A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)

Protocol Number: **UX023-CL201**
Original Protocol: **24 February 2014**
Amendment 1: **07 May 2014**
Amendment 2: **02 July 2014**
Amendment 3: **02 March 2015**
Amendment 4: **22 April 2015**
Amendment 5: **28 August 2015**
Amendment 6: **07 July 2016**
Amendment 7: **08 May 2017**

Investigational Product: KRN23 (Recombinant human IgG_1 monoclonal antibody to fibroblast growth factor 23 [FGF23])

Indication: X-linked Hypophosphatemia (XLH)

IND /EudraCT Number: 76,488/ 2014-000406-35

Sponsor:
Ultragenyx Pharmaceutical Inc.
60 Leveroni Court
Novato, CA 94949 USA

Sponsor's Responsible Medical Officer:
Javier San Martin, MD
VP, Clinical Sciences
PPD

Coordinating Investigator:
Thomas Carpenter, MD
Yale University School of Medicine
New Haven, CT 06520, USA

This study is to be performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

Protocol Amendment 1

The original version of Protocol UX023-CL201 (dated 24 February 2014) was modified by Amendment 1 (dated 07 May 2014) to incorporate changes requested by the Medicines and Healthcare Products Regulatory Agency (MHRA). Key changes impacting the conduct of the study were:

- Pregnancy testing (for female subjects of childbearing potential who had experienced menarche), contraception requirements, and follow up for pregnancies were incorporated into the protocol. Although the study enrolled pre-pubertal subjects of Tanner Stage 2 or less, contraception requirements and regular pregnancy testing for subjects entering puberty during trial participation was included as an added safety precaution, given that burosumab has been found to be associated with premature births, embryo/fetal deaths, and abortions in cynomolgus monkeys.
- Subjects were to be discontinued from study drug if they experienced new or clinically significant worsening in mineralization that was considered clinically meaningful by the investigator and/or sponsor and was related was to study drug. Ectopic mineralization is a characteristic feature of patients with XLH and is also related to the current conventional therapy treatment with oral phosphate and active forms of vitamin D. It is unknown whether burosumab may increase the risk of ectopic mineralization including nephrocalcinosis.
- The standing height inclusion criterion was broadened from < 25th percentile to < 50th percentile to include pediatric XLH subjects with significant bone disease who met all other eligibility criteria and who would previously have been excluded from participation in the study based on their stature alone.

Protocol Amendment 2

Protocol Amendment 1 (dated 07 May 2014) was modified by Protocol Amendment 2 (dated 02 July 2014) to incorporate changes requested by the US FDA and ECs. Most changes were clarifications and adjustments regarding logistical considerations, eg, windows for dosing, visits, and assessments; fasting requirements; and the formula to be used for GFR. Key changes impacting the conduct of the study were:

- The number of study sites was increased from 8 to 9.
- Tanner staging criteria was to be assessed for all subjects, for consistency of data collection and to ensure that any subjects with early pubertal status due to underlying conditions were identified.
- Subjects receiving growth hormone therapy within 3 months (previously: 12 months) of screening were excluded from the study.

Protocol Amendment 3

Protocol Amendment 2 (dated 02 July 2014) was modified by Protocol Amendment 3 (dated 02 March 2015) to allow for the enrollment of additional study subjects to provide additional safety, dose, and efficacy data in the pediatric population. Key changes impacting the conduct of the study were:

- The number of study sites was increased from 9 to 12.
- Dose Cohort 3 was expanded to include up to 30 subjects for a total study population of up to 50 subjects. "Pre-expansion subjects" (n = 36) were fully enrolled under the earlier versions of the protocol; Dose Cohort 3 "expansion subjects" (n = approximately 15) were to be enrolled under the Amendment 3.
- Added assessment of changes in rickets severity by the RSS method to complement assessments by RGI-C. Methods for blinding of radiographic assessments also were added.
- RSS at the knee of at least 1.5, as determined by a central reader, was required for inclusion in the expansion group. Requiring subjects in the expansion group to have an RSS of at least 1.5 at the knee increases the probability of seeing a meaningful reduction in rickets severity with burosumab.
- Because the enrollment criteria were adjusted to require a specific level of rickets severity, gender-related differences in the severity of skeletal disease were minimized and the requirement for gender balance was removed for the expansion group.

Protocol Amendment 4

Protocol Amendment 3 (02 March 2015) was modified by Protocol Amendment 4 (dated 22 April 2015) based on new data. Key changes impacting the conduct of the study were:

- The upper limit of the target serum phosphorus range was updated to 5.0 mg/dL (1.61 mmol/L) from 4.5 mg/dL (1.45 mmol/L). The normal reference serum phosphorus range for children aged 5 to 12 years is approximately 3.2 to 6.1 mg/dL (1.03 to 1.97 mmol/L). Increasing the upper limit of the target fasting serum phosphorus range for this study maintained the target within the low- to mid- normal range and would avoid unnecessary fluctuations in dose levels.
- Dose titration adjustments, whether upward or downward, could be made in increments of 0.3 mg/kg for the Q2W regimen (vs 0.1 mg/kg previously) and in increments of 0.4 mg/kg for the Q4W regimen (vs 0.2 mg/kg previously). The dose increments in the initial version of the protocol were selected to slowly increase the dose to prevent any unexpected or exaggerated increases in serum phosphorus. Available data showed small proportional increases in serum phosphorus with the previous titration scheme, and many dose cycles were required to reach a dose that produced serum phosphorus levels in the target range. Therefore, in the absence of any safety signal and to allow subjects to achieve their serum phosphorus target range earlier, the dose titration scheme was modified.

- Unscheduled blood draws for peak serum phosphorus measurements could be obtained at study visits if titration continues into the Treatment Period to enable appropriate dose management.
- The maximum dose of burosumab in regimen Q2W was increased to 2.0 mg/kg. In addition, the maximum allowable dose was capped at 90 mg (for both the Q2W and Q4W groups). The target therapeutic goal remained the same, ie, peak serum phosphorus levels between 3.5 and 5.0 mg/dL (1.13 and 1.62 mmol/L). This change was based on the finding that some subjects needed doses higher than 1.0 mg/dL (0.32 mmol/L) to achieve the serum phosphorus target, regardless of whether the dose was given at the Q2W or Q4W dose regimen. Approximately half of the subjects in the Q4W regimen were already receiving doses above 1.0 mg/dL (0.32 mmol/L) to achieve the proposed target serum phosphorus range, and no safety concerns were raised. The increases in serum phosphorus were proportional to the dose administered, independently of the whether the subject is receiving burosumab monthly or biweekly. No cumulative dose effect in the Q2W regimen group was observed. The maximum dose was set at 90 mg because there is limited experience in adults with burosumab doses above 90 mg.
- Changes were made in the timing of serum phosphorus, calcium, and 1,25(OH)2D measurements at Weeks 48 through 62 to better characterize the longer-term PD effects of burosumab by assessing both peak and trough measurements toward the end of the study.
- The dosing window was changed so that subjects will be dosed at Q2W or Q4W week intervals (±3 days) and no fewer than 8 days apart (previously: no fewer than 12 days apart). Adjusting the dosing window provided additional convenience to subjects and study sites without impacting safety.

Protocol Amendment 5

Protocol UX023-CL201 Amendment 4 (dated 22 April 2015) was modified by Amendment 5 (dated 28 August 2015) to extend the study duration by adding a treatment extension period, apply Q2W dosing for all subjects within the extension period, and adjust the dosing calculation. Key changes impacting the conduct of the study were:

- A 96-week Treatment Extension Period was incorporated into the study design to evaluate the long-term safety and efficacy of burosumab. It is expected that the maintenance of phosphate control will allow for continued healing of rickets and bowing and maximize growth outcomes. Changes in growth and correction of lower extremity bowing may take longer to observe than the healing of rickets, and these outcomes continued to be followed in the Treatment Extension Period.
- During the Treatment Extension Period, all subjects receive Q2W administration of burosumab. The transition of subjects to Q2W dosing reflects interim Week 40 findings related to serum phosphorus levels, rickets, and dose. Subjects in the Q2W dosing regimen showed a more stable and consistent increase in serum phosphorus levels with less fluctuation over time than in subjects who received burosumab Q4W

for whom serum phosphorus levels increased at the middle of the dose cycle (week 2) but tended to return to baseline at the end of the dose interval (week 4).

  - Subjects who had been receiving Q2W dosing continued receiving the same dose at the same dose interval.
  - Subjects who had been receiving the Q4W regimen switched to the Q2W regimen beginning with the Week 64 dose. The dose was 60% of the most recent monthly dose (rounded to the nearest 10 mg), the total dose was approximately 20% higher per month compared with the subject's Q4W dose.

- Vital signs measurements were required to be performed before any additional assessments were completed and after the subject had rested for 5 minutes. A second BP measurement was required to be obtained at the end of the study visit after all procedures have been performed.

Protocol Amendment 6

Protocol UX023-CL201 Amendment 5 (dated 28 August 2015) was modified by Amendment 6 (dated 07 July 2016) to clarify language and procedures regarding dose adjustment, to add an option for non-healthcare provider administration of study drug under certain conditions; to add reflexive genetic testing to assess additional genes associated with phenotypes overlapping with XLH if initial *PHEX* mutation analysis is negative or inconclusive; and to clarify or update study procedures and assessments. This protocol amendment was implemented at the clinical sites after the data cut-off date of 01 December 2016.

Key changes impacting the conduct of the study were:

Drug Administration

- In Section 7.1 and Section 7.2, language and procedures regarding dose adjustment were updated and clarified. The information was also reorganized for easier reference to dosing for a specific period of the study (eg, Titration Period or Treatment Extension Period). Specifically, the protocol states that after the initial dose titration is complete, during the Treatment Period and Treatment Extension Period dose adjustments may be made in any subject if specific serum phosphorus criteria are met. When post-titration dose adjustment is needed, doses should be adjusted in 10 mg total dose increments (eg, a 20-mg rounded total dose would be increased to a 30 mg total dose).
- Section 7.4.1 was updated to state that "At the discretion of the investigator and after proper training by study personnel in SC injection technique, a subject's parent or non-healthcare provider caregiver may administer burosumab to the subject under the supervision of a Home Health (HH) nurse where local regulations permit and where logistically feasible. Parents or caregivers will be instructed to follow the directions provided in the Instructions for Use. The dosing schedule will remain the same."

Inclusion Criteria

- In Section 7.3.1, inclusion criterion #10 was updated to state that sexually active male and female subjects must be willing to use 2 highly effective methods of contraception during the study. Previously it stated, "an acceptable method."

Removal of Subjects

- In Section 7.3.3, language was added to indicate that orthopedic surgery will be permitted during the Treatment Extension Period if recommended by the investigator or consulting physician and that subjects who develop hyperparathyroidism may remain on study but use of medication to suppress PTH (eg, Sensipar®, cinacalcet, calcimimetics) is not permitted at any time. Subjects should be removed from study if treatment for hyperparathyroidism becomes medically necessary.

Study Procedures and Assessments

- The Schedule of Events was updated to add serum phosphorus and serum 1,25(OH)2D measurements at Weeks 124 and 148.
- Section 7.5.3.2 was modified to add a 6MWT assessment at Week 160 and to indicate the POSNA-PODCI instrument will be administered at Weeks 88 and 160 but not at Weeks 112 and 136.
- Measurement of pre-dose serum burosumab concentration at Week 24 using retrospective samples was added to Section 7.5.4 and the Schedule of Events.
- The Schedule of Events was updated to indicate post-treatment Tanner staging will be performed beginning at Week 64 and every 6 months thereafter during the extension phase of the study.
- Bilateral AP knee X-rays were added at Week 160 to the Schedule of Events and in Section 7.5.3.1. In addition, it is noted that beginning at Week 64 and during the extension, radiographs will be evaluated for epiphyseal closure, and that RGI-C assessment of radiographs will occur at Weeks 88 and 160.

Genetic Testing

- Section 7.5.5 was modified to add that genetic testing for mutations in genes consistent with syndromes that have clinical and biochemical phenotypic overlap with XLH will be performed if the initial *PHEX* mutation analysis result is negative or inconclusive and informed consent is provided. This testing will include, but not necessarily be limited to, genes for Autosomal Dominant Hypophosphatemic Rickets (*FGF23*), Autosomal Recessive Hypophosphatemic Rickets (*DMP1*, *ENPP1*), X-Linked Recessive Hypophosphatemic Rickets (*CLCN5*), and Hereditary Hypophosphatemic Rickets with Hypercalciuria (*SLC34A3*). The investigator will be provided the genetic testing results and will determine when and whether the information should be shared with the subject.

Central Reads of Echocardiograms

- Section 7.5.5.6 was updated to state that ECHOs will be read centrally rather than locally. The central core lab will provide a study specific protocol to be followed by the sites to ensure adequate image acquisition for the assessment of mineralization.

Safety Measures

- In Section 7.5.5, ECG is listed as a general safety assessment. Previously it was listed within the safety assessments for ectopic mineralization.
- Section 7.5.5.8 was updated to add assessment of lipase in all subjects and specify additional laboratory analyses will be performed reflexively if serum amylase levels are elevated to ≥ 1.5 times the upper limit of the reference range (ULRR).
- Language in Section 7.5.5.8 regarding FGF23 assays was updated to indicate testing will be performed by a contract laboratory and not the sponsor's development partner, Kyowa Hakko Kirin Pharma, Inc.

Ethics

- Section 8.1.2 was updated to state that both the sponsor and investigator will make every effort to assure the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH GCP guidelines, and local ethical and regulatory requirements.

Statistical Analyses

- In Section 7.6.4.3, the statistical methodology for the Week 40 analysis was updated to include the GEE model rather than the Mixed Model for Repeated Measures.

Record Retention

- Section 8.4.3 was updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law.

Definition of Adverse Events

- In Section 8.5.1, language was added to clarify that hospitalizations planned prior to study enrollment (eg, for elective surgeries) are not considered SAEs but hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

Protocol Amendment 7

Protocol UX023-CL201 Amendment 6 (dated 07 July 2016) was modified by Amendment 7 (dated 08 May 2017) to extend the study duration for subjects at study sites in the United States (US); to update and clarify end of study procedures globally; and to make other minor corrections and edits. Key changes impacting the conduct of the study were:

Treatment Duration

- The study treatment period was extended for subjects at study sites in the US for up to an additional 56 weeks until September 2018; therefore, the total treatment duration varied by region. The study consisted of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks), for a total treatment duration of up to 160 weeks for subjects at study sites outside the US. In the US, the study also included a Treatment Extension Period II

(up to 56 weeks) until September 2018 for a maximum total treatment duration of up to 216 weeks. The total duration of treatment varied for the individual US subjects based on their initial time of enrollment but was not to exceed 216 weeks. For subjects at study sites in Europe, Week 160 was the final efficacy visit for the study. Additional safety follow-up phone calls and visits occurred for certain subjects.

End of Study Definition, Timing, and Procedures

- In Section 7.1 and related sections, the description of the study periods was updated to indicate that the study duration would vary by region. The study consisted of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks), for a total treatment duration of up to 160 weeks for subjects at study sites outside the US. For subjects at study sites outside the US, the Week 160 visit was their end of study (EOS) efficacy visit (referred to as EOSI). In the US, the study also included a Treatment Extension Period II (up to 56 weeks) until September 2018, at which time subjects had their EOS efficacy visit (referred to as EOS II), for a maximum total treatment duration of up to 216 weeks. A safety follow-up telephone call was to occur at 5 weeks (+ 5 days) after the EOS (I or II) efficacy visit, and a final safety visit was to occur at 10 weeks (± 1 week) after the EOS (I or II) efficacy visit for subjects who were not continuing on burosumab treatment through commercial use or another mechanism. The end of study was defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

Study Drug Administration

- Sections 7.4.1 and 7.4.6 were updated to indicate that for subjects in the US, after proper training by study personnel in subcutaneous injection technique, the subject's parent or caregiver may administer KRN23 to the subject, in the home setting without the supervision of a home health nurse during Treatment Extension Period II. Parents or caregivers were to be instructed to follow the directions provided in the Instructions for Use. The dosing schedule remained the same. Additional instructions regarding the timing of the training and implementation of the subject/caregiver administration are provided in Section 7.4.6. In addition, in Section 7.4.1, the language was updated to indicate that 1.5 mL is the maximum volume that should be administered at a single injection site, and that rotation of injections may include rotation to a different quadrant of the abdomen.

Dose Limiting Toxicity

- In Section 7.5.5.13 the definition of dose limiting toxicity (DLT) for serum phosphorus was corrected to be a confirmed serum phosphorus level of ≥ 6.5 mg/dL rather than ≥ 6.1 mg/dL.

Statistical Analyses

- In Section 7.6.4.5, Treatment Extension Period Analysis, language was updated to account for the addition of Treatment Extension Period II. Efficacy analysis was to be performed at the completion of Treatment Extension Period I for the overall population and a final analysis was to be performed at the end of the study, which is

defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

Pregnancy Testing and Contraception

- Section 7.5.5.10 and the Schedule of Events were updated to indicate that during Treatment Extension Period II, pregnancy testing will be conducted at study site visits every 12 weeks for subjects of childbearing potential. In addition, the acceptable methods of contraception were updated.

Anti-Burosumab Antibodies

- In Section 5.3, Section 7.5.5.9, and the Schedule of Events, the term HAHA (human anti-human antibody) in reference to anti- burosumab antibody testing, was replaced with the term ADA (anti-drug antibody).

2 SYNOPSIS

TITLE OF STUDY:

A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)

PROTOCOL NUMBER:

UX023-CL201

STUDY SITES:

Approximately 12 sites globally in the US and EU

PHASE OF DEVELOPMENT:

Phase 2

RATIONALE:

X-linked hypophosphatemia (XLH) is a disorder of renal phosphate wasting, and the most common heritable form of rickets. In XLH patients, high circulating levels of fibroblast growth factor 23 (FGF23) impair normal phosphate reabsorption in the kidney. Hypophosphatemia and low-normal circulating 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) levels are typical biochemical findings. Low serum phosphorus levels result in hypomineralization of bone and associated abnormalities including rickets, bowing of the legs, and short stature. The current standard of care (SOC) therapy consists of multiple daily doses of oral phosphate combined with appropriate doses of active vitamin D metabolites. SOC therapy, when taken with a high degree of compliance and monitoring, can improve the skeletal disease but often does not fully address the bone and growth abnormalities, nor does it target the pathophysiological cause of the disease, renal phosphate wasting induced by high FGF23 levels. SOC therapy also requires careful monitoring to avoid potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism. More efficacious, safer, and convenient therapies clearly are needed.

KRN23 is a recombinant fully human monoclonal IgG_1 antibody being developed to treat XLH by binding and inhibiting FGF23 activity, thereby restoring normal phosphate homeostasis. Four clinical studies have been conducted in adult patients with XLH: a single dose Phase 1 safety and tolerability study of KRN23 (KRN23-US-02), a single dose Phase 1 safety and tolerability study of KRN23 in Japan and Korea (KRN23-001), a repeat dose Phase 1/2 dose escalation study (KRN23-INT-001), and an associated treatment extension study (KRN23 INT-002). An additional open-label long-term extension study (UX023-CL203), a double-blind, placebo-controlled, Phase 3 study (UX023-CL303), and an open-label, paired bone biopsy Phase 3 study to evaluate changes in osteomalacia at the tissue level with KRN23 treatment are ongoing. The safety data from these studies have shown that KRN23 in single and repeated monthly doses up to 1.0 mg/kg was well tolerated by adult XLH subjects. KRN23 sufficiently increased serum phosphorus levels, such that improvements in bone physiology, structure and function would be expected. These data support the initiation of further studies to evaluate the therapeutic benefit of KRN23 in children who experience the most severe physical and health manifestations associated with XLH. Currently, there are no approved treatments and a high unmet medical need in pediatric XLH patients.

Adults and children with XLH have the same underlying defect but are at a different stage of the disease. In childhood, normal phosphorus levels are higher to promote bone formation, whereas

in adults, the normal range is lower, coincident with reduced demand for bone formation. Therefore, smaller, more frequent dosing may be preferred for pediatric hypophosphatemic patients to maximize treatment effects without a plateau, drive serum phosphorus levels closer to the normal range and minimize the troughs. This Phase 2 study will examine the PD, efficacy, and safety of KRN23 administered at multiple doses and dose regimens in pediatric XLH patients.

The total treatment duration will vary by region. The study will consist of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks), for a total treatment duration of up to 160 weeks for subjects at study sites outside the United States (US). For subjects at study sites outside the US the Week 160 visit will be their end of study (EOS) efficacy visit (referred to as EOS I). In the US, the study will also include a Treatment Extension Period II (up to 56 weeks) until September 2018, at which time they will have their EOS efficacy visit (referred to as EOS II), for a maximum total treatment duration of up to 216 weeks. A safety follow-up telephone call will occur at 5 weeks (+ 5 days) after the EOS (I or II) efficacy visit, and a final safety visit will occur at 10 weeks (± 1 week) after the EOS (I or II) efficacy visit for subjects that are not continuing on KRN23 treatment through commercial use or another mechanism. The end of study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

The dose response of KRN23 will be evaluated at 3 starting dose levels. Monthly (Q4) and biweekly (i.e., every other week; Q2) dosing regimens will also be compared. KRN23 dosing will be individually adjusted every 4 weeks as needed, according to serum phosphorus levels. The goal is to achieve stable serum phosphorus levels in the target range, while minimizing changes in the calcium control system. During Treatment Extension Period I (and II, if applicable), all subjects will receive KRN23 at the Q2 dosing regimen. Data collected in this study will establish a KRN23 dose and dose regimen for pediatric patients, and provide information about the PD, PK, clinical efficacy and safety of KRN23 in children with XLH.

OBJECTIVES:

The objectives of the study are to:

- Identify a dose and dosing regimen of KRN23, based on safety and PD effect, in pediatric XLH patients
- Establish the safety profile of KRN23 for the treatment of children with XLH including ectopic mineralization risk, cardiovascular effects, and immunogenicity profile
- Characterize the PK/PD profile of the KRN23 doses tested in the monthly (Q4) and biweekly (Q2) dose regimens in pediatric XLH patients
- Determine the PD effects of KRN23 treatment on markers of bone health in pediatric XLH patients
- Obtain a preliminary assessment of the clinical effects of KRN23 on bone health and deformity, muscle strength, and motor function
- Obtain a preliminary assessment of the effects of KRN23 on patient-reported outcomes, including pain, disability, and quality of life in pediatric XLH patients
- Evaluate the long-term safety and efficacy of KRN23

STUDY DESIGN AND METHODOLOGY:

UX023-CL201 is a randomized, multicenter, open-label, dose finding Phase 2 study. The study will be conducted in prepubescent children aged 5-12 years with XLH to assess the PD, efficacy, and safety of KRN23 administered via subcutaneous (SC) injections monthly (Q4, 28 days) or biweekly (Q2, 14 days) for up to 160 weeks for subjects at study sites outside the US and up to 216 weeks (until September 2018) for subjects at study sites in the US. The study will consist of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks). For subjects at study sites outside the US the Week 160 visit will be their end of study efficacy visit (EOS I). In the US, the study will also include a Treatment Extension Period II (up to 56 weeks) at the end of which the US subjects will have their EOS efficacy visit (referred to as EOS II). A safety follow-up telephone call will occur at 5 weeks (+ 5 days) after the EOS (I or II) efficacy visit, and a final safety visit will occur at 10 weeks (± 1 week) after the EOS (I or II) efficacy visit for subjects that are not continuing on KRN23 treatment through commercial use or another mechanism. The end of study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

The study initially enrolled 36 pediatric subjects with XLH and radiographic evidence of bone disease (pre-expansion subjects). The study was expanded to include additional subjects who were required to have a level of rickets severity of at least 1.5 points at the knee as defined by the Rickets Severity Score (RSS) method for a total of approximately 50 subjects overall. All subjects will discontinue oral phosphate and vitamin D metabolite therapy prior to randomization and throughout the duration of the study.

There will be 3 cohorts in this study (n = 10 in cohorts 1 and 2 [pre-expansion subjects] and n = 30 in cohort 3 [comprising both pre-expansion and expansion subjects]); each with a Q4 and Q2 dosing group (Figure 2.1). Subjects will be randomized 1:1 to the KRN23 Q4 or Q2 dosing regimens within each cohort; randomization will be stratified on subject gender. In order to maintain a level of gender balance, no more than 20 patients of either sex can be enrolled in the in the pre-expansion group. No requirement for gender balance will be applied in the expansion group. The cohorts will be enrolled sequentially. The first cohort will examine the lowest starting doses (0.2 mg/kg Q4 and 0.1 mg/kg Q2) and will be enrolled first. As an added precautionary measure in this pediatric population, the second cohort (0.4 mg/kg Q4 and 0.2 mg/kg Q2) cannot begin dosing until the fourth subject in the first cohort completes the Week 4 visit. The third cohort will be administered the highest starting doses (0.6 mg/kg Q4 and 0.3 mg/kg Q2).

Dosing During the Titration Period (Weeks 0-16)

The initial 16-week Titration Period is intended to identify the KRN23 dose required to achieve the target peak PD effect. The goal is to identify an individualized KRN23 dose that maintains serum phosphorus levels in the target range. The target fasting serum phosphorus range for this study is 3.5- 5.0 mg/dL (1.13-1.62 mmol/L), based on the peak PD effect of KRN23. The dose will be adjusted every 4 weeks, as needed, based on 2-week post-dose (peak) fasting serum phosphorus levels.

The KRN23 dose titration scheme (Table 2.1) will be used as a guideline during the Titration Period should the peak fasting serum phosphorus level fall outside of the target range.

Table 2.1: KRN23 Dose Titration Scheme

Serum Phosphorus (2 weeks Post-Dose)	Dose Adjustment[1]
< 3.5 mg/dL [2] < 1.13 mmol/L	In 2 weeks, increase dose by 0.3 mg/kg for Q2 OR 0.4 mg/kg for Q4[3]
3.5 ≤ 4.5 mg/dL 1.13 – 1.45 mmol/L	Repeat previous dose
>4.5 – 5.0 mg/dL >1.45 – 1.62 mmol/L	Repeat previous dose and then repeat serum phosphorus at 2 weeks after that dose; determine next dose based on the repeat serum phosphorus level.
> 5.0 mg/dL (1.62 mmol/L) and ≤ age adjusted ULN	In 2 weeks, decrease dose by 0.3 mg/kg for Q2 OR 0.4 mg/kg for Q4 and then repeat serum phosphorus at 2 weeks after that dose[3]
> age adjusted ULN	Skip next 2 doses for Q2 OR skip next dose for Q4, then re-initiate dosing at last dose level at which the subject's peak serum phosphorus was in range[4]

[1] Dose adjustments for subjects assigned to the Q2 regimen will only be made after 2 consecutive peak measurements.
[2] During the Treatment Period, if a subject's serum phosphorus level has not increased, as defined by a change no greater than 0.1 mg/dL, after 2 consecutive dose escalations, even if the target range has not been achieved, then the previous dose will be considered that subject's optimized dose and not escalated further.
[3] If needed, the final dose adjustment increment may be less than 0.3 mg/kg for Q2 or 0.4 mg/kg for Q4 to reach the 2.0 mg/kg maximum dose
[4] The investigator should consult with the medical monitor to determine when and how to titrate up

Dosing During the Treatment Period (Weeks 18-64)

If the serum phosphorus level is rising but has not yet reached the pre-specified target range by the end of the Titration Period, the titration can continue into the Treatment Period until the target range is reached, provided there are no safety concerns. For those subjects whose dose titration continues into the Treatment Period, 2week post-dose peak serum phosphorus levels may be measured through unscheduled blood draws at corresponding study visits (e.g., at Week 18, 26, or 34) and the dose titration scheme (Table 2.1) followed until the target range is reached.

The visit window for HH visits is ± 3 days during the Titration Period and Treatment Period. If at any time during dose titration the subject is dosed earlier than the allowable ±3-day window, the previous dose should be repeated (i.e., no titration). If a subject is dosed later than the allowable ±3-day window, dosing should be determined as if the dosing occurred within the allowable window (i.e., by using the most recent post-dose peak serum phosphorus level and the dose titration scheme).

Dosing During Treatment Extension Periods I (Week 66 up to Week 160) and II (Weeks 162 up to Week 216)

During Treatment Extension Periods I (and II, if applicable), all subjects will receive biweekly (Q2) administration of KRN23. Subjects in the Q2 dosing regimen during the Treatment Period will continue to receive KRN23 at the dose they were receiving at Week 64. At the Week 64 study visit, subjects in the Q4 dosing regimen will receive KRN23 at 60% of their established Q4 total dose level (rounded to the nearest 10 mg) and continue on that dose biweekly (Q2) through Treatment Extension Period I (and II). The visit window for HH visits is ± 5 days during Treatment Extension Period I. The window for dosing and biweekly telephone calls from the site during Treatment Extension Period II is ± 5 days.

General Dosing Guidelines

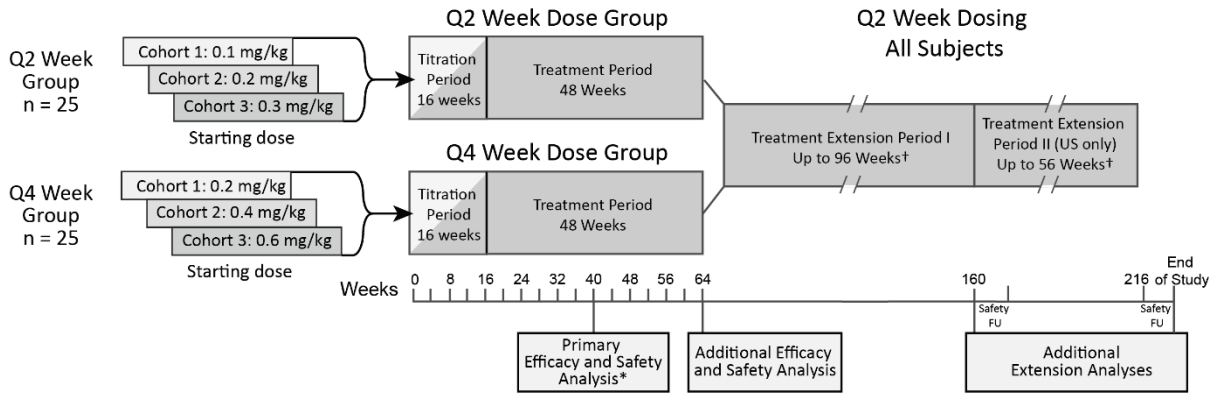
The rounding of doses to the nearest 10 mg will not be applied during the Titration Period (Week 0-16). During the Treatment Period and Treatment Extension Period I and II, dose rounding will be applied once study sites have obtained appropriate approvals. Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg. The total administered dose may differ slightly from the total calculated or rounded dose due to rounding of the volume drawn for administration (to the nearest 0.1 mL).
After the initial dose titration is complete, the dose may be increased at any time during the Treatment Period or Treatment Extension Periods I or II if a subject meets the following dose-adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range (3.2-6.1 mg/dL [1.03-1.97 mmol/L]); 2) the serum phosphorus level is < 0.5 mg/dL (0.16 mmol/L) above baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. If the subject has a single serum phosphorus measurement below the normal range and criteria 2 and 3 are met, the serum phosphorus measurement should be repeated through an unscheduled blood draw within 4 weeks and a dose adjustment made if the serum phosphorus remains below the normal range. When post-titration dose adjustment is needed during the Treatment Period or Treatment Extension Periods I and II, doses should be adjusted in 10 mg total dose increments (e.g., a 20 mg rounded total dose would be increased to a 30 mg total dose). The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen.

If serum phosphorus increases above 5.0 mg/dL (1.62 mmol/L) at any time during the study, the dose will be titrated down. During the Titration Period the dose should be titrated down according to the dose titration scheme (Table 2.1). During the Treatment Period or Treatment Extension Periods the total dose should be decreased by half. Following a dose reduction in a subject, the investigator and medical monitor will determine when and how that subject's dose will be titrated up.

If a subject does not receive a dose within 10 days of a scheduled dose for the Q2 regimen, that dose should be skipped and the next dose will be administered at the next scheduled Q2 dosing visit. If a subject does not receive a dose within 21 days of a scheduled dose for the Q4 regimen, that dose should be skipped and next dose will be administered at the next scheduled Q4 dosing visit.

At the end of the Titration Period, the population of approximately 50 subjects will consist of essentially two groups of 25 subjects, each with individually optimized dosing of KRN23 at either a Q4 week or Q2 week frequency. Analyses of safety and available PD and efficacy data are planned at the end of the Titration Period (Week 16) and at Week 24 for pre-expansion subjects. Further analyses in the pre-expansion group alone and for the overall population are planned at Week 40 and at Week 64 at the end of the Treatment Period to compare treatment outcomes to baseline (pre-dose). Analysis of long-term efficacy and safety will be conducted at the completion of Treatment Extension Period I (Weeks 64-160), and a final analysis will be performed at study completion (i.e., following Treatment Extension Period II and all needed safety follow-up visits). Figure 2.1 provides a schematic of the overall study design.

Figure 2.1: UX023-CL201 Study Schema



*Interim analyses conducted for pre-expansion subjects at Week 16 and Week 24
†An additional Safety visit will be conducted 12 weeks (± 1 week) after the date of last study drug administration if KRN23 is not being continued through another mechanism

NUMBER OF SUBJECTS PLANNED:

Approximately 50 pediatric subjects will be enrolled in the study. Subjects who withdraw or are removed from the study may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in this study must meet all of the following criteria:

1) Male or female, aged 5 – 12 years, inclusive, with open growth plates
2) Tanner stage of 2 or less based on breast and testicular development
3) Diagnosis of XLH supported by ONE of the following:
   - Confirmed *PHEX* mutation in the patient or a directly related family member with appropriate X-linked inheritance
   - Serum FGF23 level $\geq$ 30 pg/mL by Kainos assay
4) Biochemical findings associated with XLH including:
   - Serum phosphorus $\leq$ 2.8 mg/dL (0.904 mmol/L)*
   - Serum creatinine within age-adjusted normal range*
5) Standing height < 50th percentile for age and gender using local normative data.
6) Radiographic evidence of active bone disease including rickets in the wrists and/or knees, AND/OR femoral/tibial bowing,

   OR for the expansion subjects, a rickets severity score (RSS) in the knee of at least 1.5 points as determined by central read.
7) Willing to provide access to prior medical records for the collection of historical growth, biochemical and radiographic data, and disease history.
8) Provide written or verbal assent (if possible) and written informed consent by a legally

authorized representative after the nature of the study has been explained, and prior to any research-related procedures.

9) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule and comply with the assessments.

10) Females who have reached menarche must have a negative pregnancy test at Screening and undergo additional pregnancy testing during the study. If sexually active, male and female subjects must be willing to use two highly effective methods of contraception for the duration of the study.

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1) Use of a pharmacologic vitamin D metabolite or analog (e.g. calcitriol, doxercalciferol, alfacalcidiol, and paricalcitol) within 14 days prior to Screening Visit 2; washout will take place during the Screening Period

2) Use of oral phosphate within 7 days prior to Screening Visit 2; washout will take place during the Screening Period

3) Use of aluminum hydroxide antacids (e.g. Maalox® and Mylanta®), systemic corticosteroids, and thiazides within 7 days prior to Screening Visit 1

4) Use of growth hormone therapy within 3 months before Screening Visit 1

5) Use of bisphosphonates for 6 months or more in the 2 years prior to Screening Visit 1

6) Presence of nephrocalcinosis on renal ultrasound graded $\geq$ 3 based on the following scale:

   0 = Normal

   1 = Faint hyperechogenic rim around the medullary pyramids

   2 = More intense echogenic rim with echoes faintly filling the entire pyramid

   3 = Uniformly intense echoes throughout the pyramid

   4 = Stone formation: solitary focus of echoes at the tip of the pyramid

7) Planned or recommended orthopedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period

8) Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits*

9) Evidence of tertiary hyperparathyroidism as determined by the investigator

10) Use of medication to suppress PTH (e.g. Sensipar®, cinacalcet, calcimimetics) within 2 months prior to Screening Visit 1

11) Presence or history of any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study.

12) Presence of a concurrent disease or condition that would interfere with study participation or affect safety

13) Previously diagnosed with human immunodeficiency virus antibody, hepatitis B surface

antigen, and/or hepatitis C antibody

14) History of recurrent infection or predisposition to infection, or of known immunodeficiency

15) Use of a therapeutic monoclonal antibody within 90 days prior to Screening Visit 1 or history of allergic or anaphylactic reactions to any monoclonal antibody

16) Presence or history of any hypersensitivity to KRN23 excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects.

17) Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments.

* Criteria to be determined based on overnight fasting (min. 4 hours) values collected at Screening Visit 2

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION

KRN23 is a sterile, clear, colorless, and preservative-free solution in single-use 5-mL vials containing 1 mL of KRN23 at a concentration of 10 mg/mL or 30 mg/mL. Subjects will receive study drug via SC injection to the abdomen, upper arms and thighs; the injection site should be rotated with each injection including to a different quadrant of the abdomen. The maximum amount administered in a single injection should not exceed 1.5 mL. Subjects will be sequentially enrolled into the cohorts, starting with the lowest dose group, and randomized to a dosing regimen (Q2 or Q4) then individually titrated to achieve a target overnight (minimum 4 hours) fasting serum phosphorus range of 3.5- 5.0 mg/dL (1.13-1.62 mmol/L). During Treatment Extension Periods I (and II, if applicable), all subjects will receive KRN23 at the Q2 dosing regimen. The amount of KRN23 administered will be calculated based on the subject's weight. Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg. The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen. After proper training, a subject's parent or non-healthcare provider caregiver may administer KRN23 to the subject.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

The study design is open-label; all subjects will receive investigational product. No placebo or reference therapy will be administered in this study.

DURATION OF TREATMENT:

Treatment duration will vary by region. The study consists of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks), for a total treatment duration of up to 160 weeks for subjects at study sites outside the US. For subjects at study sites outside the US the Week 160 visit will be their EOS I visit. In the US, the study will also include a Treatment Extension Period II (up to 56 weeks) until September2018 for a maximum total treatment duration of up to 216 weeks at which time the subjects will have their EOS II visit.
The duration of Treatment Extension Period II will vary for individual subjects and will be determined by the time from Week 160 through the EOS II visit.

CRITERIA FOR EVALUATION:

Pharmacodynamic*:

- Serum phosphorus
- Serum $1,25(OH)_2D$
- Urinary phosphorus
- Phosphate reabsorption: ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and tubular reabsorption of phosphate (TRP)
- Bone biomarkers: procollagen type 1 N-propeptide (P1NP), carboxy-terminal cross-linked telopeptide of type I collagen (CTx), bone-specific alkaline phosphatase (BALP) and alkaline phosphatase (ALP)

  * Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable) per dosing regimen

Efficacy – Bone Health:

- Growth: standing height, sitting height, arm length and leg length will be measured. Growth percentiles based on standing height will be derived prior to and following treatment if historical data are available
- Severity of rickets and epiphyseal (growth plate) abnormalities: central readings of bilateral posteroanterior (PA) hand/wrist and anteroposterior (AP) knee radiographs using the RSS, a scale developed for nutritional rickets, and a disease-specific qualitative Radiograph Global Impression of Change (RGI-C) scoring system
- Lower extremity deformity assessed by intercondylar distance and intermalleolar distance. Specific abnormalities related to lower extremity deformity and bowing observed on standing long leg films will also be evaluated using the qualitative RGI-C scoring system
- Bone Mineral Density or Content at the cortical and trabecular compartment as assessed by XtremeCT of the forearm and tibia (performed at select sites depending on scheduling and availability of equipment)

Efficacy – Clinical Outcomes:

- Walking ability: Six Minute Walk Test (6MWT) total distance and percent of predicted normal distance walked
- Gross motor function: Bruininks-Oseretsky Test of Motor Proficiency – Second Edition (BOT-2) subtests to assess running speed, agility and strength
- Muscle strength: Bilateral hand-held dynamometry (HHD) in the following muscle groups: gross grip, knee flexors, knee extensors, hip flexors, hip extensors and hip abductors
- Functional disability and pain: Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument (POSNA PODCI)
- Health-Related Quality of Life: SF-10 for Children Health Survey (SF-10)

Pharmacokinetic:

- Serum KRN23 (pre-dose level)

Safety Assessments:

Safety will be evaluated by the incidence, frequency, and severity of adverse events (AEs) and serious adverse events (SAEs), including clinically significant changes from baseline to scheduled time points.

General Safety Variables include:

- Vital signs and weight
- Interval history and physical examinations
- GFR (calculated using the Bedside Schwartz equation)
- Chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (serum 25(OH)D, amylase, creatinine, and FGF23 [total and unbound])
- Anti-KRN23 antibody testing and dose-limiting toxicities
- Concomitant medications
- ECG

Ectopic Mineralization Safety Assessments include:

- Renal ultrasound
- ECHO
- Serum calcium, phosphorus and iPTH; urinary calcium and creatinine

Data Monitoring Committee (DMC)

An independent DMC that includes members with expertise in metabolic bone disease and the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis through the end of the Treatment Period (Week 64). The DMC will meet for approximately quarterly data reviews. During Treatment Extension Periods I and II, safety data will be reviewed by the Ultragenyx Study Safety Review Team (SSRT) on an ongoing basis.

STATISTICAL METHODS:

A full description of the statistical evaluations will be provided in the Statistical Analysis Plan.

Sample Size:

A sample size of at least 10 per cohort will provide at least 90% power to detect a serum phosphorus increase from baseline of at least 0.8 mg/dL, assuming a standard deviation of 0.7 mg/dL or smaller, at the 2-sided level of significance of 0.05. In addition, a total sample size of 50 subjects (25 subjects per Q4 or Q2 regimen) will provide at least 90% power to detect a 0.5 mg/dL difference between the two dosing regimens assuming a standard deviation of 0.4 and 2-sided level of significance of 0.05.

Phosphate and mineral control are adequately powered based on the clinical experience to date with KRN23. The degree of powering for bone health will depend on the degree of effect expected, which is not known. However, powering for adequate phosphate control should provide the potential for improved bone health based on prior experience with oral phosphate replacement therapy.

In addition, for the RSS endpoint, the expected sample size of 50 subjects will provide at least 90% power of rejecting the hypothesis of no change from baseline in knee total score when the true mean change is 0.5 with a standard deviation of 0.5, at the 2-sided level of significance of 0.05.

Pharmacodynamics and Efficacy Analysis:

Analyses of available PD and efficacy data are planned at the end of the Titration Period (Week 16) and at Week 24 for pre-expansion subjects. Further analyses in the pre-expansion group alone and for the overall population are planned at Week 40 and at Week 64 at the end of the Treatment Period to compare treatment outcomes to baseline (pre-dose). Analyses of long-term efficacy will be conducted at the completion of Treatment Extension Period I (Weeks 64-160). A final analysis will be performed at study completion (i.e., following Treatment Extension Period II and all needed safety follow-up visits).

Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard error, median, minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Changes over time and the association of the efficacy with the PD variables will be summarized and evaluated.

Safety Analysis:

All subjects who receive any amount of study drug will be included in the safety analysis. Safety of each cohort and each dose regimen within a cohort will be assessed.

Table 2.2: Schedule of Events – Titration Period Visits

	Screening		Baseline[1]	Titration Period [2]								
VISIT TYPE/NUMBER	SV1	SV2[1]	V1	HH[3] V2	V3	V4	V5	V6	V7	V8	V9	V10
WEEK	W-4 to -2	Day -1	W0	W1	W2	W4	W6	W8	W10	W12	W14	W16
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Medical History & Demographics	X											
Tanner Staging [4]	X											
PHEX mutation analysis [5]		X										
PD MEASURES												
Serum Phosphorus [6]		X[6]	X	X	X	X	X	X	X	X	X	X
$1,25(OH)_2$ D [6]			X		X						X	X
2-hour urine [6,7]			X		X		X	X			X	X
24-hour urine [8]			X									X
Bone biomarkers: P1NP, CTx, ALP, BALP [6]			X									X
EFFICACY MEASURES												
Growth (standing height, sitting height, arm length and leg length)	X[9]		X									X
Bilateral AP knee X-rays[1]	X[10, 11]											
Bilateral PA hand/wrist X-rays[1]	X[10]											
Standing long leg X-Ray[1]	X[10]											
Intercondylar and Intermalleolar distance	X[10]											
XtremeCT of forearm, tibia [12]			X[1]									
6MWT, BOT-2, HHD	X		X[1]									X
POSNA-PODCI, SF-10			X[1]									
PHARMACOKINETICS												
Serum Pre-Dose KRN23[13]			X	X[14]	X	X				X	X	X
SAFETY												
Vital Signs [15]	X		X	X	X	X	X	X	X	X	X	X
Weight	X		X		X	X	X	X	X	X	X	X
Physical Examination	X	X				X		X			X	
Interval History		X			X	X		X		X		X

	Screening		Baseline[1]	Titration Period [2]								
VISIT TYPE/NUMBER	**SV1**	**SV2[1]**	**V1**	**HH[3] V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
WEEK	**W-4 to -2**	**Day -1**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**
Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound [1]	X[10]											X
ECHO [1]			X									X
ECG [1]			X									X
Chemistry, Hematology, Urinalysis [16]	X[6]		X			X		X				X
Serum Amylase	X		X			X		X				X
Serum 25(OH) D	X											X
Serum Calcium [6]	X	X[6]	X	X	X	X	X	X	X	X	X	X
Serum Creatinine [6]		X[6]	X		X		X	X			X	X
Serum iPTH	X	X						X				
Serum FGF23 [13]	X[17]	X[17]						X				X
Anti-KRN23 antibody (ADA) [13, 18]			X									X
Pregnancy Test[19]	X		X			X		X		X		X
DOSE ADJUSTMENT (AS NEEDED)						X		X		X		X
DRUG ADMINISTRATION[20]			Q2, Q4		Q2	Q2, Q4	Q2	Q2, Q4	Q2	Q2, Q4	Q2	Q2, Q4

[1] SV2 should be conducted 14 – 35 days following SV1. SV2 and Baseline visits can be conducted on consecutive days but may be conducted up to 7 days apart. Renal ultrasound, ECHO, ECG, and x-rays may be performed within ± 3 days of clinic visit to accommodate scheduling availability. XtremeCT may be performed any time between SV1 and Baseline. Motor function tests (6MWT, BOT-2, HHD) and questionnaires (POSNA-PODCI, SF-10) may be completed at either SV2 or Baseline visit, but must be assessed on the same day. All Screening/Baseline assessments and inclusion/exclusion criteria based on local lab results must be satisfied prior to randomization and dosing.

[2] During the Titration Period (Weeks 0 – 16) subjects will return to the clinic for visits at 2 week intervals (± 3 days).

[3] HH visits may also be conducted at the clinic depending on proximity of the subject to the investigational site and local availability of HH care resources. The visit window is ± 3 days.

[4] Tanner staging will be performed on all subjects regardless of age.

[5] *PHEX* mutation analysis will be performed for all subjects. For any subject with a *PHEX* mutation analysis result of No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic, additional genetic testing will be performed to assess mutations in other genes associated with phenotypes overlapping with XLH. A new blood sample for genetic analysis may be collected if necessary.

[6] Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable) per dosing regimen. Record fasting duration on CRF. At SV2, local lab values will be used to confirm eligibility. Baseline visit samples will be sent to the central lab for data analysis.

[7] 2-hour urine collections for urinary calcium, phosphorous, and creatinine and calculation of TmP/GFR and TRP

[8] 24-hour urine collections for urinary phosphorus, calcium, and creatinine

[9] At Screening Visit 1, only standing height is required to confirm eligibility.

[10] Screening results will be treated as baseline data

[11] For the expansion subjects, screening knee x-rays must be read centrally for determination of eligibility

[12] Performed at select sites based on scheduling and availability of equipment

[13] If there is a technical or operational issue obtaining results for PK, FGF23, or ADA, an additional blood sample may be obtained at the next suitable clinic visit.

[14] Serum KRN23 samples will be taken at W1 for subjects enrolled in Cohorts 2 and 3 only.

[15] Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed.

[16] Serum chemistry panels may include PD parameters (i.e. serum phosphorus and ALP), and safety parameters of interest (i.e. calcium) to avoid duplication of testing. See Table 7.5.5.8.1 for complete list of Clinical Laboratory Assessments for Safety.

[17] If confirmation of XLH diagnosis is based on FGF23, the results may be communicated by telephone to the potential subject with instructions to begin washout of prohibited medications. If subject or directly related family member with appropriate X-linked inheritance has a confirmed *PHEX* mutation, samples for FGF23 analysis will be obtained at SV2 only and used as baseline values. If subject or qualified directly related family member does NOT have a confirmed *PHEX* mutation, FGF23 levels will be obtained at SV1 to determine eligibility and at SV2 to obtain a baseline value.

[18] If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points on a case-by-case basis, if warranted.

[19] Pregnancy testing will be performed on any female subject of childbearing potential who has experienced menarche.

[20] Subjects will be dosed at either Q2 (± 3 days and no fewer than 8 days apart) or Q4 week intervals (± 3 days and no fewer than 12 days apart). Subjects should be observed for 3-4 hours following the first dose of study drug. Subjects should be observed for 30 minutes following subsequent doses of study drug.

Table 2.3: Schedule of Events –Treatment Period Visits (Weeks 18 – 40)

	Treatment Period [21]											
VISIT TYPE/NUMBER	HH [22] V11	V12	HH V13	V14	HH V15	V16	HH V17	V18	HH V19	V20	V21	V22 [37]
WEEK	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36	W38	W40
PD MEASURES												
Serum Phosphorus [23]		X	X	X		X	X	X		X	X	X
$1,25(OH)_2$ D [23]						X					X	X
2-hour urine [23,24]				X							X	X
24-hour urine [25]												X
Bone biomarkers: P1NP, CTx, ALP, BALP [23]												X
EFFICACY MEASURES												
Growth (standing height, sitting height, arm length and leg length)				X								X
Bilateral PA hand/wrist and AP knee X-ray												X
Intercondylar and Intermalleolar distance												X
XtremeCT of forearm, tibia [26]												
6MWT, BOT-2, HHD				X								X
POSNA-PODCI, SF-10				X								X
PHARMACOKINETICS												
Serum Pre-Dose KRN23[27]				X [28]						X	X	X
SAFETY												
Vital Signs [29]	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X		X		X		X		X	X	X
Physical Examination		X						X				X
Tanner Staging												
Interval History		X		X		X		X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound												X
ECHO												X

	Treatment Period [21]											
VISIT TYPE/NUMBER	**HH [22] V11**	**V12**	**HH V13**	**V14**	**HH V15**	**V16**	**HH V17**	**V18**	**HH V19**	**V20**	**V21**	**V22 [37]**
WEEK	**W18**	**W20**	**W22**	**W24**	**W26**	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**
ECG												X
Chemistry, Hematology, Urinalysis [30]				X								X
Serum Amylase[31]				X								X
Serum Lipase[32]												X
Serum 25(OH) D								X				
Serum Calcium [23]		X	X	X		X	X	X		X	X	X
Serum Creatinine [23]				X							X	X
Serum iPTH		X				X				X		
Serum FGF23 [27]						X					X	
Anti-KRN23 antibody (ADA) [27, 33]				X						X		
Pregnancy Test [34]		X		X		X		X		X		X
DOSE ADJUSTMENT (AS NEEDED)[35]		X		X		X		X		X		X
DRUG ADMINISTRATION [36]	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2, Q4

[21] During the Treatment Period (Weeks 16 – 40) clinic visits will occur at 4 week intervals (± 3 days).

[22] HH visits may also be conducted at the clinic depending on proximity of the subject to the investigational site and local availability of HH care resources. The visit window is ± 3 days.

[23] Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable) per dosing regimen. Peak serum phosphorus may be collected as an unscheduled lab if required (to assist in dose titration) at Week 18, 26 and 34.

[24] 2-hour urine collections for urinary calcium, phosphorous, and creatinine and calculation of TmP/GFR and TRP

[25] 24-hour urine collections for urinary phosphorus, calcium, and creatinine

[26] Performed at select sites based on scheduling and availability of equipment

[27] If there is a technical or operational issue obtaining results for PK, FGF23, or ADA, an additional blood sample may be obtained at the next suitable clinic visit.

[28] Week 24 pre-dose serum KRN23 concentration will be retrospectively tested on subjects' previously collected samples, if available.

[29] Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed.

[30] Serum chemistry panels may include PD parameters (i.e., serum phosphorus and ALP), and safety parameters of interest (i.e., calcium) to avoid duplication of testing. See Table 7.5.5.8.1 for complete list of Clinical Laboratory Assessments for Safety.

[31] Reflexive assessment of amylase isoenzymes will be performed if the serum amylase level is elevated to ≥1.5 times the upper limit of the reference range (ULRR) beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[32] Serum lipase will be assessed as part of the serum chemistry panel beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[33] If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points on a case-by-case basis, if warranted.

[34] Pregnancy testing will be performed on any female subject of childbearing potential who has experienced menarche.

[35] Dose adjustments may be made at visits W20, W24, W28, W32, W36, W40 if required when following the KRN23 Dose Titration Scheme Table 2.1)

[36] Subjects will be dosed at either Q2 (± 3 days and no fewer than 8 days apart) or Q4 week intervals (± 3 days and no fewer than 12 days apart). Subjects should be observed for 3-4 hours following the first dose of study drug. Subjects should be observed for 30 minutes following subsequent doses of study drug.

[37] The Week 40 visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days

Table 2.4: Schedule of Events –Treatment Period Visits (Weeks 42 – 64)

	Treatment Period [38]											
VISIT TYPE/NUMBER	HH [39] V23	HH V24	V25	HH V26	HH V27	HH V28	HH V29	V30	HH V31	HH V32	HH V33	V34
WEEK	W42	W44	W46	W48	W50	W52	W54	W56	W58	W60	W62	W64[53]
PD MEASURES												
Serum Phosphorus [40]			X	X			X	X			X	X
$1,25(OH)_2$ D [40]							X	X			X	X
2-hour urine [40, 41]												X
24-hour urine [42]												X
Bone biomarkers: P1NP, CTx, ALP, BALP [40]												X
EFFICACY MEASURES												
Growth (standing height, sitting height, arm length and leg length)								X				X
Bilateral PA hand/wrist and AP knee X-ray												X
Standing long leg X-ray												X
Intercondylar and Intermalleolar distance												X
XtremeCT of forearm, tibia [43]												X
6MWT, BOT-2, HHD												X
POSNA-PODCI, SF-10												X
PHARMACOKINETICS												
Serum Pre-DoseKRN23 [44]								X				X
SAFETY												
Vital Signs [45]	X	X	X	X	X	X	X	X	X	X	X	X
Weight			X					X				X
Physical Examination			X					X				X
Tanner Staging												X
Interval History			X					X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound												X

	Treatment Period [38]											
VISIT TYPE/NUMBER	**HH [39] V23**	**HH V24**	**V25**	**HH V26**	**HH V27**	**HH V28**	**HH V29**	**V30**	**HH V31**	**HH V32**	**HH V33**	**V34**
WEEK	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64[53]**
ECHO												X
ECG												X
Chemistry, Hematology, Urinalysis [46]			X					X				X
Serum Amylase[47]			X					X				X
Serum Lipase[48]			X					X				X
Serum 25(OH) D			X									X
Serum Calcium [40]			X	X			X	X			X	X
Serum Creatinine [40]												X
Serum iPTH			X					X				X
Serum FGF23 [44]												X
Anti-KRN23 antibody (ADA) [43,49]								X				X
Pregnancy Test [50]			X			X		X		X		X
DOSE ADJUSTMENT (AS NEEDED)[51]		X		X		X		X		X		X
DRUG ADMINISTRATION [52]	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2

[38] During the Treatment Period (Weeks 40-64) clinic visits will occur at approximately 8-week intervals (± 3 days).

[39] HH visits may also be conducted at the clinic depending on proximity of the subject to the investigational site and local availability of HH care resources. The visit window is ± 3 days.

[40] Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable) per dosing regimen. Peak serum phosphorus may be collected as an unscheduled lab if required (to assist in dose titration).

[41] 2-hour urine collections for urinary calcium, phosphorous, and creatinine and calculation of TmP/GFR and TRP

[42] 24-hour urine collections for urinary phosphorus, calcium, and creatinine

[43] Performed at select sites based on scheduling and availability of equipment

[44] If there is a technical or operational issue obtaining results for PK, FGF23 or ADA, an additional blood sample may be obtained at the next suitable clinic visit.

[45] Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed

and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed.

[46] Serum chemistry panels may include PD parameters (i.e. serum phosphorus and ALP), and safety parameters of interest (i.e. calcium) to avoid duplication of testing. See Table 7.5.5.8.1 for complete list of Clinical Laboratory Assessments for Safety.

[47] Reflexive assessment of amylase isoenzymes will be performed if the serum amylase level is elevated to ≥1.5 times the upper limit of the reference range (ULRR) beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[48] Serum lipase will be assessed as part of the serum chemistry panel beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[49] If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points, and may include additional blood volume required to perform a neutralization assay on a case-by-case basis, if warranted.

[50] Pregnancy testing will be performed on any female subject of childbearing potential who has experienced menarche.

[51] Post-titration dose escalation during the Treatment Period will occur only for subjects who meet the following criteria: 1) two consecutive serum phosphorus measurements are below the normal range (3.2-6.1 mg/dL [1.03-1.97 mmol/L]); 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. If the subject has single serum phosphorus measurement below the normal range and criteria 2 and 3 are met, the serum phosphorus measurement should be repeated through an unscheduled blood draw within 4 weeks and a dose adjustment made if the serum phosphorus remains below the normal range.

[52] Subjects will be dosed at either Q2 (± 3 days and no fewer than 8 days apart) or Q4 week intervals (± 3 days and no fewer than 12 days apart). Subjects should be observed for 3-4 hours following the first dose of study drug. Subjects should be observed for 30 minutes following subsequent doses of study drug. Dosing will continue Q2 between the Week 64 and Week 74 study visits.

[53] The Week 64 visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days.

Table 2.5: Schedule of Events –Treatment Extension Period I Visits (Weeks 66 – 160)

			Treatment Extension Period I[54]												Safety follow up TC[71]	Safety follow up visit[72]
VISIT TYPE/NUMBER	**HH[55]**	**HH V36**	**HH V37**	**HH V39**	**HH V40**	**HH V41**	**V46**	**HH V52**	**V58**	**HH V64**	**V70**	**HH V76**	**V80**	**V82**	**V83 (EU)**	**V84 (EU)**
	Q2	**W68**	**W70**	**W74**	**W76**	**W78**	**W88[69]**	**W100**	**W112[69]**	**W124**	**W136[69]**	**W148**	**W156**	**W160[69] (EOSI)[70]**	**W165**	**W170**
PD MEASURES																
Serum Phosphorus[56,57]		X[57]		X[57]		X	X	X	X	X	X	X	X	X		X
$1,25(OH)_2D$[56,57]		X[57]		X[57]		X	X	X	X	X	X	X	X	X		X
2-hour urine[56,58]							X		X		X			X		
24-hour urine[59]							X		X		X			X		
Bone biomarkers: ALP[56]							X		X		X			X		
EFFICACY MEASURES																
Growth (standing height, sitting height, arm length and leg length)							X		X		X			X		
Bilateral PA hand/wrist X-ray							X							X		
Bilateral AP knee X-ray							X							X		
Standing long leg X-ray							X							X		
XtremeCT of forearm, tibia																
6MWT							X							X		
POSNA-PODCI, SF-10							X							X		
BOT-2																

			Treatment Extension Period I[54]												Safety follow up TC[71]	Safety follow up visit[72]
VISIT TYPE/NUMBER	**HH[55]**	**HH V36**	**HH V37**	**HH V39**	**HH V40**	**HH V41**	**V46**	**HH V52**	**V58**	**HH V64**	**V70**	**HH V76**	**V80**	**V82**	**V83 (EU)**	**V84 (EU)**
	Q2	**W68**	**W70**	**W74**	**W76**	**W78**	**W88[69]**	**W100**	**W112[69]**	**W124**	**W136[69]**	**W148**	**W156**	**W160[69] (EOSI)[70]**	**W165**	**W170**
HHD																
PHARMACOKINETICS																
Serum Pre-DoseKRN23[60]							X		X		X			X		
SAFETY																
Vital Signs[61]	X[61]	X			X		X	X	X		X		X	X		X
Weight							X		X		X		X	X		
Physical Examination							X		X		X			X		X
Tanner Staging							X		X		X			X		
Interval History							X		X		X			X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound							X		X		X			X		
ECHO							X		X		X			X		
ECG							X		X		X			X		
Chemistry, Hematology, Urinalysis[62]							X		X		X			X		X
Serum Amylase[63]							X		X		X			X		X
Serum Lipase[64]							X		X		X			X		X
Serum 25(OH) D							X		X		X			X		

			Treatment Extension Period I[54]												Safety follow up TC[71]	Safety follow up visit[72]
VISIT TYPE/NUMBER	**HH[55]**	**HH V36**	**HH V37**	**HH V39**	**HH V40**	**HH V41**	**V46**	**HH V52**	**V58**	**HH V64**	**V70**	**HH V76**	**V80**	**V82**	**V83 (EU)**	**V84 (EU)**
	Q2	**W68**	**W70**	**W74**	**W76**	**W78**	**W88[69]**	**W100**	**W112[69]**	**W124**	**W136[69]**	**W148**	**W156**	**W160[69] (EOSI)[70]**	**W165**	**W170**
Serum Calcium[56, 57]		X		X		X	X		X		X			X		X
Serum Creatinine[56]							X		X		X			X		
Serum iPTH							X		X		X			X		
Serum FGF23[60]							X		X		X			X		X
Anti-KRN23 antibody (ADA)[60,65]							X		X		X			X		
Pregnancy Test[66]	X	X		X		X	X	X	X	X	X	X	X	X		
DOSE TITRATION[67]		X	X	X	X	X	X	X	X	X	X	X	X	X[67]		
DRUG ADMINISTRATION[68]	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2	Q2[68]		

54 During the Treatment Extension Period (Weeks 66-160) clinic visits will occur at approximately 24-week intervals (± 5 days)

55 In addition to the specific visits noted, HH visits will be conducted every 2 weeks (i.e., starting at Week 66), for administration of study drug (Q2) and reporting of concomitant medications and adverse events. The visit window is ± 5 days. HH visits may also be conducted at the clinic depending on proximity of the subject to the investigational site and local availability of HH care resources.

56 Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable) per dosing regimen. Peak serum phosphorus may be collected as an unscheduled lab if necessary.

57 Blood collection for assessment of serum phosphorus, $1,25(OH)_2D$, and serum calcium will be collected at Weeks 68 and Week 74 only for the subjects transitioning from Q4 to Q2 dosing.

58 2-hour urine collections for urinary calcium, phosphorous, and creatinine and calculation of TmP/GFR and TRP

59 24-hour urine collections for urinary phosphorus, calcium, and creatinine

60 If there is a technical or operational issue obtaining results for PK, FGF23, or ADA, an additional blood sample may be obtained at the next suitable clinic visit.

61 Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed

and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed. At HH visits during Weeks 66-160, vital signs will be measured every 4 weeks starting at Week 68.

[62] Serum chemistry panels may include PD parameters (i.e. serum phosphorus and ALP), and safety parameters of interest (i.e. calcium) to avoid duplication of testing. See Table 7.5.5.8.1 for complete listing of Clinical Laboratory Assessments for Safety.

[63] Reflexive assessment of amylase isoenzymes will be performed if the serum amylase level is elevated to ≥1.5 times the upper limit of the reference range (ULRR) beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[64] Serum lipase will be assessed as part of the serum chemistry panel beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[65] If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points, and may include additional blood volume required to perform a neutralization assay on a case-by-case basis, if warranted.

[66] Pregnancy testing will be performed on any female subject of childbearing potential who has experienced menarche. A urine pregnancy test will be given every 4-6 weeks at HH visits in addition to those visits indicated.

[67] Dose titration during the Treatment Extension Period will apply only to subjects meeting the following criteria: 1) two consecutive serum phosphorus measurements are below the normal range (3.2-6.1 mg/dL [1.03-1.97 mmol/L]); 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. If the subject has single serum phosphorus measurement below the normal range and criteria 2 and 3 are met, the serum phosphorus measurement should be repeated through an unscheduled blood draw within 4 weeks and a dose adjustment made if the serum phosphorus remains below the normal range.

[68] Subjects will be dosed at Q2 week intervals (± 5 days and no fewer than 8 days apart). Subjects should be observed for 3-4 hours following the first dose of study drug. Subjects should be observed for 30 minutes following subsequent doses of study drug. For subjects outside the US, no study drug will be administered at the Week 160/EOS I visit.

[69] The Week 88, 112, 136, and 160/EOS I visits may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days.

[70] For subjects at study sites outside the US, the Week 160 visit will be their End of Study efficacy visit (EOS I). No study drug will be administered under the current protocol. If a subject will be continuing KRN23 treatment under commercial use or another mechanism, the first dose of that treatment should not be administered until after completion of all EOS I assessments.

[71] To be completed for those subjects at sites outside the US who complete EOS I and do not continue on KRN23 treatment immediately through commercial use or through another mechanism. Site personnel will initiate a safety follow-up telephone call at 5 weeks (+ 5 days) after the EOS I visit to collect information on whether KRN23 has been started through another mechanism and, if not, any ongoing or new AEs, serious AEs, or concomitant medications.

[72] An additional safety visit will take place 10 weeks ±1 week after the EOS I visit for those subjects who discontinue treatment before Week 160 or for those subjects at sites outside the US who complete EOS I and do not continue on KRN23 through commercial use or another mechanism. This safety visit will not occur for subjects in the US who continue into Treatment Extension Period II or subjects who complete EOS I and are documented to be continuing on KRN23 on commercial use or through another mechanism. Every reasonable effort should be made to have subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic for the final safety visit will be given the option of having a final safety telephone call for the collection of any ongoing or new AEs, serious AEs, or concomitant medications.

Table 2.6: Schedule of Events–Treatment Extension Period II Visits (Week 162 – End of Study)[73]

	Q2W	Q12W	Q24W	EOS II Visit[86]	ET Visit[87]	Safety Follow Up TC [88]	Safety Follow Up Visit[89]
PD MEASURES							
Serum Phosphorus[74]		X		X	X		X
$1,25(OH)_2D$[74]		X		X	X		X
2-hour urine[74, 75]			X	X	X		
24-hour urine[76]			X	X	X		
Bone biomarkers: ALP[74]			X	X	X		
EFFICACY MEASURES							
Growth (standing height, sitting height, arm length and leg length)			X	X	X		
Bilateral PA hand/wrist X-ray				X	X		
Bilateral AP knee X-ray				X	X		
Standing long leg X-ray				X	X		
XtremeCT of forearm, tibia					X		
6MWT				X	X		
POSNA-PODCI, SF-10			X	X	X		
BOT-2					X		
HHD					X		
PHARMACOKINETICS							
Serum Pre-Dose KRN23[77]				X	X		
SAFETY							
Vital signs[78]		X		X	X		X
Weight		X		X	X		
Physical examination		X		X	X		X
Tanner staging				X	X		
Concomitant medications[79]	X			X	X	X	X

	Q2W	Q12W	Q24W	EOS II Visit[86]	ET Visit[87]	Safety Follow Up TC [88]	Safety Follow Up Visit[89]
Adverse Events[79]	X			X	X	X	X
Renal Ultrasound				X	X		
ECHO				X	X		
ECG				X	X		
Chemistry, Hematology, Urinalysis[80]		X		X	X		X
Serum Amylase[81]		X		X	X		X
Serum Lipase[82]		X		X	X		X
Serum 25(OH)D		X		X	X		
Serum Calcium[74]		X		X	X		X
Serum Creatinine[74]		X		X	X		
Serum iPTH			X	X	X		
Serum FGF23[77]				X	X		X
Anti-KRN23 antibody (ADA)[77, 83]				X	X		
Pregnancy Test[84]		X		X	X		
DOSE TITRATION[85]		X					
DRUG ADMINISTRATION[79]	X						

[73] During Treatment Extension Period II (Weeks 162-EOS), clinic visits will occur at 12-week intervals (± 5 days) starting at Week 172. Telephone calls from the site will occur every 2 weeks (± 5 days) to confirm administration of study drug by the subject's caregiver (Q2), and reporting of concomitant medications and adverse events. The visit window is ± 5 days. Telephone visits may also be conducted at the clinic depending on proximity of the subject to the investigational site.

[74] Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable). Peak serum phosphorus may be collected as an unscheduled lab if necessary.

[75] 2-hour urine collections for urinary calcium, phosphorous, and creatinine and calculation of TmP/GFR and TRP

[76] 24-hour urine collections for urinary phosphorus, calcium, and creatinine

[77] If there is a technical or operational issue obtaining results for PK, FGF23, or ADA, an additional blood sample may be obtained at the next suitable clinic visit.

[78] Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed.

[79] During Treatment Extension Period II, study drug will be administered by the subject's parent or caregiver at Q2 week intervals (± 5 days and no fewer than 8 days apart). Study drug administration will be confirmed by the study site during biweekly telephone calls to the subject. Adverse event and concomitant medicine information will also be collected during these biweekly telephone calls.

[80] Serum chemistry panels may include PD parameters (i.e. serum phosphorus and ALP), and safety parameters of interest (i.e. calcium) to avoid duplication of testing. See Table 7.5.5.8.1 for complete listing of Clinical Laboratory Assessments for Safety.

[81] Reflexive assessment of amylase isoenzymes will be performed if the serum amylase level is elevated to ≥1.5 times the upper limit of the reference range (ULRR) beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[82] Serum lipase will be assessed as part of the serum chemistry panel beginning at Week 40 or the first scheduled time point after appropriate approvals are obtained.

[83] If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points, and may include additional blood volume required to perform a neutralization assay on a case-by-case basis, if warranted.

[84] Pregnancy testing will be performed for any female subject of childbearing potential who has experienced menarche. Pregnancy testing will be performed at site visits every 12 weeks as indicated.

[85] Dose titration during Treatment Extension Period II will apply only to subjects meeting the following criteria: 1) two consecutive serum phosphorus measurements are below the normal range (3.2-6.1 mg/dL [1.03-1.97 mmol/L]); 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. If the subject has a single serum phosphorus measurement below the normal range and criteria 2 and 3 are met, the serum phosphorus measurement should be repeated through an unscheduled blood draw at the study site within 4 weeks and a dose adjustment made if the serum phosphorus remains below the normal range.

[86] The EOS II visit will be the End of Study efficacy visit for subjects in the US and should occur before September 30, 2018. The EOS II visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days. Radiography (x-rays) of wrists and knees, 6MWT, and ECHO will not be performed at the EOS II Visit if the assessment was conducted within 3 months of termination. Radiography (x-rays) of standing long legs will not be performed at the EOS II visit if a postbaseline assessment was conducted within 12 months of termination.

[87] The ET visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days. Radiography (x-rays) of wrists and knees, XtremeCT, 6MWT, BOT-2, HHD and ECHO will not be performed at the ET Visit if the assessment was conducted within 3 months of termination. Radiography (x-rays) of standing long legs will not be performed at the ET visit if a postbaseline assessment was conducted within 12 months of termination. BOT-2 and HHD will not be performed if the ET Visit occurs after Week 64. XtremeCT will be performed for ET visits occurring between Week 40 and Week 64 at select sites based on scheduling and availability of equipment.

[88] To be completed for those subjects who complete EOS II and do not continue on KRN23 treatment immediately on commercial use or through another mechanism. Site personnel will initiate a safety follow-up telephone call 5 weeks (+ 5 days) after the EOS II visit to collect information on whether KRN23 has been started through another mechanism and, if not, any ongoing or new AEs, serious AEs, or concomitant medications.

[89] A safety visit will take place 10 weeks ±1 week after the ET or EOS II visit for those subjects who discontinue treatment after Week 160 and before the EOS II visit or for those subjects within the US who complete EOS II and do not continue on KRN23 through commercial use or another mechanism. This safety visit will not occur for subjects in the US who complete EOS II and are documented to be continuing on KRN23 on commercial use or through another mechanism. Every reasonable effort should be made to have subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic for the final safety visit will be given the option of having a final safety telephone call for the collection of any ongoing or new AEs, serious AEs, or concomitant medications.

3 TABLE OF CONTENTS

List of Tables

List of Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

25(OH)D	25-hydroxyvitamin D
1,25$(OH)_2$D	1,25-dihydroxyvitamin D
6MWT	Six Minute Walk Test
ADA	Anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AP	anteroposterior
BALP	bone-specific alkaline phosphatase
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition
BUN	blood urea nitrogen
°C	degrees Celsius
CFR	Code of Federal Regulations
CRF	case report form
CT	computed tomography
CTx	carboxy-terminal cross-linked telopeptide of type I collagen
Dl	deciliter
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECLA	electrochemiluminescent assay
EDC	electronic data capture
EEI	energy expenditure index
EOS	end of study
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice

GMP	Good Manufacturing Practice
HH	Home Health
HHD	hand-held dynamometry
HIPAA	Health Insurance Portability and Accountability Act
Hyp	hypophosphatemic
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
iPTH	intact parathyroid hormone
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Randomization System
kg	kilogram
KHK	Kyowa Hakko Kirin Pharma, Inc.
L	liter
LS	least squares
LVH	left ventricular hypertrophy
m	meter
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mm Hg	millimeters of mercury
mmol	millimole
MVIC	maximum voluntary isometric contraction
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no adverse effect level
P1NP	procollagen type 1 N-propeptide
PA	posteroanterior
PD	pharmacodynamic (s)
PHEX	Phosphate regulating gene with homology to endopeptidases located on the X chromosome
PHS-10	Physical Summary Score
PK	pharmacokinetic(s)
PODCI	Pediatric Outcomes Data Collection Instrument

POSNA	Pediatric Orthopedic Society of North America
PSS-10	Psychosocial Summary Score
PT	Preferred Term
PTH	parathyroid hormone
Q2	biweekly, once every two weeks
Q4	monthly
RBC	red blood cell
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-10	SF-10 for Children Health Survey
SOC	standard of care
SSRT	Study Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TmP/GFR	ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
TRP	tubular reabsorption of phosphate
ULN	upper limit of normal
ULRR	Upper limit of the reference range
US	United States
WBC	white blood cell
XLH	X-linked hypophosphatemia

Definition of Terms

Investigational Product is defined as, “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

The terms “Investigational Product” and “study drug” may be used interchangeably in the protocol.

5 INTRODUCTION

X-linked hypophosphatemia (XLH) is a disorder of renal phosphate wasting, and the most common heritable form of rickets. In XLH patients, a defect in the phosphate sensing mechanism in osteocytes leads to the production of aberrantly high circulating levels of fibroblast growth factor 23 (FGF23) that causes an inappropriate loss of phosphate reabsorption in the kidney. The impact of FGF23 on the kidney causes hypophosphatemia and low-normal circulating 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels. The low serum phosphorus levels result in hypomineralization of bone and associated abnormalities including rickets, bowing of the legs and short stature.

The current standard of care consists of oral phosphate and $1,25(OH)_2D$ (calcitriol) replacement. Treatment can improve rickets disease but provides limited benefit in some patients or in other aspects of the disease and does not treat the underlying cause (Carpenter et al. 2011). The treatment regimen requires balancing the benefits of treatment with complicated monitoring and potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism (Carpenter et al. 2011). By blocking the action of the aberrantly elevated FGF23, the reabsorption of phosphate could potentially be normalized, offering an effective and safe treatment option for patients with XLH.

Proof-of-concept studies in a relevant murine model support the use of an anti-FGF23 monoclonal antibody (mAb) as a treatment for XLH. Experiments in both juvenile and adult Hyp mice provided evidence that treatment with an anti-FGF23 mAb normalized or ameliorated many of the characteristic abnormalities associated with XLH (Aono et al. 2009); (Aono et al. 2011). KRN23 is a fully human IgG_1 mAb that binds to and inhibits FGF23. The Sponsor and development partner, Kyowa Hakko Kirin Pharma, Inc. (KHK) are investigating KRN23 as a potential therapeutic candidate for the treatment of XLH, a disease distinguished by high levels of serum FGF23.

KHK has conducted a series of nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies supporting the investigation of KRN23 in adults and children. Three clinical studies have been conducted in adult patients with XLH: a single dose Phase 1 safety and tolerability study of KRN23, a repeat dose Phase 1/2 dose escalation study, and associated treatment extension study. The current Phase 2 study will evaluate the pharmacodynamics (PD) of KRN23 to determine the appropriate dose range and dose regimen, and establish the safety profile of KRN23 in children with XLH. Effects on phosphate homeostasis and the clinical impact of KRN23 on skeletal disease, growth and physical function will also be examined.

5.1 Overview of XLH

XLH, also described as vitamin D-resistant rickets, is a rare genetic metabolic disorder. The incidence of XLH is 3.9-5 per 100,000 live births (Davies et al. 1981); (Beck-Nielsen et al. 2009). XLH is the most common inherited form of rickets and the most common inherited defect in renal tubular phosphate transport. There is a great deal of variability in the manifestations of XLH. In the mildest cases, only hypophosphatemia is evident (Holm et al. 2012). In more severe disease, hypophosphatemia leads to decreased mineralization of newly formed bone and the clinical findings of rickets. Surgical correction of limb deformities is often required.

Patients with XLH often present during childhood with rickets due to hypophosphatemia and frequently develop skeletal abnormalities (e.g. bowed legs), impaired growth, and short adult stature (Tenenhouse et al. 2001). As young patients age and progress into adulthood, the symptom pattern evolves due to the decreasing phosphate needs for bone growth. Adult XLH patients suffer from bone pain and osteomalacia, increased risk of bone fractures, joint abnormalities and joint pain, enthesopathy, and osteoarthritis (Carpenter et al. 2011).

XLH is transmitted as an X-linked dominant disorder, although autosomal recessive and dominant forms of hypophosphatemia have also been observed (Dixon et al. 1998). Mutations resulting in the loss of function of PHEX (Phosphate regulating gene with Homology to Endopeptidases located on the X chromosome) form the genetic basis for XLH (Carpenter et al. 2011). Approximately 20% of *PHEX* mutations are *de novo* (i.e. not inherited from a parent) based on genetic testing and clinical observations in non-familial XLH patients (Dixon et al. 1998); (Whyte et al. 1996).

Patients with XLH have hypophosphatemia due to excessive FGF23 levels (Jonsson et al. 2003); (Yamazaki et al. 2002); however the precise mechanism by which PHEX disruption results in elevated FGF23 is complex and not fully understood (Carpenter et al. 2011); (Rowe 2012). FGF23 plays an important role as a specific regulator of serum phosphorus; its major function is to reduce serum phosphorus levels by inhibiting renal proximal tubular phosphate reabsorption (Fukumoto 2008); (Razzaque et al. 2007). FGF23 also decreases serum 1,25 dihydroxyvitamin D [$1,25(OH)_2D$] levels by inhibiting 1-alpha-hydroxylase activity in the kidney, thereby decreasing intestinal absorption of phosphate and calcium. Both actions by FGF23 on the tubular reabsorption and intestinal absorption via vitamin D metabolism lead to a decrease in serum phosphorus levels.

Current treatment options for patients with XLH are directed at correcting osteomalacia and replacing lost serum phosphorus by administering oral phosphate supplements and an active vitamin D metabolite (e.g. calcitriol) several times per day. However, the resulting transient yet pronounced increases in serum phosphorus lower serum ionized calcium causing compensatory increases in parathyroid hormone (PTH). The combination of increased urinary phosphate excretion and increased PTH can increase the risk for extra-osseus calcifications and precipitation of calcium-phosphate in the kidney. The administration of oral phosphate also increases serum FGF23 concentrations (Imel et al. 2010); (Carpenter et

al. 2010), which is the underlying cause of hypophosphatemia in patients with XLH and could further suppress phosphate reabsorption and drive further complications. Treatment with oral phosphate supplements and calcitriol therefore requires frequent and continued monitoring of patients. Serum and urine mineral metabolites levels and imaging studies are required to assess toxicity and secondary complications, including nephrocalcinosis, hypercalciuria, and hyperparathyroidism (Carpenter et al. 2011).

5.2 Brief Overview of KRN23 Development

A brief overview of existing information on KRN23 is provided below; a comprehensive review of the data is contained in the Investigator's Brochure (IB) provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

5.2.1 Brief Description of KRN23

KRN23 is a recombinant human IgG_1 monoclonal antibody that binds to and inhibits the activity of FGF23. KRN23 is expressed in Chinese hamster ovary dihydrofolate reductase deficient cells. The secreted KRN23 antibody is recovered from the culture medium and purified using a series of chromatographic and filtration steps. Based on the amino acid sequence, the predicted molecular mass of KRN23 is approximately 140 kilodaltons (kDa). Nonclinical studies demonstrated KRN23 possesses high binding affinity to the N-terminal domain of FGF23. KRN23 binds to FGF23 from humans, cynomolgus monkeys and rabbits, but not to other species tested.

5.2.1.1 Mechanism of Action in XLH

Patients with XLH have hypophosphatemia due to excessive serum FGF23 levels. FGF23 reduces serum phosphorus levels by two distinct mechanisms of action (Fukumoto 2008); (Razzaque et al. 2007); (Yamazaki et al. 2008). The primary mechanism is to inhibit phosphate reabsorption in the proximal tubule of the kidney. The secondary mechanism is to decrease phosphate absorption by the small intestine through the inhibition of $1,25(OH)_2D$ production in the kidney.

KRN23 has the potential to block or reduce FGF23 action and improve phosphate metabolism in XLH patients. KRN23 binds the amino-terminal domain of FGF23 that interacts with the FGFR1-binding portion of the combination FGFR1/Klotho receptor, preventing FGF23 from binding and signaling its receptor. Both intact and fragmented FGF23 polypeptides are immunoprecipitated with KRN23 (Yamazaki et al. 2008).
By inhibiting FGF23, KRN23 restores tubular reabsorption of phosphate (TmP/GFR) from the kidney and increases the production of $1,25(OH)_2D$ that also enhances intestinal absorption of phosphate. The dual action on kidney reabsorption and intestinal absorption, improves serum phosphorus levels, which is expected to improve bone mineralization and reduce the diverse bone and non-bone manifestations associated with hypophosphatemia in XLH patients.

5.2.2 Nonclinical Studies

The Hyp mouse is a murine homologue of XLH with a deletion in the 3' region of the *Phex* gene (Liu et al. 2007); (Perwad et al. 2005). In addition to hypophosphatemia, rickets and associated developmental abnormalities, these animals display elevated serum FGF23 levels and increased expression of FGF23 in the bone. Since KRN23 does not bind murine FGF23, the pharmacological effects of murine anti-FGF23 mAbs were examined in juvenile and adult Hyp mice (Aono et al. 2009); (Aono et al. 2011). In juvenile Hyp mice, anti-FGF23 treatment corrected hypophosphatemia and ameliorated the rachitic bone phenotypes (Aono et al. 2009). In adult Hyp mice, anti-FGF-23 treatment increased serum phosphate and $1,25(OH)_2D$ levels, and increased grip strength and spontaneous movement (Aono et al. 2011). These studies provide proof-of-concept that treatment with antibodies targeting FGF23 may reverse or ameliorate the characteristic abnormalities associated with XLH.

KRN23 binds to human, rabbit, and monkey FGF23 with comparable affinities. In a GLP study, KRN23 cross-reactivity was evaluated against a full panel of human, rabbit (32 tissues), and cynomolgus monkey (33 tissues) tissues by immunohistochemistry. No specific KRN23 staining was observed suggesting untoward direct-effects of KRN23 are not expected in any tissues of normal humans, rabbits, or cynomolgus monkeys.

A series of nonclinical pharmacology, PK, and toxicity studies have been conducted in rabbits and cynomolgus monkeys to support the use of KRN23 in adults and children. Findings of potential clinical significance and relevance to this protocol are summarized below; additional information is provided in the IB.

- The no adverse effect level (NOAEL) in a 40-week toxicity study in adult cynomolgus monkeys was 0.03 mg/kg KRN23 for males and 0.3 mg/kg KRN23 for females. The NOAEL in a 40-week toxicity study in juvenile cynomolgus monkeys and a single-dose study in rabbits was 0.3 mg/kg KRN23.
- Soft tissue and organ mineralization was a consistent finding associated with prolonged and excessive serum phosphate levels including the kidney where nephrocalcinosis was observed at the highest dose tested and reversibility of mineralization could not be established.
- The most prominent pharmacologic actions of KRN23 were dose-dependent changes in serum inorganic phosphorus and $1,25(OH)_2D$ in rabbits and juvenile, adult and pregnant cynomolgus monkeys.
- No gross or histopathological abnormalities were observed at the IV infusion sites or SC injection sites in the 40-week repeat dose toxicity studies in adult and juvenile cynomolgus monkeys.
- KRN23 demonstrated consistent and predictable PK behavior in both rabbits and cynomolgus monkeys based on the results of single and repeat dose studies where exposure was by either the IV or SC route.

The NOAEL was the same in juvenile and adult monkeys suggesting no difference in sensitivity to the adverse effects of KRN23. The results from single- and repeat-dose toxicology studies in rabbits and juvenile, adult and pregnant cynomolgus monkeys suggest the primary toxicological effects of KRN23 are associated with prolonged and excessive antagonism of the normal regulatory actions of FGF23 on renal tubular phosphate reabsorption and vitamin D metabolism.

5.2.3 Previous Clinical Studies

Four clinical studies have been conducted in adult patients with XLH: a single dose Phase 1 safety and tolerability study of KRN23 (KRN23-US-02), a single dose Phase 1 safety and tolerability study of KRN23 in Japan and Korea (KRN23-001), a repeat dose Phase 1/2 dose escalation study (KRN23-INT-001), and an associated treatment extension study (KRN23-INT-002). An additional open-label long-term extension study (UX023-CL203), a double-blind, placebo-controlled, Phase 3 study (UX023-CL303), and an open-label, paired bone biopsy Phase 3 study to evaluate changes in osteomalacia at the tissue level with KRN23 treatment are ongoing. Details of study parameters and PK, PD, clinical efficacy and safety results are provided in the IB.

Data from clinical studies to date are consistent with the model that KRN23 blocks FGF23 action, leading to a sustained increase in serum phosphorus levels due to increased tubular reabsorption of phosphate (TmP/GFR) and increased intestinal absorption caused by increased $1,25(OH)_2D$. Single and repeat-dose clinical studies indicate SC administration of KRN23 consistently increased and sustained serum phosphorus levels and TmP/GFR, without a major impact on urine calcium levels or vitamin D metabolism. The data from the long-term extension study suggest KRN23 could provide sustained increases in serum phosphorus levels sufficiently such that improvements in bone physiology, structure and function would be expected.

Repeated doses of KRN23 up to 1.0 mg/kg every 4 weeks were well tolerated by adult XLH subjects throughout the Phase 1/2 dose escalation and associated treatment extension study. No deaths or life threatening treatment emergent AEs have been reported. In the extension study, SAEs reported for 3 subjects were unlikely to be or were not study drug related: breast cancer, hypertensive crisis, and cervical spinal stenosis. Throughout the long-term extension study, treatment-related AEs were reported for 14 subjects (63.6%) treated with KRN23 and included injection site reaction (5 subjects, 22.7%), arthralgia (3 subjects, 13.6%), restless legs syndrome (3 subjects, 13.6%), and injection site pain (2 subjects, 9.1%). No discernible clinically significant trends of lab abnormalities suggestive of a treatment-related adverse effect were noted. Overall, no immunogenicity or patterns of dose-limiting toxicity have been associated with KRN23 treatment.

5.3 Summary of Overall Risks and Potential Benefits

KRN23 is a recombinant human IgG_1 mAb. Although KRN23 is a fully human antibody, there is still a potential risk of anti-drug antibody (ADA) production against KRN23. It is

important to monitor for the presence of ADA, especially when repeat-doses of KRN23 are given. No positive anti-KRN23 antibodies have been detected following IV or SC administration of KRN23 at the dose levels tested. Following SC administration of KRN23, injection site pain and urticaria have been reported.

Based on the anticipated actions of KRN23, subjects could experience hyperphosphatemia for a certain period of time due to excessive pharmacologic effects of KRN23. While no clinically relevant changes in laboratory values suggestive of a treatment-related adverse effect have been observed for KRN23, careful attention should be paid to serum levels of phosphorus and other related factors, such as calcium, $1,25(OH)_2D$, and iPTH.

Nephrocalcinosis was observed in some toxicology studies; it may occur due to an excessive increase in serum phosphorus and/or a potential increase in serum calcium. Many XLH patients develop nephrocalcinosis as a result of SOC therapy. Potential subjects with nephrocalcinosis severe enough to impair renal function will not be enrolled in the study. The presence of nephrocalcinosis will be examined prior to KRN23 treatment and will be monitored closely throughout the study.

An analysis of the risk of ectopic calcification from the non-clinical and clinical program suggests that the serum phosphorus and calcium levels achieved in KRN23 clinical studies would not likely be associated with a clinical risk of ectopic mineralization, and that a safety margin exists relative to the mineral levels achieved during nonclinical toxicology experiments. Clinical data using renal ultrasound and ultra-fast CT scans of the heart have not identified a clinically significant increase or the appearance of novel calcifications in the most susceptible organs. Risks to subjects are mitigated by careful, detailed, and controlled monitoring of serum phosphorus levels and other biochemically-related factors in serum, such as calcium, $1,25(OH)_2D$, and iPTH. Surveillance via imaging modalities (i.e. renal ultrasound and echocardiogram [ECHO]) further monitor risks for the subjects.

KRN23 treatment results in elevation and accumulation of bound FGF23, but this does not appear to have any effect on phosphate metabolism despite an apparent associated increase in free FGF23. Although elevated free FGF23 has been associated with left ventricular hypertrophy (LVH) in patients with advanced chronic kidney disease (Faul et al. 2011); (Faul 2012); (Gutierrez 2013); (Wolf 2012), these findings have not been observed following anti-FGF23 treatment in the Hyp mouse model or as assessed by ECG in XLH patients in the KRN23 clinical program. Some reports have suggested that XLH patients on oral phosphate therapy have signs of LVH which likely increases FGF23 without any mitigation (Nehgme et al. 1997); (Carpenter et al. 2010). Cardiac monitoring has been incorporated into the study design to assess the potential risk.

The nonclinical and clinical experience with KRN23 indicates treatment induces expected PD effects, including increased serum phosphorus, TmP/GFR, and serum $1,25(OH)_2D$ levels, without negatively impacting urine calcium levels. Data from the long-term extension study suggest KRN23 could provide sustained increases in serum phosphorus levels sufficiently such that improvements in bone physiology, structure and function would be expected.

KRN23 treatment has been well tolerated, with no deaths, study drug related SAEs, or immunogenicity reported to date. Overall, based on the scientific rationale, unmet medical need, and results from nonclinical studies and clinical studies to date, continued clinical investigation of KRN23 in patients with XLH is warranted.

5.4 Study Rationale

The current standard of care (SOC) therapy consists of multiple daily doses of oral phosphate combined with appropriate doses of active vitamin D metabolites. SOC therapy, when taken with a high degree of compliance and monitoring, can improve the skeletal disease but often does not fully address the bone and growth abnormalities nor does it target the pathophysiological cause of the disease: renal phosphate wasting induced by high FGF23 levels. SOC therapy also requires careful monitoring to avoid potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism. More efficacious, safer, and convenient therapies clearly are needed.

KRN23 is a recombinant fully human monoclonal IgG_1 antibody being developed to treat XLH by binding and inhibiting FGF23 activity, thereby restoring normal phosphate homeostasis. Four clinical studies have been conducted in adult patients with XLH: a single dose Phase 1 safety and tolerability study of KRN23 (KRN23-US-02), a single dose Phase 1 safety and tolerability study of KRN23 in Japan and Korea (KRN23 001), a repeat dose Phase 1/2 dose escalation study (KRN23-INT-001), and an associated treatment extension study (KRN23 INT-002). An additional open-label long-term extension study (UX023-CL203), a double-blind, placebo-controlled, Phase 3 study (UX023-CL303), and an open-label, paired bone biopsy Phase 3 study to evaluate changes in osteomalacia at the tissue level with KRN23 treatment are ongoing. The safety data from these studies has shown that KRN23 in single and repeated monthly doses up to 1.0 mg/kg was well tolerated by adult XLH subjects. KRN23 sufficiently increased serum phosphorus levels, such that improvements in bone physiology, structure and function would be expected. These data support the initiation of further studies to evaluate the therapeutic benefit of KRN23 in children who experience the most severe physical and health manifestations associated with XLH. Currently, there are no approved treatments and a high unmet medical need in pediatric XLH patients.

Adults and children with XLH have the same underlying defect but are at a different stage of the disease. In childhood, normal phosphorus levels are higher to promote bone formation, whereas in adults, the normal range is lower, coincident with reduced demand for bone formation. Therefore, smaller, more frequent dosing may be preferred for pediatric hypophosphatemic patients to maximize treatment effect without a plateau, drive serum phosphorus levels closer to the normal range and minimize the troughs. This Phase 2 study will examine the PD, efficacy, and safety of KRN23 administered at multiple doses and dose regimens in pediatric XLH patients.

The dose response of KRN23 will be evaluated at 3 starting dose levels. Monthly (Q4) and biweekly (i.e. every other week; Q2) dosing regimens will also be compared. KRN23 dosing

will be individually adjusted every 4 weeks as needed, according to serum phosphorus levels. The goal is to achieve stable serum phosphorus levels in the target range, while minimizing changes in the calcium control system. During Treatment Extension Periods I (and II, if applicable), all subjects will receive KRN23 at the Q2 dosing regimen. Data collected in this study will establish a KRN23 dose and dose regimen for pediatric patients, and provide information about the PD, PK, clinical efficacy and safety of KRN23 in children with XLH.

6 STUDY OBJECTIVES

The objectives of the study are to:

- Identify a dose and dosing regimen of KRN23, based on safety and PD effect in pediatric XLH patients
- Establish the safety profile of KRN23 for the treatment of children with XLH including ectopic mineralization risk, cardiovascular effects, and immunogenicity profile
- Characterize the PK/PD of the KRN23 doses tested in the monthly (Q4) and biweekly (Q2) dose regimens in pediatric XLH patients
- Determine the PD effects of KRN23 treatment on markers of bone health in pediatric XLH patients
- Obtain a preliminary assessment of the clinical effects of KRN23 on bone health and deformity, muscle strength, and motor function
- Obtain a preliminary assessment of the effects of KRN23 on patient-reported outcomes, including pain, disability, and quality of life in pediatric XLH patients
- Evaluate the long-term safety and efficacy of KRN23

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

UX023-CL201 is a randomized, multicenter, open-label, dose finding Phase 2 study. The study will be conducted in prepubescent children aged 5-12 years with XLH to assess the PD and safety of KRN23 administered via subcutaneous (SC) injections monthly (Q4, 28 days, and no fewer than 12 days apart) or biweekly (Q2, 14 days, and no fewer than 8 days apart) for up to 160 weeks for subjects at study sites outside the US and up to 216 weeks (until September 2018) for subjects at study sites in the US. The study will consist of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks). For subjects at study sites outside the US the Week 160 visit will be their end of study efficacy visit (EOS I). In the US, the study will also include a Treatment Extension Period II (up to 56 weeks) at the end of which the US subjects will have their EOS efficacy visit (referred to as EOS II). A safety follow-up telephone call will occur at 5 weeks (+ 5 days) after the EOS (I or II) efficacy visit, and a final safety visit will occur at 10 weeks (± 1 week) after the EOS (I or II) efficacy visit for subjects that are not continuing on KRN23 treatment through commercial use or another mechanism. The end of study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study. During Treatment Extension Period I (and II, if applicable), all subjects will receive KRN23 with Q2 administration.

The study initially enrolled 36 pediatric subjects with XLH and radiographic evidence of bone disease (pre-expansion subjects). The study was expanded to include additional subjects who were required to have a level of rickets severity of at least 1.5 points at the knee as defined by the Rickets Severity Score (RSS) method for a total of approximately 50 subjects overall (Thacher et al. 2000).

Potential subjects will come in to the site for an initial screening visit and sign informed consent. Once the diagnosis of XLH and radiographic evidence of active bone disease (pre-expansion subjects) or a RSS of at least 1.5 points at the knee (expansion subjects) have been confirmed, subjects will discontinue oral phosphate and vitamin D metabolite therapy prior to randomization and throughout the duration of the study (Section 7.4.5.1).
Subjects who successfully pass the initial screening requirements will return to the site for a second screening visit a minimum of 14 days after vitamin D metabolite treatment has been stopped and a minimum of 7 days after oral phosphate treatment has been stopped (as applicable); the remaining screening assessments to confirm eligibility will be performed.
The Baseline visit may occur up to 7 days after the second screening visit.
All Screening/Baseline assessments and inclusion/exclusion criteria based on local lab results must be satisfied prior to randomization and dosing.

There will be 3 cohorts in this study (n = 10 in cohorts 1 and 2 [pre-expansion subjects] and n = 30 in cohort 3 [comprising both pre-expansion and expansion subjects]); each with a Q4 and Q2 dosing group. Subjects will be randomized 1:1 to the Q4 or Q2 dosing regimens within each cohort; randomization will be stratified on subject gender. In order to maintain a

level of gender balance, no more than 20 patients of either sex can be enrolled in the pre-expansion group. No requirement for gender balance will be applied in the expansion group. The cohorts will be enrolled sequentially. The first cohort will examine the lowest doses (0.2 mg/kg Q4 and 0.1 mg/kg Q2) and will be enrolled first. As an added precautionary measure in this pediatric population, the second cohort (0.4 mg/kg Q4 and 0.2 mg/kg Q2) cannot begin dosing until the fourth subject in the first cohort completes the Week 4 visit. The third cohort will be administered the highest starting doses (0.6 mg/kg Q4 and 0.3 mg/kg Q2).

Dosing During the Titration Period (Weeks 0-16)

The initial 16-week Titration Period is intended to identify the KRN23 dose required to achieve the target peak PD effect. The goal is to identify an individualized KRN23 dose that maintains serum phosphorus levels in the target range for a given subject.

The target fasting serum phosphorus range for this study is 3.5- 5.0 mg/dL (1.131.62 mmol-/L), based on the peak PD effect of KRN23. The dose will be adjusted every 4 weeks, as needed, based on 2-week post-dose fasting serum phosphorus levels. The KRN23 dose titration scheme will be used as a guideline should the peak fasting serum phosphorus level fall outside of the target range (Table 7.4.4.1).

Dosing During the Treatment Period (Weeks 18-64)

If the serum phosphorus level is rising but has not yet reached the pre-specified target range by the end of the Titration Period, the titration may continue into the Treatment Period until the target range is reached, provided there are no safety concerns. For those subjects whose dose titration continues into the Treatment Period, 2-week post-dose peak serum phosphorus levels may be measured through unscheduled blood draws at corresponding study visits (e.g., at Week 18, 26, or 34) and the titration scheme (Table 7.4.4.1) followed until the target range is reached.

The visit window for HH visits is ± 3 days during the Titration Period and Treatment Period. If at any time during dose titration the subject is dosed earlier than the allowable ±3-day window, the previous dose should be repeated (i.e. no titration). If a subject is dosed later than the allowable ±3-day window, dosing should be determined as if the dosing occurred within the allowable window (i.e. by using the most recent post-dose peak serum phosphorus level and the dose titration scheme).

Dosing During Treatment Extension Period I (Week 66 up to Week 160) and II (Week 162 up to Week 216)

During Treatment Extension Period I (and II, if applicable), all subjects will receive biweekly (Q2) administration of KRN23. Subjects in the Q2 dosing regimen during the Treatment Period will continue to receive KRN23 at the KRN23 dose they were receiving at Week 64. At the Week 64 study visit, subjects in the Q4 dosing regimen will receive KRN23 at 60% of their established total Q4 dose level (rounded to the nearest 10 mg) and continue on that dose biweekly (Q2) through the Extension Period.

The visit window for HH visits is ± 5 days during Treatment Extension Period I. The window for dosing and telephone calls from the site during Treatment Extension Period II is ± 5 days.

General Dosing Guidelines

The rounding of doses to the nearest 10 mg will not be applied during the Titration Period (Weeks 0-16). During the Treatment Period and Treatment Extension Periods I and II, dose rounding will be applied once study sites have obtained appropriate approvals. Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg. The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen. The total administered dose may differ slightly from the total calculated or rounded dose due to rounding of the volume drawn for administration (to the nearest 0.1 mL). After the initial dose titration is complete, the dose may be increased at any time during the Treatment Period or Treatment Extension Periods I or II if a subject meets the following dose adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range (3.2-6.1 mg/dL [1.03-1.97 mmol/L]); 2) the serum phosphorus level is < 0.5 mg/dL above baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. If the subject has a single serum phosphorus measurement below the normal range and criteria 2 and 3 are met, the serum phosphorus measurement should be repeated through an unscheduled blood draw within 4 weeks and a dose adjustment made if the serum phosphorus measurement remains below the normal range. When post-titration dose adjustment is needed during the Treatment Period or Treatment Extension Periods I or II, doses may be adjusted in 10 mg total dose increments (e.g., a 20 mg rounded total dose would be increased to a 30 mg total dose). The dose level should not exceed 2.0 mg/kg (Q2).

If serum phosphorus increases above 5.0 mg/dL (1.62 mmol/L) at any time, the dose will be titrated down. During the Titration Period the dose should be titrated down according to the dose titration scheme (Table 7.4.4.1). During the Treatment Period or Treatment Extension Periods I or II, the total dose should be decreased by 10 mg. Following a dose reduction in a subject, the investigator and medical monitor will determine when and how that subject's dose will be titrated up.

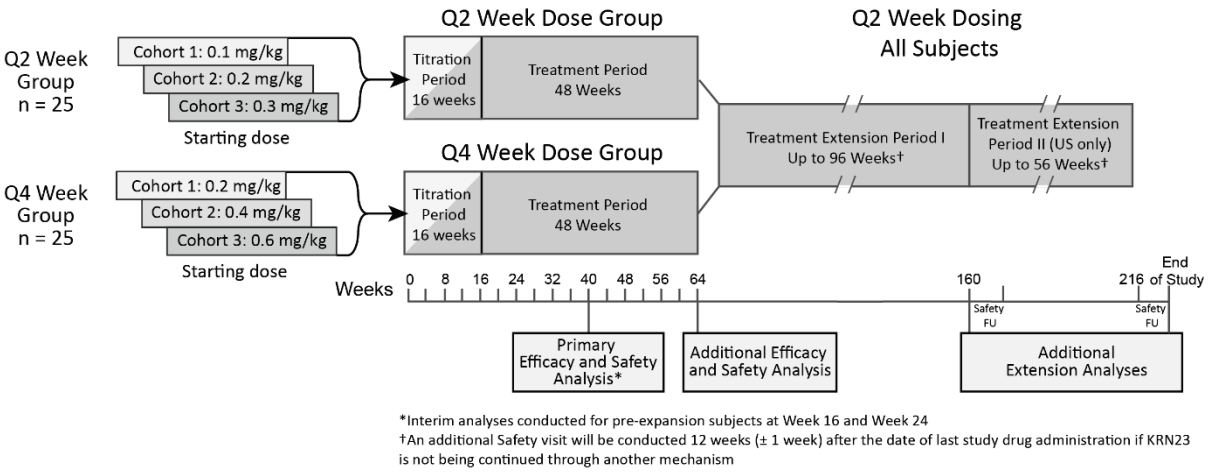
If a subject does not receive a dose within 10 days of a scheduled dose for the Q2 regimen, that dose should be skipped and next dose will be administered at the next scheduled Q2 dosing visit. If a subject does not receive a dose within 21 days of a scheduled dose for the Q4 regimen, that dose should be skipped and the next dose will be administered at the next scheduled Q4 dosing visit.

At the end of the Titration Period, the population of 50 subjects will consist of essentially two groups of 25 subjects, each with individually optimized dosing of KRN23 at either a Q4 week or Q2 week frequency. Analyses of safety and available PD and efficacy data are planned at the end of the Titration Period (Week 16) and at Week 24 for pre-expansion subjects. Further analyses in the pre-expansion group alone and for the overall population are planned at Week 40 and at Week 64 at the end of the Treatment Period to compare treatment outcomes to baseline (pre-dose). Analyses of long-term safety and efficacy will be conducted

at the completion of Treatment Extension Period I (Weeks 64-160). A final analysis will be performed at study completion (i.e., following Treatment Extension Period II and all needed safety follow-up visits).

Figure 7.1.1 provides a schematic of the overall study design.

Figure 7.1.1: UX023-CL201 Study Schema



7.2 Discussion of Study Design, Including Choice of Control Group

Patients with XLH who receive standard oral phosphate and calcitriol therapy are monitored and doses are individually adjusted based on the patient's response to treatment (Carpenter et al. 2011). The goal of this study is to identify a KRN23 dose and dose regimen, while investigating PD, PK, safety and clinical efficacy in pediatric subjects. Evaluations of additional biomarkers will also be performed to provide supportive evidence and confirm surrogate endpoints of efficacy and safety.

The sample size is intended to provide the maximum amount of information regarding KRN23 tolerability and dosing regimen in pediatric patients, along with indicators of long-term safety and efficacy. Randomization will be used to assign subjects to monthly (Q4) or biweekly (Q2) dosing regimens within each dose cohort, and stratify by gender; no more than 20 subjects of either gender will be enrolled in the pre-expansion group. There will be no requirement for gender balance in the expansion. Since all subjects will receive the same investigational product, blinding is unnecessary; study drug will be provided open-label.

The Titration Period is intended to initiate KRN23 at three starting dose levels, and escalate the dose for each subject in a progressive fashion over 16 weeks in order to maximize safety and tolerability in the pediatric study population. The goal of the Titration Period is to determine the optimal KRN23 dosing regimen and identify an acceptable dose to maintain the overnight fasting serum phosphorus level in the target range, while avoiding secondary complications. An initial analysis of safety and select PD data will be conducted at Week 16 for initial signals of PD and safety.

After 16 weeks of individual dose titration, subjects will enter a 48-week Treatment Period at an optimized KRN23 dose level. Dose titration may continue into the Treatment Period if necessary. The goal of the Treatment Period is to assess ongoing safety and sustained PD, PK, and clinical efficacy. The duration of treatment is intended to define whether KRN23 is safe for long-term use and provide sufficient insight on sustained clinical effects and improvements in rickets and active bone disease in pediatric XLH patients.

The main efficacy comparison will focus on dose finding and determining whether Q4 or Q2 dosing provides the optimal profile of phosphate control with acceptable levels of other bone mineral metabolites. In addition, the effect of the two regimens on bone health will be compared. While the lack of a placebo control group may introduce difficulties in discerning natural disease progression from treatment effectiveness, a placebo-controlled study of 64-weeks duration is difficult to conduct and possibly not ethical given the need for ongoing disease management in developing children. Use of SOC as a parallel active-control group would be reasonable, but might require a substantially larger trial size and a longer time frame to conduct. Given that the severity of rickets on x-rays of the wrists and knees will be scored in a blinded fashion using the RSS method, it is not necessary to subject pediatric patients to placebo in this Phase 2 study.

The goal of Treatment Extension Period I (up to 96 weeks) is to evaluate the long-term safety and efficacy of KRN23. All subjects will receive KRN23 at a Q2 dosing regimen. Beginning at Week 64, subjects previously assigned to Q4 dosing will receive KRN23 at 60% of their established Q4 dose level (rounded to the nearest 10 mg) and continue on that dose biweekly (Q2). It is expected that the maintenance of phosphate control during the Treatment Extension Period will allow for continued healing of rickets and bowing and maximize growth outcomes. Changes in growth and correction of lower extremity bowing may take longer to observe than the healing of rickets; thus, these outcomes will continue to be followed in Treatment Extension Period I.

The goal of Treatment Extension Period II is to continue to provide KRN23 treatment to subjects in the US through September 2018 while also continuing to collect long-term safety and efficacy data.

7.3 Selection of Study Population

The study will be conducted in approximately 50 prepubescent pediatric XLH subjects (aged 5 – 12 years) whom are likely to benefit from KRN23 treatment. The inclusion criteria are structured to enroll subjects with XLH, typically presenting with similar biochemical and clinical characteristics, including reduced serum phosphorus levels and radiographic evidence of rickets and/or bowing. The enrollment of patients with active rachitic disease should be prioritized due to the potential for a positive treatment effect in this population; expansion subjects will be required to have a level of rickets severity of at least 1.5 points at the knee as defined by the RSS.

Children with XLH undergo a normal pubertal growth spurt. Post-pubertal height is predicted by pre-pubertal height, indicating that loss of height potential generally occurs prior to puberty. Thus, initiation of therapy at early ages is recommended to achieve improved height outcomes (Carpenter et al. 2011). Specific inclusion criteria were designed to enroll patients with open growth plates who have not yet entered puberty (Tanner Stage ≤ 2), to maximize detection of treatment effects on bone growth. However, children younger than 5 were not included due to requirements for frequent blood draws and routine monitoring of 24-hour urine to accurately assess dose-finding and treatment effectiveness.

The Sponsor has taken reasonable measures to ensure the protection and safety of this population. Patients with evidence of tertiary hyperparathyroidism or nephrocalcinosis will be excluded. Appropriate pediatric expertise will be available at all trial sites, and site personnel will be focused on minimizing risk, fear, pain and distress during conduct of the study. However, a series of frequent blood draws are required during the Titration Period to ensure subject safety and to assist in the determination of the appropriate dose and dose regimen since KRN23 has not been previously administered to the pediatric XLH population.

7.3.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1) Male or female, aged 5 – 12 years, inclusive, with open growth plates
2) Tanner stage of 2 or less based on breast and testicular development
3) Diagnosis of XLH supported by ONE of the following:
   - Confirmed *PHEX* mutation in the patient or a directly related family member with appropriate X-linked inheritance
   - Serum FGF23 level ≥ 30 pg/mL by Kainos assay
4) Biochemical findings associated with XLH including:
   - Serum phosphorus ≤ 2.8 mg/dL (0.904 mmol/L)*
   - Serum creatinine within age-adjusted normal range*
5) Standing height < 50th percentile for age and gender using local normative data
6) Radiographic evidence of active bone disease including rickets in the wrists and/or knees, AND/OR femoral/tibial bowing,

   OR, for expansion subjects, a RSS score in the knee of at least 1.5 points as determined by central read
7) Willing to provide access to prior medical records for the collection of historical growth, biochemical and radiographic data, and disease history

8) Provide written or verbal assent (if possible) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures

9) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule and comply with the assessments

10) Females who have reached menarche must have a negative pregnancy test at Screening and undergo additional pregnancy testing during the study. If sexually active, male and female subjects must be willing to use two highly effective methods of contraception for the duration of the study

*Criteria to be determined based on overnight fasting (min. 4 hours) values collected at Screening Visit 2

7.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1) Use of a pharmacologic vitamin D metabolite or analog (e.g. calcitriol, doxercalciferol, alfacalcidiol, and paricalcitol) within 14 days prior to Screening Visit 2; washout will take place during the Screening Period

2) Use of oral phosphate within 7 days prior to Screening Visit 2; washout will take place during the Screening Period

3) Use of calcimimetics, aluminum hydroxide antacids (e.g. Maalox® and Mylanta®), systemic corticosteroids, and thiazides within 7 days prior to Screening Visit 1

4) Use of growth hormone therapy within 3 months before Screening Visit 1

5) Use of bisphosphonates for 6 months or more in the 2 years prior to Screening Visit 1

6) Presence of nephrocalcinosis on renal ultrasound graded $\geq$ 3 based on the following scale:

   0 = Normal

   1 = Faint hyperechogenic rim around the medullary pyramids

   2 = More intense echogenic rim with echoes faintly filling the entire pyramid

   3 = Uniformly intense echoes throughout the pyramid

   4 = Stone formation: solitary focus of echoes at the tip of the pyramid

7) Planned or recommended orthopedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period

8) Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits *

9) Evidence of tertiary hyperparathyroidism as determined by the investigator

10) Use of medication to suppress PTH (e.g. Sensipar®, cinacalcet, calcimimetics) within 2 months prior to Screening Visit 1

11) Presence or history of any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study

12) Presence of a concurrent disease or condition that would interfere with study participation or affect safety

13) Previously diagnosed with human immunodeficiency virus antibody, hepatitis B surface antigen, and/or hepatitis C antibody

14) History of recurrent infection or predisposition to infection, or of known immunodeficiency

15) Use of a therapeutic monoclonal antibody within 90 days prior to Screening Visit 1 or history of allergic or anaphylactic reactions to any monoclonal antibody

16) Presence or history of any hypersensitivity to KRN23 excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects

17) Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments

* Criteria to be determined based on overnight fasting (min. 4 hours) values collected at Screening Visit 2

7.3.3 Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The investigator may withdraw a subject at any time at their discretion. Ultragenyx must be notified of all subject withdrawals as soon as possible. Ultragenyx also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual subject or investigator due to poor enrollment or noncompliance, as applicable.

Subjects may be removed from the study for the following reasons:

- Occurrence of an unacceptable AE
- An illness that, in the judgment of the investigator or Ultragenyx, might place the subject at risk or invalidate the study
- At the request of the subject, investigator, or Ultragenyx, for administrative or other reasons
- Protocol deviation or noncompliance

During Treatment Extension Period I (Weeks 66-160) and II (Weeks 160 up to Week 216), orthopedic surgery will be permitted if recommended by the investigator or consulting physician. Subjects who develop secondary or tertiary hyperparathyroidism may also remain on study; however, use of medication to suppress PTH (e.g., Sensipar®, cinacalcet, calcimimetics) is not permitted at any time during the study (Section 7.4.5.1). Subjects should be removed from study if treatment for hyperparathyroidism becomes medically necessary.

If the reason for removal of a subject from the study is an AE, the AE and any related test or procedure results will be recorded in the source documents and transcribed onto the Case Report Form (CRF). Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within 30 days after the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation. An additional follow-up safety telephone call will take place 5 weeks (+ 5 days) after the subject's EOS (I or II) efficacy visit to collect information on any ongoing or new AEs, SAEs, or concomitant medications. An additional safety visit will occur 10 weeks ±1 week (approximately 5 times the elimination half-life) after the date of the subject's EOS (I or II) visit for a subject who has not continued KRN23 therapy under commercial use or another mechanism. Subjects who are unable to return to the clinic for the final safety visit will be given the option of providing blood and urine samples as part of a HH visit.

Subjects who withdraw or are removed from the study after receiving study drug may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

7.3.3.1 Stopping Rules

A DMC will be constituted for Study UX023-CL201 and will act in an advisory capacity to monitor the safety of KRN23 on a routine basis until the end of the Treatment Period (Week 64) (Section 7.6.7). The DMC may provide advice to Ultragenyx in any determination of whether study enrollment should be paused or if the study should be halted. During Treatment Extension Periods I and II, safety data will be reviewed by the Ultragenyx Study Safety Review Team (SSRT) as described in Section 8.5.5.1.

Individual subjects who experience any unexpected and possibly, probably, or definitely drug-related SAEs (Section 8.5.3) that represent a change in the nature or an increase in frequency of the serious event from their prior medical history will be assessed as to whether the subject will continue on the study.

Individual subjects will be monitored for ectopic mineralization by renal ultrasound and echocardiogram. If new or clinically significant worsening in mineralization is considered

clinically meaningful by the investigator and/or sponsor and related to study drug, the subject will be discontinued from the study.

Regulatory Authorities, as well as the IRB/EC will be informed should unexpected and possibly, probably, or definitely drug-related SAEs occur. A full clinical evaluation of the event will be performed in order to make a decision regarding what actions to take, including whether to recommend stopping the study. Regulatory Authorities, as well as IRBs/ECs, will be informed if the study is paused or stopped.

7.4 Treatments

There will be 3 cohorts in this study (n = 10 in cohorts 1 and 2 [pre-expansion subjects] and n = 30 in cohort 3 [comprising both pre-expansion and expansion subjects]); each with a Q4 and Q2 dosing group. Subjects will be randomized 1:1 to the Q4 or Q2 dosing regimens within each cohort; randomization will be stratified on subject gender. Starting doses for all 3 cohorts are below the highest doses studied in adult XLH subjects (i.e., 1 mg/kg administered monthly). The cohorts will be enrolled sequentially. The first cohort will examine the lowest doses (0.2 mg/kg Q4 and 0.1 mg/kg Q2) and will be enrolled first. As an added precautionary measure in this pediatric population, the second cohort (0.4 mg/kg Q4 and 0.2 mg/kg Q2) cannot begin dosing until the fourth subject in the first cohort completes the Week 4 visit. The third cohort will be administered the highest starting doses (0.6 mg/kg Q4 and 0.3 mg/kg Q2). The goal is to identify an individualized KRN23 dose which maintains serum phosphorus levels in the target range.

The amount of KRN23 administered will be calculated based on the subject's weight. The rounding of doses to the nearest 10 mg will not be applied during the Titration Period (Week 0-16). During the Treatment Period and Treatment Extension Period, dose rounding will be applied once study sites have obtained appropriate approvals. Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg. The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen.

During Treatment Extension Periods I and II, all subjects will receive KRN23 at a Q2 dosing regimen. Selection of doses, dose titration, and dose adjustments are described in Section 7.4.4.

7.4.1 Investigational Product

KRN23 is supplied as a sterile, clear, colorless and preservative-free solution in single-use 5 mL vials containing 1 mL of KRN23 at a concentration of 10 mg/mL or 30 mg/mL. At the study site, KRN23 should be securely stored at 2- 8°C and protected from light. It should not be frozen. In the home setting, study drug should be handled as directed by the study personnel.

Trained personnel will administer study drug by SC injection to the abdomen, upper arms or thighs; the injection site should be rotated with each injection including to a different

quadrant of the abdomen. If the dose level exceeds 1 mL in volume, the dose may be administered at two injection sites. However, the maximum volume administered at a single injection site should not exceed 1.5 mL. After proper training by study personnel in SC injection technique, a subject's parent or non-healthcare provider caregiver may administer KRN23 to the subject. Parents or caregivers will be instructed to follow the directions provided in the Instructions for Use. The dosing schedule will remain the same.

The study drug is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations.

7.4.2 Reference Therapy

The study design is open-label; all subjects will receive investigational product. No placebo or reference therapy will be administered in this study.

7.4.3 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. Three treatment cohorts (n = 10 in cohorts 1 and 2 [pre-expansion subjects] and n = 30 in cohort 3 [comprising both pre-expansion and expansion subjects]) will be sequentially enrolled, each with a Q4 and Q2 dosing group. Once the full allotment of subjects has been enrolled into a cohort (defined as completion of informed consent), the next cohort may begin enrolling. Subjects will be randomized 1:1 to the Q4 or Q2 dosing regimens within each cohort via an Interactive Web Response System (IWRS) based on a randomization schedule developed by an independent third-party vendor. Randomization will be stratified on gender; no more than 20 subjects of either gender will be enrolled in the pre-expansion group. No requirement for gender balance will be applied in the expansion group.

The IWRS will be programmed such that a subject in the 2nd cohort cannot be randomized until the fourth subject in the 1st cohort has completed the Week 4 study visit and a safety review has been completed. Sites and investigators will be notified if dosing of new or existing subjects will be paused between cohort 1 and 2, and if so, when they can resume dosing.

7.4.4 Selection of Doses and Study Duration

A multiple-dose, dose escalation Phase 1/2 study (KRN23-INT-001) was conducted in adult XLH subjects. KRN23 was well tolerated following SC administration of 4 intra-subject escalating doses (0.05 mg/kg → 0.1 mg/kg → 0.3 mg/kg →0.6 mg/kg) administered once per 28 days. The proportion of KRN23-treated subjects with serum phosphorus levels in the target range (> 2.5 to ≤ 3.5 mg/dL) increased with KRN23 dose level but did not exceed the upper limit of normal (4.5 mg/dL) in any subject at any time point. A direct PK-PD relationship between serum KRN23 concentrations and serum phosphorus levels was noted in the study. In an associated extension study (KRN-INT-002), doses up to 1.0 mg/kg

KRN23 administered monthly were well tolerated by adult XLH subjects over a period of 48 weeks.

Adults and children with XLH have the same underlying defect but are at a different stage of the disease. In childhood, normal phosphorus levels are higher to promote bone formation, whereas in adults, the normal range is lower, coincident with reduced demand for bone formation. Successful treatment of XLH requires sustained increases in serum phosphorus levels (Carpenter et al. 2011). Smaller, more frequent dosing may be preferred for pediatric hypophosphatemic patients to maximize treatment effect by maintaining serum phosphorus levels closer to the normal range and minimize the troughs. Therefore, the key objectives of this study are to determine both the optimal KRN23 dosing regimen for pediatric XLH patients and identify an acceptable dose that will allow for the improvement in rickets and associated clinical consequences, while avoiding hypercalciuria, hypercalcemia and hyperparathyroidism.

The dose-finding goal of this study is to identify an individualized KRN23 dose that maintains serum phosphorus levels in the target range. Dose finding will be conducted progressively in three distinct dosing cohorts, each evaluating a different starting dose level and dose regimen (Q4 or Q2). Starting doses for all three cohorts are below the highest doses studied in adult XLH (1 mg/kg administered monthly). Dose escalation will be individually titrated based on PD effects on serum phosphorus, safety and tolerability. During the Titration and Treatment Periods, dosing will be initiated and titrated in a stepwise, controlled fashion over a 16-week period to achieve serum phosphorus levels in a target range below the age-adjusted upper limit of normal.

The amount of KRN23 administered will be calculated based on the subject's weight. The rounding of doses to the nearest 10 mg will not be applied during the Titration Period (Week 0-16). During the Treatment Period and Treatment Extension Periods I and II, dose rounding will be applied once study sites have obtained appropriate approvals. Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg. The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen.

Since phosphorus requirements in growing children are greater than in adults, the design provides the provision to increase the dose level as high as 2.0 mg/kg for the Q4 regimen and 2.0 mg/kg for the Q2 regimen to a maximum dose of 90 mg. Previous studies with KRN23 in adult XLH patients did not show any "off target" effects; therefore, the safety profile is expected to be related solely to the PD effect, essentially increased serum phosphorus. Since the serum phosphorus target range is defined well below the upper limit of normal, the likelihood of a dose-related safety issue is low. The efficacy data on phosphate control from these previous studies also suggest there is a plateau in effect between 0.6 -1.0 mg/kg, which may or may not be the case in pediatric patients in whom phosphate metabolism is clearly different. Therefore, the protocol allows limited flexibility to adapt to incrementally higher doses, if the expected doses based on adult data are inadequate to achieve an acceptable increase in serum phosphorus within the accepted safe range.

The target fasting serum phosphorus range for this study is 3.5 – 5.0 mg/dL (1.13 -1.62 mmol/L), based on the peak PD effect of KRN23, which is approximately 14 days post-dose. The target range represents the low- to mid-range of normal values in children. Consultations with physicians who are expert in the field indicate this level is sufficient to improve rickets and other bone defects (T. Carpenter, personal communication), while minimizing the risk of ectopic mineralization. With additional treatment experience gained during the study, it was determined that achieving serum phosphorus levels within the target range (3.5-5.0 mg/dL) may not be required to achieve positive outcomes. Therefore, once a stable dose is reached, the need for dose escalation during the Treatment Period and the Extension Period will be based on achieving a serum phosphorus level above the lower limit of the normal range (3.2 mg/dL) or at least 0.5 mg/dL above baseline.

During the Titration Period the dose will be adjusted every 4 weeks, as needed, based on 2-week post-dose fasting serum phosphorus levels. During the Titration Period doses will be adjusted according to the titration scheme detailed below. The titration scheme (Table 7.4.4.1) will be used as a guideline for dose adjustments should the peak fasting serum phosphorus level fall outside of the target range. If the serum phosphorus level is rising but has not yet reached the pre-specified target range by the end of the Titration Period, the titration can continue into the Treatment Period until the target range is reached, provided there are no safety concerns. For those subjects whose dose titration continues into the Treatment Period, 2-week post-dose peak serum phosphorus levels may be measured through unscheduled blood draws at corresponding study visits (e.g., at Week 18, 26, or 34) and the titration scheme followed (Table 7.4.4.1) until the target level is achieved. During the Treatment Extension Period, all subjects will receive biweekly (Q2) administration of KRN23. Subjects in the Q2 dosing regimen during the Treatment Period will continue to receive KRN23 at the KRN23 dose they were receiving at Week 62. At the Week 64 study visit, subjects in the Q4 dosing regimen will receive KRN23 at 60% of their established total Q4 dose level (rounded to the nearest 10 mg) and continue on that dose biweekly (Q2).

During the Treatment Period and Treatment Extension Period I (and II, if applicable), dose rounding will be applied once study sites have obtained appropriate approvals. Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg. The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen. The total administered dose may differ slightly from the total calculated or rounded dose due to rounding of the volume drawn for administration (to the nearest 0.1 mL).

After the initial dose titration is complete, the dose may be increased at any time during the Treatment Period or the Treatment Extension Periods if a subject meets the following dose adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range (3.2-6.1 mg/dL [1.03-1.97 mmol/L]); 2) the serum phosphorus level is < 0.5 mg/dL above baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. If the subject has a single serum phosphorus measurement below the normal range and criteria 2 and 3 are met, the serum phosphorus measurement should be repeated through an unscheduled blood draw within

4 weeks and a dose adjustment made if the serum phosphorus remains below the normal range. When post-titration dose adjustments are needed during the Treatment Period or Treatment Extension Periods, doses may be adjusted in 10 mg total dose increments (e.g., a 20 mg rounded total dose would be increased to a 30 mg total dose). The dose level should not exceed 2.0 mg/kg for either the Q4 regimen or the Q2 regimen. If serum phosphorus increases above 5.0 mg/dL (1.62 mmol/L) at any time, the dose will be titrated down. During the Titration Period the dose should be titrated down according to the dose titration scheme (Table 7.4.4.1). During the Treatment Period or Treatment Extension Periods I or II, the total dose should be decreased by half. Following a dose reduction in a subject, the investigator and medical monitor will determine when and how that subject's dose will be titrated up. When dose titration is applied due to safety concerns, the investigator judgment prevails.

During the Titration Period, the Treatment Period, and Treatment Extension Period I, if a subject does not receive a dose within 10 days of a scheduled dose for the Q2 regimen, that dose should be skipped and next dose will be administered at the next scheduled Q2 dosing visit. During the Titration Period or the Treatment Period, if a subject does not receive a dose within 21 days of a scheduled dose for the Q4 regimen, that dose should be skipped and next dose will be administered at the next scheduled Q4 dosing visit.

During Treatment Extension Period II, if a subject does not receive a dose within 10 days of a scheduled dose for the Q2 regimen, that dose should be skipped and next dose will be administered on the next scheduled Q2 dosing day.

Table 7.4.4.1: KRN23 Initial Dose Titration Scheme

Serum Phosphorus (2 weeks Post-Dose)	Dose Adjustment [1,5]
< 3.5 mg/dL [2] < 1.13 mmol/L	In 2 weeks, increase dose by 0.3 mg/kg for Q2 OR 0.4 mg/kg for Q4[3]
3.5 – 4.5 mg/dL 1.13 – 1.45 mmol/L	Repeat previous dose
>4.5 – 5.0 mg/dL >1.45 – 1.62 mmol/L	Repeat previous dose and then repeat serum phosphorus in at 2 weeks after that dose; determine next dose based on the repeat serum phosphorus level.
> 5.0 mg/dL (1.45 mmol/L) and ≤ age adjusted ULN	In 2 weeks, decrease dose by 0.3 mg/kg for Q2 OR 0.4 mg/kg for Q4 and then repeat serum phosphorus at 2 weeks after that dose[3]
> age adjusted ULN	Skip next 2 doses for Q2 OR skip next dose for Q4, then re-initiate dosing at last dose level at which the subject's peak serum phosphorus was in range[4]

1 Dose adjustments for subjects assigned to the Q2 regimen will only be made after 2 consecutive peak measurements.

2 During the Treatment Period, if a subject's serum phosphorus level has not increased, as defined by a change no greater than 0.1 mg/dL, after 2 consecutive dose escalations, even if the target range has not been achieved, then the previous dose will be considered that subject's optimized dose and not escalated further.

3 If needed, the final dose adjustment increment may be less than 0.3 mg/kg for Q2 or 0.4 mg/kg for Q4 to reach the 2.0 mg/kg maximum dose

4 The investigator should consult with the medical monitor to determine when and how to titrate up

5 Calculated doses below 15 mg will be adjusted to 15 mg. Calculated doses ≥15 mg will be rounded to the nearest 10 mg up to a maximum dose of 90 mg.

The planned duration of treatment in this study will vary by region. The study consists of an individual dose Titration Period (16 weeks) a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks) for a total treatment duration of up to 160 weeks for subjects at study sites outside the US. For subjects at study sites outside the US the Week 160 visit will be their EOS I visit. In the US, the study will also include Treatment Extension Period II (up to 56 weeks) until September 2018 for a maximum total treatment duration of up to 216 weeks. The duration of Treatment Extension Period II will vary for individual subjects and will be determined by the time from Week 160 through their EOS II visit. For each US subject, the study site will schedule an End of Study visit to take place before 30 September 2018 with assessments performed as indicated on the Schedule of Events (Table 2.6). The end of study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

7.4.5 Prior and Concomitant Therapy

Throughout the study, there should be no significant changes to a subject's diet or medication schedule unless medically indicated. Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except those listed in Section 7.4.5.1. All concomitant medications taken during the study will be

recorded in the CRF with indication, dose information, and dates of administration. Any changes to concomitant medication will also be documented.

7.4.5.1 Prohibited Medications

To be eligible for the study, subjects must agree to discontinue use of certain medications for the indicated timeframe prior to randomization. These medications will remain prohibited throughout the conduct of the study. Any subject who resumes or requires the use of any of these medications before the EOSI/II efficacy visit will be discontinued from the study.

- Pharmacologic vitamin D metabolites or analogs (e.g. calcitriol, doxercalciferol, alfacalcidiol, and paricalcitol) (14 day washout required)
- Oral phosphate (7 day washout required)
- Adjunctive growth hormone (3 month washout required)
- Aluminum hydroxide antacids (e.g. Maalox® and Mylanta®) or thiazide (7 day washout period), thiazide (7 day washout required)
- Bisphosphonate therapy
- Chronic use of systemic corticosteroids (short courses acceptable if indicated)
- PTH suppressors (e.g. Sensipar®, cinacalcet, calcimimetics)
- Any mAb therapy (other than study drug)

NOTE: Oral phosphate treatment must be down-titrated slowly to avoid hypercalciuria. Vitamin D metabolites or analogs may be discontinued without titration.

7.4.5.2 Permitted Medications

Other than the medications specifically prohibited in this protocol, subjects may receive concomitant medications as required. If serum 25-hydroxyvitamin D (25(OH)D) levels fall below 20 ng/mL, oral supplementation may be provided. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening visit will be reviewed and recorded.

7.4.6 Treatment Compliance

Trained personnel will administer study drug by SC injection at the investigational site or during HH visits as indicated in the Schedule of Events (Table 2.2, Table 2.3, Table 2.4, Table 2.5, and Table 2.6). During the Treatment Period and the Treatment Extension Period I, at the discretion of the investigator and after proper training by study personnel in SC injection technique, a subject's parent or non-healthcare provider caregiver may administer KRN23 to the subject under the supervision of a HH nurse where local regulations permit and where logistically feasible. Parents or caregivers will be instructed to follow the directions provided in the Instructions for Use. Confirmation of dosing will be communicated

to the study site during scheduled biweekly telephone calls. Site personnel will record the related information about each administration of study drug on the CRF.

During Treatment Extension Period II, study drug will be administered Q2 at home by a parent or other non-healthcare provider caregiver between site visits. The parents or caregivers of subjects in the US who have not been previously trained on study drug administration will be trained beginning at the Week 156 site visit. The parent/caregiver will administer the study drug to the subject under the supervision of a healthcare provider at that visit. The parent/caregiver will subsequently administer study drug to the subject under the supervision of a healthcare provider at the Week 158 HH visit and at the Week 160 site visit. Thereafter, study drug will be administered by a parent or caregiver at home, except for study weeks that correspond to a site visit when parent/caregiver administration is optional.
The parent or caregiver must have demonstrated competency in administration of SC injections before unsupervised home administration will be permitted. For subjects whose parent/caregiver prefers not to administer study drug, study drug may be administered at the study site. Parents or caregivers will be instructed to follow the directions provided in the Instructions for Use. The study site will schedule a telephone call with the subject's parent/caregiver every two weeks on the designated day to confirm drug administration has occurred and the confirmation will be recorded on the CRF. If a subject does not receive a dose within 10 days of a scheduled dose for the Q2 regimen, that dose should be skipped and the next dose will be administered at the next scheduled Q2 dosing day. Empty vials will be returned to the study site as directed by study personnel for drug accountability records.

7.5 Study Procedures and Assessments

7.5.1 Schedule of Events

The schedule of visits and assessments are provided in Table 2.2, Table 2.3, Table 2.4, Table 2.5, and Table 2.6. HH visits may also be conducted at the investigational site depending on the preference of the subject and proximity of the subject to the clinic. Refer to the Study Reference Manual for additional details and a recommended schedule of specific assessments.

Potential subjects will come in to the site for an initial screening visit and provide informed consent. All pre-expansion subjects will have x-rays obtained and read locally at Screening Visit 1 to determine if the subject meets the eligibility criteria. If radiographic evidence of active bone disease is not present, the subject will be considered a screen failure.
For expansion subjects, knee x-rays collected at Screening Visit 1 will be read centrally for the determination of eligibility. Patients with radiographic evidence of active bone disease and expansion subjects with confirmed rickets severity eligibility by central read who also have a confirmed *PHEX* mutation (or a confirmed *PHEX* mutation in an appropriate directly related family member) can start the process of weaning from SOC therapy (Section 7.4.5.1) and return to the site within 2-4 weeks for Screening Visit 2 and the Baseline visit.
Total FGF23 levels in serum will be determined for those subjects who do not have *PHEX* mutation confirmation (self or appropriate family member) available at study entry.

Patients who have radiographic evidence of bone disease, but do NOT have a confirmed *PHEX* mutation or an appropriate family member with a confirmed *PHEX* mutation (referred to as "sporadic" XLH cases) will wait until the FGF23 results are available to confirm the diagnosis of XLH before starting the process of weaning from SOC therapy. "Sporadic" patients with FGF23 levels < 30 pg/mL will also be considered a screen failure.

Subjects who successfully pass the initial screening requirements will return to the site for Screening Visit 2 following discontinuation of SOC therapy: a minimum of 14 days after vitamin D metabolite treatment has been stopped and a minimum of 7 days after oral phosphate treatment has been stopped. Screening Visit 2 should be conducted 14 – 35 days following Screening Visit 1. The remaining screening assessments to confirm eligibility will be performed; Screening Visit 2 and Baseline visits can be conducted on consecutive days pending the availability of biochemical laboratory results, but may be conducted no more than 7 days apart. Motor function tests (6MWT, BOT-2, HHD) and questionnaires (POSNA-PODCI, SF-10) may be completed at either Screening Visit 2 or the Baseline visit, but must be assessed on the same day. At Screening/Baseline, renal ultrasound, ECHO, ECG, and x-rays and may be performed ± 3 days of the clinic visit to accommodate scheduling availability. XtremeCT may be performed any time between Screening Visit 1 and the Baseline visit and performed ± 10 days of the Week 64 or Early Termination visit if it occurs between Week 40 and Week 64; however, all Screening/Baseline assessments and inclusion/exclusion criteria based on local lab results must be satisfied prior to randomization and dosing.

Through Week 158, subjects may be monitored between site visits through a series of HH visits depending on the preference of the subject and the proximity of the subject to the site. The visit window for HH visits is ± 3 days during the Titration Period and Treatment Period and ± 5 days during the Treatment Extension Period. During the Titration Period of the study (Weeks 0 – 16), subjects will return to the clinic for visits at 2 week intervals (± 3 days and no fewer than 8 days apart for the Q2 dose group and no fewer than 12 days apart for the Q4 dose group). During Weeks 16 – 40 of the Treatment Period, clinic visits will occur at 4-week intervals (± 3 days). During Weeks 40-64, clinic visits will occur at approximately 8-week intervals (± 3 days). During the Treatment Extension Period I (Weeks 64 up to Week160), clinic visits will occur at approximately 24-week intervals (±5 days).

During Treatment Extension Period II, clinic visits will occur at approximately 12-week intervals (±5 days). Study sites will schedule biweekly telephone calls with the subject's parent/caregiver to confirm administration of study drug, and for collection of adverse events and concomitant medication information.

For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination visit procedures within 4 weeks of discontinuation. X-rays and ECHO will not be performed at the Early Termination visit if post-treatment test(s) have been performed within 3 months of Early Termination. Similarly, the 6MWT, BOT-2, and HHD will not be performed at the Early Termination visit if post-treatment test(s) have been performed within 3 months of Early Termination or if Early Termination

occurs after Week 64. XtremeCT will only be performed at ET visits occurring between Week 40 and Week 64 (inclusive). The Week 40, Week 64, Week 88, Week 112, Week 136, Week 160/EOS I and, if applicable, EOS II, and Early Termination visits (if applicable) may be conducted over a period of 2 days due to the volume of testing; required blood draws may be split across the 2 days.

A safety follow-up telephone call will occur at 5 weeks (+ 5 days) after the EOS (I or II) efficacy visit for a subject who has not continued KRN23 therapy under commercial use or another mechanism to collect information on any ongoing or new AEs, SAEs, or concomitant medications. An additional safety visit will occur 10 weeks ±1 week (approximately 5 times the elimination half-life) after the after the EOS (I or II) efficacy visit for a subject who has not continued KRN23 therapy under commercial use or another mechanism. Subjects who are unable to return to the clinic for the final safety visit will be given the option of having a final safety telephone call for the collection of any new or ongoing AEs, SAEs or concomitant medications.

7.5.2 Pharmacodynamic Measures

KRN23 binds to and inhibits FGF23. As a phosphaturic hormone, FGF23 plays an important role as a specific regulator of serum phosphorus levels. Serum phosphorus is designated as the primary biomarker of KRN23 efficacy in this study.

To assess the spectrum of KRN23 biological activity on phosphate homeostasis and markers of bone health, and optimize dose level and regimen, a panel of PD markers (Table 7.5.2.1) will be assessed as indicated in the Schedule of Events (Table 2.2, Table 2.3, Table 2.4, and Table 2.5 and Table 2.6).

Table 7.5.2.1: Pharmacodynamic Measures

Serum PD Markers*	Urine PD Markers*	Phosphate Reabsorption	Bone Biomarkers†
Phosphorus	Phosphorus (24 hr)	TmP/GFR	P1NP
$1,25(OH)_2D$		TRP	CTx
			BALP
			ALP

* Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable) per dosing regimen
†Only ALP will be measured during the Treatment Extension Period.

The local lab at the investigational site will be used to assess PD parameters required for study eligibility (except FGF23). Where possible, PD parameters (serum phosphorus and ALP) will be assessed as part of the standard clinical laboratory tests for safety (Section 7.5.5.8).

Two-hour fasting urine collection is required to assess phosphate reabsorption (TmP/GFR and TRP) based on simultaneous urine and blood creatinine and phosphorus concentrations, and is applicable in both fasting and non-fasting children (Alon et al. 1994). The duration of fasting time for all PD parameters will be recorded on the CRF.

Refer to the Study Reference Manual for additional details on PD parameters.

7.5.3 Clinical Efficacy Measures

Clinical efficacy measures will evaluate the effect of KRN23 on bone health and functional outcome in children with XLH. Measures of growth, healing of rickets in the wrists and knees, and correction of skeletal deformity in the legs (including tibial/femoral bowing) will provide an overall assessment of KRN23 treatment on bone health. Assessments of walking ability, muscle strength, gross motor function, and self-reported pain and disability will provide insight into the effect of KRN23 on clinical outcomes. XtremeCT of the forearm and tibia will be performed as an exploratory efficacy measure of bone mineral density/content at select sites.

Refer to the Study Reference Manual for additional details on clinical efficacy measures.

7.5.3.1 Efficacy – Bone Health

The primary goals of treatment in children with XLH are to correct or improve rickets/osteomalacia, radiographic abnormalities, and skeletal deformities (Carpenter et al. 2011). Important endpoints to establish therapeutic efficacy of KRN23 include the evaluation of growth as measured by changes in height and limb length, and radiographic evaluation of the severity of rickets and lower limb deformities. Beginning at Week 64 and during Treatment Extension Periods I and II, radiographs will be evaluated for epiphyseal closure.

Growth: Short stature is one of the predominant features in growing children with XLH. Growth of the legs and trunk has been shown to be uncoupled in XLH and related to serum phosphate levels (Zivicnjak et al. 2011). Growth will be measured by changes in standing height (and percentiles) prior to and following treatment. Standing height measurements prior to treatment will be abstracted from medical records where available. At Screening Visit 1, standing height will be measured to confirm study eligibility. To assess growth during KRN23 treatment, standing height, sitting height, arm length, and leg length will be measured by a physical therapist at Baseline and Week 16, 24, 40, 56, 64 88, 112, 136, and 160/EOS I; and, if applicable, every 12 weeks during Treatment Extension Period II, and at the EOS II (or Early Termination) visit.

Severity of Rickets and Epiphyseal Abnormalities: XLH causes rickets in the wrists and/or knees and other bone abnormalities. Bilateral anteroposterior (AP) knee radiographs will be taken at Screening Visit 1, and the Weeks 40, 64, 88, 160/EOS I, and, if applicable, at the EOS II study visits (or Early Termination if post-baseline radiographs have not been obtained within 3 months of termination). Bilateral posteroanterior (PA) hand/wrist radiographs will be taken at Screening Visit 1, and the Weeks 40, 64, 88, 160/EOS I, and, if

applicable, at the EOS II (or Early Termination) visits if post-baseline radiographs have not been obtained within 3 months of termination. For pre-expansion subjects, radiographs will be interpreted at the investigational site to determine eligibility; for expansion subjects, knee radiographs will read centrally for eligibility determination. The Screening Visit 1 radiographs will also be treated as baseline data. Changes in the severity of rickets and epiphyseal (growth plate) abnormalities will be assessed by central readings using two methods.

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 and cupping and the proportion of the growth plate affected (Thacher et al. 2000). With the RSS method, each radiograph is scored individually by a central rater who is blinded to subject number and radiograph sequence. As an additional blinding measure, and to provide context to the treatment data, at the Week 40 and Week 64 evaluation, the central rater will also score wrist and knee radiographs from a historical reference group consisting of children with a confirmed diagnosis of XLH with similar clinical characteristics to the cohort enrolled in this study.

As a complementary analysis to the RSS rating, a disease-specific qualitative Radiograph Global Impression of Change (RGI-C) scoring system will be used. Pairs of wrist, knee and standing long leg images from treated subjects will be presented to a rater with the Screening image on the left and the later image (Week 40, 64, 88, 160/EOS I, and, if applicable, EOS II (or Early Termination)) on the right. Raters will be asked to assess change in rickets severity in the wrists and knees and extent of bowing in the legs using a 7-point ordinal RGI-C scale score ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets). Ratings will be performed by 3 independent pediatric radiologists who are blinded to subject number. Radiographs from KRN23-treated subjects may also be compared with radiographs from a historical reference group in a blinded fashion at the Week 40 and Week 64 analyses depending on the availability of data from a comparable group of subjects. The historical reference group would consist of radiographs of the wrists, knees and legs of children between the ages of 5 and 12 years with a confirmed diagnosis of XLH and similar clinical characteristics to the subject population enrolled in this study. To keep the radiologists blinded to group (i.e., KRN23 treatment or historical reference group), X-ray pairs will be presented for review in random order and the radiologists will not be provided access to the protocol, patient identifiers, or information related to KRN23 or SOC treatment.

Lower Extremity Deformity: Clinical manifestations of XLH vary in severity, but patients most commonly present in childhood with genu varum or genu valgus deformities of the legs from prolonged weight bearing on softened bones. Progressive bowing, knock knees, and antero-medial rotational torsion of tibiae are the predominant skeletal features of XLH in growing children (Carpenter et al. 2011). To assess lower extremity deformity and/or trabeculation, as well as other disease-specific lower extremity abnormalities, standing long leg x-rays will be taken at Screening Visit 1, Week 64, 88, 160/EOS I, and, if applicable EOS II (or Early Termination) if post-baseline x-rays have not been obtained within 12 months.

Radiographs will be interpreted at the investigational site to determine eligibility; the Screening Visit 1 radiographs will also be treated as baseline data. Central readings of the standing long leg X-rays will be performed and ratings assigned using a disease-specific qualitative RGI-C scoring system. To further assess the severity of genu varum (bowing of the legs) and genu valgum (knock knees), the intercondylar distance (distance between the knees) and intermalleolar distance (distance between the ankles) will be obtained at Screening Visit 1, and Weeks 40, 64, 88, 160/EOS I, and, if applicable, EOS II, (or Early Termination) study visits. Beginning at Week 88 the measurement of intercondylar and intermalleolar distance will be performed using the standing long leg radiographs. The measurement will be made at EOS II (or early termination) only if standing long-leg x-rays have not been obtained within 12 months.

Bone Mineral Density or Content: XtremeCT (SCANCO Medical AG) is designed to perform high-resolution peripheral quantitative computed tomography studies for direct comparisons of density and structure characteristics over time. As an exploratory efficacy measure, XtremeCT of the forearm and tibia will be performed to assess bone mineral density or content at the cortical and trabecular compartment. XtremeCT will be performed at Baseline (Week 0) and Week 64 (or Early Termination if the ET visit is performed between Week 40 and Week 64). XtremeCT will be performed at select sites depending on scheduling and the availability of equipment. XtremeCT administration procedures will be standardized and results will be read locally by trained site personnel.

7.5.3.2 Efficacy – Clinical Outcomes:

Gross motor impairment, including diminished walking ability, pain and muscle weakness are potential complications associated with XLH-related skeletal deformities. Endpoints to establish clinical outcomes associated with KRN23 treatment include walking ability, gross motor function and muscle strength. Functional disability, pain, and health-related quality of life will also be assessed using validated questionnaires.

Walking Ability: The Six Minute Walk Test (6MWT) will be administered at Screening Visit 1 (for practice), Baseline (Week 0), Weeks 16, 24, 40, 64, 88, 160/EOS I, and EOS II visit (if applicable) (or Early Termination). The 6MWT will not be performed at the EOS (or Early Termination) visit if post-baseline 6MWT has been obtained within 3 months of the visit. The 6MWT will be administered by a trained clinician in accordance with general principles set forth in the American Thoracic Society guidelines (ATS 2002). Subjects will be instructed to walk the length of a pre-measured course for six consecutive minutes. The total distance walked at the end of six minutes will be recorded in meters. The percent of predicted normal values will be calculated using published normative data based on age, gender, and height (Geiger et al. 2007).

Gross Motor Function: The Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition (BOT-2) is a standardized, norm-referenced test of fine and gross motor skills in individuals 4-21 years of age (Bruininks et al. 2005). Only the subtests for running speed/agility and strength will be administered. The BOT-2 will be assessed at Screening Visit 1 (for practice), Baseline (Week 0), Weeks 16, 24, 40, and 64 (or Early Termination if post-baseline BOT-2 has not been obtained within 3 months of termination and Early Termination occurs at or before Week 64). The BOT-2 will not be performed during Treatment Extension Periods I or II.

Muscle Strength: Hand-held dynamometry (HHD) will be used to assess muscle strength. HHD testing will be administered at Screening Visit 1 (for practice), Baseline (Week 0), Weeks 16, 24, 40, and 64 (or Early Termination if post-baseline HHD has not been obtained within 3 months of termination and Early Termination occurs at or before Week 64). HHD testing will not be performed during Treatment Extension Periods I or II. Formal training will be conducted with the trained clinicians administering the HHD testing to standardize technique and minimize variability. The maximum voluntary isometric contraction (MVIC) against a dynamometer will be used to measure bilateral strength in the following muscle groups: knee flexors, knee extensors, hip flexors, hip extensors and hip abductors, as well as gross grip strength.

Functional Disability and Pain: The Pediatric Outcomes Data Collection Instrument (PODCI) was developed by the Pediatric Orthopedic Society of North America (POSNA) (Daltroy et al. 1998) will be used to assess functional disability. The POSNA-PODCI was developed to measure the functional health of pediatric and adolescent patients with a variety of musculoskeletal disorders. The instrument is designed to assess overall health, pain, and ability to participate in normal daily activities, as well as in more vigorous activities associated with young people. The questionnaire will be completed by the subject's caregiver. If possible, the same individual caregiver should complete the assessment throughout the study for consistency. The POSNA-PODCI will be administered at Baseline (Week 0), Weeks 24, 40, 64, 88, and 160/EOS I; and, if applicable, every 12 weeks during Treatment Extension Period II, and at the EOS II (or Early Termination) visit.

Health-Related Quality of Life: Individuals with XLH are affected by skeletal abnormalities which may impact their physical and mental health status. The SF-10 for Children Health Survey (SF-10) is a caregiver-completed questionnaire designed to assess physical and psychosocial health-related quality of life in healthy and ill children (Saris-Baglama et al. 2006). The 10 items were adapted from the Child Health Questionnaire and utilize a 4-week recall period. Responses are used to generate 2 component summary scores: physical summary score (PHS-10) and psychosocial summary score (PSS-10). Higher global scores are associated with better quality of life. The SF-10 will be administered during the Baseline visit (Week 0), Weeks 24, 40, 64, 88, and 160/EOS I; and, if applicable, every 12 weeks during Treatment Extension Period II and at the EOS II (or Early Termination) visit. Every attempt should be made to ensure that the responder completing the first administration completes subsequent administrations to minimize variability.

7.5.4 Drug Concentration Measurements

To assess KRN23 concentration and possible accumulation, serum pre-dose levels will be evaluated as a PK parameter in this study. A pre-dose blood sample will be obtained at Baseline (Week 0), during the Titration Phase (Weeks 1, 2, 4, 12, 14, and 16), during the stable dose Treatment Period (Weeks 24, 36, 38, 40, 56, and 64), during the Treatment Extension Period at Weeks 88, 112, 136, and 160/EOS I, and, if applicable, at the EOS II visit. At Week 1, the serum KRN23 sample will only be taken for subjects enrolled in Cohorts 2 and 3. Week 24 pre-dose serum KRN23 concentration will be retrospectively tested on subjects' previously collected samples, if available. For each sample collection, the time elapsed since last study drug administration will be recorded on the CRF.

7.5.5 Safety Measures & General Assessments

General assessments include Tanner staging for breast and testicular development, medical history and demographics, and *PHEX* mutation analysis. If the initial result for *PHEX* mutation analysis is negative or inconclusive (i.e., No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic), and informed consent is provided, additional genetic testing will be performed to assess mutations in other genes associated with phenotypes overlapping with XLH. This testing will include, but not necessarily be limited to, genes for Autosomal Dominant Hypophosphatemic Rickets (*FGF23*), Autosomal Recessive Hypophosphatemic Rickets (*DMP1, ENPP1*), X-Linked Recessive Hypophosphatemic Rickets (*CLCN5*), and Hereditary Hypophosphatemic Rickets with Hypercalciuria (*SLC34A3*). The investigator will be provided the genetic testing results and will determine when and whether the information should be shared with the subject.

Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from baseline to scheduled time points in vital signs, weight, interval history and physical examination, GFR, clinical laboratory evaluations (including additional KRN23/XLH biochemical parameters of interest), concomitant medications, and ECG. Ectopic mineralization safety assessments include renal ultrasound and ECHO; serum calcium, phosphorus and iPTH, and urinary calcium and creatinine. The development of anti-KRN23 antibodies and dose limiting toxicities (DLTs) will also be assessed. Refer to the Study Reference Manual for additional details on safety assessments.

7.5.5.1 Medical History

General medical information includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, and surgeries. The review will also include an assessment of symptoms and conditions associated with XLH and SOC treatment.

Subjects must be willing to provide access to prior medical records for the collection of historical growth, biochemical and radiographic data, as well as disease history. The specific diagnosis of XLH will be recorded, along with date of onset, clinical presentation, and date and method of diagnosis. Any available family history of XLH will be noted.

XLH treatment history and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Treatments may include calcitriol and oral phosphate, and growth hormone or other adjunctive therapy. Medications include investigational, prescription, over-the-counter, herbal and nutritional supplements. Any relevant concomitant therapy, including physical/occupational therapy will be recorded.

7.5.5.2 Interval History

Each interval history is intended to record any signs, symptoms, or events experienced by the subject that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including clinical manifestations of XLH) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments. Interval history may identify under-reported AEs, and will be collected at the study visits indicated in the Schedule of Events (Table 2.2, Table 2.3, Table 2.4, Table 2.5, and Table 2.6).

7.5.5.3 Vital Signs and Weight

Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital signs measurements will be performed before any additional assessments are completed and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed. All vital sign measurements will be performed at every site visit (except Screening Visit 2, and including Early Termination or the Safety Follow Up visit, if applicable) and at HH visits through Week 62. At HH visits between Weeks 66-160, vital signs will be measured every 4 weeks, beginning at Week 68. During Treatment Extension Period II (if applicable), vital signs will be measured at site visits only.

A cohort of subjects who had elevated post-baseline BP measurement ($\geq 95^{th}$ percentile for height, age, and sex) on 3 or more site visits were asked to do home monitoring of blood pressure for a period of time. The measurements will be conducted by a subject's parents or guardians in between study visits. An automated blood pressure recording device was issued to parents or guardians with instructions to measure their child's blood pressure twice per day, three days per week for one month; record the date, time, and value of the measurements, and return the record to the site at the next study visit.

At each site visit (except Screening Visit 2 and the Safety Follow Up visit, if applicable), weight (in kilograms) will be obtained using a scale. Weight measurements will be used to calculate the appropriate KRN23 dose to be administered on a mg/kg basis. Weight will not be collected at HH visits.

7.5.5.4 Physical Examination

Complete physical examinations will be performed at both Screening visits and the Week 4, 8, 14, 20, 32, 40, 46, 56, 64, 88, 112, 136, and 160/EOS I visits; and, if applicable, every 12 weeks during Treatment Extension Period II, at the EOS II (or Early Termination) visit, and at the Safety Follow Up visit. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

7.5.5.5 Renal Ultrasound and Glomerular Filtration Rate

Renal ultrasounds will be conducted at Screening Visit 1 and Weeks 16, 40, 64, 88, 112, 136, 160/EOS I, and, if applicable, at the EOS II (or Early Termination) visit. Ultrasonographic findings of nephrocalcinosis will be graded on a 5-point scale (Verge et al. 1991).
The ultrasound will be interpreted by qualified personnel at the investigational site for purposes of inclusion criteria. Results obtained at Screening Visit 1 will serve as baseline data. However, central readings will be performed for all post-treatment renal ultrasounds to evaluate changes in calcifications and all other renal abnormalities from baseline (i.e. screening assessment).

The glomerular filtration rate (GFR) will be calculated at Baseline, Weeks 16, 40, 64, 88, 112, 136, and 160/EOS I; and, if applicable, every 24 weeks during Treatment Extension Period II; and at the EOS II (or Early Termination) visit. GFR will be calculated by using the Bedside Schwartz equation (Schwartz et al. 2009).

7.5.5.6 Echocardiogram

ECHO will be performed at Baseline and Weeks 16, 40, 64, 88, 112, 136, 160/EOS I, and, if applicable, at the EOS II (or Early Termination) visit if not performed within 3 months of termination. The goal is twofold: 1) assess for evidence of ectopic mineralization in the heart and aorta, and 2) evaluate for signs of LVH or cardiac dysfunction. Additional tests may be performed if any abnormalities are detected or if medically indicated. ECHO administration procedures will be standardized and results will be read centrally by trained personnel who are blinded to the dose and dose regimen of the subjects.

7.5.5.7 Electrocardiogram

A standardized 12-lead ECG will measure PR, QRS, QT, and QTc at Baseline, Weeks 16, 40, 64, 88, 112, 136, 160/EOS I, and, if applicable, at the EOS II (or Early Termination) visit. The goal is to evaluate both for LVH changes, as well as for changes in conductivity and intervals. ECG administration procedures will be standardized and results will be read centrally by qualified personnel at an imaging facility. The ECG results will be assessed for any clinically significant abnormality or relevant changes from baseline.

7.5.5.8 Clinical Laboratory Tests for Safety

A comprehensive serum metabolic panel (Chem-20), complete blood count, and urinalysis will be used as routine screens to assess KRN23 safety. Certain analytes (i.e. ALP and serum phosphorus) in the routine Chem-20 panel are also designated as PD/efficacy parameters in this study (Section 7.5.2). KRN23/XLH biochemical parameters of interest include serum 25(OH)D, amylase, lipase, total calcium, creatinine, FGF23 (total and unbound), iPTH; and urinary calcium and creatinine. Reflexive testing for amylase isoenzymes will be performed if serum amylase levels are elevated by ≥1.5 times the upper limit of the reference range (ULRR).

FGF23 concentrations will be measured using a validated electrochemiluminescent assay (ECLA) developed by the Sponsor's development partner, KHK, and transferred to a contract laboratory.

Blood and urine samples will be collected at screening, baseline, and regular intervals throughout the study as indicated in the Schedule of Events (Table 2.2, Table 2.3, Table 2.4 and Table 2.5, and Table 2.6). The local lab at the investigational site will be used to assess safety parameters required for study eligibility (except FGF23). Fasting for a minimum of 4 hours (overnight) is required prior to each blood draw; the duration of fasting will be recorded on the CRF. Twenty-four hour urine collection is required to assess urinary phosphorus:creatinine and calcium:creatinine ratios; urinary phosphorus (a PD parameter, Section 7.5.2) will also be obtained from 24-hour urine samples.

Clinical laboratory parameters to be assessed for safety are provided in Table 7.5.5.8.1. See Study Reference Manual for details on sample collection and processing.

Table 7.5.5.8.1: Clinical Laboratory Assessments for Safety

Chemistry	Hematology	Urinalysis
25(OH) D	Hematocrit	Appearance
Alanine aminotransferase (ALT)	Hemoglobin	Color
Alkaline phosphatase (ALP)*	Platelet count	pH
Amylase	Red blood cell (RBC) count	Specific gravity
Amylase isoenzymes†	White blood cell (WBC) count	Ketones
Aspartate aminotransferase (AST)	Mean corpuscular volume (MCV)	Protein
Bilirubin (direct and total)	Mean corpuscular hemoglobin (MCH)	Glucose
Blood urea nitrogen (BUN)	MCH concentration	
Calcium (total)		**24-hour Urine**
Chloride		Calcium
Carbon dioxide (CO_2)		Calcium/creatinine ratio
Cholesterol (total)		Creatinine
Creatinine		Phosphorus/creatinine ratio
Gamma-glutamyl transpeptidase (GGT)		Phosphorus
Glucose		
FGF23 (total and unbound)		
Intact parathyroid hormone (iPTH)		**2-hour Urine**
Lactate deyhydrogenase (LDH)		Calcium
Lipase		Phosphorus
Phosphorus*		Creatinine
Potassium		Pregnancy Test (if applicable)
Protein (albumin and total)		
Sodium		
Uric acid		

* Also designated as PD/efficacy parameter
† Will be assessed reflexively if amylase levels are ≥1.5 ULRR

Subjects who experience a SAE possibly or probably related to study drug or other AE of concern may, at the discretion of the Investigator (and/or medical monitor), have additional blood samples taken for safety laboratory tests.

7.5.5.9 Anti-KRN23 Antibody Screening

To determine the immunogenicity profile of KRN23 in children with XLH, blood samples will be obtained for analysis of anti-KRN23 antibodies (ADA) at the Baseline (Week 0), Week 16, 24, 36, 56, 64, 88, 112, 136, 160/EOS I, and, if applicable, EOS II (or Early Termination) visits. The concentration of anti-KRN23 antibodies in human serum will be determined using a validated sandwich ELISA and a 2-tiered strategy: screening assay and specificity confirmation assay. If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points on a case-by-case basis, if warranted.

7.5.5.10 Pregnancy Testing

Female subjects who have reached menarche prior to or during the study will have urine pregnancy tests at screening, baseline, and approximately every 4 to 6 weeks thereafter. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result. Female subjects with a positive serum pregnancy test at Screening will not be enrolled in the study. Female subjects with a positive serum pregnancy test at Baseline or any subsequent visit will be discontinued from the study. Females who have not experienced menarche will not undergo pregnancy testing. During Treatment Extension Period II, female subjects who have reached menarche will perform a urine pregnancy test at clinic visits every 12 weeks.

Experience with KRN23 in pregnant women is limited. The study drug may involve risks to a pregnant female or unborn baby which are currently unknown. Female participants of child-bearing potential must consent to use a highly effective method of contraception as listed below from the period following the signing of the informed consent through 12 weeks after stopping the study drug. Sexually active male participants with female partners of childbearing potential must consent to use a condom with spermicide or one of the highly effective methods of contraception listed below from the period following the signing of informed consent through 12 weeks after stopping the study drug.

Highly effective methods of contraception (CTFG 2014) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (e.g. oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (e.g. oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Male sterilization, also called vasectomy
- Sexual abstinence (i.e., refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, when this is in line with the preferred and usual lifestyle of the subject)

7.5.5.11 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. Female subjects who, at any time during the study, have a positive serum pregnancy test will be discontinued from the study. The investigator must make every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee. In the event of a pregnancy in the partner of a subject, the investigator should make every effort to obtain the female partner's consent for release of protected health information.

Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy.

7.5.5.12 Concomitant Medications/Therapies

Concomitant medications and therapies will be reviewed and recorded in the subject's CRF at each study visit to the investigational site, beginning at the initial Screening visit and continuing through the final safety follow up visit. Concomitant medications and therapies will also be assessed during HH visits during Weeks 18-158. Between study site visits during Treatment Extension Period II (Week 162 to End of Study), concomitant medications and therapies will be reviewed by telephone call from the study site every 2 weeks and recorded in the subject's CRF. Concomitant medications and therapies will also be collected during the safety follow-up telephone call (as defined in Section 7.5.1) and recorded on the subject's CRF. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded. Therapies (physical therapy, occupational therapy as well as mobility and walking devices, including AFOs, braces, cane, crutches, walker, wheelchair etc.) utilized during the 30 days prior to Screening will also be reviewed and recorded. At each subsequent visit or biweekly telephone call, change in medications and therapies since the previous visit will be recorded. A discussion of concomitant medications and therapies is provided in Section 7.4.5.

7.5.5.13 Dose Limiting Toxicity

A DLT is defined as the occurrence of any of the following:

- Unexpected SAEs occurring during treatment considered to be either definitely, probably, or possibly related to the investigational product
- A confirmed serum phosphorus level of ≥ 6.5 mg/dL (defined as hyperphosphatemia) at any time after dosing

If a subject experiences a DLT, the planned dosing for that subject will be evaluated by the Investigator and Medical Monitor. The outcome of this investigation will determine the subjects' continuation or withdrawal from the study.

7.5.5.14 Adverse Events

All AEs will be recorded from the time the subject signs the informed consent through the final safety follow-up telephone call or safety visit (as defined in Section 7.5.1).
The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit, subjects will be asked about any new or ongoing AEs since the previous visit. Assessments of AEs will occur at each visit to the investigational site, at HH visits during Weeks 18-158, and during biweekly telephone calls during Treatment Extension Period II.

Clinically significant changes from baseline in physical examination findings, vital signs, clinical laboratory parameters, renal ultrasounds, GFR, ECHO and ECGs will be recorded as AEs or SAEs, if appropriate.

7.5.6 Appropriateness of Measures

The assessments and timing of assessments used in this study, and the variables analyzed, are typical of those used to evaluate hypophosphatemia, renal reabsorption, vitamin D metabolism, and skeletal defects in subjects with XLH. The primary goals of treatment in pediatric XLH patients are to improve growth and correct or minimize rickets/osteomalacia, radiographic abnormalities, and skeletal deformities (Carpenter et al. 2011). KRN23 binds to and inhibits FGF23; total and unbound FGF23 levels will be monitored throughout the study. FGF23 plays an important role in phosphate homeostasis, as such, serum phosphorus levels will be the primary PD marker of KRN23 efficacy in this study.

Additional assessments are included both as PD and safety indicators of potential secondary complications associated with treatment, including serum calcium, $1,25(OH)_2D$ and urinary calcium and creatinine, as hypercalciuria may occur in the absence of hypercalcemia. Intact PTH (iPTH) levels and TmP/GFR are routinely measured as a part of SOC in XLH, as secondary hyperparathyroidism is common. Biomarkers of bone formation (P1NP, ALP, BALP) and resorption (CTx) may provide an indication of treatment effect. The relatively extensive panel of biomarkers has been included in this Phase 2 study to provide the most information on relevant clinical laboratory parameters for endpoint confirmation and analysis. Where possible, timing of assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing.

Radiographs are routinely recommended during the initial evaluation of XLH, and to evaluate healing of rickets and skeletal deformities. Performance measures such as the 6MWT and BOT-2 have been successfully used in other clinical development programs. Additional age-appropriate, patient-reported outcomes were included to assess functional disability, pain, and health-related quality of life (i.e. POSNA-PODCI and SF-10).

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, serum chemistry, concomitant medications, and other routine clinical and laboratory procedures. Routine, non-invasive procedures will provide relevant indicators of possible renal and cardiac risk; renal ultrasounds and ECHO will be used to detect any calcinosis in susceptible organs. Since elevated free FGF23 has been associated with LVH in patients with chronic kidney disease, ECHO and ECGs will examine the potential risk in XLH subjects.

The study will be conducted in a pediatric population, as such additional safety measures including HH visits and a DMC have been incorporated into the study design. Where possible, measures to minimize pain and distress to the subject have been considered for this study protocol. However, a series of frequent blood draws are required during the Titration

Period to ensure subject safety and determine appropriate KRN23 dosing. These assessments are imperative for safety since KRN23 has not previously been tested in children, and the PK of the Q2 regimen has not been established. Should a subject complete all assessments at all study visits, the maximum blood volume obtained throughout the 226-week maximum total study duration is estimated to be approximately 350 mL. Any unscheduled blood draws would be in addition to this volume.

7.6 Statistical Methods and Determination of Sample Size

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, spurious, or unused data, and the detailed method for analyses will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

7.6.1 Determination of Sample Size

A sample size of at least 10 per cohort will provide at least 90% power to detect a serum phosphorus increase from baseline of at least 0.8 mg/dL, assuming a standard deviation of 0.7 mg/dL or smaller, at the 2-sided level of significance of 0.05. In addition, a total sample size of 50 subjects (25 subjects per monthly [Q4] or Q2 week regimen) will provide at least 90% power to detect a 0.5 mg/dL difference between the two dosing regimens assuming a standard deviation of 0.4 and 2-sided level of significance of 0.05.

Phosphate and mineral control are adequately powered based on the clinical experience to date with KRN23. The degree of powering for bone health will depend on the degree of effect expected which is not known. However, powering for adequate phosphate control should provide the potential for improved bone health based on prior experience with oral phosphate replacement therapy (Carpenter et al. 2011).

In addition, for the RSS endpoint, the expected sample size of 50 subjects will provide at least 90% power of rejecting the hypothesis of no change from baseline in knee total score when the true mean change is 0.5 with a standard deviation of 0.5, at the two-sided 0.05 level of significance.

7.6.2 Analysis Populations

7.6.2.1 Efficacy Analysis Set

The Intent to Treat (ITT) population will consist of all subjects who receive at least one dose of study therapy and have at least one pre- and post- study drug measurement.

7.6.2.2 Safety Analysis Set

The safety analysis set will consist of all subjects who receive at least one dose of study therapy.

7.6.2.3 Pharmacokinetic and Pharmacodynamic Analysis Set

The analyses sets will consist of all subjects who receive at least one dose of therapy and have evaluable plasma data.

7.6.3 Principles

Descriptive statistics will be used to summarize the data. For continuous variables, the mean, the standard error, median, minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Statistical tests will use 2-sided alpha =0.05 significance level. Two-sided 95% confidence intervals will also be presented.

7.6.3.1 Subject Accountability

The number of subjects who received study treatment will be summarized. The reason for study treatment discontinuation and study discontinuation will be summarized as well.

7.6.3.2 Demographic and Baseline Characteristics

Demographics (age, gender, and race) and other baseline disease characteristics will be summarized using descriptive statistics for the Safety Analysis Set.

7.6.3.3 Baseline

For parameters/assessments scheduled to be performed on the same day as the first study treatment, the baseline value is the last value measured before the first administration of study treatment on that day. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of study treatment, the baseline value is the value from the screening period measured closest to the day of first administration of study treatment.

7.6.3.4 Dose and Dose Regimen Evaluation

At the end of the Titration Period, the population of 50 subjects will consist of essentially two groups of 25 subjects, each with individually optimized dosing of KRN23 at either a Q4 week or Q2 week frequency. Analyses of safety and available PD and efficacy data are planned at the end of the Titration Period (Week 16) and at Week 24 for pre-expansion subjects. Further analyses in the pre-expansion group alone and for the overall population are planned at Week 40 and at Week 64 at the end of the Treatment Period to compare treatment outcomes to baseline (pre-dose). Analyses of long-term efficacy and safety will be conducted during and at the completion of the Treatment Extension Period (Weeks 64-160).

Details on planned analysis of dose and dose regimen will be provided in the SAP.

7.6.3.5 Pharmacodynamic Parameters

PD parameters will be summarized at baseline and at each time point. Additionally, the maximum and minimum observed post-baseline values will be summarized along with the change from baseline to the maximum observed value, minimum observed value, and last observed value.

7.6.3.6 Clinical Efficacy Endpoints

Efficacy parameters will be summarized at baseline and at each observed time that are collected. The following endpoints will be examined:

- Healing of rickets as measured by bilateral PA hand/wrist and AP knee radiographs scored with the 10-point RSS. RSS total score (max = 10 points) as well as scores for the knees (max = 6 points) and wrists (max = 4 points) will be determined. Subgroup analyses will be conducted based on baseline rickets severity, including a subgroup analysis of subjects with an RSS score of $\geq$1.5 points at the knee.
- Healing of rickets in the wrists and knees as measured by an XLH-specific RGI-C scale.
- Correction of lower limb bowing and deformities as measured by standing long leg radiographs scored with an XLH-specific RGI-C scale and measures of intercondylar and intermalleolar distance
- Increased growth as measured by the change in standing height, sitting height, arm length, and leg length and changes in standing height growth percentiles post-treatment as compared to the pre-treatment period (using historical growth data for standing height where available)
- Improved mineralization and increased cortical thickness in the forearm and lower leg as measured by XtremeCT evaluation of the forearm and tibia (where evaluable)
- Improved walking ability as measured by change in the distance walked on the 6MWT in meters and percent predicted normal values and change in EEI
- Improved gross motor function as measured by change in BOT-2 running speed/agility and strength subtest scores (raw, scaled, and normative scores)
- Increased muscle strength as measured by changes in raw and % predicted normal scores for bilateral gross grip, knee flexors/extensors, hip flexors/extensors and hip abductors assessed by HHD
- Reduction in functional disability and pain as measure by changes in POSNA global and subscale scores
- Improved health-related quality of life as measured by changes in the SF-10 PHS-10 score

7.6.4 Pharmacodynamic and Efficacy Analyses

7.6.4.1 Week 16 Analysis

PD and safety data will be summarized for each cohort and each dose regimen within a cohort after pre-expansion subjects have completed the Titration Period (Week 16).

7.6.4.2 Week 24 Analysis

An analysis will be conducted to review the PK/PD, dose response, differences in the PD response between the two dose regimens (Q2 and Q4)) and to evaluate initial efficacy and overall safety. Data will be summarized for each cohort and each dose regimen within a cohort after pre-expansion subjects have completed the Week 24.

7.6.4.3 Week 40 Analysis

An analysis will be performed when all pre-expansion subjects have completed the Week 40 visit. The analysis will be repeated for the entire study population when expansion subjects have completed the Week 40 visit. All efficacy analyses will be performed on the Efficacy Analysis Set. All PD analyses will be performed on the PD Analysis Set.

For each cohort and each dosing regimen, all the PD and efficacy parameters will be analyzed using the data collected during the Treatment Period. These will be the primary analyses. Any changes from baseline will utilize the values at Week 0, the values prior to treatment with study drug. The treatment comparison will be performed using the Wilcoxon rank-sum on appropriate endpoints.

ANCOVA models of change from baseline (Week 0) to Week 40 endpoints will be used to estimate the treatment effect and will include dosing regimen and baseline measurement as covariate. The ANCOVA will present least squares (LS) mean estimates, 2-sided 95% confidence intervals for mean changes and p-values between dosing regimen comparisons. The effect of other covariates such as age and gender will also be examined.

Generalized Estimation Equations (GEE) Model will be used to fit observed measurements at all scheduled visits. The model will include the dosing regimen and baseline as covariates. To model the covariance structure within subjects, the exchangeable covariance matrix will be selected initially. If the exchangeable covariance structure leads to non-convergence, Quasi-Likelihood Information Criterion (QIC) will be used to select the best covariance structure.

The association between efficacy and PD endpoints will be performed using the change from baseline of the PD parameters at Week 40 as covariate in the ANCOVA or repeated measure models. In addition, the Pearson correlation will be calculated.

7.6.4.4 Week 64 Analysis

Similar analyses will be performed for the Week 64 data as described in Section 7.6.4.3.

7.6.4.5 Treatment Extension Period Analyses

Additional analyses to evaluate long-term efficacy will be performed at the completion of Treatment Extension Period I for the overall population as described in Section 7.6.4.2. Some assessments will not be continued beyond the Treatment Period of the study and therefore will not be analyzed in the either of the Treatment Extension Periods.

A final analysis will be performed at the end of the study. Some assessments will not be continued beyond the Treatment Period or Treatment Extension Period I of the study and therefore will not be analyzed in Treatment Extension Period II.

7.6.5 Pharmacokinetic Analyses

Summary statistics will be generated for pre-dose PK parameters for each cohort and dose regimen.

7.6.6 Safety Analyses

Analysis of safety data will be conducted at Weeks 16, 24, 40, 64, at the completion of the Treatment Extension Period I, and at the end of the study. Additional safety analyses may be conducted as needed. Safety of each cohort and each dose regimen within a cohort will be assessed. Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from baseline to scheduled time points in vital signs and weight, interval history and physical examinations, renal ultrasound, GFR, ECHO, and ECG findings; chemistry, hematology, and urinalysis; and anti-KRN23 antibody testing. Safety data will be periodically reviewed by the DMC through the end of the Treatment Period (Week 64). During Treatment Extension Periods I and II, safety data will be reviewed by the SSRT on an ongoing basis (Section 8.5.5.1).

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class, Preferred Term (PT), relationship to study drug, and severity. All reported AEs with onset during the treatment (i.e. treatment-emergent AEs) will be included in the analysis. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. The numbers (frequency) and incidence rates of AEs and SAEs will be summarized during exposure to KRN23 throughout the study including the continuation period. Special attention will be given to those subjects who died, discontinued treatment due to an AE, or experienced a SAE (e.g. summaries, listings, and narrative preparation may be provided, as appropriate).

Clinical laboratory data will be summarized by the type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of

laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any markedly abnormal laboratory results will be provided. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

The SAP will provide additional details on the planned safety analyses.

7.6.7 Data Monitoring Committee

An independent DMC that includes members with expertise in metabolic bone disease and the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis through the end of the Treatment Period (Week 64). The DMC will also meet for approximately quarterly data reviews. During Treatment Extension Periods I and II, safety data will be reviewed by the SSRT on an ongoing basis (Section 8.5.5.1).

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee

The IRB/Ethics Committee (EC) must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, and the associated informed consent forms (ICFs) must be submitted to the IRB/EC for review and must be approved before screening of any subject into the study. Study drug may not be shipped to the investigator until Ultragenyx or its designee has received a copy of the letter or certificate of approval from the IRB/EC for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/EC and Ultragenyx or its designee for review and approval prior to implementation. IRB/EC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/EC should be notified immediately and the amendment forwarded to the IRB/EC for review and approval.

8.1.2 Ethical Conduct of Study

This protocol is written in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The sponsor and investigator will make every effort to assure the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the sponsor and investigator will follow whichever law or guideline affords the greater protection to the individual subject. 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 this protocol and the IB, prior to the initiation of the study.

8.1.3 Subject Information and Consent

Appropriate forms for documenting written informed consent will be provided by the investigator and reviewed and approved by Ultragenyx or its designee before submission to the IRB/EC. Ultragenyx or its designee must receive a copy of the IRB/EC's approval of the ICF before the shipment of study drug to the study site.

It is the investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent 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 that the subject is completely free to refuse to enter the study or to withdraw

from it at any time. Subjects under the age of 18 years (or 16 years, depending on the region) will provide written assent (if possible), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

Receipt of written informed consent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

8.2 Investigators and Study Administrative Structure

Each investigator must provide Ultragenyx and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-investigators listed on Form FDA 1572.

Ultragenyx and/or its designee will be responsible for managing and monitoring the clinical trial to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's trained designated representative (the monitor) will conduct regular visits to the clinical site, to perform source document verification. The monitor will verify the investigator's ongoing qualifications, inspect clinical site facilities, and inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

A Coordinating Investigator will be identified for multicenter trials. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data.
The Coordinating Investigator will read and sign the Clinical Study Report.

8.3 Investigational Product Accountability

While at the clinical site, study drug must be stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging.
The storage facility must be available for inspection by the study monitor at any time during the study. In the home setting, study drug should be handled as directed by study personnel.

A drug accountability record must be maintained for all study drug received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. During Treatment Extension Period II, subject caregivers will retain empty vials and return them to the study site as directed by study personnel for drug accountability. Following the close-out of the study, all unused study drug must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the study drug.

8.4 Data Handling and Record Keeping

8.4.1 Case Report Forms and Source Documents

The investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated electronic data capture (EDC) system will be used for entry of the data into electronic CRFs. Data must be recorded on CRFs approved by Ultragenyx or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by Ultragenyx-authorized users, and data entries and changes will be captured in an electronic audit trail.
An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee.
The investigator must allow direct access to all source documents.

8.4.2 Data Quality Assurance

Monitoring and auditing procedures developed by Ultragenyx and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's designated representative (the monitor) will contact the investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents including progress notes, laboratory test reports and other subject records. Instances of missing or uninterruptable data will be resolved in coordination with the investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by

e-mail, telephone, facsimile, and/or mail. The investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least two years after the last approval of a marketing application or for at least two years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

All study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 25 years. Ultragenyx must be notified and will assist with retention should the Investigator/institution be unable to continue maintenance of subject files for the full 25 years. All study records must be stored in a secure and safe facility.

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the investigator or Ultragenyx, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the current Investigators Brochure’s Reference Safety Information (RSI) or is not listed at the specificity or severity that has been observed.

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the investigator or Ultragenyx, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Note that hospitalizations planned prior to study enrollment (e.g. for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the NCI CTCAE.
The majority of AEs can be graded using this system.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions.

- Mild (Grade 1): Awareness of signs or symptoms, but easily tolerated and of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate (Grade 2): Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe (Grade 3): Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
- Life-threatening (Grade 4): Events that place the participant at immediate risk of death or are disabling.
- Death (Grade 5): Events that result in death.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

The investigator will assess the potential relationship of the AE to study drug using the following descriptions.

Categories of attributions for "Not Related" events:

- ***Definitely Not Related:*** This category applies to an AE that ***is clearly not related*** to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exposure to study drug and/or a causal relationship is considered biologically implausible.
- ***Probably Not Related:*** This category applied to an AE that ***is doubtfully related*** to the investigational agent/procedure. That is, an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), known consequences of the disease under investigation or the relationship in time suggest that a causal relationship is unlikely.

Categories of attributions for "Related" events:

- ***Possibly Related:*** This category applies to an AE that ***may be related*** to the investigational agent/procedure. That is the AE follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
- ***Probably Related:*** This category applies to an AE that ***is likely related*** to the investigational agent/procedure. That is, the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, and is strongly associated with study drug exposure. An alternative explanation is less likely, e.g., concomitant drugs(s), concomitant medication(s).
- ***Definitely Related:*** This category applies to an AE that ***is clearly related*** to the investigational agent/procedure. That is, the AE is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s), known consequences of the disease under investigation

or the relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Definitely Not or Probably Not Related will be considered Unrelated.

8.5.4 Adverse Event Reporting to Ultragenyx

8.5.4.1 General

All AEs (i.e. any new or worsening in severity or frequency of a preexisting condition) with onset after the subject signs consent for study participation must be promptly documented on the AE eCRF via the EDC system. The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is adequate. Details of the AE must include severity, relationship to study drug, duration, and outcome.

All AEs will be collected from the time the subject signs informed consent through the final safety follow-up telephone call or safety visit (as defined in Section 7.5.1). In addition, the Investigator should report any AE that occurs after this time period that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing at the final safety follow-up telephone call or safety visit (as defined in Section 7.5.1) should have a comment in the source document by the Investigator that the event has recovered, recovered with sequelae, or stabilized.

8.5.4.2 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

Ultragenyx or its designee must be notified of the occurrence of any SAE that occurs during the reporting period within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. SAEs will be reported by completing and submitting SAE report forms to Ultragenyx or designee.

Follow-up SAE information must be submitted in a timely manner as additional information becomes available. All SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected.

All deaths, regardless of causality, occurring from signing of the informed consent until the final safety follow-up telephone call or safety visit (as defined in Section 7.5.1) are to be reported as SAEs to Ultragenyx or its designee within 24 hours of knowledge.

8.5.4.3 Pregnancy Reports

Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is

known. Pregnancy associated SAEs will be processed and submitted, as necessary, as per the suspected unexpected serious adverse reaction (SUSAR) reporting process indicated in Section 8.5.5.2.

8.5.5 Communication Plan

8.5.5.1 Review of Safety Data

The Ultragenyx SSRT, Medical Monitor and investigator(s) will actively review safety data during the course of the study. The SSRT and Medical Monitor will review safety data and a meeting will be convened after the first four (4) subjects in the first cohort have been treated for four (4) weeks. This safety data review will be completed prior to a decision to initiate enrollment of the second cohort. As an added precautionary measure, the IWRS will be placed on hold to ensure that subjects cannot be enrolled into cohort 2. The Ultragenyx Medical Monitor will authorize in writing when enrollment to the second cohort may start. Subsequent safety data review by the SSRT will occur approximately quarterly or more frequently, as needed. Safety data for review will, at a minimum, include listings of all SAEs, treatment-emergent AEs, grade 2 or greater laboratory values, deaths, and AEs leading to study discontinuation.

To facilitate prompt risk mitigation activities, the SSRT will immediately evaluate:

- Any observations that may materially influence the risk-benefit analysis of KRN23
- Any significant safety issues that have been identified from safety analysis of cohort and/or cumulative data
- Any actions taken by any country's Regulatory Authority due to safety issues

Potential safety signals identified during the SSRT reviews or any other process during the conduct of the study will be escalated to the appropriate internal Ultragenyx safety governing bodies. Any action indicated by Ultragenyx safety governing bodies will be communicated accordingly to all stakeholders, e.g. Regulatory Authorities, Ethics Committees, and Investigators.

An independent DMC will act in an advisory capacity to monitor subject safety on a routine basis through the end of the Treatment Period (Week 64). The DMC may meet on an approximately quarterly basis, or as needed, to review aggregate safety data and provide advice regarding the safety of subjects and the continuing scientific validity of the study. The DMC may also be asked to review SUSARs that represent changes in the nature or an increase in the frequency of events and may provide recommendations regarding continued subject participation.

8.5.5.2 Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit SUSARs to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), Ethics Committees, and

investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight (8) days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

Principal Investigators are required to report any urgent safety matters to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the Regulatory Authorities, Ethics Committees, and Investigators of any events (e.g. change to the safety profile of KRN23, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the ICF through the final safety follow-up telephone call or safety visit (as defined in Section 7.5.1).

The Investigator will notify the IRBs/Research Ethics Boards (REB)/ECs of SAEs and urgent safety matters, in accordance with IRB/REB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

Non-SUSARs will be maintained in the Ultragenyx safety database and provided in annual and/or periodic reports as per local laws and regulations. Ultragenyx or its designee will prepare and submit annual safety reports and/or other aggregate periodic summary reports to Regulatory Authorities and Ethics Committees, as per local laws and regulations.

8.5.6 Urgent Safety Measures

The regulations governing clinical studies state that the sponsor and investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee (EC) is notified at the same time." The reporting period for urgent safety measures is the period from the signing of the ICF through the final safety follow-up telephone call or safety visit (as defined in Section 7.5.1). Investigators are required to report any urgent safety measures to Ultragenyx within 24 hours.

8.5.7 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: PPD e-mail: PPD	PPD Telephone: PPD Mobile: PPD e-mail: PPD

8.6 Financing and Insurance

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with the study site.

8.7 Publication Policy

Any publication or presentation by the investigator and/or the Institution based on data or results resulting from the Ultragenyx study shall only be done in strict accordance with the Publication section in the Clinical Trial Agreement executed between Ultragenyx and the Institution and/or the investigator.

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10 SIGNATURE PAGE

Protocol Title: A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)

Protocol Number: UX023-CL201 Amendment 7

I have read Protocol UX023-CL201. I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Investigator Signature Date

Printed Name: _____

Accepted for the Sponsor:

As the Sponsor representative, I confirm that Ultragenyx will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure the investigator is informed of all relevant information that becomes available during the conduct of this study.

PPD

PPD

Date

Javier San Martin, MD
Vice President, Clinical Sciences
Ultragenyx Pharmaceutical Inc.