



Clinical trial results:

An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2018-001983-49 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 10 September 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 22 March 2020 |
| First version publication date | 22 March 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | UX023-CL205 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02750618 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Ultragenyx Pharmaceutical Inc. |
| Sponsor organisation address | 60 Leveroni Court, Novato, California, United States, 94949 |
| Public contact | Medical Information, Ultragenyx Pharmaceutical Inc, 1 8887568567, medinfo@ultragenyx.com |
| Scientific contact | Medical Information, Ultragenyx Pharmaceutical Inc, 1 8887568567, medinfo@ultragenyx.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? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 September 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 September 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are to:

- Establish the safety profile of KRN23 for the treatment of XLH in children between 1 and 4 years old
- Determine the pharmacodynamic (PD) effects of KRN23 treatment on serum phosphorus and other PD markers that reflect the status of phosphate homeostasis in children between 1 and 4 years old with XLH

Protection of trial subjects:

The trial was designed, conducted, recorded, and reported 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 investigators made every effort to ensure that the study was conducted in full conformance with Helsinki principles, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, current Food and Drug Administration (FDA) regulations, EU Clinical Trial Directive 2001/20/EC, and local ethical and regulatory requirements. Each investigator was thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in the protocol and Investigator's Brochure, prior to the initiation of the study. The method of obtaining and documenting informed consent and the contents of the informed consent form (ICF) complied with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act regulations, and all other applicable regulatory requirements. Investigators were responsible for preparing the ICF and submitting it to the Sponsor for approval prior to submission to the Institutional Review Board (IRB). All ICFs were written in regional language and contained the minimum elements for consent as mandated by the ICH guidelines. An IRB-approved ICF was provided by the Sponsor prior to initiation of the study. Investigators obtained signed written informed consent from each potential study subject prior to the conduct of any study procedures and after the methods, objectives, requirements, and potential risks of the study were fully explained to each potential subject. Consent for participation could be withdrawn at any time for any reason by the subject.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 05 May 2016 |
| 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 | United States: 13 |
| Worldwide total number of subjects | 13 |
| EEA total number of subjects | 0 |

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) | 3 |
| Children (2-11 years) | 10 |
| 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: -

Pre-assignment

Screening details:

The study enrolled approximately 10 pediatric subjects between 1 and 4 years old, inclusive, with clinical findings consistent with XLH including hypophosphatemia and radiographic evidence of rickets, and a confirmed PHEX mutation or variant of uncertain significance.

Period 1

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

Arms

| | |
|-----------|---------------|
| Arm title | Burosumab Q2W |
|-----------|---------------|

Arm description:

Burosumab subcutaneous (SC) injections every 2 weeks (Q2W) for a total of 160 weeks.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | burosumab |
| Investigational medicinal product code | UX023 |
| Other name | KRN23, Crysvida®, UX023 |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The amount of drug administered will be calculated based on a subject's weight. All subjects will receive KRN23 at a Q2W dosing regimen.

| Number of subjects in period 1 | Burosumab Q2W |
|--------------------------------|---------------|
| Started | 13 |
| Completed Week 40 | 13 |
| Completed Week 64 | 13 |
| Completed | 12 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Burosumab Q2W |
|-----------------------|---------------|

Reporting group description:

Burosumab subcutaneous (SC) injections every 2 weeks (Q2W) for a total of 160 weeks.

| Reporting group values | Burosumab Q2W | Total | |
|------------------------|---------------|-------|--|
| Number of subjects | 13 | 13 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---------|----|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 2.94 | | |
| standard deviation | ± 1.146 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 9 | 9 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 2 | |
| Not Hispanic or Latino | 11 | 11 | |
| Unknown or Not Reported | 0 | 0 | |
| Race | | | |
| Units: Subjects | | | |
| White | 12 | 12 | |
| Black or African American | 1 | 1 | |
| Serum Phosphorus | | | |
| Units: mg/dL | | | |
| arithmetic mean | 2.51 | | |
| standard deviation | ± 0.284 | - | |
| Rickets Severity Score (RSS) Total Score | | | |
| The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 2.92 | | |
| standard deviation | ± 1.367 | - | |
| Recumbent length/ Standing height | | | |
| Growth is measured by recumbent length for subjects < 2 years of age or those unable or unwilling to stand for the measurement. | | | |
| Units: cm | | | |
| arithmetic mean | 89.15 | | |
| standard deviation | ± 7.597 | - | |
| Recumbent length/ Standing height (Z | | | |

| | | | |
|---|-----------|---|--|
| score) | | | |
| <p>Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. The Z-score indicates the number of standard deviations away from a reference population (from the Centers for Disease Control [CDC] growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.</p> | | | |
| Units: Z score | | | |
| arithmetic mean | -1.378 | | |
| standard deviation | ± 1.1947 | - | |
| Recumbent length/ Standing height (percentile) | | | |
| Units: percentile | | | |
| arithmetic mean | 18.044 | | |
| standard deviation | ± 25.2644 | - | |
| Serum Alkaline Phosphatase (ALP) | | | |
| Units: U/L | | | |
| arithmetic mean | 548.5 | | |
| standard deviation | ± 193.80 | - | |

End points

End points reporting groups

| | |
|--|---------------|
| Reporting group title | Burosumab Q2W |
| Reporting group description: Burosumab subcutaneous (SC) injections every 2 weeks (Q2W) for a total of 160 weeks. | |

Primary: Change From Baseline at Week 40 in Serum Phosphorus

| | |
|-----------------|--|
| End point title | Change From Baseline at Week 40 in Serum Phosphorus ^[1] |
|-----------------|--|

End point description:

The Generalized Estimation Equation (GEE) model includes the change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure.

Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set: all participants who received at least one dose of study drug and had evaluable blood samples.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 40

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: GEE statistical analysis is presented in the data table.

| | | | | |
|-------------------------------------|-----------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: mg/dL | | | | |
| least squares mean (standard error) | 0.96 (± 0.117) | | | |

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|-----------------------------------|---|
| Attachments (see zip file) | Statistical Analysis 1 for Change From Baseline at Week 40 in |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Adverse Events (AEs), Treatment Emergent AEs (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation

| | |
|-----------------|--|
| End point title | Number of Participants With Adverse Events (AEs), Treatment Emergent AEs (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation ^[2] |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug related. A serious AE was defined as an AE that at any dose, in the view of either the Investigator or Sponsor, results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or disability, a congenital anomaly/birth defect, or other important medical events (according to the investigator). An AE was considered a TEAE if it occurred on or after the first dose and was not present prior to the first dose, or it was present prior to the first dose but increased in severity during the study.

Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), grade 5 (death).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From first dose of study drug through the end of the study (at Week 160). Maximum duration of exposure to study drug was 160 weeks.

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 are presented per protocol.

| | | | | |
|--|-----------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: participants | | | | |
| Adverse Event Starting during Screening Period | 5 | | | |
| TEAEs | 13 | | | |
| Related TEAEs | 5 | | | |
| Serious TEAEs | 1 | | | |
| Serious Related TEAEs | 0 | | | |
| Grade 3 or 4 TEAEs | 2 | | | |
| TEAE Leading to Study Discontinuation | 0 | | | |
| TEAE Leading to Treatment Discontinuation | 0 | | | |
| TEAE Leading to Death | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic Global Impression of Change (RGI-C) Score at Week 40

| | |
|-----------------|---|
| End point title | Radiographic Global Impression of Change (RGI-C) Score at Week 40 |
|-----------------|---|

End point description:

Changes in the severity of rickets and bowing were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The Analysis of Covariance (ANCOVA) model includes the RGI-C score as the dependent variable, age and RSS at baseline as covariates.

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

End point timeframe:

Week 40

| | | | | |
|-------------------------------------|---------------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 2.21 (\pm 0.071) | | | |

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| Attachments (see zip file) | Statistical Analysis 1 for Radiographic Global Impression of |
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Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Score at Week 64

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|-----------------|------------------------|
| End point title | RGI-C Score at Week 64 |
|-----------------|------------------------|

End point description:

Changes in the severity of rickets and bowing were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The GEE model includes the RGI-C score as the dependent variable, visit as a factor, age and RSS at baseline as covariates, with exchangeable covariance structure.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

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

End point timeframe:

Week 64

| | | | | |
|-------------------------------------|---------------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 2.23 (\pm 0.111) | | | |

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|-----------------------------------|--|
| Attachments (see zip file) | Statistical Analysis 1 for RGI-C Score at Week 64.docx |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rickets at Week 40 as Assessed by the RSS Total Score

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|-----------------|---|
| End point title | Change From Baseline in Rickets at Week 40 as Assessed by |
|-----------------|---|

End point description:

The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity. The ANCOVA model includes the RGI-C score as the dependent variable, age and RSS at baseline as covariates.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

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

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|----------------------|
| End point timeframe: |
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|-------------------|
| Baseline, Week 40 |
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|-------------------------------------|-----------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -1.75 (± 0.116) | | | |

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|-----------------------------------|---|
| Attachments (see zip file) | Statistical Analysis 1 for Change From Baseline in Rickets at |
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rickets at Week 64 as Assessed by the RSS Total Score

| | |
|-----------------|---|
| End point title | Change From Baseline in Rickets at Week 64 as Assessed by the RSS Total Score |
|-----------------|---|

End point description:

The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity. The GEE model includes the change from baseline in RSS as the dependent variable, visit as a factor, age and RSS at baseline as covariates, with exchangeable covariance structure.

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|----------------|-----------|
| End point type | Secondary |
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|----------------------|
| End point timeframe: |
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|-------------------|
| Baseline, Week 64 |
|-------------------|

| | | | | |
|-------------------------------------|----------------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -2.02 (\pm 0.115) | | | |

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|-----------------------------------|---|
| Attachments (see zip file) | Change From Baseline in Rickets at Week 64 as Assessed by |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Lower Limb Deformity Score at Week 40

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|-----------------|---|
| End point title | RGI-C Lower Limb Deformity Score at Week 40 |
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End point description:

Changes in the severity of lower extremity skeletal abnormalities were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The ANCOVA model includes the RGI-C score as the dependent variable, age and RSS at baseline as covariates.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

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

End point timeframe:

Week 40

| | | | | |
|-------------------------------------|---------------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 1.21 (\pm 0.155) | | | |

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| Attachments (see zip file) | Statistical Analysis 1 for RGI-C Lower Limb Deformity Score at |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Lower Limb Deformity Score at Week 64

| | |
|-----------------|---|
| End point title | RGI-C Lower Limb Deformity Score at Week 64 |
|-----------------|---|

End point description:

Changes in the severity of lower extremity skeletal abnormalities were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The GEE model includes the RGI-C score as the dependent variable, visit as a factor, age and RSS at baseline as covariates, with exchangeable covariance structure.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 64 | |

| | | | | |
|-------------------------------------|---------------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 1.51 (\pm 0.123) | | | |

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|-----------------------------------|--|
| Attachments (see zip file) | Statistical Analysis 1 for RGI-C Lower Limb Deformity Score at |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Recumbent Length/Standing Height

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|-----------------|--|
| End point title | Change From Baseline Over Time in Recumbent Length/Standing Height |
|-----------------|--|

End point description:

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement at given time point.

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|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12, 24, 40, 64, 88, 112, 136, 160 | |

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | Burosumab Q2W | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 ^[3] | | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12; n=13 | 1.44 (\pm 2.009) | | | |

| | | | | |
|----------------|----------------------|--|--|--|
| Week 24; n=13 | 2.52 (\pm 1.518) | | | |
| Week 40; n=13 | 4.29 (\pm 2.451) | | | |
| Week 64; n=13 | 7.22 (\pm 3.157) | | | |
| Week 88; n=13 | 10.30 (\pm 3.400) | | | |
| Week 112; n=13 | 13.25 (\pm 3.724) | | | |
| Week 136; n=11 | 15.41 (\pm 3.699) | | | |
| Week 160; n=12 | 18.96 (\pm 4.206) | | | |

Notes:

[3] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in Recumbent Length/Standing Height as Assessed by Height-for-Age Z-Scores

| | |
|-----------------|---|
| End point title | Change from Baseline Over Time in Recumbent Length/Standing Height as Assessed by Height-for-Age Z-Scores |
|-----------------|---|

End point description:

Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. The Z-score indicates the number of standard deviations away from a reference population (from the CDC growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement at given time point.

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

End point timeframe:

Baseline, Weeks 12, 24, 40, 64, 88, 112, 136, 160

| End point values | Burosumab Q2W | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 ^[4] | | | |
| Units: Z score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12; n=13 | -0.082 (\pm 0.4964) | | | |
| Week 24; n=13 | -0.208 (\pm 0.4540) | | | |
| Week 40; n=13 | -0.276 (\pm 0.6647) | | | |
| Week 64; n=13 | -0.264 (\pm 0.8755) | | | |
| Week 88; n=13 | -0.212 (\pm 0.9115) | | | |
| Week 112; n=13 | -0.174 (\pm 0.9273) | | | |

| | | | | |
|----------------|------------------------|--|--|--|
| Week 136; n=11 | -0.321 (\pm 0.9123) | | | |
| Week 160; n=12 | -0.172 (\pm 0.9048) | | | |

Notes:

[4] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Recumbent Length/Standing Height as Assessed by Percentiles

| | |
|-----------------|---|
| End point title | Change From Baseline Over Time in Recumbent Length/Standing Height as Assessed by Percentiles |
|-----------------|---|

End point description:

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement at given time point.

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

End point timeframe:

Baseline, Weeks 12, 24, 40, 64, 88, 112, 136, 160

| End point values | Burosumab Q2W | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: percentiles | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12; n=13 | -0.006 (\pm 11.6149) | | | |
| Week 24; n=13 | -4.940 (\pm 13.1323) | | | |
| Week 40; n=13 | -5.283 (\pm 20.1675) | | | |
| Week 64; n=13 | -4.980 (\pm 23.4412) | | | |
| Week 88; n=13 | -4.155 (\pm 23.9126) | | | |
| Week 112; n=13 | -3.000 (\pm 24.7569) | | | |
| Week 136; n=11 | -7.026 (\pm 24.8583) | | | |
| Week 160; n=12 | -3.628 (\pm 25.5113) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Serum Alkaline Phosphatase (ALP)

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|--|--|
| End point title | Change From Baseline Over Time in Serum Alkaline Phosphatase (ALP) |
| End point description: | |
| The GEE model includes the change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure. | |
| PK/PD Analysis Set: all participants who received at least one dose of study drug and had evaluable blood samples at given time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 12, 20, 40, 48, 56, 64, 76, 88, 100, 112, 124, 136, 148, 160 | |

| End point values | Burosumab Q2W | | | |
|-------------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: U/L | | | | |
| least squares mean (standard error) | | | | |
| Week 4; n=13 | -82.91 (\pm 23.348) | | | |
| Week 12; n=13 | -83.84 (\pm 45.263) | | | |
| Week 20; n=13 | -161.38 (\pm 12.924) | | | |
| Week 40; n=13 | -214.99 (\pm 13.628) | | | |
| Week 48; n=12 | -226.58 (\pm 11.491) | | | |
| Week 56; n=13 | -216.45 (\pm 16.165) | | | |
| Week 64; n=13 | -216.76 (\pm 12.705) | | | |
| Week 76; n=13 | -231.22 (\pm 15.964) | | | |
| Week 88; n=12 | -237.78 (\pm 12.837) | | | |
| Week 100; n=13 | -218.14 (\pm 15.340) | | | |
| Week 112; n=13 | -233.91 (\pm 11.098) | | | |
| Week 124; n=12 | -252.22 (\pm 8.312) | | | |
| Week 136; n=12 | -267.89 (\pm 13.124) | | | |
| Week 148; n=12 | -248.05 (\pm 12.653) | | | |
| Week 160; n=12 | -248.47 (\pm 10.990) | | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Statistical Analysis 15 for Change From Baseline Over Time in |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over Time in Serum ALP

| | |
|--|---|
| End point title | Percent Change From Baseline Over Time in Serum ALP |
| End point description: PK/PD Analysis Set: all participants who received at least one dose of study drug and had evaluable blood samples at given time point. | |
| End point type | Secondary |
| End point timeframe: Baseline, Weeks 4, 12, 20, 40, 48, 56, 64, 76, 88, 100, 112, 124, 136, 148, 160 | |

| End point values | Burosumab Q2W | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4; n=13 | -12.47 (\pm 16.620) | | | |
| Week 12; n=13 | -5.00 (\pm 60.124) | | | |
| Week 20; n=13 | -24.76 (\pm 18.883) | | | |
| Week 40; n=13 | -36.25 (\pm 12.787) | | | |
| Week 48; n=13 | -37.29 (\pm 13.936) | | | |
| Week 56; n=13 | -35.80 (\pm 16.568) | | | |
| Week 64; n=13 | -35.95 (\pm 14.851) | | | |
| Week 76; n=13 | -38.36 (\pm 15.621) | | | |
| Week 88; n=12 | -39.08 (\pm 12.987) | | | |
| Week 100; n=13 | -37.42 (\pm 12.466) | | | |
| Week 112; n=13 | -39.05 (\pm 13.808) | | | |
| Week 124; n=12 | -43.11 (\pm 12.493) | | | |
| Week 136; n=12 | -47.01 (\pm 11.752) | | | |
| Week 148; n=12 | -43.47 (\pm 11.321) | | | |
| Week 160; n=12 | -42.35 (\pm 13.574) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through the end of the study (at Week 160). Maximum duration of exposure to study drug was 160 weeks.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Burosumab Q2W |
|-----------------------|---------------|

Reporting group description:

Burosumab SC injections Q2W for a total of 160 weeks.

| Serious adverse events | Burosumab Q2W | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Infections and infestations | | | |
| Tooth Abscess | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Burosumab Q2W | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 13 (100.00%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration | | | |

| | | | |
|-----------------------------|------------------|--|--|
| site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Injection Site Bruising | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 3 | | |
| Injection Site Erythema | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 4 | | |
| Injection Site Pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Injection Site Pruritus | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Injection Site Reaction | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 13 (84.62%) | | |
| occurrences (all) | 54 | | |
| Vaccination Site Reaction | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Immune system disorders | | | |
| Food Allergy | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypersensitivity | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 4 | | |
| Reproductive system and breast disorders | | | |
| Penile Erythema subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Penile Pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Adenoidal Disorder subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Chronic Throat Clearing subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Cough subjects affected / exposed occurrences (all) | 11 / 13 (84.62%) 40 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 11 | | |
| Nasal Congestion subjects affected / exposed occurrences (all) | 8 / 13 (61.54%) 9 | | |
| Nasal Discharge Discolouration subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Oropharyngeal Pain subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 10 | | |
| Productive Cough subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 4 | | |
| Respiratory Tract Congestion | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 4 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 7 / 13 (53.85%) | | |
| occurrences (all) | 35 | | |
| Sinus Congestion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Sneezing | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 3 | | |
| Throat Irritation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Wheezing | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 7 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Amylase Increased | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Blood 25-Hydroxycholecalciferol Decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Blood Parathyroid Hormone Increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Blood Phosphorus Decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Heart Rate Abnormal | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Lipase Increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Vitamin D Decreased | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| White Blood Cell Count Increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod Bite | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 8 | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Fall | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 6 | | |
| Laceration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Lip Injury | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Skin Abrasion | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 5 | | |
| Tooth Fracture | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Tooth Injury | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Traumatic Tooth Displacement | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Congenital, familial and genetic disorders | | | |
| Skull Malformation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Syringomyelia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | | |
| occurrences (all) | 15 | | |
| Hypersomnia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 4 | | |
| Periodic Limb Movement Disorder | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Deafness Unilateral | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Ear Haemorrhage | | | |

| | | | |
|------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Ear Pain | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 17 | | |
| Excessive Cerumen Production | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Motion Sickness | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Otorrhoea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Ocular Hyperaemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal Discomfort | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 4 | | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | | |
| occurrences (all) | 12 | | |
| Aphthous Ulcer | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 5 | | |
| Constipation | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 3 | | |
| Dental Caries | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | | |
| occurrences (all) | 9 | | |
| Epigastric Discomfort | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gingival Blister | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gingival Erythema | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gingival Pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Loose Tooth | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Oral Pain | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 6 | | |
| Post-Tussive Vomiting | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Teething | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Toothache | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 6 | | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 13 (53.85%) | | |
| occurrences (all) | 15 | | |
| Vomiting Projectile | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis Contact | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Rash | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 3 | | |
| Rash Papular | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Skin Disorder | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Swelling Face | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 8 | | |

| | | | |
|---|---|--|--|
| Urticaria Papular subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Polyuria subjects affected / exposed occurrences (all) Urinary Incontinence subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back Pain subjects affected / exposed occurrences (all) Bone Pain subjects affected / exposed occurrences (all) Foot Deformity subjects affected / exposed occurrences (all) Knee Deformity subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain In Extremity subjects affected / exposed occurrences (all) | 4 / 13 (30.77%) 13 1 / 13 (7.69%) 1 3 / 13 (23.08%) 6 1 / 13 (7.69%) 1 3 / 13 (23.08%) 3 1 / 13 (7.69%) 2 9 / 13 (69.23%) 40 | | |
| Infections and infestations | | | |

| | | | |
|----------------------------------|-----------------|--|--|
| Atypical Pneumonia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Croup Infectious | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Ear Infection | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | | |
| occurrences (all) | 7 | | |
| Enterobiasis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Eye Infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal Viral Infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Genital Candidiasis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gingival Abscess | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Hand-Foot-And-Mouth Disease | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------------|------------------|--|--|
| Impetigo | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 3 | | |
| Influenza | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 3 | | |
| Molluscum Contagiosum | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 3 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 5 | | |
| Otitis Media | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Pharyngitis Streptococcal | | | |
| subjects affected / exposed | 8 / 13 (61.54%) | | |
| occurrences (all) | 22 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Tooth Abscess | | | |
| subjects affected / exposed | 10 / 13 (76.92%) | | |
| occurrences (all) | 24 | | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 9 / 13 (69.23%) | | |
| occurrences (all) | 11 | | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Viral Infection | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|-----------------------|--|--|
| Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 15 | | |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Increased Appetite subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Polydipsia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 28 March 2016 | <p>1. Burosumab dose and dose justification: As a result of additional clinical data available since the time the original protocol was written, the dose of burosumab was changed. The starting dose of burosumab was changed to 0.8 mg/kg Q2W. The dose may then be increased to 1.2 mg/kg at any time during the study if a subject met the following dose adjustment criteria: 1) 2 consecutive serum phosphorus measurements were below the normal range; 2) serum phosphorus had increased by < 0.5 mg/dL from Baseline; and 3) the subject had not missed a dose of study drug that would have accounted for the decrease in serum phosphorus. Previously the protocol had specified a starting dose of 0.3 mg/kg Q2W for the first 2 doses and a target dose of 0.6 mg/kg Q2W.</p> <p>2. Study Population: The inclusion criteria were modified to add PHEX mutation or VUS in either the patient or in a directly related family member with appropriate X-linked inheritance to confirm presence of XLH and to avoid including patients with syndromes that have clinical and biochemical phenotypic overlap with XLH. The criterion of intact fibroblast growth factor 23 (iFGF23) level ≥ 30 pg/mL by Kainos assay was eliminated because it was unnecessary in addition to genetic confirmation. The exclusion criteria were modified to add presence of nephrocalcinosis grade 4 on renal ultrasound (ie, stone formation). Presence of stone formation was added as an exclusion criterion based on regulatory agency request.</p> |
| 28 March 2016 | <p>(continued)</p> <p>3. Prohibited Medications: The washout period required for subjects receiving oral phosphate and active vitamin D standard therapy was reduced from 14 days to 7 days. Oral phosphate is typically given 4–5 times daily in XLH due to its rapid clearance from the body (Carpenter et al. 2011). Prescribing information for oral calcitriol notes a half life of 27.4 hours in children (Rocaltrol 2008); therefore, a 7-day washout was deemed sufficient to remove phosphate and active vitamin D from the body and minimizes the duration of time that a patient is off therapy.</p> <p>4. Study Procedures and Assessments:</p> <p>a. Screening Visit 2 was removed from the Schedule of Events. Assessments previously indicated to be performed at Screening Visit 2 were rescheduled to be performed at the Baseline visit. This change was made to reduce the burden of multiple visits on subjects and their families.</p> <p>b. The Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument was removed as an assessment in the study because the questionnaire could be administered to subjects less than 2 years of age and most of the items were only relevant for subjects 5 years of age or older. Therefore, the amount of data to be collected from this instrument in this study of children 1 to 4 years old was likely minimal.</p> <p>c. The frequency and schedule of renal ultrasounds was modified. Renal ultrasounds were to be conducted at Screening, Week 40, and Week 64. Renal ultrasound assessment was moved from Baseline to Screening because renal stone formation had been added as an exclusion criterion. The Week 12 renal ultrasound was removed to minimize patient burden in these young patients.</p> <p>d. The frequency and schedule for measurement of FGF23 levels was modified to Baseline, Week 24, and Week 64. This change was made to minimize blood volumes collected and to align with the Phase 3 pediatric protocol.</p> |

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| 28 March 2016 | <p>(continued)</p> <p>e. Assessment of ADA was added at the Baseline Visit. ADA assessment was needed both before and after burosumab administration to distinguish between background signal and ADAs induced by administration of burosumab.</p> <p>f. The instructions for the measurement of BP were updated. BP was to be measured only in subjects who were ≥ 3 years of age. Previously, BP was measured one time each at the beginning and end of site visits in all subjects. At the Screening Visit, BP was to be measured 3 times, 30 seconds apart at the beginning of each visit; 3 additional BP measurements, 30 seconds apart, were to be obtained at the end of the study visit after all procedures had been performed. Elevated BP measurements were noted in some subjects in the Phase 2 pediatric UX023-CL201 study prior to administration of burosumab and in some subjects post administration of burosumab. To help ensure accurate pre-treatment and post-treatment BP measurements in this study, multiple assessments of BP were to be obtained at each site visit. The United States Department of Health and Human Services guidelines for Blood Pressure Measurement in Children was used as a reference.</p> <p>5. Safety Measurements: Assessment of serum lipase in addition to serum amylase was added for all subjects. Amylase is produced by several organs including the pancreas and salivary gland and so elevated amylase levels are not diagnostic in the absence of other information. In ongoing and completed burosumab studies at Baseline, mild elevations of amylase ($<2\times$ the upper limit of the reference range [ULRR]) have been noted. Post treatment mild shifts in amylase elevation ($< 2\times$ULRR) has been noted without association with GI symptoms. No AEs of pancreatitis have been observed. The additional testing of serum lipase were to aid in a determination of whether the elevations were from pancreatic or salivary gland sources.</p> |
| 28 March 2016 | <p>(continued)</p> <p>6. Data Monitoring Committee: Details of the DMC were updated. Specifically, the amended protocol stated that the independent DMC was to include members with expertise in metabolic bone disease, cardiology, and nephrology and the conduct of clinical trials in children. The FDA requested the inclusion of DMC members with expertise in pediatric cardiology and nephrology in addition to metabolic bone disease.</p> <p>7. Record Retention: The record retention language was updated to state that all study records must have been retained for at least 25 years after the end of the clinical trial or in accordance with national law. This administrative change was made to reflect changes to European Union clinical trial regulations and current regulations by other health authorities.</p> |
| 12 June 2017 | <p>1. Study Objectives: The additional study objective was modified from "Pre-dose KRN23 drug concentration levels" to "KRN23 drug concentration levels (PK)" to clarify that burosumab drug concentration levels were to be assessed throughout the study.</p> <p>2. Overall Study Design and Plan: The provision to maintain gender balance was modified from "no more than 7 subjects" to "no more than 70% of subjects". The original protocol planned sample size was 10 subjects, therefore 7 subjects (ie, 70% of the study population) were originally selected. The change more accurately reflected the total enrollment of 13 subjects (9 male; 69%).</p> <p>3. Study Duration: An Extension Period of 96 weeks was added for continued assessment of the long-term safety and efficacy of burosumab in younger children.</p> <p>4. Removal of Subjects: Language was added to allow orthopedic surgery during the Extension Period if recommended by the investigator or consulting physician. In addition, subjects who developed hyperparathyroidism were allowed to remain on study, but use of medication to suppress parathyroid hormone (eg, Sensipar®, cinacalcet, calcimimetics) was not permitted at any time. Subjects were to be removed from study if treatment for hyperparathyroidism became medically necessary.</p> |

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| 12 June 2017 | <p>(continued)</p> <p>5. Treatment: Updates were made to allow for a parent or caregiver to administer burosumab to the subject after proper training by study personnel in SC injection technique and documentation of proficiency. Additional updates were made to describe the timing of dose adjustments during the Extension Period and to describe methods for monitoring treatment compliance in the home setting via telephone contact and physical inventory of empty vials at site visits for study drug accountability. Allowing subjects' parents or caregivers to administer burosumab in the home setting was expected to reduce the burden on the subjects. Instructions for Use (IFU) were thoughtfully developed with input from XLH patients and were used to guide parents and caregivers through the injection process. The IFU was provided to sites and IRBs for approval prior to the initiation of parent/caregiver administration. To avoid potential errors with any dose adjustments, dose changes during the Extension Period were to be initially implemented at the clinic visits. Site personnel collected information on treatment compliance in the home setting and monitored the home administration via telephone contact.</p> <p>6. Study Procedures and Assessments: Changes to study procedures are described below; a new Schedule of Events table was included to describe visits and assessments during the Extension Period.</p> |
| 12 June 2017 | <p>(continued)</p> <p>a. During the Extension Period, clinic visits were to occur at approximately 12-week intervals (± 5 days). Home health or telephone visits were to occur every 2 weeks. For telephone visits, study sites scheduled biweekly telephone calls with the subjects' parent/caregiver to confirm administration of study drug, and for collection of AEs and concomitant medication information. Site personnel initiated a safety follow-up telephone call 5 weeks ($+5$ days) after the Week 160 visit to determine if the subject was receiving burosumab therapy under commercial use or another mechanism and to collect information on any ongoing or new AEs, serious TEAEs, and concomitant medications for subjects not receiving burosumab. The additional safety visit (10 weeks ± 5 days after Week 160) applied to subjects who discontinued treatment early or chose not to continue burosumab therapy as commercial product or through another mechanism once the study ended. These additional clinic visits and telephone calls were included in the Extension Period to monitor long-term safety, compliance, and efficacy at an interval deemed appropriate for the age of the population and duration of treatment.</p> <p>b. As previously communicated by memorandum (20 October 2016), updates were made to remove TmP/GFR and TRP (tubular reabsorption of phosphate) as estimates of renal phosphate reabsorption due to the breadth of available data and burden of obtaining urine samples in this study population (under 5 years of age).</p> <p>c. As previously communicated by memorandum (20 October 2016), the Week 22 serum calcium assessment was removed from the Schedule of Events.</p> <p>d. As previously communicated by memorandum (05 April 2016), updates were made such that blood pressure was to be obtained for subjects aged 3 years or above (at study entry or beginning when the subject turned 3 years of age). The provision for training on blood pressure measurements at the site initiation visit was removed.</p> |

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| 12 June 2017 | <p>(continued)</p> <p>e. As previously communicated by memorandum (13 December 2016), updates were made to indicate that the scope of the genitourinary exam should have been noninvasive and as per age-appropriate standard of care, at the investigator's discretion based on clinical judgement.</p> <p>f. ECG was changed from an ectopic mineralization assessment to a general safety assessment. ECG was performed to evaluate for changes associated with left ventricular hypertrophy. Ectopic mineralization was not expected to affect ECG parameters and ECG was inadvertently listed in that section in the original protocol.</p> <p>g. Updates were made such that concomitant medications and therapies were reviewed between site visits by telephone call from the study site every 2 weeks and recorded in the subject's CRF. Inclusion of telephone calls provided a mechanism to track use of concomitant medications and therapies at a consistent frequency during the Extension Period.</p> <p>7. Statistical Analysis and Data Monitoring Committee: The statistical models for efficacy analysis were updated to incorporate Baseline adjustment and repeated measures at multiple time points. A newly added section described the timing of planned analyses for the study and more precisely defined the end of the study. Updates were made to stipulate that the Data Monitoring Committee was to review safety data through the Treatment Period (Week 64); long-term safety during the Extension Period was to be reviewed by the Ultragenyx SSRT on an ongoing basis.</p> <p>8. Investigators and Study Administrative Structure: As previously communicated by memorandum (30 September 2016), updates were made to include language describing the Coordinating Investigator for the study. The Coordinating Investigator is Erik Imel, MD, Indiana University School of Medicine.</p> |
| 12 June 2017 | <p>(continued)</p> <p>9. Reporting and Follow-up of Adverse Events: Language was revised to reflect the revised study design and safety follow-up procedures. The reporting periods of AEs were defined as those from the time the subjects signs informed consent through "the final protocol-defined safety follow-up telephone call or safety visit". Previously, these were defined as those through "12 weeks (approximately 5 times the elimination half-life) following the last dose of study drug."</p> <p>10. Nomenclature: Clarification was made in the Schedules of Events to change the explanation of anti-burosumab antibodies from human anti-human antibodies (HAHA) to the more correct and specific term, anti-drug antibodies (ADA).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported