



## Clinical trial results:

### A Phase 3b Open-label Study of the Anti-FGF23 Antibody, Burosumab (KRN23) in Adult Patients with X-linked Hypophosphatemia (XLH)

#### Summary

EudraCT number	2018-000202-37
Trial protocol	FR GB IT
Global end of trial date	07 April 2022

#### Results information

Result version number	v1 (current)
This version publication date	06 April 2023
First version publication date	06 April 2023

#### Trial information

##### Trial identification

Sponsor protocol code	BUR02
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03920072
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Kyowa Kirin Pharmaceutical Development Ltd
Sponsor organisation address	Galabank Business Park, Galashiels, United Kingdom, TD1 1QH
Public contact	Kyowa Kirin Pharmaceutical Development Ltd, Kyowa Kirin Pharmaceutical Development Ltd, kkd.clintrial.82@kyowakirin.com
Scientific contact	Kyowa Kirin Pharmaceutical Development Ltd, Kyowa Kirin Pharmaceutical Development Ltd, kkd.clintrial.82@kyowakirin.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	26 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2022
Global end of trial reached?	Yes
Global end of trial date	07 April 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To continue to evaluate the long-term efficacy and safety of burosumab as a treatment for adult patients with XLH and to provide continued treatment for subjects previously enrolled in UX023-CL303 and UX023-CL304 clinical trials.

Protection of trial subjects:

This protocol was written in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The Sponsor and investigator made every effort to assure the study described in this protocol was conducted in full conformance with those principles, current Food and Drug Administration (FDA) regulations, ICH Good Clinical Practices (GCP) guidelines and local ethical and regulatory requirements. The investigator made sure he or she was thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in the protocol and the IB, prior to the initiation of the study. It was the investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent was obtained after the methods, objectives, requirements and potential risks of the study had been fully explained to each potential subject. The investigator explained to each subject that the subject was completely free to refuse to enter the study or to withdraw from it at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2018
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	United Kingdom: 9
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	35
EEA total number of subjects	26

Notes:

### Subjects enrolled per age group

In utero	0
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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)	35
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Adult XLH patients (18 to 70 years) from Europe who had participated in either study UX023-CL303 or UX023-CL304. Subjects were moved to this study as soon as possible after completion of UX023-CL303 or UX023 CL304.

### Pre-assignment

Screening details:

Screening visits could occur up to 4 weeks before the baseline visit. Informed consent, Inclusion/Exclusion criteria, medical history, demographics and height were collected. Clinical labs were collected as well as a lateral foot x-ray and patient reported outcomes.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Overall trial
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Burosumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Burosumab was supplied as a sterile, clear, colorless and preservative-free solution in single-use 5 mL vials containing 1 mL of burosumab at a concentration of 30 mg/mL.

Burosumab was administered via SC injection, without dilution, to the abdomen, upper arms or thighs, at the same dose as the last administered during UX023-CL303 or UX023-CL304. The dose remained fixed for the duration of the study, provided serum phosphate levels did not exceed the upper limit of normal (ULN), as measured by the central laboratory, and body weight did not change by >20% from the baseline measurement. The dose was to be recalculated to account for the new body weight if it changed by >20%.

The dose was increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg) if the trough serum phosphate concentration remained below the lower limit of normal (LLN).

Number of subjects in period 1	Overall trial
Started	35
Completed	25
Not completed	10
Consent withdrawn by subject	4
Transfer to commercial burosumab	6



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	35	35	
Age categorical			
Units: Subjects			
Adults (18-64 years)	35	35	
Gender categorical			
Units: Subjects			
Female	23	23	
Male	12	12	
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	35	35	
Unknown or Not reported	0	0	
Race			
Units: Subjects			
American Indian or Alaska Native		0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander		0	
Black or African American		0	
White	34	34	
More than one race		0	
Unknown or not reported		0	

### Subject analysis sets

Subject analysis set title	Placebo in the Double-blinded Period - UX023-CL303
Subject analysis set type	Full analysis

Subject analysis set description:

Thirty-five subjects who completed study UX023-CL303 or UX023-CL304 were screened for this study (34 subjects from UX023-CL303 and 1 subject from UX023-CL304). All 35 subjects met the eligibility criteria and were enrolled. Of the 35 subjects, 18 subjects had received placebo during the double-blind period of UX023-CL303 (following the double-blind period, they received burosumab in the open-label periods of that study). This is the Placebo in the Double-blinded Period - UX023-CL303 Analysis set

Subject analysis set title	Burosumab in Double-blinded Period - UX023-CL303 and CL304
Subject analysis set type	Full analysis

Subject analysis set description:

Thirty-five subjects who completed study UX023-CL303 or UX023-CL304 were screened for this study (34 subjects from UX023-CL303 and 1 subject from UX023-CL304). All 35 subjects met the eligibility criteria and were enrolled. Of the 35 subjects, 17 subjects had either received burosumab during the double-blind period of UX023-CL303 or were from study UX023-CL304 (a single-arm study on burosumab). This is the Burosumab in the double-blinded period from UX023-CL303 and CL304 analysis set.

Subject analysis set title	All (Placebo + Burosumab)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Thirty-five subjects who completed study UX023-CL303 or UX023-CL304 were screened for this study (34 subjects from UX023-CL303 and 1 subject from UX023-CL304). All 35 subjects met the eligibility criteria and were enrolled. All 35 subjects received at least one dose of burosumab and were included in this analysis set.

<b>Reporting group values</b>	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Number of subjects	18	17	35
Age categorical Units: Subjects			
Adults (18-64 years)	18	17	35
Gender categorical Units: Subjects			
Female	10	13	23
Male	8	4	12
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	18	17	35
Unknown or Not reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	17	17	34
More than one race	0	0	0
Unknown or not reported	0	0	0

## End points

### End points reporting groups

Reporting group title	Overall trial
Reporting group description: -	
Subject analysis set title	Placebo in the Double-blinded Period - UX023-CL303
Subject analysis set type	Full analysis

#### Subject analysis set description:

Thirty-five subjects who completed study UX023-CL303 or UX023-CL304 were screened for this study (34 subjects from UX023-CL303 and 1 subject from UX023-CL304). All 35 subjects met the eligibility criteria and were enrolled. Of the 35 subjects, 18 subjects had received placebo during the double-blind period of UX023-CL303 (following the double-blind period, they received burosumab in the open-label periods of that study). This is the Placebo in the Double-blinded Period - UX023-CL303 Analysis set

Subject analysis set title	Burosumab in Double-blinded Period - UX023-CL303 and CL304
Subject analysis set type	Full analysis

#### Subject analysis set description:

Thirty-five subjects who completed study UX023-CL303 or UX023-CL304 were screened for this study (34 subjects from UX023-CL303 and 1 subject from UX023-CL304). All 35 subjects met the eligibility criteria and were enrolled. Of the 35 subjects, 17 subjects had either received burosumab during the double-blind period of UX023-CL303 or were from study UX023-CL304 (a single-arm study on burosumab). This is the Burosumab in the double-blinded period from UX023-CL303 and CL304 analysis set.

Subject analysis set title	All (Placebo + Burosumab)
Subject analysis set type	Full analysis

#### Subject analysis set description:

Thirty-five subjects who completed study UX023-CL303 or UX023-CL304 were screened for this study (34 subjects from UX023-CL303 and 1 subject from UX023-CL304). All 35 subjects met the eligibility criteria and were enrolled. All 35 subjects received at least one dose of burosumab and were included in this analysis set.

### Primary: Number of Subjects Achieving Mean Trough Serum Phosphate Level Above the LLN as Assessed by Central Laboratories

End point title	Number of Subjects Achieving Mean Trough Serum Phosphate Level Above the LLN as Assessed by Central Laboratories <sup>[1]</sup>
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#### End point description:

Number of subjects achieving mean trough serum phosphate level above the LLN (as assessed by the central or local laboratory as a result of the COVID-19 pandemic) in adults with X linked Hypophosphatemia (XLH) at EOS/ET.

End point type	Primary
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#### End point timeframe:

Baseline through to end of study/end of trial.

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics only for this study due to number of patients enrolled. Based on central laboratory data, 28 of the 35 subjects (80.0%) achieved mean trough serum phosphate level above the LLN.

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	18	17	35
Units: Count of participant	28	12	16	28



## Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of Subjects Achieving Mean Trough Serum Phosphate Level Above the LLN as Assessed by Local Laboratories

End point title	Proportion of Subjects Achieving Mean Trough Serum Phosphate Level Above the LLN as Assessed by Local Laboratories <sup>[2]</sup>
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End point description:

Proportion of subjects achieving mean trough serum phosphate level above the LLN as assessed by local laboratories (due to the COVID-19 pandemic)

End point type	Primary
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End point timeframe:

From Baseline through to end of study/end of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics only for this study due to number of patients enrolled. Overall, the results from local laboratories were consistent with the central laboratory: 14 of the 17 subjects (82.4%) had mean trough serum phosphate level above the LLN.

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	12	5	17
Units: Count of Participants	14	9	5	14

## Statistical analyses

No statistical analyses for this end point

### Secondary: Calcaneal Enthesopathy

End point title	Calcaneal Enthesopathy
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End point description:

Total Calcaneal enthesopathy burden at EOS/ET.

End point type	Secondary
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End point timeframe:

From baseline to end of study/end of treatment.

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	15	14	29
Units: units on a scale				
arithmetic mean (standard deviation)	100.74 ( $\pm$ 48.250)	93.97 ( $\pm$ 39.910)	107.99 ( $\pm$ 56.476)	100.74 ( $\pm$ 48.250)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to EOS/ET in Calcaneal enthesopathy

End point title	Change from baseline to EOS/ET in Calcaneal enthesopathy
End point description:	Change from baseline to EOS/ET in Calcaneal enthesopathy
End point type	Secondary
End point timeframe:	From Baseline to end of study/end of treatment

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	15	14	29
Units: score on a scale				
arithmetic mean (standard deviation)	100.74 ( $\pm$ 48.250)	93.97 ( $\pm$ 39.910)	107.99 ( $\pm$ 56.476)	100.74 ( $\pm$ 48.250)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Timed Up and Go (TUG) test, change from baseline (seconds)

End point title	Timed Up and Go (TUG) test, change from baseline (seconds)
End point description:	Timed Up and Go (TUG) test, change from baseline (seconds) to end of study/end of treatment
End point type	Secondary
End point timeframe:	Baseline to end of study/end of treatment

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	18	13	31
Units: Units on a scale				
arithmetic mean (standard deviation)	-1.36 (± 3.156)	-1.54 (± 2.571)	-1.12 (± 3.927)	-1.36 (± 3.156)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Brief Pain Inventory (BPI) Worst Pain, Change From Baseline.

End point title	Brief Pain Inventory (BPI) Worst Pain, Change From Baseline.
End point description:	Brief Pain Inventory (BPI) Worst Pain, change from baseline to Week 96
End point type	Secondary
End point timeframe:	From baseline to Week 96

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	10	12	22
Units: score on a scale				
arithmetic mean (standard deviation)	-0.58 (± 1.820)	-0.39 (± 1.554)	-0.73 (± 2.072)	-0.58 (± 1.820)

### Statistical analyses

No statistical analyses for this end point

### Secondary: BPI Pain Severity Score, Change From Baseline

End point title	BPI Pain Severity Score, Change From Baseline
End point description:	BPI Pain Severity score, change from baseline to Week 96.
End point type	Secondary

End point timeframe:  
From baseline to week 96

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	10	11 <sup>[3]</sup>	21
Units: score on a scale				
arithmetic mean (standard deviation)	-0.42 (± 1.907)	-0.33 (± 1.663)	-0.50 (± 2.185)	-0.42 (± 1.907)

Notes:

[3] - 11

### Statistical analyses

No statistical analyses for this end point

### Secondary: Brief Fatigue Inventory (BFI), Change From Baseline

End point title	Brief Fatigue Inventory (BFI), Change From Baseline
End point description:	Brief Fatigue Inventory (BFI), change from baseline to Week 96
End point type	Secondary
End point timeframe:	From baseline to Week 96

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	9	12	21
Units: score on a scale				
arithmetic mean (standard deviation)	-0.64 (± 1.726)	0.34 (± 1.013)	-1.38 (± 1.817)	-0.64 (± 1.726)

### Statistical analyses

No statistical analyses for this end point

### Secondary: WOMAC Stiffness Score, Change From Baseline

End point title	WOMAC Stiffness Score, Change From Baseline
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End point description:	
WOMAC Stiffness score, change from baseline to end of study to end of treatment	
End point type	Secondary
End point timeframe:	
From baseline to end of study/end of treatment	

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	17	14	31
Units: score on a scale				
arithmetic mean (standard deviation)	-14.52 (± 22.615)	-19.85 (± 23.410)	-8.04 (± 20.573)	-14.52 (± 22.615)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Trough Serum Phosphate

End point title	Trough Serum Phosphate
End point description:	
Trough serum phosphate at end of study/end of treatment	
End point type	Secondary
End point timeframe:	
Trough serum phosphate at end of study/end of treatment	

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	18	15	33
Units: units on a scale(mmol/L)				
arithmetic mean (standard deviation)	0.787 (± 0.1529)	0.754 (± 0.1768)	0.826 (± 0.1116)	0.787 (± 0.1529)

### Statistical analyses

No statistical analyses for this end point

**Secondary: Serum Burosumab Concentrations (Pharmacokinetics)**

End point title	Serum Burosumab Concentrations (Pharmacokinetics)
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End point description:

Serum burosumab concentrations (Pharmacokinetics) at end of study/end of treatment

End point type	Secondary
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End point timeframe:

end of study/end of treatment

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	18	15	33
Units: units on a scale (ng/mL)				
arithmetic mean (standard deviation)	6153.69 ( $\pm$ 2469.532)	6056.40 ( $\pm$ 2703.828)	6270.45 ( $\pm$ 2244.012)	6153.69 ( $\pm$ 2469.532)

**Statistical analyses**

No statistical analyses for this end point

**Secondary: BPI Pain Interference Score, Change From Baseline**

End point title	BPI Pain Interference Score, Change From Baseline
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End point description:

BPI Pain Interference score, change from baseline to Week 96.

End point type	Secondary
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End point timeframe:

From baseline to Week 96

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	10	12	22
Units: score on a scale				
arithmetic mean (standard deviation)	0.27 ( $\pm$ 2.115)	-0.23 ( $\pm$ 2.381)	-0.31 ( $\pm$ 1.975)	-0.27 ( $\pm$ 2.115)

**Statistical analyses**

No statistical analyses for this end point

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**Other pre-specified: Actual Walking Distance, Change From Baseline (Meters)**

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End point title	Actual Walking Distance, Change From Baseline (Meters)
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End point description:

Actual Walking Distance, Change From Baseline (Meters) to end of study/end of treatment

End point type	Other pre-specified
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End point timeframe:

Baseline to end of study/end of treatment

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End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	18	12	30
Units: score on a scale				
arithmetic mean (standard deviation)	23.80 ( $\pm$ 78.208)	22.78 ( $\pm$ 70.863)	25.33 ( $\pm$ 91.435)	23.80 ( $\pm$ 78.208)

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**Statistical analyses**

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No statistical analyses for this end point

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**Other pre-specified: Treatment-emergent Adverse Events (TEAEs)**

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End point title	Treatment-emergent Adverse Events (TEAEs)
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End point description:

Treatment-emergent adverse events (TEAEs) Baseline to EOS/ET

End point type	Other pre-specified
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End point timeframe:

From baseline to end of study/to end of treatment

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End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	18	17	35
Units: Count of participants	34	17	17	34

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Treatment-emergent Adverse Events (TEAEs) Related to Burosumab

End point title	Treatment-emergent Adverse Events (TEAEs) Related to Burosumab
End point description: Treatment-emergent adverse events (TEAEs) related to burosumab Baseline to end of study/end of treatment	
End point type	Other pre-specified
End point timeframe: From Baseline to end of study/end of treatment	

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	18	17	35
Units: count of participants	16	9	7	16

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Treatment-emergent Hyperphosphatemia Adverse Events

End point title	Treatment-emergent Hyperphosphatemia Adverse Events
End point description: Baseline to end of study/end of treatment	
End point type	Other pre-specified
End point timeframe: Treatment-emergent hyperphosphatemia Adverse Events Baseline to end of study/end of treatment	

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	18	17	35
Units: Count of participants	0	0	0	0



## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Anti-burosumab Antibody

End point title	Anti-burosumab Antibody
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End point description:

Anti-burosumab antibody Week 0 to EOS

End point type	Other pre-specified
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End point timeframe:

From week 0 to EOS

End point values	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	18	17	35
Units: Count of Participants	3	1	2	3

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Increase in Ectopic Mineralization Grade in Echocardiogram

End point title	Increase in Ectopic Mineralization Grade in Echocardiogram
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End point description:

Increase in ectopic mineralization grade in echocardiogram Baseline to EOT

End point type	Other pre-specified
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End point timeframe:

Baseline to End of trial

<b>End point values</b>	Overall trial	Placebo in the Double-blinded Period - UX023-CL303	Burosumab in Double-blinded Period - UX023-CL303 and CL304	All (Placebo + Burosumab)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	13	9	22
Units: Count of participants	1	0	1	1

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Baseline visit through to the safety follow up call

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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### Reporting groups

Reporting group title	Placebo in Double blinded Period from UX023-CL303
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Reporting group description:

18 subjects received placebo during the double-blind period of UX023-CL303.

Reporting group title	Burosumab in Double-blinded Period From UX023-CL303 & CL304
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Reporting group description:

17 subjects either received burosumab during the double-blind period of UX023 CL303 or were from study UX023-CL304 (a single-arm study on burosumab, 1 subject).

Reporting group title	All (Placebo + Burosumab)
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Reporting group description:

All 35 subjects received at least one dose of burosumab and were included in the Full analysis set (FAS).

<b>Serious adverse events</b>	Placebo in Double blinded Period from UX023-CL303	Burosumab in Double-blinded Period From UX023-CL303 & CL304	All (Placebo + Burosumab)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)	3 / 17 (17.65%)	6 / 35 (17.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Procedural failure			

subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum intestinal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	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 %

<b>Non-serious adverse events</b>	Placebo in Double blinded Period from UX023-CL303	Burosumab in Double-blinded Period From UX023- CL303 & CL304	All (Placebo + Burosumab)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	17 / 17 (100.00%)	34 / 35 (97.14%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)	1 / 17 (5.88%)	4 / 35 (11.43%)
occurrences (all)	4	1	5
injection site hematoma			

subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	1 / 17 (5.88%) 1	3 / 35 (8.57%) 3
Injection site hypersensitivity subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 14	3 / 17 (17.65%) 7	6 / 35 (17.14%) 21
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3	1 / 17 (5.88%) 1	3 / 35 (8.57%) 4
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 17 (5.88%) 1	2 / 35 (5.71%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 17 (0.00%) 0	3 / 35 (8.57%) 3
Rhinorrhea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 17 (5.88%) 2	2 / 35 (5.71%) 3
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 17 (0.00%) 0	2 / 35 (5.71%) 2
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 17 (0.00%) 0	2 / 35 (5.71%) 2
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 17 (0.00%) 0	2 / 35 (5.71%) 2
Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 17 (11.76%) 2	3 / 35 (8.57%) 3
Blood parathyroid hormone increased			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 2	2 / 35 (5.71%) 2
Lipase increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 2	2 / 35 (5.71%) 2
Vitamin D decreased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 17 (11.76%) 2	3 / 35 (8.57%) 3
Injury, poisoning and procedural complications			
Ligament sprain subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3	1 / 17 (5.88%) 1	3 / 35 (8.57%) 4
Post vaccination syndrome subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 2	2 / 35 (5.71%) 2
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 17 (5.88%) 1	2 / 35 (5.71%) 2
Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 5	3 / 17 (17.65%) 3	5 / 35 (14.29%) 8
Hypoesthesia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 2	2 / 35 (5.71%) 2
Migraine subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 17 (5.88%) 1	2 / 35 (5.71%) 2
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 5	2 / 35 (5.71%) 5
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	2 / 17 (11.76%) 3	3 / 35 (8.57%) 5

Toothache subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 4	0 / 17 (0.00%) 0	3 / 35 (8.57%) 4
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3	0 / 17 (0.00%) 0	2 / 35 (5.71%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	7 / 18 (38.89%) 10	6 / 17 (35.29%) 10	13 / 35 (37.14%) 20
Arthritis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	1 / 17 (5.88%) 1	2 / 35 (5.71%) 3
Back pain subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	3 / 17 (17.65%) 4	5 / 35 (14.29%) 6
Enthesopathy subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 17 (0.00%) 0	2 / 35 (5.71%) 2
Muscular weakness subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	1 / 17 (5.88%) 1	2 / 35 (5.71%) 3
Myalgia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	1 / 17 (5.88%) 1	3 / 35 (8.57%) 3
Osteoarthritis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 17 (5.88%) 1	2 / 35 (5.71%) 2
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 2	2 / 35 (5.71%) 2
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	3 / 17 (17.65%) 4	3 / 35 (8.57%) 4

COVID-19			
subjects affected / exposed	0 / 18 (0.00%)	2 / 17 (11.76%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Cystitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Ear infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Influenza			
subjects affected / exposed	2 / 18 (11.11%)	1 / 17 (5.88%)	3 / 35 (8.57%)
occurrences (all)	2	1	3
Nasopharyngitis			
subjects affected / exposed	2 / 18 (11.11%)	4 / 17 (23.53%)	6 / 35 (17.14%)
occurrences (all)	2	5	7
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Tooth abscess			
subjects affected / exposed	2 / 18 (11.11%)	3 / 17 (17.65%)	5 / 35 (14.29%)
occurrences (all)	2	4	6
Amylase increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 17 (5.88%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Blood phosphorus decreased			
subjects affected / exposed	1 / 18 (5.56%)	2 / 17 (11.76%)	3 / 35 (8.57%)
occurrences (all)	1	4	5
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	3 / 18 (16.67%)	6 / 17 (35.29%)	9 / 35 (25.71%)
occurrences (all)	3	7	10
Vitamin D deficiency			
subjects affected / exposed	9 / 18 (50.00%)	10 / 17 (58.82%)	19 / 35 (54.29%)
occurrences (all)	14	13	27



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2019	Amendment 2: Duration of treatment was extended. An Inclusion criterion was updated. Collection of patient reported outcome data frequency was increased. An interim analysis was included. Pharmacokinetic samples were added.
24 April 2020	Amendment 3: Additional blood sampling of peak serum phosphate was added. Clarification on central versus local reading of ECHO, ECG and renal ultra sounds was added. Details on data cuts were added. Collection of details of PHEX analysis was removed. The specific serum phosphate lower limit of normal value used by the central laboratory was updated. Data retention timelines were updated.
25 June 2021	Amendment 4: Amendment 4 was to reduce the burden on the patients and hospital staff during the COVID-19 pandemic. The frequency of some assessments was reduced from every 3 months to every 6 months, and the Six Minute Walk Test and Timed Up and Go test were made optional. Investigators following discussion with the Sponsor could transition patients off the study sooner than the study end date of December 2021 or before commercial product was reimbursed. This was only considered if there was a clear mechanism via which the patient could continue, if they wished, to access burosumab until reimbursement was complete in their country.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported