



Clinical trial results:

A Phase 1/2, Open-label, Multicenter, Non-randomized Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Burosumab in Pediatric Patients from Birth to Less than 1 Year of Age with X-linked Hypophosphatemia (XLH)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2019-000469-19 |
| Trial protocol | GB FR DE SE AT IT |
| Global end of trial date | 04 October 2023 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 20 April 2024 |
| First version publication date | 20 April 2024 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | BUR-CL207 |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Kyowa Kirin Pharmaceutical Development Ltd |
| Sponsor organisation address | Galabank Business Park, London, 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) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001659-PIP01-15 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 05 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 October 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 October 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of burosumab in pediatric subjects with X-linked Hypophosphatemia (XLH) starting treatment below 12 months of age with up to 48 weeks of exposure.

Protection of trial subjects:

This protocol is written in accordance with the principles established by the 18th World Medical General Assembly(Helsinki, 1964) and subsequent amendments and clarifications adopted by the general assemblies. The Sponsor and the investigators will make every effort to assure the study described in the protocol is 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 will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug as described in the protocol and investigational brochure, prior to the initiation of the study. It is the investigators responsibility to obtain signed written consent from each potential study subject legal representative prior to conduct of any study procedures. The written informed consent will be obtained after the methods, objectives, requirements and potential risks of the study have been fully explained to each potential subject. The investigator must explain to each subject what the subject is 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 March 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | Italy: 3 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 12 |

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) | 16 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Pediatric XLH patients under 1 year at initiation of treatment with burosumab, with serum phosphate below the lower limit of normal as assessed by local labs

Pre-assignment

Screening details:

Screening visit could occur up to 4 weeks before the baseline visit and could be split into two visits if required. Informed consent, Inclusion/Exclusion criteria, medical history, demographics, vital signs and weight, local and central labs were collected as well as renal ultrasound.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1 |

Arm description:

Subjects aged between 6 months and 1 year on a starting dose of 0.4mg/kg.

| | |
|--|------------------|
| 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 is a sterile clear, colorless and preservative-free solutions supplied in a single use 5ml vial containing 1ml of burosumab at a concentration of 10 mg/ml, 20 mg/ml and 30 mg/ml. Burosumab was administered Q2W as a subcutaneous injection with a maximum volume of 1ml per injection site. Burosumab dose was calculated on actual body weight. The administered dose may be rounded based on the estimated volume to be drawn for administration (rounding up to nearest 1ml). Dose increases were allowed in 0.4mg/kg increases up to a maximum dose of 2mg/kg upon agreement with sponsors medical monitor and the chairperson of the data safety monitoring board. Burosumab dosing will be adjusted based on the pharmacodynamic response based on serum phosphate levels

| | |
|------------------|----------|
| Arm title | Cohort 2 |
|------------------|----------|

Arm description:

Subjects aged between 6 months and 1 year at initiation of treatment with burosumab at a starting dose of 0.8mg/kg

| | |
|--|------------------|
| 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 is a sterile clear, colorless and preservative-free solutions supplied in a single use 5ml vial containing 1ml of burosumab at a concentration of 10 mg/ml, 20 mg/ml and 30 mg/ml. Burosumab was administered Q2W as a subcutaneous injection with a maximum volume of 1ml per injection site. Burosumab dose was calculated on actual body weight. The administered dose may be rounded based on the estimated volume to be drawn for administration (rounding up to nearest 1ml). Dose increases

were allowed in 0.4mg/kg increases up to a maximum dose of 2mg/kg upon agreement with sponsors medical monitor and the chairperson of the data safety monitoring board. Burosumab dosing will be adjusted based on the pharmacodynamic response based on serum phosphate levels

| | |
|--|------------------|
| Arm title | Cohort 3 |
| Arm description: | |
| Subjects under 6 months of age at initiation of burosumab with a starting dose of 0.4mg/kg | |
| 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 is a sterile clear, colorless and preservative-free solutions supplied in a single use 5ml vial containing 1ml of burosumab at a concentration of 10 mg/ml, 20 mg/ml and 30 mg/ml. Burosumab was administered Q2W as a subcutaneous injection with a maximum volume of 1ml per injection site. Burosumab dose was calculated on actual body weight. The administered dose may be rounded based on the estimated volume to be drawn for administration (rounding up to nearest 1ml). Dose increases were allowed in 0.4mg/kg increases up to a maximum dose of 2mg/kg upon agreement with sponsors medical monitor and the chairperson of the data safety monitoring board. Burosumab dosing will be adjusted based on the pharmacodynamic response based on serum phosphate levels

| Number of subjects in period 1 | Cohort 1 | Cohort 2 | Cohort 3 |
|---------------------------------------|----------|----------|----------|
| Started | 3 | 9 | 4 |
| Completed | 3 | 8 | 4 |
| Not completed | 0 | 1 | 0 |
| Consent withdrawn by subject | - | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: | |
| Subjects aged between 6 months and 1 year on a starting dose of 0.4mg/kg. | |
| Reporting group title | Cohort 2 |
| Reporting group description: | |
| Subjects aged between 6 months and 1 year at initiation of treatment with burosumab at a starting dose of 0.8mg/kg | |
| Reporting group title | Cohort 3 |
| Reporting group description: | |
| Subjects under 6 months of age at initiation of burosumab with a starting dose of 0.4mg/kg | |

| Reporting group values | Cohort 1 | Cohort 2 | Cohort 3 |
|--|----------|----------|----------|
| Number of subjects | 3 | 9 | 4 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 3 | 9 | 4 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 4 | 2 |
| Male | 2 | 5 | 2 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 16 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 16 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |

| | | | |
|--------------------|---|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | | |
| Male | 9 | | |

End points

End points reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: Subjects aged between 6 months and 1 year on a starting dose of 0.4mg/kg. | |
| Reporting group title | Cohort 2 |
| Reporting group description: Subjects aged between 6 months and 1 year at initiation of treatment with burosumab at a starting dose of 0.8mg/kg | |
| Reporting group title | Cohort 3 |
| Reporting group description: Subjects under 6 months of age at initiation of burosumab with a starting dose of 0.4mg/kg | |

Primary: Primary

| | |
|--|------------------------|
| End point title | Primary ^[1] |
| End point description: Incidence, frequency, and severity of AEs and SAEs, including clinically significant changes in laboratory and imaging assessments, from Baseline to scheduled timepoints (measured throughout the study up to Week 48). | |
| End point type | Primary |
| End point timeframe: Baseline through to Week 48 | |

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: The primary objective for this study was to characterize the safety profile of burosumab in pediatric subjects starting treatment from birth to <12 months of age. Accordingly, the primary endpoint of this study was to assess the incidence, frequency, and severity of AEs and SAEs, including clinically significant changes in laboratory and imaging assessments, from Baseline to scheduled timepoints (measured throughout the study up to Week 48).

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 9 | 4 | |
| Units: Adverse Events | 51 | 93 | 40 | |

Statistical analyses

No statistical analyses for this end point

Secondary: To characterize the affect of burosumab on serum phosphate

| | |
|--|--|
| End point title | To characterize the affect of burosumab on serum phosphate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Change from baseline over time (week 20, week 26, 32, 40 and 48) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|--------------------|--------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 8 | 4 | |
| Units: millimole(s)/litre | | | | |
| arithmetic mean (standard deviation) | 16.875 (± 16.0982) | 21.869 (± 14.1200) | 13.743 (± 9.4988) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Characterize the effect of burosumab on serum 1,25{OH}2D

End point title Characterize the effect of burosumab on serum 1,25{OH}2D

End point description:

End point type Secondary

End point timeframe:

Change from baseline to week 20, week 26, week 32, week 40 and week 48

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|-----------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 4 | |
| Units: millimole(s)/litre | | | | |
| arithmetic mean (standard deviation) | 3.67 (± 27.335) | -2.50 (± 55.026) | 31.13 (± 44.150) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change overtime in serum ALP

End point title Change overtime in serum ALP

End point description:

End point type Secondary

End point timeframe:

Change from Baseline overtime and at week 48

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 8 | 4 | |
| Units: unit(s) per litre | | | | |
| arithmetic mean (standard deviation) | 151.3 (± 552.81) | -274.5 (± 102.20) | -276.8 (± 169.34) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in radiographic appearance of rickets severity as assessed by the RGI-C scoring system (global))

| | |
|-----------------|---|
| End point title | Change in radiographic appearance of rickets severity as assessed by the RGI-C scoring system (global)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change in baseline to Week 48

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 2 | 9 | 4 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 1.50 (± 0.707) | 2.00 (± 0.0) | 1.75 (± 0.500) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in rickets severity assessed by total RSS

| | |
|-----------------|--|
| End point title | Change from baseline in rickets severity assessed by total RSS |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Baseline to Week 48

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 2 | 7 | 4 | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | -3.50 (\pm 0.00) | 1.86 (\pm 0.802) | 2.13 (\pm 1.436) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in lower extremities skeletal abnormalities as determined by RGI-C long leg score

| | |
|-----------------|--|
| End point title | Change from baseline in lower extremities skeletal abnormalities as determined by RGI-C long leg score |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Baseline to Week 48

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 4 | 2 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | () | 1.25 (\pm 0.500) | 1.50 (\pm 0.707) | |

Notes:

[2] - 0 subjects were included as data not reported for long leg X-Ray at EoT

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in recumbent length at week 48 in cm

| | |
|-----------------|---|
| End point title | Change from baseline in recumbent length at week 48 in cm |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from baseline to week 48

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|-------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 4 | |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 13 (\pm 0.000) | 10.43 (\pm 1.618) | 13.50 (\pm 2.082) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 48 height-for-age z-score

| | |
|---------------------------------|--|
| End point title | Change from baseline at week 48 height-for-age z-score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from baseline to week 48 | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 4 | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -1.09 (\pm 1.586) | -1.73 (\pm 0.609) | -1.44 (\pm 0.860) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 48 in height-for-age percentiles

| | |
|---------------------------------|---|
| End point title | Change from baseline to week 48 in height-for-age percentiles |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Change from baseline to week 48 | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--------------------------------------|----------------------|------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 7 | 4 | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 76.20 (± 151.833) | -129.37 (± 431.598) | 4.96 (± 49.597) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to end of study

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 2 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 3 |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------------|----------------|---------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (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 |
| Congenital, familial and genetic disorders | | | |
| Craniosynostosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (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 |

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

| Non-serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 9 / 9 (100.00%) | 4 / 4 (100.00%) |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 6 / 9 (66.67%) | 3 / 4 (75.00%) |
| occurrences (all) | 21 | 19 | 7 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vaccination site reaction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Selective IgA immunodeficiency | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 9 (22.22%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 3 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 3 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Productive cough subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Investigations | | | |
| Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 3 / 9 (33.33%) 3 | 0 / 4 (0.00%) 0 |
| Vitamin D decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 4 / 9 (44.44%) 4 | 0 / 4 (0.00%) 0 |
| Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 1 / 4 (25.00%) 1 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Blood phosphorus decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Creatine urine increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Serum ferritin decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 4 (50.00%) 2 |
| Joint dislocation subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Thermal burn | | | |

| | | | |
|---|---|---|--|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Congenital, familial and genetic disorders Craniosynostosis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Ear swelling subjects affected / exposed occurrences (all) Middle ear effusion subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 |
| Eye disorders Papilloedema subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea | 0 / 3 (0.00%) 0 2 / 3 (66.67%) 2 0 / 3 (0.00%) 0 | 3 / 9 (33.33%) 4 1 / 9 (11.11%) 3 1 / 9 (11.11%) 1 | 1 / 4 (25.00%) 4 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Teething | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Retching | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Eczema asteatotic | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Skin lesion subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Renal and urinary disorders Nephrocalcinosis subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 4 / 9 (44.44%) 6 | 3 / 4 (75.00%) 6 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 3 / 9 (33.33%) 5 | 3 / 4 (75.00%) 5 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 3 | 5 / 9 (55.56%) 5 | 0 / 4 (0.00%) 0 |
| COVID-19 subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 4 / 9 (44.44%) 4 | 1 / 4 (25.00%) 1 |
| Bronchiolitis subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 | 2 / 4 (50.00%) 2 |
| Varicella subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 2 / 9 (22.22%) 2 | 0 / 4 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 9 (22.22%) 2 | 0 / 4 (0.00%) 0 |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 | 1 / 4 (25.00%) 1 |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Roseola | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Erythema infectiosum | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 02 April 2020 | <ul style="list-style-type: none">• The requirement that targeted radiographic assessments to diagnose and monitor skeletal abnormalities identified during routine standard of care assessments be reported as an unscheduled visit in the eCRF and evaluated centrally was removed as there was no requirement to collect these data as part of the study. Any skeletal abnormalities identified during the study were reported as AEs or SAEs, as appropriate.• A new Clinical Trial Manager was appointed. |
| 26 June 2020 | <ul style="list-style-type: none">• Serum creatinine and serum calcium were collected at the same timepoints as for spot urine in order to be able to calculate the TmP/GFR and the creatinine/calcium ratio. No additional blood sampling was required.• Following recommendation by the DSMB and because formula milk contained higher levels of phosphate, the nutritional status (i.e., breast fed, bottle fed with formula milk, weaned, dietary changes, etc) of the subject was recorded at intervals throughout the study.• The procedure for increasing a patient's dose was clarified.• The Baseline renal ultrasound was moved to Screening as it formed part of the inclusion criteria.• In order to allow pharmacies sufficient time to prepare the first dose an additional weight measurement was taken at Screening. In addition, the study schedule of events table was corrected to include weight measurements on Day 14 and Week 6.• In cases where the genetic testing for PHEX mutation was required, the testing was performed during Screening or within the first 20 weeks on the study, rather than within the first 24 weeks on the study.• The serum phosphate analysis used to determine the patient's hypophosphatemia status for the inclusion criteria was conducted by a local laboratory.• The requirement to enter AE information in the eCRF within 24 hours was removed.• It was clarified that a Laboratory Manual detailing blood sample collection, preparation, labeling, and storage was only provided for the Central Laboratory.• All subjects were assessed for the occurrence of AEs from the time following the first dose of investigational product until 56 days after the last dose or until Week 76 (whichever was longer).• Details on the reporting of any COVID-19 infections were included. |

| | |
|-----------------|--|
| 27 January 2021 | <ul style="list-style-type: none"> The planned treatment duration was updated from at least 64 weeks to up to 48 weeks since the safety and efficacy of burosumab had previously been demonstrated in other clinical trials included in the marketing authorization. A 48 week study did not limit access of the patient to treatment as the product was indicated for patients from 12 months of age, and given that the study provided for a 30-day Screening period followed by 48 weeks of treatment, this ensured that any patient completing the study were more than 12 months old at study completion. Consequently, the frequency and timing of certain assessments were amended. The study design had been revised to remove Cohort 4 and the Expansion Part (Part 2). There was more flexibility for dosing of subjects <6 months of age in Cohort 3, allowing the starting dose to be increased to 0.8 mg/kg if deemed safe and appropriate. The requirement to offer subjects participation in a 96-week follow-up extension study was removed, as data on effects of long-term treatment were available from 3 studies in pediatric XLH subjects aged 1 to 12 years (UX023 CL201, UX023 CL205, and UX023 CL301); therefore, there was no need for a further extension study after completion of BUR CL207. Subjects were offered long term follow-up in the Kyowa Kirin Registry upon consent by their legally authorized representative in territories where this was available at the time the subject completed 48 weeks of treatment. The exploratory endpoint to measure time to appearance of radiological abnormalities due to XLH was removed as it could not be evaluated with only 2 X rays. Day 3 and Day 11 visits were removed to reduce the burden of visits for families and the site during the initial 2 weeks and PK timepoints had been updated to match PD timepoints. The Burosumab Dosing Recommendations tables were removed for simplification. |
| 13 October 2022 | <ul style="list-style-type: none"> The minimum number of evaluable subjects to be enrolled into the study was updated to at least 14 in line with the PIP commitment. Exclusion criterion 3 was updated to remove the wording "and estimated GFR (eGFR, calculated using the Bedside Schwartz equation) below the age-adjusted normal range", since this equation was not developed and validated in infants below 12 months of age and is thus not applicable to the patient population to be enrolled in this study. A timepoint was added at Week 26 for 1,25(OH)2D as it had previously not been included in error. Subgroup analysis performed for age group was removed as analyses would only be performed by cohort. Wording was updated regarding the marketing authorization and clinical studies completion statuses. Wording was added to the Study Schedule of Events to clarify that if spot urine could not be collected this would not be a protocol deviation. The requirement for the calculation of percentiles for age-adjusted normal ranges to be provided for each Investigational Site before enrolling the first subject was deleted. The Sponsor Medical Monitor contact details were updated. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported