kabi.com
Scientific contact	Clinical Development, Fresenius Kabi SwissBioSim GmbH, +41 793075735, medinfo_biosim@fresenius-kabi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate equivalent efficacy and pharmacodynamics (PD) of the proposed biosimilar denosumab FKS518 to US- licensed Prolia (US-Prolia, Amgen) in women with postmenopausal osteoporosis (PMO).

Protection of trial subjects:

Before initiating a study and enrolling any patient, the Investigator/institution obtained written and dated approval/favorable opinion from the Independent Ethics Committees (IECs) for the clinical study protocol/amendment(s), informed consent form (ICF) and any subsequent ICF updates, and any written information to be provided to participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 280
Country: Number of subjects enrolled	Bulgaria: 81
Country: Number of subjects enrolled	Czechia: 50
Country: Number of subjects enrolled	Estonia: 25
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	Georgia: 72
Worldwide total number of subjects	553
EEA total number of subjects	481

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	254
From 65 to 84 years	298
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 553 participants were randomised in the study at 64 centers across 6 countries (Bulgaria, Czech Republic, Estonia, Georgia, Hungary, and Poland) between June 2021 and January 2022.

Pre-assignment

Screening details:

The study included a Screening Period of maximum 28 days prior to first drug (FKS518 and US-Prolia) 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, and Week 52.

Period 1

Period 1 title	Core Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Core Treatment Period FKS518

Arm description:

Participants received FKS518 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52).

Arm type	Experimental
Investigational medicinal product name	FKS518
Investigational medicinal product code	
Other name	Proposed denosumab biosimilar
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

FKS518 60 mg, subcutaneously.

Arm title	Core Treatment Period US-Prolia
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Arm description:

Participants received US-Prolia 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52).

Arm type	Active comparator
Investigational medicinal product name	US-Prolia
Investigational medicinal product code	
Other name	Denosumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

US-Prolia 60 mg, subcutaneously.

Number of subjects in period 1	Core Treatment Period FKS518	Core Treatment Period US-Prolia
Started	277	276
Completed	252	249
Not completed	25	27
Consent withdrawn by subject	17	22
Adverse event, non-fatal	1	3
Discontinued Treatment Prior to Week 52	4	1
Not Specified	3	1

Period 2

Period 2 title	Transition Period (TP)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Transition Period: FKS518 (was on FKS518 in CTP)

Arm description:

Participants treated with FKS518 during Core Treatment Period received FKS518 60 mg subcutaneously on Week 52 during the Transition Period (Week 52 to Week 78).

Arm type	Experimental
Investigational medicinal product name	FKS518
Investigational medicinal product code	
Other name	Proposed denosumab biosimilar
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

FKS518 60 mg, subcutaneously.

Arm title	Transition Period: FKS518 (switched from US -Prolia in CTP)
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Arm description:

Participants treated with US-Prolia during Core Treatment Period were re-randomised to receive FKS518 60 mg subcutaneously on Week 52 during the Transition Period (Week 52 to Week 78).

Arm type	Experimental
Investigational medicinal product name	FKS518
Investigational medicinal product code	
Other name	Proposed Biosimilar to Denosumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

FKS518 60 mg, subcutaneously.

Arm title	Transition Period: US-Prolia (was on US -Prolia in CTP)
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Arm description:

Participants treated with US-Prolia during Core Treatment period were re-randomised to receive US-Prolia 60 mg subcutaneously on Week 52 during the Transition Period (Week 52 to Week 78).

Arm type	Experimental
Investigational medicinal product name	US-Prolia
Investigational medicinal product code	
Other name	Denosumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

US-Prolia 60 mg, subcutaneously.

Number of subjects in period 2	Transition Period: FKS518 (was on FKS518 in CTP)	Transition Period: FKS518 (switched from US -Prolia in CTP)	Transition Period: US-Prolia (was on US -Prolia in CTP)
Started	252	124	125
Completed	245	122	122
Not completed	7	2	3
Consent withdrawn by subject	6	1	2
Adverse event, non-fatal	-	1	1
Not Specified	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Core Treatment Period FKS518
Reporting group description: Participants received FKS518 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52).	
Reporting group title	Core Treatment Period US-Prolia
Reporting group description: Participants received US-Prolia 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52).	

Reporting group values	Core Treatment Period FKS518	Core Treatment Period US-Prolia	Total
Number of subjects	277	276	553
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	65.2 ± 6.44	65.8 ± 6.47	-
Gender categorical Units: Subjects			
Female	277	276	553
Male	0	0	0
Race Units: Subjects			
White	277	276	553
Lumbar spine bone mineral density (LS-BMD) by dual energy Xray absorptiometry (DXA) Units: g/cm2 arithmetic mean standard deviation	0.7872 ± 0.06381	0.7929 ± 0.05962	-

End points

End points reporting groups

Reporting group title	Core Treatment Period FKS518
Reporting group description: Participants received FKS518 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52).	
Reporting group title	Core Treatment Period US-Prolia
Reporting group description: Participants received US-Prolia 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52).	
Reporting group title	Transition Period: FKS518 (was on FKS518 in CTP)
Reporting group description: Participants treated with FKS518 during Core Treatment Period received FKS518 60 mg subcutaneously on Week 52 during the Transition Period (Week 52 to Week 78).	
Reporting group title	Transition Period: FKS518 (switched from US -Prolia in CTP)
Reporting group description: Participants treated with US-Prolia during Core Treatment Period were re-randomised to receive FKS518 60 mg subcutaneously on Week 52 during the Transition Period (Week 52 to Week 78).	
Reporting group title	Transition Period: US-Prolia (was on US -Prolia in CTP)
Reporting group description: Participants treated with US-Prolia during Core Treatment period were re-randomised to receive US-Prolia 60 mg subcutaneously on Week 52 during the Transition Period (Week 52 to Week 78).	

Primary: Percentage Change From Baseline in LS-BMD by DXA

End point title	Percentage Change From Baseline in LS-BMD by DXA
End point description: Bone density was measured at the lumbar spine from L1 through L4. Decreased BMD is associated with risk of fracture. Intention-to-Treat (ITT) Analysis Set: The ITT Analysis Set included all randomised participants. Participants were analysed according to their randomised treatment.	
End point type	Primary
End point timeframe: Baseline and Week 52	

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	276		
Units: Percentage Change				
least squares mean (standard error)	5.74 (± 0.315)	5.07 (± 0.321)		

Statistical analyses

Statistical analysis title	FKS518 and US-Prolia
Statistical analysis description: FKS518 was considered equivalent to US-Prolia if the 95% CI for the difference in mean percent change from baseline to Week 52 in LS-BMD laid entirely within the equivalence interval of [-1.45%; 1.45%].	
Comparison groups	Core Treatment Period FKS518 v Core Treatment Period US-Prolia
Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Mean difference (final values)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	0.317
Notes: [1] - Difference : FKS518 - US-Prolia	

Primary: Area Under the Effect Curve (AUEC) of Serum C-terminal Cross-linking Teloepetide of Type 1 Collagen (CTX)

End point title	Area Under the Effect Curve (AUEC) of Serum C-terminal Cross-linking Teloepetide of Type 1 Collagen (CTX)
End point description: 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. ITT Analysis Set: The ITT Analysis Set included all randomised participants. Participants were analysed according to their randomised treatment.	
End point type	Primary
End point timeframe: Baseline to Week 26	

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	276		
Units: ng*h/L				
geometric mean (confidence interval 95%)	1895 (1849 to 1941)	1875 (1828 to 1923)		

Statistical analyses

Statistical analysis title	Comparison of FKS518 and US-Prolia
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Statistical analysis description:

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].

Comparison groups	Core Treatment Period US-Prolia v Core Treatment Period FKS518
Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	ratio of geometric LSM
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.04

Notes:

[2] - Ratio of FKS518 / US Prolia

Secondary: Percentage Change From Baseline in BMD at Femoral Neck and Total Hip by DXA

End point title	Percentage Change From Baseline in BMD at Femoral Neck and Total Hip by DXA
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End point description:

The proximal femur (inclusive of femoral neck and total hip) DXA scans were obtained from the left side when possible. If the right side had to be used (e.g., due to implants) or was inadvertently used at Baseline, then it had to be used consistently throughout the study. Data reported are for one half of the body only.

ITT Analysis Set: The ITT Analysis Set included all randomised participants. Participants were analysed according to their randomised treatment.

End point type	Secondary
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End point timeframe:

Baseline and Week 52

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	276		
Units: Percentage change				
least squares mean (standard error)				
BMD at Femoral Neck at Week 52	2.07 (± 0.284)	1.85 (± 0.291)		
BMD at Total Hip at Week 52	2.97 (± 0.217)	2.88 (± 0.223)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Serum Procollagen Type 1 N-

terminal Propeptide (P1NP)

End point title	Percentage Change From Baseline in Serum Procollagen Type 1 N-terminal Propeptide (P1NP)
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End point description:

P1NP is a bone biomarker. Serum samples were collected for analysis of P1NP to evaluate bone formation (P1NP) in response to treatment with FKS518 and US-Prolia. A decrease in the serum levels of P1NP is expected following treatment and is suggestive of improvement.

Pharmacodynamic (PD) Analysis Set: All participants who received at least 1 dose of investigational product, had a quantifiable baseline PD marker concentration, and enough samples not impacted by protocol deviations to calculate the PD parameter. Only participants with available data are included.

End point type	Secondary
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End point timeframe:

Baseline and Week 52 pre dose

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: Percentage change				
least squares mean (standard error)	-65.27 (\pm 2.491)	-63.25 (\pm 2.536)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Serum C-terminal Cross-linking Telo peptide of Type 1 Collagen (CTX)

End point title	Percentage Change From Baseline in Serum C-terminal Cross-linking Telo peptide of Type 1 Collagen (CTX)
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End point description:

Serum CTX is a bone biomarker. Serum samples were collected for analysis of CTX to evaluate bone resorption in response to treatment with FKS518 or US-Prolia. A decrease in the serum levels of CTX is expected following treatment with FKS518 and is suggestive of improvement.

PD Analysis Set: All participants who received at least 1 dose of investigational product, had a quantifiable baseline PD marker concentration, and enough samples not impacted by protocol deviations to calculate the PD parameter. Only participants with available data are included.

End point type	Secondary
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End point timeframe:

Baseline and Week 52 pre dose

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	235		
Units: Percentage change				
least squares mean (standard error)	-68.16 (\pm 4.241)	-64.47 (\pm 4.330)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)
End point description:	
Treatment-emergence was defined as AEs that began or increased in severity or frequency on or after the date of first administration of IP in a given treatment Period (Core or Transition) up to the Early Termination/End of Study Visit.	
Safety Analysis Set (SAS): The SAS included all participants who received at least 1 dose of IP. The Transition Period Safety Analysis Set (TP-SAS) included all participants who received at least 1 dose of IP during the course of the TP. Participants were analysed according to the actual treatment they received.	
End point type	Secondary
End point timeframe:	
Day 1 to Week 78	

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia	Transition Period: FKS518 (was on FKS518 in CTP)	Transition Period: FKS518 (switched from US -Prolia in CTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	252	124
Units: Number of Participants	185	189	106	58

End point values	Transition Period: US-Prolia (was on US -Prolia in CTP)			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: Number of Participants	47			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Treatment-Emergent Serious Adverse Event (TESAE)

End point title	Number of Participants Who Experienced a Treatment-Emergent Serious Adverse Event (TESAE)
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End point description:

Treatment-emergence was defined as SAEs 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.

SAS: SAS included all participants who received at least 1 dose of IP. Participants were analysed according to the actual treatment they received.

End point type	Secondary
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End point timeframe:

Day 1 to Week 78

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia	Transition Period: FKS518 (was on FKS518 in CTP)	Transition Period: FKS518 (switched from US -Prolia in CTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	252	124
Units: Count of Participants	43	50	8	6

End point values	Transition Period: US-Prolia (was on US -Prolia in CTP)			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: Count of Participants	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Treatment-emergent Adverse Event of Special Interest (AESI)

End point title	Number of Participants Who Experienced a Treatment-emergent Adverse Event of Special Interest (AESI)
End point description: A Treatment-emergent AESI is defined as drug-related hypersensitivity/allergic reactions (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3 or reported as serious adverse events [SAEs]) and AEs leading to IP discontinuation or study withdrawal. SAS: SAS included all participants who received at least 1 dose of IP. Participants were analysed according to the actual treatment they received.	
End point type	Secondary
End point timeframe: Day 1 to Week 78	

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia	Transition Period: FKS518 (was on FKS518 in CTP)	Transition Period: FKS518 (switched from US -Prolia in CTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	252	124
Units: Count of Participants	0	7	0	1

End point values	Transition Period: US-Prolia (was on US -Prolia in CTP)			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: Count of Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Injection Site Reaction (ISR)

End point title	Number of Participants Who Experienced an Injection Site Reaction (ISR)
End point description: Local tolerability in terms of ISRs was assessed by inspection of the skin and appendages in proximity to the site of administration. The injection site was the abdomen, and the IP was injected slowly. This local tolerability assessment was performed by the Investigator or designee to determine the presence of e.g., erythema, rash, tenderness, swelling, itching, bruising, pain, extravasation, phlebitis, or other types of reaction. The Investigator was also requested to ask participants during assessment about any such reactions that may have occurred since last assessment. SAS: The SAS included all participants who received at least 1 dose of IP. Participants were analysed according to the actual treatment they received.	
End point type	Secondary
End point timeframe: Day 1 to Week 78	

End point values	Core Treatment Period FKS518	Core Treatment Period US-Prolia	Transition Period: FKS518 (was on FKS518 in CTP)	Transition Period: FKS518 (switched from US -Prolia in CTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	252	124
Units: Count of Participants	1	2	1	0

End point values	Transition Period: US-Prolia (was on US -Prolia in CTP)			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: Count of Participants	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 78

Adverse event reporting additional description:

SAS: The SAS included all participants who received at least 1 dose of IP. The TP-SAS included all participants who received at least 1 injection of study drug (FKS518 or US-Prolia) during the course of the Transition Period. Participants were analysed according to the actual treatment they received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	FKS518
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Reporting group description:

Participants received FKS518 60 mg subcutaneously on Day 1 and Week 26 during the Core Treatment Period (Baseline to Week 52) and were re-randomized to receive FKS518 60 mg subcutaneously on Week 52 during the Transition Period. This Reporting Group is used to report the results of the Overall period (Baseline to Week 78).

Reporting group title	Core Treatment Period: US-Prolia; TP: FKS518
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Reporting group description:

Participants who were originally randomised to receive US-Prolia during core treatment period (Baseline to Week 52) were re-randomised to continue to receive an administration of FKS518 subcutaneously; 60 mg on Week 52 during transition treatment period. This Reporting Group is used to report the results of the Overall period (Baseline to Week 78).

Reporting group title	US-Prolia
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Reporting group description:

Participants who were originally randomised to receive US-Prolia during the Core Treatment Period (Baseline to Week 52) were re-randomised to receive administration of US-Prolia 60 mg, subcutaneously, on Week 52 during the Transition Period. This Reporting Group is used to report the results of the Overall period (Baseline to Week 78).

Serious adverse events	FKS518	Core Treatment Period: US-Prolia; TP: FKS518	US-Prolia
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 277 (18.05%)	27 / 124 (21.77%)	33 / 152 (21.71%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 277 (0.00%)	1 / 124 (0.81%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			

subjects affected / exposed	0 / 277 (0.00%)	1 / 124 (0.81%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngeal cancer			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour of the lung metastatic			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral papilloma			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			

subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 277 (0.00%)	1 / 124 (0.81%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Hydrometra			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectocele			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal osteoarthritis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Asymptomatic COVID-19			
subjects affected / exposed	3 / 277 (1.08%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	37 / 277 (13.36%)	25 / 124 (20.16%)	22 / 152 (14.47%)
occurrences causally related to treatment / all	1 / 37	0 / 25	0 / 22
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 277 (0.00%)	0 / 124 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	FKS518	Core Treatment Period: US-Prolia; TP: FKS518	US-Prolia
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 277 (42.24%)	71 / 124 (57.26%)	58 / 152 (38.16%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 277 (5.42%)	5 / 124 (4.03%)	2 / 152 (1.32%)
occurrences (all)	25	5	2
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	18 / 277 (6.50%) 19	10 / 124 (8.06%) 11	7 / 152 (4.61%) 7
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	17 / 277 (6.14%) 18	5 / 124 (4.03%) 5	5 / 152 (3.29%) 5
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	15 / 277 (5.42%) 20 10 / 277 (3.61%) 10	9 / 124 (7.26%) 11 9 / 124 (7.26%) 12	4 / 152 (2.63%) 4 5 / 152 (3.29%) 5
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	13 / 277 (4.69%) 15 34 / 277 (12.27%) 45 6 / 277 (2.17%) 6 30 / 277 (10.83%) 43 25 / 277 (9.03%) 35	9 / 124 (7.26%) 9 33 / 124 (26.61%) 42 7 / 124 (5.65%) 8 20 / 124 (16.13%) 26 11 / 124 (8.87%) 12	2 / 152 (1.32%) 2 20 / 152 (13.16%) 25 4 / 152 (2.63%) 5 21 / 152 (13.82%) 25 16 / 152 (10.53%) 21

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2021	<p>Version 2.0:</p> <ul style="list-style-type: none">-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 participants who have received a COVID-19 vaccine within 4 weeks before randomization or if COVID-19 vaccination was ongoing at the time of screening.-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.
23 September 2021	<p>Version 5:</p> <ul style="list-style-type: none">-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 participant at an unacceptable risk, was updated to clarify that participants 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:<ul style="list-style-type: none">▪ 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 participants 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.
17 January 2023	<p>Version 6.0:</p> <ul style="list-style-type: none">-A Coordinating Investigator was included in the protocol.-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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported