A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH)

Protocol Number: UX023-CL301
Original Protocol: 04 April 2016
Amendment 1 (Global): 03 November 2017

Investigational Product:	KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])
Indication:	X-linked Hypophosphatemia (XLH)
IND Number:	76,488
EudraCT Number:	2016-000600-29
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Sponsor's Responsible Medical Officer:	Javier San Martin, MD VP, Clinical Sciences Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA USA 94949 PPD
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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

UX023-CL301 Amendment 1 (Global)

03 November 2017

The original version of Protocol UX023-CL301 (dated 04 April 2016) has been modified by Amendment 1 (Global) to extend the duration of the study, to clarify procedures, and to incorporate changes based on additional information acquired since the beginning of the study from the clinical investigators and from Health Authorities. The major changes to the protocol are summarized below; additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Overall Study Design and Plan

a. Treatment Periods and Treatment Duration: A Treatment Extension Period was added to the study for subjects in Europe, the US, Canada, and Australia (Section 7.1). All subjects who continue into the Treatment Extension Period will receive KRN23 (refer to Summary of Change Item #1b). The total treatment duration will vary by region. For subjects at study sites in Japan and Korea, the final visit for the study (ie, the end of the Treatment Period) will be Week 64 (final dose of KRN23 at Week 62); subjects in these countries will be enrolled into a separate clinical trial of KRN23 or will receive KRN23 through another mechanism. For subjects in Europe, the US, Canada, and Australia, the study consists of the Treatment Period (64 weeks) and the Treatment Extension Period (up to 76 weeks) for a total treatment duration of up to 140 weeks.
For subjects in Europe and Australia, the Treatment Extension Period will end in September 2018; subjects will be enrolled into separate clinical trials of KRN23 or will receive KRN23 through another mechanism. For subjects in the US and Canada, the Treatment Extension Period will end in September 2018 and June 2019, respectively, when commercial KRN23 is expected to be available; subjects will receive commercial KRN23 or will receive KRN23 through another mechanism. The total duration of treatment in this study for subjects in Europe, the US, Canada, and Australia will vary based on the subjects' initial date of enrollment but will not exceed 140 weeks.

Rationale: It is important to prevent treatment interruption in children with XLH to maximize their bone health and growth potential. The 76-week Treatment Extension Period has been added to provide KRN23 treatment until KRN23 is expected to be commercially available in regions of the clinical sites participating in the study.

b. Treatment in Treatment Extension Period (subjects in Europe, the US, Canada, and Australia only). After completion of the 64-week Treatment Period, subjects who were randomized to KRN23 will continue treatment with KRN23, and subjects randomized to active control will cross over to receive open-label KRN23 at the starting dose and regimen administered to subjects in the KRN23 arm. Subjects in the active control arm will discontinue treatment the day after the Week 64 visit to allow washout of oral phosphate and active vitamin D treatments before their first dose of KRN23 at Week 66 (Synopsis [Study Design and Methodology, Duration of Treatment], Section 7.6 and subsections)

   Rationale: This change implements the extension of treatment as noted in the original protocol, "Subjects from either treatment groups who complete the active controlled Treatment Period of the study (64 weeks) may be eligible for an extension study and receive KRN23 treatment for up to an additional 96 weeks or until the study drug is commercially available."

c. Procedures: Evaluation of PD parameters, rickets, growth, and safety will continue in the Treatment Extension period. The description of the timing of the planned analyses has been clarified, and additional analyses time points have been added for the Treatment Extension Period at Weeks 88, Week 112, and end of study (Synopsis [Study Design and Methodology, Duration of Treatment], Section 7.6 and subsections). All AEs will be recorded from the time the informed consent is signed through 12 weeks following the last dose of study drug, unless the subject enrolls in another clinical study of KRN23, is treated with commercially available KRN23, or is treated with KRN23 through another mechanism, at which point the collection of AEs within this study is no longer applicable (however, AEs will continue to be reported either under another KRN23 protocol or per post-approval requirements for safety monitoring, as applicable).

   Rationale: Describes planned evaluations of the safety and efficacy parameters that will continue to be followed while subjects remain on study and receive treatment.

d. End of Study: In Section 7.1 and related sections, the description of the study periods has been updated to describe the end of study procedures for different regions. For subjects in Japan and Korea, the End of Study (EOS) Visit is Week 64 (referred to as "Week 64/EOS I"). Subjects in Europe, the US, Canada, and Australia will have an EOS visit that includes efficacy assessments (EOS II). (refer to Summary of Change Item #1e). (Synopsis [Study Design and Methodology], Section 7.4.4, and Section 7.5.1).

   Rationale: These changes clarify the end of study procedures for different regions.

e. Safety follow-up: All subjects are expected to continue KRN23 treatment post-study in another clinical trial, through commercial use, or through another mechanism; post-study safety follow-up calls and safety visits will occur only for subjects who are not documented to be continuing on KRN23 at the EOS visits. A safety follow-up telephone call will occur at 5 weeks (+5 days) after the Week 64/EOS I or EOS II visit, as applicable, to determine if KRN23 therapy has been started in another clinical trial, as commercial product, or through another mechanism; if KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue KRN23 therapy, an additional safety visit will occur 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit. The end of the study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study (Synopsis [Study Design and Methodology], Section 7.4.4, and Section 7.5.1).

   Rationale: These changes clarify the post-study procedures.

f. Clarified that "at least" (rather than "approximately") 20 subjects age 1 to < 5 years will be included (Synopsis [Study Design and Methodology], Section 7.1 and Section 7.3).

   Rationale: Clarifies the intent of the protocol to have at least 20 subjects enrolled who are age 1 to < 5 years.

g. The maximum proportion of female subjects was increased from 60% to 70% (Synopsis [Study Design and Methodology], Section 7.1, and Section 7.3).

   Rationale: The proportion of female subjects allowed into the study was increased to better reflect the gender distribution of X-linked dominant disease and study experience.

h. Specified that the terms "study drug" and "investigational product" refer to KRN23, and "active control" and "active control arm" refer to oral phosphate/active vitamin D therapy (Section 4, Definition of Terms).

   Rationale: Clarification of nomenclature.

i. Added a substudy to assess pre- and post-prandial serum phosphorus and calcium concentrations. Assessments for this substudy will occur at a single clinic visit anytime 10 to 14 days after a KRN23 dose; this clinic visit may take the place of a Home Health visit. Approximately 20 subjects, age ≥ 3 years, will fast overnight for a minimum of 8 hours, and fasting serum will be collected prior to a breakfast of a standardized meal. Dietary phosphate will be estimated based on the calculated phosphate content and the amount of food consumed. Serum samples will be drawn 1 and 2 hours after the completion of the meal. (Synopsis [Study Design and Methodology, Exploratory Assessments], Table 2.1 - Table 2.3 [footnote #12], Section 7.1, Section 7.5.3.8, new Section 7.5.4.3)

Rationale: KRN23 blocks FGF23 action, leading to a sustained increase in serum phosphorus levels due to increased phosphate reabsorption at the distal renal tubule (measured as TmP/GFR) and increased intestinal absorption caused by increased $1,25(OH)_2D$. The effect of burosumab on postprandial physiological excursions of serum phosphorus has not been studied. The substudy was added to evaluate the post-prandial increases in serum phosphorus during KRN23 treatment.

2. Selection of Study Population

a. Inclusion Criterion #4 was revised to "Serum creatinine below age-adjusted upper normal limit" (Synopsis [Diagnosis and Criteria for Inclusion and Exclusion], Section 7.3.1).

Rationale: The criterion was revised to align with the original intent that subjects with serum creatinine values higher than the age-adjusted upper limit of normal should not be included in the study. Low serum creatinine is not a concern and should not be a consideration for eligibility.

b. Inclusion Criterion #6 was revised to indicate that conventional therapy should be discontinued "…7 days prior to the Randomization Visit" rather than "…prior to the Screening Visit" (Synopsis [Diagnosis and Criteria for Inclusion and Exclusion], Section 7.3.1).

Rationale: The change in the window will give subjects more time to meet this requirement. It is clinically immaterial whether subjects meet the requirement prior to the Screening visit or prior to Randomization Visit.

c. Inclusion Criterion #10 was updated to require sexually active male subjects with female partners of childbearing potential to use a condom with spermicide or a highly effective method of contraception (rather than 2 methods) for the duration of the study plus 12 weeks after stopping the study drug.

Rationale: Changes to contraception and pregnancy testing language were made to align with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials.

d. Exclusion Criterion #1 was revised to specify that Tanner stage 4 or higher is assessed through physical examination in any of the following: genitals, breast, or pubic hair (Synopsis [Diagnosis and Criteria for Inclusion and Exclusion], Section 7.3.2).

Rationale: Added to specify physical exam requirements.

e. Exclusion Criterion #7 was corrected to "Planned orthopedic surgery, including osteotomy or implantation or removal of staples, 8-plates, or any other hardware, within the first 40 weeks of the study" (Synopsis [Diagnosis and Criteria for Inclusion and Exclusion], Section 7.3.2).

Rationale: The language was corrected to match the language in the Synopsis. "Recommended" terminology was removed to provide greater specificity for the criteria. Also the timeframe of the surgery prior to Screening was clarified to match the Synopsis.

3. Schedule of Events (Tables 2.1-2.3)

a. Added Table 2.3, Schedule of Events – Treatment Extension Period Weeks 66-140

Rationale: To define assessments for the 76-week Treatment Extension Period

b. Additional assessments at clinic visits at Weeks 52, 76, 88, 100, 112, 124, and 140 have been added to Urine Pregnancy Test for females administered KRN23 who have reached menarche.

Rationale: The additional assessments were added for female subjects of childbearing potential administered KRN23 (ie, those assigned to KRN23 initially and those who cross over to KRN23 in the Treatment Extension Period).

c. Clarified that all study visits will be scheduled relative to the Baseline visit, with an allowable variance of ±3 days for each visit (with the exception of the Screening and Safety Follow-up Visits) to accommodate scheduling; clarified that KRN23 dosing should occur no sooner than 8 days after the last dose administered, and that the Safety Follow-up Visit visit has an allowable variance of ±7 days (Table 2.1 - Table 2.3 [footnote #1], Section 7.4.1, and Section 7.5.1).

Rationale: Provides clarity to facilitate subject scheduling.

d. Changed "within 7 days" to "after 7 days" to describe the time frame when subjects may return to the site after weaning from oral phosphate/ active vitamin D therapy (Section 7.5.1).

Rationale: For consistency with Section 7.4.5.1 and the intent of the protocol

4. Study Drug

a. Specified that subjects may resume KRN23 at half of the last dose received (ie, half the dose of either 0.8 or 1.2 mg/kg) following withdrawal from KRN23 due to increased serum phosphorus levels above the upper limit of normal (ULN), with a maximum dose of 40 mg (Synopsis [Study Design and Methodology; Investigational Product(s), Dose and Mode of Administration], Section 7.1 and Section 7.4.1). The maximum allowable dose of KRN23 was defined as 90 mg per administration. Additional language has been added to define the term "unscheduled serum phosphorus assessment."

Rationale: The language on KRN23 dose, including the maximum dose requirements and definition of an unscheduled serum phosphorus assessment, provides greater specificity and clarity consistent with the original intent of the protocol.

b. Changed criterion 2 for dose escalation, from "serum phosphorus has increased by < 0.5 mg/dL from baseline" to "serum phosphorus has increased by ≤ 0.5 mg/dL from baseline" (Synopsis [Study Design and Methodology; Investigational Product(s), Dose and Mode of Administration], Section 7.1 and Section 7.4.1).

Rationale: Based on investigator input and clinical experience thus far in the study, some subjects with low serum phosphorus at Baseline who have met the other dose escalation criteria and who have responded to KRN23 (increase in serum phosphorus of 0.5 mg/dL) would likely benefit from a higher dose of KRN23.

c. Buttocks are included as a potential injection site for the administration of KRN23, and guidance provided to clarify the rotation of injection sites (Synopsis [Investigational Product(s), Dose and Mode of Administration], Section 7.4.1).

Rationale: Buttocks were added to the list of potential injection sites to allow for flexibility in administration. In addition, the text regarding injection site rotation was clarified to provide guidance the rotation of the site with each injection. While the Sponsor's preference is to rotate the site of injection to minimize the risk for an injection site reaction, this is not always possible in practice in a pediatric population based on subject fat distribution and subject preference. The injection location should be rotated at each visit.

5. Prohibited Medications

    a. Clarified that active vitamin D, not vitamin D supplementation, is prohibited in the KRN23 treatment arm (Section 7.4.5.1).

    Rationale: The original protocol stated that subjects in the KRN23 treatment arm were prohibited from receiving oral phosphates and vitamin D for the duration of the study. This has been corrected to oral phosphates and active vitamin D because vitamin D supplementation is allowed during the study to correct for clinically meaningful low nutritional vitamin D laboratory values.

6. Efficacy Assessments

    a. Provided additional information regarding the collection of historical radiograph images and recumbent length/standing height data prior to Screening (Section 7.5.1).

    Rationale: Provides greater specificity to the data collection process. The radiographs will be used to evaluate rickets severity and to determine how much rickets fluctuate over time in patients who were treated with oral phosphate/active vitamin D prior to study enrollment. The recumbent length/standing height data will be used to evaluate growth over time in patients who were treated with oral phosphate/active vitamin D prior to study enrollment.

    b. A new section, Change in Lower Extremity Abnormalities, has been added to describe how this endpoint will be evaluated (Section 7.5.2.2.2).

    Rationale: To provide details on how changes in lower extremity abnormalities will be measured over time.

    c. Provided greater clarity about how growth will be assessed (Section 7.5.2.2.3). At each time point, height will be assessed 3 times; an average of the 3 measurements will be calculated. For subjects < 2 years old, recumbent length will be used as the growth measurement. For subjects ≥ 2 years old, standing and sitting heights will be collected for growth measurement. (Table 2.1 - Table 2.3 [footnote #5], Section 7.5.2.2.3).

    Rationale: To describe how height will be measured.

    d. The method used to calculate the ratio of the maximum renal tubular reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) was updated to Payne, 1998 (Section 7.5.2.2.4).

    Rationale: The protocol was updated to include the appropriate reference.

e. Version 2.0 of the PROMIS instrument will be used (rather that Version 1.0) (Section 7.5.2.2.5).

Rationale: To reflect the study use of the updated version of PROMIS (Version 2.0).

f. Clarified the process for a subject ≥ 8 years old at Screening who has difficulty completing the PROMIS self-report (Section 7.5.2.2.5).

Rationale: To allow completion of the PROMIS Parent Proxy while maintaining consistent practice in cases where a child 8 to ≤ 12 years old may not be able to perform the PROMIS self-report.

7. PK and ADA Assessments

a. Specified that subjects randomized to receive active control during the study will not have a blood sample drawn for these assessments (Section 7.5.2.2.6 and Section 7.5.3.8.2).

Rationale: PK and ADA assessments are relevant to subjects in the KRN23 treatment arm and are not necessary for subjects in the active control arm during the Treatment Period.

8. Safety Assessments

a. Clarified the acceptable method for measuring blood pressure and updated the literature reference (Tables 2.1-2.3 [footnote #14] and Section 7.5.3.2).

Rationale: The National Heart, Lung, and Blood Institute (NHBLI) guidelines specifically recommend auscultation as the preferred method for measuring blood pressure and have reported that automated devices do not always closely match with those obtained by auscultation.

b. Specified that the genitourinary exam should be non-invasive, age-appropriate, and consistent with the investigator's standard of care, and that the purpose of the exam is establish and monitor Tanner staging (Section 7.5.3.5).

Rationale: To clarify the scope and purpose of the genitourinary exam.

c. Added the definition of a highly effective contraceptive method (Section 7.5.3.9).

Rationale: Changes to contraception and pregnancy testing language were made to align with the CTFG recommendations related to contraception and pregnancy testing in clinical trials.

d. Clarified "dental events" as "dental caries, tooth extraction, root canal, dental abscesses, and gingivitis" (Synopsis [Exploratory Assessments], Table 2.1 - Table 2.3 [footnote #19], Section 7.5.4.2).

Rationale: To specify the events to be evaluated for the assessment of dental health.

e. Clarified serious adverse event (SAE) reporting for the active control arm (Section 8.5.5.1) and added Appendix 1, which serves as reference safety information (RSI) for the oral phosphate and active vitamin D products used in the active control arm of this study.

Rationale: The study allows use of different oral phosphate and active vitamin D products that are approved in several European Union (EU) Member States with different Summaries of Product Characteristics (SmPCs). Per CT3 section 7.2.3.2. (54) and CTFG, the sponsor is required to select the most appropriate SmPC, with reference to subject safety, as the RSI. The Sponsor has selected the SmPCs in Appendix 1 to serve as RSI for the active control arm of the study, based on factors including widespread use, consistency of safety information across multiple countries, and marketing authorization holder.

f. Clarified the visits at which subject weight is determined (Table 2.1 - Table 2.3 [footnote #15], Section 7.5.3.4).

Rationale: The instruction is clarified to match the original intent of the protocol to use the most recent in clinic weight as the basis for dose calculation.

g. Section 8.5.5.3, Pregnancy Reporting, was deleted

Rationale: Text was redundant with text in Section 8.5.4.3, Pregnancy in Subject or Partner, and Requirements for Immediate Reporting.

9. Investigators and Study Administrative Structure

a. Included a requirement for a Coordinating Investigator (Section 8.2).
The Coordinating Investigator is Erik Imel, MD (Indiana University School of Medicine).

Rationale: Regulatory guidance in the EU requires designation of a Coordinating Investigator for a multicenter clinical trial.

2 SYNOPSIS

TITLE OF STUDY: A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH)
PROTOCOL NUMBER: UX023-CL301
STUDY SITES: Approximately 30 sites globally
PHASE OF DEVELOPMENT: Phase 3
RATIONALE FOR THIS STUDY: X-linked hypophosphatemia (XLH) is a disorder of renal phosphate wasting, defective bone mineralization, and impaired growth plate or endochondral ossification caused by inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), and is the most common form of heritable rickets. In the absence of functional PHEX, release of fibroblast growth factor 23 (FGF23) by osteocytes is greatly increased, leading to impaired conservation of phosphate and consequent hypophosphatemia. FGF23 also suppresses 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production, resulting in decreased intestinal absorption of calcium and phosphate. Chronic low serum phosphorus levels result in defective bone mineralization and the 2 major pathologic consequences of the hypophosphatemia, rickets and osteomalacia. Rickets and osteomalacia are both disorders of bone mineralization; however, rickets is a disease of the growth plates specifically characterized by deficient mineralization as well as by delayed endochondral ossification, leading to reduced growth and skeletal deformities. The goal of therapy in children with XLH is to correct or minimize rickets, radiographic abnormalities, and skeletal deformities, and to promote maximal growth potential while preventing the lifelong bone- and joint-related complications of rickets. Published retrospective data suggest that earlier treatment leads to better outcomes for children with XLH (Makitie et al. 2003), (Quinlan et al. 2012). Although there are no approved treatments specific for XLH, the most common therapy for children with XLH consists of multiple daily doses of oral phosphate combined with doses of active vitamin D analogs, the most common being calcitriol and alfacalcidol. Dosing is individualized and depends on tolerability of the phosphate dose and the age, size, and growth of the child. The goal of therapy with phosphate and active vitamin D is to sufficiently supplement the body's pool of phosphate to allow mineralization of bone and improve skeletal outcomes; however, because supplementation therapy does not address the mechanism of urinary phosphate wasting, increasing phosphate through supplementation also increases renal phosphate throughput and urinary phosphate concentrations, thus raising the risk of nephrocalcinosis. More therapeutic options that are efficacious, safe, and convenient, and that target the underlying pathophysiology of XLH (ie, renal phosphate wasting induced by high FGF23 levels), are needed.

KRN23 is a recombinant human IgG_1 monoclonal antibody that binds to and inhibits the activity of FGF23. Phase 1 and Phase 2 studies in adults and children (aged 5-12 years) with XLH have shown that KRN23 increases serum phosphorus and $1,25(OH)_2D$ levels and the ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR). Initial 40-week Phase 2 data (UX023-CL201) in children with XLH (aged 5-12 years) suggest that KRN23 treatment also improves rickets severity with a favorable safety profile. The 40-week interim analysis demonstrated that KRN23 significantly improved rickets across the 2 dosing groups, with subjects in the every 2 weeks (Q2W) dosing group having better outcomes that may reflect the more steady levels of serum phosphorus, $1,25(OH)_2D$, and other PD parameters observed with Q2W dosing than with every 4 weeks (Q4W) dosing of KRN23.

Data from the ongoing pediatric Phase 2 study helped establish the dose regimen and provided information for the design of this Phase 3 clinical trial in children with XLH. Interim data from the pediatric Phase 2 study suggested KRN23, administered Q2W at approximately 0.8 mg/kg for 40 weeks, increased serum phosphorus by an average of 0.7 mg/dL; increases of > 0.5 mg/dL were seen in 83.3% of subjects. Serum $1,25(OH)_2D$ concentrations and TmP/GFR levels also increased, demonstrating overall improved phosphorus homeostasis. The increases in serum phosphorus and $1,25(OH)_2D$ were sufficient to provide substantial healing of rickets. No subjects have experienced serum phosphorus levels above the upper limit of normal. The Q2W dosing regimen was chosen for this Phase 3 study because it appeared to produce a more stable and consistent increase in serum phosphorus levels with less fluctuation over time than the Q4W dosing regimen, and a safety profile that was not substantially different from the Q4W dosing regimen.

The objectives of this study are to evaluate the effects of KRN23 on improving rickets, maximizing growth, and restoring phosphorus homeostasis compared with active control (oral phosphate/active vitamin D therapy), as well as to evaluate the safety of KRN23, in children with XLH (aged 1 to ≤ 12 years) with confirmed evidence of rickets. In addition, this study will evaluate whether every 2 week dosing of KRN23 improves functional outcomes and quality of life in children with XLH.

OBJECTIVES:

Primary Objectives:

- Evaluate the effect of KRN23 therapy in improving rickets in children with XLH compared with active control (oral phosphate/active vitamin D)

Secondary Efficacy Objectives:

Evaluate the effects of KRN23 as compared with active control on:

- Growth velocity and lower extremity deformity
- Pharmacodynamic markers that reflect the status of phosphorus homeostasis, including serum $1,25(OH)_2D$, serum and urinary phosphorus, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and tubular reabsorption of phosphate (TRP)
- Biochemical markers of bone turnover that reflect rickets severity (alkaline phosphatase [ALP])
- Walking ability and patient-/parent-reported pain, fatigue, and physical function/mobility

Pharmacokinetic Objective:

Assess the PK of KRN23 throughout the dosing cycle

Safety Objective:

Evaluate the safety and tolerability profile of KRN23 in the treatment of children with XLH (aged 1 to ≤ 12 years), including adverse events (AEs) (eg, nephrocalcinosis), as compared with active control, and immunogenicity profile

Treatment Extension Period Objective:

To evaluate the long-term safety and efficacy of KRN23

STUDY DESIGN AND METHODOLOGY:

UX023-CL301 is a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of KRN23 with active control (oral phosphate/active vitamin D therapy) in children with clinical evidence consistent with XLH (aged 1 to ≤ 12 years), including demonstrated hypophosphatemia, radiographic evidence of rickets (≥ 2.0 points RSS total score), and *PHEX* mutation or variants of uncertain significance. Patients will also be required to have open epiphyses and have received oral phosphate/active vitamin D therapy for ≥ 12 consecutive months (for children ≥ 3 years of age) or ≥ 6 consecutive months (for children < 3 years of age) 7 days prior to the Randomization Visit. Approximately 60 subjects will be randomized 1:1 to receive open-label KRN23 administered by subcutaneous injection or oral phosphate and active vitamin D therapy for a total of 64 weeks in the Treatment Period. Randomization will be stratified by baseline rickets severity (RSS total score ≤ 2.5 vs > 2.5) and age (< 5 vs ≥ 5 years). At least 20 subjects aged 1 to < 5 years will be included (approximately 10 in each treatment arm), and no more than 10 subjects between the ages of 1 to < 3 years will be enrolled. The age range of eligible subjects will be monitored for enrollment for age distribution. No more than 70% female subjects will be enrolled. All subjects will washout of oral phosphate and active vitamin D therapy for 7 days prior to randomization.

Treatment Period (Weeks 0 – 64) – All Subjects

Subjects randomized to KRN23 will remain off of oral phosphate/active vitamin D therapy throughout the duration of the study. Subjects assigned to the KRN23 treatment group will receive KRN23 at a starting dose of 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) 2 consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by ≤ 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of KRN23 that would account for the decrease in serum phosphorus. The maximum allowable dose of KRN23 per administration is 90 mg. At any time during the study, if serum phosphorus increases above the upper limit of normal (ULN) for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received (ie, half of either 0.8 mg/kg or 1.2 mg/kg; maximum dose per administration: 40 mg). Serum phosphorus will be followed through unscheduled serum phosphorus assessments (approximately 2 weeks post-dose and assessed by the central laboratory; the assessments may be repeated as necessary). A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

Subjects assigned to active control will typically receive multiple daily doses of oral phosphate and active vitamin D. Because of the variability in the doses and dosing frequencies of oral phosphates and active vitamin D therapies in clinical practice, these treatments will be individualized for each subject at the investigator's discretion; general guidance is provided based on expert recommendations in the US and Europe. Detailed information about the brand, starting dosages, and any changes in oral phosphate and active vitamin D therapy will be determined by the treating Investigator within the guidelines (provided in Section 7.1 and summarized below) and recorded at every site visit. US guidelines generally recommend a calcitriol dosage of 20 to 30 ng/kg/day in 2 to 3 divided doses and an elemental phosphorus dose of 20 to 40 mg/kg/day (in 3 to 5 divided doses), acknowledging that some children require more, whereas some do well with less (Carpenter et al. 2011). European guidelines recommend an alfacalcidol dosage of 1 to 2 µg/day (once daily) and a phosphate supplemental dose of 45 to 70 mg/kg/day (in 3 to 4 divided doses) (Linglart et al. 2014). Calcitriol and alfacalcidol dosages should be adjusted based on the clinical and laboratory values that guide best possible treatment.

For subjects in Japan and Korea, the Week 64 visit at the end of the Treatment Period will be the End of Study (EOS) Visit ("Week 64/EOS I"); subjects in these countries will be enrolled into a separate clinical trial of KRN23 or will receive KRN23 through another mechanism. Post-study safety follow-up calls and safety visits will occur only for subjects who are not documented to be continuing on KRN23 at the Week 64/EOS I Visit. A safety follow-up telephone call will occur at 5 weeks (+5 days) after the Week 64/EOS I Visit to determine if KRN23 therapy has been started in another clinical trial or through another mechanism; if KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue KRN23 therapy, an additional safety visit will occur 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit.

Treatment Extension Period (Weeks 66 – 140) – Subjects in Europe, the US, Canada, and Australia

After completion of the 64-week Treatment Period, subjects in Europe, the US, Canada, and Australia who were randomized to KRN23 will continue treatment with KRN23 at their previous dose and regimen in the Treatment Extension Period. Subjects in Europe, the US, Canada, and Australia who were randomized to active control will cross over to receive KRN23 at the starting dose and regimen administered to subjects in the KRN23 arm (starting dose of 0.8 mg/kg Q2W; dose may be increased to 1.2 mg/kg Q2W).

Before their first dose of KRN23 at Week 66, subjects who were in the active control arm in the Treatment Period will discontinue treatment the day after the Week 64/EOS I visit to allow washout of oral phosphate and active vitamin D treatments. These subjects must have serum phosphorus < 3.2 mg/dL (< 1.03 mmol/L) (ie, below the lower limit of normal) to continue on study and receive KRN23 in the Treatment Extension Period. If hypophosphatemia is not observed, the subject should be retested for serum phosphorus within a week to ensure that the test result was not due to a technical issue. If hypophosphatemia is still not observed after test and retest, the subject will be discontinued

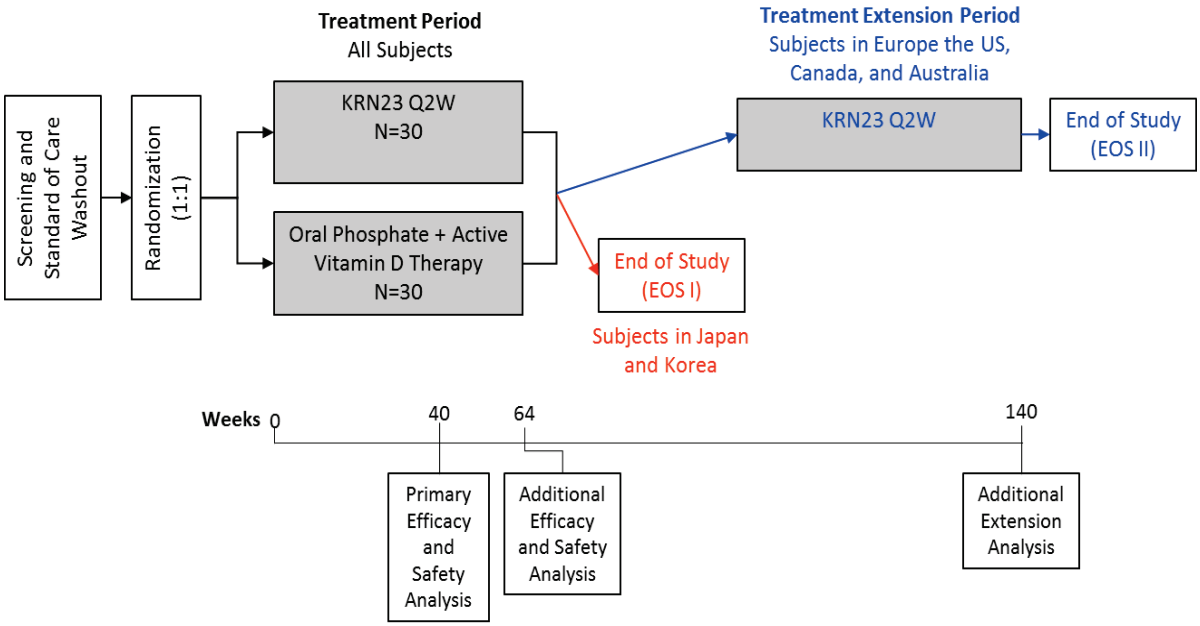
from the study. The assessment of serum phosphorus to document hypophosphatemia before administration of the first dose of KRN23 in subjects originally assigned to active control will be done at the local laboratory so that KRN23 can be administered the same day. A sample will also be drawn for a serum phosphorus assessment at the central laboratory. For subjects crossing over to KRN23 treatment, the Weeks 66 and 68 visits will be in-clinic visits.

For subjects in Europe and Australia, the Treatment Extension Period will end in September 2018, and subjects will be enrolled into separate clinical trials of KRN23 or will receive KRN23 through another mechanism. For subjects in the US and Canada, the Treatment Extension Period will end in September 2018 and June 2019, respectively, when commercial KRN23 is expected to be available; subjects will receive commercial KRN23 or will receive KRN23 through another mechanism. Subjects leaving the study will have an EOS visit that includes efficacy assessments (EOS II). Post-study safety follow-up calls and safety visits will occur only for subjects who are not documented to be continuing on KRN23 at the EOS II Visit. A safety follow-up telephone call will occur at 5 weeks (+5 days) after the EOS II Visit to determine if KRN23 therapy has been started in another clinical trial, as commercial product, or through another mechanism; if KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue KRN23 therapy, an additional safety visit will occur 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit.

The study will be conducted in a pediatric population. Where possible, measures to minimize pain and distress to the subject have been considered for this study protocol including the use of home health visits (KRN23 group only). At every home health visit for subjects in the KRN23 treatment arm, all subjects randomized to the active control arm will receive a phone call to assess adverse events and concomitant medications. Home Health visits are not applicable to subjects in Japan or Korea. Where possible, timing of assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing. The primary analysis will be at Week 40; analyses at Week 64/EOS I and Week 140/EOS II will assess the durability of treatment effect, additional efficacy outcomes, and long term safety. The end of the study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

Figure 2.1 provides a schematic of the overall study design.

Figure 2.1: UX023-CL301 Study Schema



Pre- and post-prandial serum concentrations of phosphorus and calcium will be assessed at a single clinic visit anytime 10 to 14 days after a KRN23 dose; this clinic visit may take the place of a Home Health visit. Approximately 20 subjects, age ≥ 3 years, will fast overnight for a minimum of 8 hours, and fasting serum will be collected prior to a breakfast containing predefined ranges of phosphate, calories, and carbohydrate representative of a typical Western diet for children. Dietary phosphate will be estimated based on the amount of food consumed. Serum samples will be drawn 1 and 2 hours after the completion of the meal.

NUMBER OF SUBJECTS PLANNED:

Approximately 60 pediatric subjects will be enrolled in the study.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

Note: All laboratory evaluations required for study eligibility will be determined centrally

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

1) Male or female, aged 1 to ≤ 12 years with radiographic evidence of rickets with a minimum rickets severity score (RSS) total score of 2 as determined by central read
2) *PHEX* mutation or variant of uncertain significance in either the patient or in a directly related family member with appropriate X-linked inheritance
3) Biochemical findings associated with XLH: Serum phosphorus < 3.0 mg/dL (< 0.97 mmol/L)*

4) Serum creatinine below the age-adjusted upper limit of normal *
5) Serum 25(OH)D above the lower limit of normal (≥16 ng/mL) at the Screening Visit**
6) Have received both oral phosphate and active vitamin D therapy for ≥ 12 consecutive months (for children ≥3 years of age) or ≥ 6 consecutive months (for children <3 years of age) 7 days prior to the Randomization Visit
7) Willing to provide access to prior medical records for the collection of historical growth and radiographic data and disease history.
8) Provide written or verbal assent (as appropriate for the subject and region) 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. Female subjects of childbearing potential must be willing to use a highly effective method of contraception for the duration of the study plus 12 weeks after stopping the study drug. Sexually active male subjects with female partners of childbearing potential must consent to use a condom with spermicide or a highly effective method of contraception for the duration of the study plus 12 weeks after stopping the study drug.

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

1) Tanner stage 4 or higher in any of the following: genitals, breast, or pubic hair, based on physical examination
2) Height percentile > 50th based on country-specific norms
3) Use of aluminum hydroxide antacids (eg, Maalox® and Mylanta®), systemic corticosteroids, acetazolamide, and thiazides within 7 days prior to the Screening Visit
4) Current or prior use of leuprorelin (eg, Lupron®, Viadur®, Eligard®), triptorelin (TRELSTAR®), goserelin (Zoladex®), or other drugs known to delay puberty
5) Use of growth hormone therapy within 12 months before the Screening Visit
6) Presence of nephrocalcinosis on renal ultrasound grade 4 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 orthopedic surgery, including osteotomy or implantation or removal of staples, 8-plates, or any other hardware, within the first 40 weeks of the study
8) Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits*

9) Evidence of hyperparathyroidism (parathyroid hormone [PTH] levels 2.5X upper limit of normal [ULN])

10) Use of medication to suppress PTH (eg, cinacalcet, calcimimetics) within 2 months prior to the Screening Visit

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

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

15) 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

16) 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

OR, in Japan, use of any investigational product or investigational medical device within 4 months 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 the Screening and/or Baseline Visit.

** If 25(OH)D levels are below the normal range, 25(OH)D supplementation will be prescribed. Assuming a subject meets all other eligibility requirements, the subject may be rescreened after a minimum of 7 days of treatment.

INVESTIGATIONAL PRODUCT(S), 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. The starting dose will be 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) 2 consecutive serum phosphorus measurements are below the normal range; 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. The maximum allowable dose of KRN23 per administration is 90 mg. At any time during the study, if serum phosphorus increases above the upper limit of normal (ULN) for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received (ie, half of either 0.8 mg/kg or 1.2 mg/kg; maximum dose per administration: 40 mg). Serum phosphorus will be followed through unscheduled serum phosphorus assessments (approximately 2 weeks post-dose and assessed by the central laboratory; the assessments may be repeated as necessary). A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above. KRN23 will be administered via subcutaneous

(SC) injection to the abdomen, upper arms, thighs, or buttocks; the injection site should be rotated with each injection.

ACTIVE CONTROL, DOSE, AND MODE OF ADMINISTRATION:

The first 64 weeks of the study is designed as an open-label comparison with active control (oral phosphate and active vitamin D therapy). Active control will be administered on an individualized basis at the discretion of the investigator. However, general guidance will be provided based on expert recommendations in the US and Europe (see Section 7.1 for more information). The brand, starting dosages, and any changes in oral phosphate and active vitamin D therapy will be determined and recorded at every site visit. US expert guidelines generally recommend a calcitriol dosage of 20 to 30 ng/kg/day in 2 to 3 divided doses and an elemental phosphorus dose of 20 to 40 mg/kg/day (in 3 to 5 divided doses), acknowledging that some children require more, whereas some do well with less (Carpenter et al. 2011). European expert guidelines recommend an alfacalcidol dosage of 1 to 2 µg/day (once daily) and a phosphate supplemental dose of 45 to 70 mg/kg/day (in 3 to 4 divided doses) (Linglart et al. 2014). Calcitriol and alfacalcidol dosages should be adjusted based on the clinical and laboratory values that guide best possible treatment.

DURATION OF TREATMENT:

Treatment duration will vary by region. The study consists of a Treatment Period (64 weeks) for all subjects and a Treatment Extension Period (up to 76 weeks) for subjects in Europe, the US, Canada, and Australia. For subjects in Japan and Korea, the planned duration of treatment in this study is 64 weeks, and the Week 64 visit at the end of the Treatment Period will be the EOS I visit. For subjects in Europe, the US, Canada, and Australia, the planned duration of treatment is up to 140 weeks (64 weeks in the Treatment Period and up to 76 weeks in the Treatment Extension period). In Europe, the US, and Australia, treatment in the Treatment Extension Period will end by September 2018; in Canada, treatment in the Treatment Extension Period will end by June 2019. The duration of Treatment Extension Period will vary for individual subjects and will be determined by the time from Week 64/EOS I through the EOS II visit. The maximum duration of treatment is 140 weeks.

CRITERIA FOR EVALUATION:

Primary Efficacy Endpoint:

The primary endpoint will be compared between the KRN23 and active control groups:

- Change in rickets at Week 40 as assessed by the RGI-C global score

Secondary Efficacy Endpoints:

The following secondary endpoints will be compared between the KRN23 and active control groups:

- Proportion of subjects with a mean RGI-C global score ≥ +2.0 (substantial healing) at Week 40 and Week 64
- Change in rickets at Week 64 as assessed by the RGI-C global score
- Change from baseline in RSS total score at Weeks 40 and 64

- Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as assessed by the RGI-C long leg score at Weeks 40 and 64
- Change in standing height (or recumbent length in children < 2 years) from baseline to Weeks 24, 40, and 64 in cm
- Change in height-for-age z-scores from baseline to Weeks 24, 40, 64
- Change in growth velocity from pre-treatment and post-treatment at Weeks 40 and 64 in cm/yr
- Pharmacodynamic* assessments including
    - Change from baseline over time in serum phosphorus
    - Change from baseline over time in serum $1,25(OH)_2D$, urinary phosphorus, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and tubular reabsorption of phosphate (TRP)
    - Change and percent change from baseline over time in biochemical markers of bone turnover that reflects rickets severity (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
- Pain, fatigue and physical function: Change from baseline in the PROMIS (Patient-Reported Outcomes Measurement Information System) Pediatric Pain Interference, Physical Function Mobility and Fatigue domain scores (for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40 and 64
- Pain intensity: Change from baseline in the Faces Pain Scale- Revised (FPS-R) (for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40 and 64
- Walking ability: Change from baseline in the Six Minute Walk Test (6MWT) total distance and percent of predicted normal (for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40, and 64

Pharmacokinetic:

- Serum KRN23 concentration

Safety Assessments:

Safety will be evaluated and compared with active control by the incidence, frequency, and severity of AEs and serious adverse events (SAEs), including clinically significant changes from baseline to scheduled time points for the following variables:

- Vital signs and weight
- Physical examinations
- eGFR (calculated using the Bedside Schwartz equation)
- Renal ultrasound to evaluate nephrocalcinosis
- Echocardiogram (ECHO) (for subjects ≥ 5 years of age)

- Chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (serum 25(OH)D; lipase; amylase; creatinine; serum calcium and iPTH, and urinary calcium and creatinine)
- Anti-KRN23 antibody testing and dose-limiting toxicities
- Concomitant medications
- ECG

Exploratory Assessments:

- Health-related quality of life: Change from baseline in the SF-10 for Children Health Survey (SF-10; for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40, and 64
- Dental evaluation to assess the number of dental events such as dental caries, tooth extraction, root canal, dental abscesses, and gingivitis
- Pre- and post-prandial serum phosphorus and calcium concentrations at a single visit

Long-term Assessments in Treatment Extension Period:

- At Weeks 88, 112, and 140, efficacy, safety, pharmacokinetic, and exploratory assessments will be conducted as noted in the Schedule of Events.

Data Monitoring Committee
An independent DMC that includes members with expertise in metabolic bone disease, cardiology, and nephrology, and the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial. The DMC will meet at least twice a year during the active-controlled period. The roles and responsibilities of the DMC will be defined in the DMC Charter.

STATISTICAL METHODS:

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

Sample Size:

This Phase 3 study is powered to test the effect of KRN23 on improvement of rickets using RGI-C global score at Week 40 against the active control group based on the assumption of a mean RGI-C global score of 1.80 in the KRN23 group, 1.40 in the active control group, and a common standard deviation of 0.50. Given these assumption, a total sample size of 60 (30 per group) will provide approximately 80% power to detect such a difference in the mean RGI-C global score at Week 40 between treatment groups using a 2-sample t-test with a 2-sided alpha level of 0.05. A 10% drop-out rate is incorporated in the sample size calculation.

Efficacy Analysis:

The Full Analysis Set will include all randomized subjects who received at least 1 dose of assigned medication, and the Full Analysis Set will be used for both efficacy and safety analyses. For efficacy analyses, subjects will be analyzed by the randomized treatment group. The primary efficacy endpoint will be tested to compare the mean RGI-C global score between the KRN23 and active control groups.

At the Week 40 Analysis (the primary efficacy analysis time point), the primary hypothesis of the primary endpoint is to test whether there is a difference between the KRN23 and active control groups in the mean RGI-C global scores at Week 40. An Analysis of Covariance (ANCOVA) model with treatment group adjusting for baseline rickets severity and age will be used to test this hypothesis at a 2-sided alpha level of 0.05. The proportion of RGI-C responders will be summarized for each treatment group.

At the Week 64 Analysis (secondary analysis), RGI-C global score over time will be analyzed using the repeat measurement model that includes treatment group, visit, treatment group by visit interaction, and adjusted for baseline rickets severity and age.

The change from baseline in RSS total score over time will be analyzed using the same method as that of the RGI-C global score.

Analyses of other efficacy and PD measures will be performed at Week 40, Week 64, and Week 140. Endpoints will be summarized descriptively by each treatment group. Treatment comparison will be performed using the repeat measurement model including treatment group, visit, treatment group by visit interaction, adjusting for baseline age, rickets severity. Other baseline covariates may be considered for adjustment.

Safety Analysis:

Full Analysis Set will be used for the safety analysis. Subjects will be analyzed based on the actual treatment received. Safety variables including AEs, SAEs safety laboratory assessments, vital signs, renal ultrasound, ECG, ECHO, and anti-KRN23 antibody will be summarized descriptively by treatment group.

Table 2.1: Schedule of Events – Treatment Period Weeks 1-30

	Screening/ Baseline[1]		Treatment Period															
VISIT ID	**SV**	**BL V1**	**V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**HH V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**HH V13**	**V14**	**HH V15**	**HH V16**	**HH V17**
TIME (WEEK/DAY)	**W-8 to BL**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**	**W28**	**W30**
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Medical History, Demographics	X																	
Parents' Heights	X																	
Tanner Staging	X																	
PHEX mutation analysis[2]	X																	
Randomization		X																
KRN23 Administration[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Active Control[3,4]		Administered at the discretion of the treating Investigator																
EFFICACY MEASURES																		
Growth (standing height [or length], sitting height)[5]		X													X			
Growth velocity		X																
Bilateral AP knee x-rays [6, 7]	X																	
Bilateral PA hand/wrist x-rays[6,7]	X																	
Standing long leg x-ray[7]		X																
6MWT[8] (aged ≥ 5 years at Screening Visit)	X	X													X			

	Screening/ Baseline[1]		Treatment Period															
VISIT ID	**SV**	**BL V1**	**V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**HH V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**HH V13**	**V14**	**HH V15**	**HH V16**	**HH V17**
TIME (WEEK/DAY)	**W-8 to BL**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**	**W28**	**W30**
PROMIS Pediatric Pain Interference, Fatigue and Physical Function Mobility (aged ≥ 5 years at Screening Visit)[9]		X													X			
Faces Pain Scale – Revised (aged ≥ 5 years at Screening Visit)		X													X			
SF-10 (aged ≥ 5 years at Screening Visit)[10]		X													X			
PD MEASURES																		
Serum Phosphorus[11, 12]	X	X	X	X	X		X		X		X				X			
Serum $1,25(OH)_2D$[11]		X	X	X	X		X		X		X				X			
ALP	X	X			X		X				X				X			
PHARMACOKINETICS																		
Serum KRN23 concentration [13]			X	X	X		X				X				X			
SAFETY MEASURES																		
Vital Signs [14]	X	X			X		X				X				X			
Weight [15]	X	X	X		X		X				X				X			
Physical Examination	X	X					X				X				X			
Concomitant Medication [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening/ Baseline[1]		Treatment Period															
VISIT ID	**SV**	**BL V1**	**V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**HH V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**HH V13**	**V14**	**HH V15**	**HH V16**	**HH V17**
TIME (WEEK/DAY)	**W-8 to BL**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**	**W28**	**W30**
Adverse Events [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound	X														X			
ECG		X													X			
ECHO (aged ≥ 5 years)		X																
Chemistry[16], Hematology, Urinalysis[11]	X	X			X		X				X				X			
Serum 25(OH)D	X	X		X							X							
Serum Calcium[11, 12]	X	X		X	X		X				X				X			
Serum Creatinine[11]	X	X		X	X		X				X				X			
Serum iPTH	X	X			X		X				X				X			
Serum iFGF23		X													X			
2-hr Urine[11,18]		X			X		X				X				X			
24-hr Urine[11,18] (aged ≥ 5 years)		X					X				X				X			
Dental assessment [19]		X			X		X				X				X			
Immunogenicity (ADA) [13]		X			X		X				X				X			
Urine Pregnancy Test [20]	X	X			X						X				X			

See footnotes after Table 2.3

Table 2.2: Schedule of Events – Treatment Period Weeks 32-64 and Safety Follow-up

	Treatment Period																		Safety Follow Up TC [21]	Safety Follow Up Visit [22]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**		
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ EOS I [23]**	**W69**	**W74**
Tanner staging						X												X		
KRN23 Administration[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [23]		
Active Control[3,4]	Administered at the discretion of the treating Investigator																			
EFFICACY MEASURES																				
Growth (standing height [or length], sitting height)[5]						X												X		
Growth velocity						X												X		
Bilateral AP knee x-rays [6,7]						X												X		
Bilateral PA hand/ wrist x-rays [6,7]						X												X		
Standing long leg x-ray[7]						X												X		
6MWT[8] (aged ≥ 5 years at Screening Visit)						X												X		

	Treatment Period																		Safety Follow Up TC [21]	Safety Follow Up Visit [22]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**		
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ EOS I [23]**	**W69**	**W74**
PROMIS Pediatric Pain Interference, Fatigue and Physical Function Mobility (aged ≥ 5 years at Screening Visit)[9]						X												X		
Faces Pain Scale – Revised (FPS-R) (aged ≥ 5 years at Screening Visit)						X												X		
SF-10 (aged ≥ 5 years at Screening Visit)[10]						X												X		
PD MEASURES																				
Serum Phosphorus[11, 12]	X	X				X						X						X		X
Serum $1,25(OH)_2D$[11]	X	X				X						X						X		X
ALP	**X**					X						**X**						X		X
PHARMACOKINETICS																				
Serum KRN23 concentration [13]		X				X												X		

	Treatment Period																		Safety Follow Up TC [21]	Safety Follow Up Visit [22]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**		
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ EOS I [23]**	**W69**	**W74**
SAFETY MEASURES																				
Vital Signs [14]	X					X						X						X		X
Weight [15]	X					X						X						X		
Physical Examination	X					X						X						X		X
Concomitant Medication [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound						X												X		
ECG						X												X		
ECHO (aged ≥ 5 years)						X												X		
Chemistry [17], Hematology, Urinalysis[11]	X					X						X						X		X
Serum 25(OH)D						X												X		
Serum Calcium[11, 12]	X					X						X						X		X
Serum Creatinine[11]	X					X						X						X		X
Serum iPTH	X					X						X						X		
Serum iFGF23																		X		X
2-hr Urine[11,18]	X					X						X						X		

	Treatment Period																		Safety Follow Up TC [21]	Safety Follow Up Visit [22]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**		
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ EOS I [23]**	**W69**	**W74**
24-hr Urine[11,18] (aged ≥ 5 years)	X					X						X						X		
Dental assessment [19]	X					X						X						X		X
Immunogenicity (ADA) [13]						X												X		
Urine Pregnancy Test [20]						X						**X**						X		X

See footnotes after Table 2.3

Table 2.3: Schedule of Events – Treatment Extension Period Weeks 66-140 and Safety Follow-up

	Treatment Extension Period											
VISIT ID	**V36**	**V37**	**HH [24]**	**V41**	**V47**	**V53**	**V59**	**V65**	**V73**		**Safety Follow Up TC [28]**	**Safety Follow Up Visit [29]**
TIME (WEEK/DAY)	**W66 [25]**	**W68 [25]**	**Q2W**	**W76**	**W88**	**W100**	**W112**	**W124**	**W140/ EOS II [26]**	**ET Visit [27]**		
Tanner staging					X		X		X	X		
KRN23 Administration	X [30]	X	X	X	X	X	X	X				
EFFICACY MEASURES												
Growth (standing height [or length], sitting height)[5]				X	X	X	X	X	X	X		
Growth velocity				X	X	X	X	X	X	X		
Bilateral AP knee x-rays[6,7]					X		X		X	X		
Bilateral PA hand/wrist x-rays[6,7]					X		X		X	X		
Standing long leg x-ray[7]					X		X		X	X		
6MWT[8] (aged ≥ 5 years at Screening Visit)					X		X		X	X		
PROMIS Pediatric Pain Interference, Fatigue and Physical Function Mobility (aged ≥ 5 years at Screening Visit)[9]					X		X		X	X		
Faces Pain Scale – Revised (FPS-R) (aged ≥ 5 years at Screening Visit)					X		X		X	X		
SF-10 (aged ≥ 5 years at Screening Visit)[10]					X		X		X	X		
PD MEASURES												
Serum Phosphorus[11, 12]	X [30]	X		X	X	X	X	X	X	X		X
Serum $1,25(OH)_2D$[11]		X		X	X	X	X	X	X	X		X
ALP		**X**		X	X	X	X	X	X	X		X
PHARMACOKINETICS												
Serum KRN23 concentration [13]		X			X		X		X	X		
SAFETY MEASURES												
Vital Signs [14]	X	X		X	X	X	X	X	X	X		X

	Treatment Extension Period											
VISIT ID	**V36**	**V37**	**HH [24]**	**V41**	**V47**	**V53**	**V59**	**V65**	**V73**		**Safety Follow Up TC [28]**	**Safety Follow Up Visit [29]**
TIME (WEEK/DAY)	**W66 [25]**	**W68 [25]**	**Q2W**	**W76**	**W88**	**W100**	**W112**	**W124**	**W140/ EOS II [26]**	**ET Visit [27]**		
Weight [15]		X		X	X	X	X	X	X	X		
Physical Examination		X		X	X	X	X	X	X	X		X
Concomitant Medication [16]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [16]	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound					X		X		X	X		
ECG					X		X		X	X		
ECHO (aged ≥ 5 years)					X		X		X	X		
Chemistry [17], Hematology, Urinalysis[11]		X		X	X	X	X	X	X	X		X
Serum 25(OH)D				X	X	X	X	X	X	X		
Serum Calcium[11, 12]		X		X	X	X	X	X	X	X		X
Serum Creatinine[11]		X		X	X	X	X	X	X	X		X
Serum iPTH		X			X		X		X	X		
Serum iFGF23					X		X		X	X		X
2-hr Urine[11,18]		X			X		X		X	X		
24-hr Urine[11,18] (aged ≥ 5 years)		X			X		X		X	X		
Immunogenicity (ADA) [11]					X		X		X	X		
Urine Pregnancy Test [20]				X	X	X	X	X	X	X		X

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; 6MWT = Six Minute Walk Test; ADA = anti-drug antibodies; ALP = alkaline phosphatase; AP = anteroposterior; BP = blood pressure; ECG = electrocardiogram; ECHO = echocardiogram; EOS I = End of Study I (for subjects in Japan and Korea); EOS II = End of Study II (for subjects in Europe, the US, Canada, and Australia); ET = End of Treatment; FPS-R = Faces Pain Scale – Revised; HH = Home Health; iFGF23 = intact fibroblast growth factor 23; iPTH = intact parathyroid hormone; PA = posteroanterior; PD = pharmacodynamic; PROMIS = Patient-Reported Outcomes Measurement Information System; SF-10 = Short Form 10; TC = teleconference; V = visit; W = week

1. All study visits will be scheduled relative to the Baseline visit, with an allowable variance of ±3 days for each visit (with the exception of the Screening and the Safety Follow-up Visits) to accommodate scheduling. All Screening/Baseline assessments and inclusion/exclusion criteria must be satisfied prior to randomization and dosing. The Screening Visit window may be up to 8 weeks for *PHEX* mutation analysis and washout of oral phosphate and active vitamin D therapy. KRN23 dosing should occur no sooner than 8 days since the last dose administered.
2. *PHEX* mutation analysis will be performed in all subjects. Potential subjects with prior confirmation of a *PHEX* mutation or variant of uncertain significance in either self or a family member with appropriate X-linked inheritance who meet other eligibility requirements may enroll before screening *PHEX* mutation results are returned.
3. Patients will be randomized 1:1 to either the KRN23 treatment arm or the active control arm (oral phosphate/active vitamin D therapy).
4. Active control will be administered at the discretion of the treating Investigator. Subjects randomized to the active control arm will visit the clinic at Weeks 1, 4, 8, 16, 24, 32, 40, 52, and 64. Active control will be discontinued after the Week 64 visit to allow washout of oral phosphate and active vitamin D treatments before the first dose of KRN23 at Week 66 for subjects originally randomized to active control.
5. In subjects < 2 years old, recumbent length will be measured instead of standing and sitting height. At each time point, height will be assessed 3 times and each assessment will be recorded onto the subject chart and eCRF. An average of the 3 measurements will be calculated. Pre-study recumbent length/standing height data will be collected as discussed in Section 7.5.1.
6. Screening results will be treated as Baseline data.
7. AP knee and PA hand/wrist x-rays will be acquired for all subjects and standing long leg x-rays will be acquired for all qualifying subjects. Pre-study radiographs will be collected as discussed in Section 7.5.1.
8. 6MWT will be conducted only for subjects ≥ 5 years of age at the Screening Visit. If a subject is < 5 years of age at the Screening Visit, the 6MWT will not be assessed when the subject is over 5 years of age during the post-baseline visits.
9. For the PROMIS Pediatric Pain Interference, Fatigue, and Physical Function Mobility scales, the parent or legal guardian will complete a Parent/Legal Guardian form for subjects ages 5 to < 8 years of age at the Screening Visit. Subjects ≥ 8 years of age at the Screening Visit will complete a pediatric self-report form. Parent/Legal Guardian forms will be used for the duration of the study for subjects < 8 years of age at the Screening Visit who had a baseline assessment, even when a subject turns 8 during the study. If a subject ≥ 8 years of age at screening has difficulty completing the PROMIS self-report, the investigator may allow the PROMIS interview to be administered by trained clinic staff or allow the parent to complete the PROMIS Parent Proxy version. The reason should be carefully documented and consistent practice of administration should be maintained for every visit from Baseline.
10. If a subject is < 5 years of age at the Screening Visit and therefore has no baseline data, SF-10 will not be administered even when the subject turns 5 during the study.
11. Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable). Record fasting duration on CRF. Serum phosphorus may be collected as an unscheduled laboratory assessment if necessary. Details for blood and urine collection can be found in the central laboratory manual.
12. Pre- and post-prandial serum phosphorus and calcium concentrations will be assessed at a single clinic visit anytime 10 to 14 days after a KRN23 dose; this clinic visit may take the place of a Home Health visit. Approximately 20 subjects, age ≥ 3 years, will fast overnight for a minimum of 8 hours, and fasting serum will be collected prior to a breakfast containing predefined ranges of phosphate, calories, and carbohydrate representative of a typical Western diet for children. Serum samples will be drawn 1 and 2 hours after the completion of the meal (refer to Table 7.5.4.3.1).

13. Serum KRN23 concentrations and ADA assessment will be performed only for subjects randomized to KRN23 during the Treatment Period and for all subjects during the Treatment Extension Period. If 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.
14. Vital sign measurements consist of seated systolic/diastolic blood pressure (BP) measured in millimeters of mercury (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Vital signs will be obtained at the beginning of each visit before any additional assessments are completed and after the subject has rested for 5 minutes. BP measurements will only be obtained at clinic visits and only for subjects ≥3 years of age. At the Screening Visit and at Baseline, 2 sets of 3 BP measurements will be obtained – the first set will be done at the beginning of the visit and the second set at end of the visit after all site procedures are completed. BP measurements should be obtained by auscultation (ie, manually and without using an automated device) dafter the subject has rested for 5 minutes and a second and third BP measurement should be obtained, each performed 30 seconds apart.
15. The subject's weight collected at in-clinic visits will be the basis of the KRN23 dose calculation until the next in-clinic weight collection.
16. Adverse events and concomitant medications information will be collected at HH visits for subjects in the KRN23 arm during the Treatment Period and for all subjects during the Treatment Extension Period (HH visits are not applicable to subjects in Japan or Korea). For subjects in the active control arm during the Treatment Period, adverse events and concomitant medications information will be collected by telephone call.
17. Serum chemistry panels may include PD parameters (ie, serum phosphorus and ALP), and safety parameters of interest (ie, calcium) to avoid duplication of testing.
18. Both 2-hr and 24-hr urine will be used for measurements of urinary phosphorus, creatinine, and calcium; 2-hr urine will be used for the derivation of TmP/GFR and TRP. For subjects < 5 years of age, spot urine may be collected in place of the 2-hr urine samples for measurements of urinary calcium, phosphorus, and creatinine.
19. Separate dental assessments are not required and will be captured under AEs as dental issues arise. At each clinic visit, an oral examination will be conducted and subjects will be proactively asked if they had any dental events such as dental caries, tooth extraction, root canal, dental abscesses, and gingivitis.
20. Pregnancy testing will be performed on any female subject of childbearing potential who has experienced menarche.
21. To be completed for those subjects who complete Week 64 and do not continue on KRN23 treatment immediately on a clinical trial or through another mechanism. For subjects in Japan and Korea, site personnel will initiate a safety follow-up telephone call 5 weeks (+5 days) after the Week 64/EOS I Visit to determine if KRN23 therapy has been started in another clinical trial or through another mechanism. If KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected.
22. For subjects in Japan and Korea who complete the Week 64/EOS I Visit and do not continue on KRN23 on a separate clinical trial or through another mechanism, a safety visit will take place 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit. This safety visit will not occur for subjects who are documented to be continuing on KRN23 on a separate clinical trial or another mechanism.
23. The Week 64/EOS I Visit is the end of the study for subjects in Japan and Korea. KRN23 will be administered at the Week 64 visit for subjects in Europe, the US, Canada, and Australia in the KRN23 arm; these subjects will continue into the Treatment Extension Period. For subjects Japan and Korea in the KRN23 arm, KRN23 will not be administered at the Week 64/EOS I visit.
24. HH visits will be conducted every 2 weeks (Q2W). At the HH visit, study drug will be administered (Q2W); information regarding concomitant medications and adverse events will be collected. The visit window is ±5 days. For subjects originally randomized to KRN23 and who continue on KRN23 in the Treatment Extension Period, the first HH visit will be at Week 66. For subjects originally randomized to active control and who cross over to KRN23 in the Treatment Extension Period, the Weeks 66 and 68 visits are clinic visits; the Week 70 HH visit will be the first HH visit for these subjects.

25. The Weeks 66 and 68 clinic visits are for subjects originally randomized to active control and who cross over to KRN23 in the Treatment Extension Period. For subjects originally randomized to KRN23 and who continue to receive KRN23 in the Treatment Extension period, the Weeks 66 and 68 visits are Q2W HH visits.
26. The EOS II visit will be the End of Study efficacy visit for subjects in Europe, the US, Canada, and Australia. EOS II should occur before 30 September 2018 for subjects in Europe, the US, and Australia and before 30 June 2019 for subjects in Canada. 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 wrists and knees will not be performed at the EOS II Visit if the assessment was conducted within 6 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.
27. For subjects who discontinue prior to completing the study (in either the Treatment Period or the Treatment Extension Period), every reasonable effort should be made to perform the ET Visit procedures within 4 weeks of early discontinuation. 6MWT and ECHO will not be performed at the ET Visit if the assessment was conducted within 3 months of termination. Radiography (x-rays) of wrists and knees will not be performed at the ET Visit if the assessment was conducted within 6 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.
28. To be completed for those subjects who complete EOS II and do not continue on KRN23 treatment immediately on a clinical trial or through another mechanism. For subjects in Europe, the US, Canada, and Australia, site personnel will initiate a safety follow-up telephone call 5 weeks (+5 days) after the EOS II Visit to determine if KRN23 therapy has been started in another clinical trial, through commercial use, or through another mechanism. If KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected.
29. For subjects in Europe, the US, Canada, and Australia who complete the ET or EOS II Visit and do not continue on KRN23 on another clinical trial, through commercial use, or through another mechanism, a safety visit will take place 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit. This safety visit will not occur for subjects who are documented to be continuing on KRN23 on a separate clinical trial or another mechanism.
30. Subjects originally randomized to active control will have serum phosphorus assessed at the local laboratory to document hypophosphatemia before administration of the first dose of KRN23. A sample will also be drawn for a serum phosphorus assessment at the central laboratory.

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Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
6MWT	Six Minute Walk Test
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
AP	anteroposterior
BALP	bone-specific alkaline phosphatase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTx	carboxy-terminal cross-linked telopeptide of type I collagen
dL	deciliter
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECLA	electrochemiluminescent assay
EDC	electronic data capture
EOS	End of Study
ET	End of Treatment
EU	European Union
eGFR	estimated glomerular filtration rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration

FGF23	fibroblast growth factor 23
FPS-R	Faces Pain Scale – Revised
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
Hyp	hypophosphatemic
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
iFGF23	intact fibroblast growth factor 23
IND	Investigational New Drug (application)
iPTH	intact parathyroid hormone
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	Interactive Web Randomization System
Kg	kilogram
KHK	Kyowa Hakko Kirin Co., Ltd
L	liter
LVH	left ventricular hypertrophy
M	meter
mAb	monoclonal antibody
Mg	milligram
mm Hg	millimeters of mercury
mmol	millimole
NaPi-IIa	sodium/phosphate cotransporter IIa

NaPi-IIc	sodium/phosphate cotransporter IIc
NCI	National Cancer Institute
NOAEL	no adverse effect level
P1NP	procollagen type 1 N-propeptide
PA	posteroanterior
PD	pharmacodynamic (s)
PHEX	phosphate-regulating gene with homologies to endopeptidases on the X chromosome
PK	pharmacokinetic(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
PTH	parathyroid hormone
Q2W	once every 2 weeks
Q4W	once every 4 weeks
RBC	red blood cell
RGI-C	Radiographic Global Impression of Change
RSI	Reference Safety Information
RSS	Rickets Severity Score
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-10	Short Form 10
SmPC	Summary of Product Characteristics
SV	Screening Visit
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
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" are used interchangeably in the protocol and refer to KRN23.

The terms "Active Control" or "Active Control Arm" refer to oral phosphate/active vitamin D therapy.

5 INTRODUCTION

X-linked hypophosphatemia (XLH) is a disorder of hypophosphatemia, renal phosphate wasting, defective bone mineralization, and impaired growth plate or endochondral ossification caused by inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), and is the most common form of heritable rickets. In the absence of functional PHEX, release of fibroblast growth factor 23 (FGF23) by osteocytes is greatly increased, leading to impaired conservation of phosphate by the kidney and consequent hypophosphatemia. FGF23 also suppresses 1,25-dihydroxyvitamin D (1,25(OH)2D) production resulting in decreased intestinal absorption of calcium and phosphate.

Chronic hypophosphatemia leads to rickets in children and osteomalacia in adults, the 2 major pathologic features of XLH. Rickets and osteomalacia are both disorders of bone mineralization; however, rickets is a disease of the growth plates specifically characterized by deficient mineralization as well as by delayed endochondral ossification, leading to reduced growth and skeletal deformities (Shore et al. 2013). Osteomalacia occurs in both children and adults wherein low levels of phosphorus prevent normal mineralization of osteoid, resulting in low bone turnover and poor quality bone (Shore et al. 2013). Published data suggest that earlier treatment leads to better outcomes. In retrospective studies, children beginning treatment before age 1 had consistently higher z scores and lower alkaline phosphatase levels than children starting treatment later in life (Makitie et al. 2003), (Quinlan et al. 2012).

There is no available medicine that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphatemia in XLH. The most common therapy for pediatric XLH patients consists of multiple daily doses of oral phosphate often combined with doses of active vitamin D analogs, the most common being calcitriol and alfacalcidol. Dosing is individualized and depends on tolerability of the phosphate dose and the age, size, and growth of the child. Doses may be further adjusted based on the efficacy response to treatment or evidence of secondary complications (Carpenter et al. 2011). Treatment is typically discontinued in adolescence once longitudinal bone growth is complete. The goal of therapy with oral phosphate/active vitamin D is to sufficiently supplement the body's pool of phosphate to allow mineralization of bone and improve skeletal outcomes; however, because supplementation therapy does not address the mechanism of urinary phosphate wasting, increasing phosphate through supplementation also increases renal phosphate throughput and urinary phosphate concentrations, thus raising the risk of nephrocalcinosis. Therefore, an opportunity exists for more targeted treatment of XLH by blocking the action of aberrantly elevated FGF23 to normalize serum phosphorus and prevent long term consequences of chronic hypophosphatemia.

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 hypophosphatemic 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 IgG1 mAb that binds to and inhibits FGF23. The Sponsor and development partner, Kyowa Hakko Kirin Co., Ltd. (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. Four clinical studies of KRN23 have been completed in adult patients with XLH: 2 single-dose Phase 1 safety and tolerability studies, a repeat dose Phase 1/2 dose escalation study, and an associated treatment extension study. An additional open-label, long-term extension study is ongoing. A Phase 2 study (UX023-CL201) in pediatric XLH subjects aged 5 to 12 years receiving KRN23 at multiple doses up to 2.0 mg/kg every 2 weeks (Q2W) or every 4 weeks (Q4W) is ongoing and no new safety concerns have been identified. Studies in both adults and children (aged 5-12 years) with XLH have shown that KRN23 increases serum phosphorus and $1,25(OH)_2D$ levels and ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR). Initial 40-week data from the pediatric Phase 2 study also suggest that KRN23 treatment improves rickets severity with a favorable safety profile. The 40-week interim analysis demonstrated that KRN23 significantly improved rickets across the 2 dosing groups, with subjects in the Q2W dosing group having better outcomes that may reflect the more steady levels of serum phosphorus, $1,25(OH)_2D$, and other PD parameters observed with Q2W dosing than with Q4W dosing of KRN23.

Data from the pediatric Phase 2 study were used to establish the dosing regimen and provided information for the design of the current Phase 3 study. This Phase 3 study will be conducted in children with XLH (aged 1 to ≤ 12 years) with confirmed evidence of rickets to evaluate the efficacy (ie, improvement in rickets) and safety profile of KRN23 treatment, and to compare KRN23 treatment with active control (oral phosphate/active vitamin D therapy). In addition, this study will evaluate whether every 2 week dosing of KRN23 improves growth velocity, restores phosphorus homeostasis, and improves functional outcomes and quality of life in children with XLH. A Treatment Extension Period, which provides for continued treatment until KRN23 is expected to be commercially available, will also allow evaluation of subject who cross over from active control to KRN23.

5.1 Overview of XLH

XLH is a rare, genetic disorder that is serious, chronically debilitating, and represents an unmet medical need. This genetic deficiency is estimated to occur in about 1:20,000 live births (Burnett et al. 1964), (Imel et al. 2005), (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. XLH is transmitted as an X-linked dominant disorder (Dixon et al. 1998). Mutations resulting in the loss of function of PHEX form the genetic basis for XLH (Carpenter et al. 2011). More than 300 different *PHEX* gene mutations have been identified in patients with XLH (PHEXdb); however, few definitive correlations have been observed between specific mutations and phenotypic severity.

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 $1,25(OH)_2D$ 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.

Patients with XLH often present during childhood with rickets due to hypophosphatemia and frequently develop skeletal abnormalities (eg, 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 decreased phosphate requirements 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). There is a great deal of variability in the manifestations of XLH. In more severe disease, hypophosphatemia leads to decreased mineralization of newly formed bone and rickets. Surgical correction of limb deformities is often required (Santos et al. 2013), (Zivicnjak et al. 2011).

Although there is no approved therapy for XLH that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphatemia., the most common treatment for pediatric XLH patients consists of multiple daily doses of oral phosphate often combined with doses of active vitamin D metabolites (eg, calcitriol and alfacalcidol). General guidelines for treatment of children with XLH with oral phosphates and active vitamin D therapy are published in both the US and Europe, as described in Table 7.1.1 and Table 7.1.2.

No consensus exists regarding treatment of adult patients with XLH (Linglart et al. 2014). The use of oral phosphate and vitamin D may be initiated for the treatment of osteomalacia, bone/joint pain, and pseudofractures in symptomatic patients, although evidence of efficacy in adults is limited (Sullivan et al. 1992). Treatment with oral phosphate and active vitamin D 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 IgG1 monoclonal antibody (mAb) 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 2 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 phosphorus homeostasis in XLH patients. KRN23 binds the amino-terminal domain of FGF23 that interacts with the FGF-binding portion of the combination FGFR1/Klotho receptor, preventing FGF23 from binding to and signaling from 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 (as measured by the ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate [TmP/GFR]) from the kidney and increases the production of $1,25(OH)_2D$ that also enhances intestinal absorption of phosphate. It is expected that by directly inhibiting excess FGF23, the underlying cause of XLH, and thereby improving phosphorus homeostasis and healing rickets, KRN23 has the potential to significantly alter the natural history of the disease.

5.2.2 Nonclinical Studies

The hypophosphatemic (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-FGF23 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 characteristic abnormalities associated with XLH.

KRN23 binds to human, rabbit, and monkey FGF23 with comparable affinities. In a study conducted under Good Laboratory Practice (GLP) conditions, 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 intravenous (IV) infusion sites or subcutaneous (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 Clinical Studies

Multiple clinical studies of FGF23 in adults or children with XLH are completed or ongoing. 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 (UX023-CL304) 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. A Phase 2 dose-finding, pharmacodynamic (PD) and safety study in pediatric XLH patients aged 5 to 12 years (UX023-CL201) and an open-label, Phase 2 safety, PD, and efficacy study in 1-to-4-year-old children with XLH (UX023-CL205) are also ongoing.

Data from clinical studies to date are consistent with the proposed mechanism of action: that KRN23 blocks FGF23 action, leading to a sustained increase in serum phosphorus levels due to increased 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 (Carpenter et al. 2014), (Imel et al. 2015). Data from the long-term extension study in adults suggest KRN23 could provide sustained increases in serum phosphorus levels such that improvements in bone physiology, structure, and function would be expected (Imel et al. 2015).

Repeated doses of KRN23 up to 1.0 mg/kg were well tolerated by adult XLH subjects throughout the Phase 1/2 dose escalation study and associated treatment extension study (Imel et al. 2015). In the extension study, serious adverse events (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 (2 subjects, 9.1%), 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.

Similar to the adult studies, interim analyses from the Phase 2 pediatric study (UX023-CL201) showed KRN23 treatment up to 2 mg/kg Q2W or Q4W increased serum phosphorus, TmP/GFR, and $1,25(OH)_2D$ levels. A 40-week interim analysis of the first 36 subjects enrolled demonstrated that KRN23 significantly improved rickets from baseline

to Week 40 by 30% (p=0.0076) as assessed by the Thacher Rickets Severity Score (RSS), with greater improvements seen with Q2W dosing (44% reduction; p=0.0126) than with Q4W dosing (14% reduction). The greatest improvement was observed in a subset of patients (n=18) with clear evidence of rickets at baseline (baseline RSS ≥1.5) (59% reduction with Q2W dosing and 47% reduction with Q4W dosing; p<0.0001 for both dose groups). Consistency in the rickets results was observed using the Radiographic Global Impression of Change (RGI-C; -3=worsening; +3=complete healing), with rickets improving by +1.56 points (p<0.0001) in the Q2W dosing group and by +1.20 points (p<0.0001) in the Q4W dosing group at Week 40. In the subgroup with a baseline RSS ≥1.5, RGI-C improved by +2.0 points (p<0.0001) in patients who received Q2W dosing, indicating substantial healing of rickets, and by +1.70 (p<0.0001) in patients who received Q4W dosing.
The 40-week analysis also revealed that the Q4W dosing group showed a peak in serum phosphorus at 2 weeks after dosing followed by a decrease in serum phosphorus levels before the next dose (though remaining above baseline), whereas the Q2W regimen showed stable serum phosphorus levels slowly increasing over time. Overall, the dose-response and PD results observed in the pediatric study were consistent with the adult XLH data generated to date. None of the subjects had serum phosphorus levels above the normal range in either dosing group. Most treatment-related adverse events (AE) were mild, most commonly a transient injection site reaction (39%). One child experienced a serious AE and was hospitalized for fever/muscle pain that improved and continues in the trial. No clinically meaningful changes occurred in serum or urine calcium, serum iPTH, or renal ultrasound.

5.3 Summary of Overall Risks and Potential Benefits

KRN23, a fully human mAb that binds and inhibits FGF23, is being developed as a potential therapeutic candidate for XLH, a rare genetic disease characterized by chronic hypophosphatemia and elevated levels of FGF23. By blocking the activity of FGF23, KRN23 can restore phosphate, vitamin D, and bone metabolism homeostasis, and has the potential to improve the lives of children with this disorder by correcting or minimizing rickets, radiographic abnormalities, and skeletal deformities, and by promoting maximal growth potential while preventing the lifelong bone- and joint-related complications of rickets.
This therapeutic approach directly targets the inherent dysregulation in XLH (ie, excess FGF23). In contrast, supplementation therapy with phosphate and/or active vitamin D is only partially effective and carries a significant burden and risk of ectopic mineralization, particularly nephrocalcinosis.

Clinical studies to date have demonstrated that KRN23 treatment blocks FGF23 action and leads to a sustained increase in serum phosphorus levels due to increased TmP/GFR. Increased $1,25(OH)_2D$ was also observed, as expected, based on the inhibition of the excess of FGF23. Bone formation and resorption markers also increased. Interim data in children with XLH suggest that KRN23 treatment also improves rickets. KRN23 was well tolerated in the population studied. No major safety concerns were observed; there was no evidence of immunogenicity, and no evidence of left ventricular hypertrophy (LVH) based on electrocardiogram (ECG) even though FGF23 levels were increased following KRN23 treatment. Although ectopic mineralization is a known risk related to XLH disease and is

exacerbated by oral phosphate and/or active vitamin D supplementation, KRN23 does not appear to be associated with progression of cardiac or renal ectopic mineralization beyond the natural course of pre-existing disease.

KRN23 administered SC Q2W or Q4W as doses up to 2 mg/kg achieved the desired PD effect in children and evidence of a clinical effect in healing rickets, positioning KRN23 as a drug that could be administered twice per month by SC injection, which is a convenient and acceptable therapeutic regimen for a chronic condition.

In conclusion, KRN23 inhibits the effects of FGF23, restoring phosphate, vitamin D and bone metabolism homeostasis. In children with XLH, interim data suggest that KRN23 treatment improves rickets. By targeting FGF23 and increasing serum phosphorus levels, it is expected that rickets severity in children with XLH will be healed or reduced, leading to improved clinical outcomes and the quality of life of children with XLH. To date, KRN23 has a favorable safety profile without evidence of increased ectopic mineralization or other concerns associated with the excess of FGF23. KRN23 has the potential to be an effective and safe treatment option for patients with XLH.

5.4 Study Rationale

XLH is a disorder of hypophosphatemia, renal phosphate wasting, defective bone mineralization, and impaired growth plate or endochondral ossification caused by inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), and is the most common form of heritable rickets. In the absence of functional PHEX, release of FGF23 by osteocytes is greatly increased. Excess circulating FGF23 impairs conservation of phosphate by down-regulating NaPi-IIa and NaPi-IIc in the renal tubule cells and suppressing $1,25(OH)_2D$ production, resulting in decreased intestinal absorption of calcium and phosphate. Chronic low serum phosphorus levels lead to rickets in children and osteomalacia in both children and adults, the 2 major pathologic outcomes of the hypophosphatemia. Rickets is a disorder of open growth plates characterized by both defective bone mineralization and defective endochondral ossification, leading to reduced growth and skeletal deformities. Osteomalacia is characterized by a lack of proper mineralization, a prolonged mineralization process, and an accumulation of osteoid tissue with a consequent deterioration of bone remodeling (Shore et al. 2013).

Although there is no approved therapy for XLH that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphatemia, the most common therapy for children with XLH consists of multiple daily doses of oral phosphate often combined with doses of active vitamin D analogs, the most common being calcitriol and alfacalcidol. Dosing is individualized and depends on tolerability of the phosphate dose and the age, size, and growth of the child. The goal of therapy with phosphate and active vitamin D is to sufficiently supplement the body's pool of phosphate to allow mineralization of bone and improve skeletal outcomes; however, because supplementation therapy does not address the mechanism of urinary phosphate wasting, increasing phosphate through supplementation also increases renal phosphate throughput and urinary phosphate concentrations, thus raising the

risk of nephrocalcinosis. More therapeutic options that are efficacious, safe, and convenient, and that target the underlying pathophysiology of XLH (ie, renal phosphate wasting induced by high FGF23 levels), are needed.

KRN23 is a recombinant human IgG_1 mAb that binds to and inhibits the activity of FGF23. By inhibiting FGF23, KRN23 restores tubular reabsorption of phosphate from the kidney and increases the production of $1,25(OH)_2D$ that enhances intestinal absorption of calcium and phosphate (Carpenter et al. 2014). It is expected that by directly inhibiting excess FGF23-the underlying cause of XLH-improving phosphorus homeostasis, and healing rickets, KRN23 has the potential to significantly alter the natural history of the disease. A Phase 1 study established the PK profile of KRN23. A Phase 1/2 study and associated extension study evaluated the PD of KRN23 on phosphate metabolism and related measures of the phosphate-calcium mineral control system. The safety data from these studies have shown that KRN23 in single and repeated every 4 week 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, to drive serum phosphorus levels closer to the normal range, and to minimize the troughs.

A Phase 2 study (UX023-CL201) in pediatric XLH subjects aged 5 to 12 years receiving KRN23 at multiple doses up to 2.0 mg/kg every 2 weeks (Q2W) or every 4 weeks (Q4W) is ongoing and no new safety concerns have been identified. Interim data from the Phase 2 pediatric study showed that KRN23 treatment for 40 weeks leads to significant improvement in rickets severity, with the greatest improvement observed with Q2W dosing in those subjects with higher rickets severity at baseline. KRN23 treatment also improved serum phosphorus, TmP/GFR, and serum $1,25(OH)_2D$ levels, consistent with results observed in studies of adults with XLH. The 40-week analysis also revealed that the Q4W dosing group showed a peak in serum phosphorus at 2 weeks after dosing followed by a decrease in serum phosphorus levels before the next dose (though remaining above baseline), whereas the Q2W regimen showed stable serum phosphorus levels slowly increasing over time. Overall, the dose-response, serum phosphorus, and other pharmacodynamic results observed in the pediatric study were consistent with the adult XLH data generated to date. There have been no discontinuations from the study for any reason. Most treatment-related adverse events (AE) were mild, most commonly a transient injection site reaction (39%). One child experienced a serious AE and was hospitalized for fever/muscle pain that improved and continues in the trial. There have been no deaths or discontinuations from the study for any

reason. No clinically meaningful changes occurred in serum or urine calcium, serum iPTH, or renal ultrasound. The current Phase 3 study will be conducted in children with XLH (aged 1 to ≤12 years) who have radiographic evidence of rickets (≥ 2.0 points RSS total score), open epiphyses, and have received oral phosphate/active vitamin D therapy for ≥ 12 consecutive months (for children ≥ 3 years of age) or ≥ 6 consecutive months (for children < 3 years of age), 7 days prior to the Randomization Visit. The design is intended to evaluate the efficacy (change in rickets severity) and safety of KRN23 treatment compared with active control (oral phosphate/active vitamin D therapy). In addition, this study will evaluate whether every 2 week dosing of KRN23 improves growth velocity, restores phosphorus homeostasis, and improves functional outcomes and quality of life in children with XLH.

RGI-C global score at Week 40 was selected as the primary efficacy measure as this endpoint directly assesses improvements in rickets, which is the basis for, and correlates with the major morbidities patients with XLH suffer from during their lifespan.

6 STUDY OBJECTIVES

Primary Objective:

- Evaluate the effect of KRN23 therapy in improving rickets in children with XLH compared with the active control (oral phosphate/active vitamin D)

Secondary Efficacy Objectives:

Evaluate the effects of KRN23 as compared with the active control on:

- Growth velocity and lower extremity deformity
- Pharmacodynamic markers that reflect the status of phosphorus homeostasis, including serum $1,25(OH)_2D$, serum and urinary phosphorus, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and tubular reabsorption of phosphate (TRP)
- Biochemical markers of bone turnover that reflect rickets severity (alkaline phosphatase [ALP])
- Walking ability and patient-/parent-reported pain, fatigue, and physical function/mobility

Pharmacokinetic Objective:

Assess the PK of KRN23 throughout the dosing cycle

Safety Objective:

Evaluate the safety and tolerability profile of KRN23 in the treatment of children with XLH (aged 1 to ≤ 12 years), including adverse events (AEs) (eg, nephrocalcinosis), as compared with active control, and immunogenicity profile

Treatment Extension Period Objective:

To evaluate the long-term safety and efficacy of KRN23

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

UX023-CL301 is a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of KRN23 with the active control (oral phosphate/active vitamin D therapy) in pediatric patients with XLH. The study will be conducted in children with clinical evidence consistent with XLH (aged 1 to ≤ 12 years), including demonstrated hypophosphatemia, radiographic evidence of rickets (≥ 2.0 points RSS total score), and *PHEX* mutation or variants of uncertain significance. Patients will also be required to have open epiphyses and have received oral phosphate/active vitamin D therapy for ≥ 12 consecutive months (for children ≥ 3 years of age) or ≥ 6 consecutive months (for children < 3 years of age), 7 days prior to the Randomization Visit. Approximately 60 subjects will be randomized 1:1 to receive open-label KRN23 administered by subcutaneous injection or active control for a total of 64 weeks in the Treatment Period. Randomization will be stratified by baseline rickets severity (RSS total score ≤ 2.5 vs > 2.5) and age (< 5 vs ≥ 5 years). At least 20 subjects aged 1 to < 5 years will be included (approximately 10 in each treatment arm), and no more than 10 subjects between the ages of 1 to < 3 years will be enrolled. The age range of eligible subjects will be monitored for enrollment for age distribution. No more than 70% female subjects will be enrolled. All subjects will washout of oral phosphate and active vitamin D therapy for 7 days prior to randomization. Subjects randomized to KRN23 will remain off of oral phosphate/active vitamin D therapy throughout the duration of the study.

Treatment Extension Period (Weeks 66 – 140) – All Subjects

Subjects assigned to the KRN23 treatment group will receive KRN23 at a starting dose of 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) 2 consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by ≤ 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of KRN23 that would account for the decrease in serum phosphorus. The maximum allowable dose of KRN23 per administration is 90 mg. At any time during the study, if serum phosphorus increases above the upper limit of normal (ULN) for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received (ie, half of either 0.8 mg/kg or 1.2 mg/kg; maximum dose per administration: 40 mg). Serum phosphorus will be followed through unscheduled serum phosphorus assessments (approximately 2 weeks post-dose and assessed by the central laboratory; the assessments may be repeated as necessary). A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

Subjects assigned to active control will typically receive multiple daily doses of oral phosphate and active vitamin D. Because of the variability in the doses and dosing frequencies of oral phosphates and active vitamin D therapies in clinical practice, these treatments will be individualized for each subject at the investigator's discretion, but the

following general guidance is provided based on expert recommendations in the US and Europe (in Table 7.1.1 and Table 7.1.2). Detailed information about the brand, starting dosages, and any changes in oral phosphate and active vitamin D therapy will be determined by the treating Investigator within the guidelines and recorded at every site visit. US expert guidelines generally recommend a calcitriol dosage of 20 to 30 ng/kg/day in 2 to 3 divided doses and an elemental phosphorus dose of 20 to 40 mg/kg/day (in 3 to 5 divided doses), acknowledging that some children require more, whereas some do well with less (Carpenter et al. 2011). European expert guidelines recommend an alfacalcidol dosage of 1 to 2 µg/day (once daily) and a phosphate supplemental dose of 45 to 70 mg/kg/day (in 3 to 4 divided doses) (Linglart et al. 2014). Calcitriol and alfacalcidol dosages should be adjusted based on the clinical and laboratory values that guide best possible treatment.

Table 7.1.1: Oral Phosphate and Active Vitamin D Agents in Common Use for XLH Treatment

Phosphate Preparations	Phosphorus content	Potassium (K) content	Sodium (Na) content
Neutaphos - powder (for mixing with liquid)	250 mg/packet	270 mg	164 mg
Neutraphos-K - powder (for mixing with liquid)	250 mg/packet	556	0
K-Phos Original -uncoated tablet (to mix in liquid, acidifying)	114 mg/tablet	144	0
K-Phos MF - coated tablet (mixing not required, acidifying)	126	45	67
K-Phos #2 (double strength of K-Phos MF)	250	90	133
K-Phos Neutral-tablet (non-acidifying, mixing not required)	250	45	298
Phospha-Soda-solution (small doses may be given undiluted)	127 mg/ml	0	152
Joulie's solution Prepared by compounding pharmacies	30 mg/ml	0	17.5-20

Vitamin D and Related Agents	
Vitamin D (1 mcg vitamin D = 40 IU) (calciferol; Drisdol®)	Solution: 8000 IU/ml Tablets: 25,000 and 50,000 IU
Dihydrotachysterol (DHT, Hytakerol®)	Solution: 0.2 mg/5ml Tablets: 0.125, 0.2, and 0.4 mg
1,25 dihydroxyvitamin D calcitriol, Rocaltrol®	0.25 and 0.5 mcg capsules 1 mcg/ml solution
Calcijex®	Ampules for IV use containing solutions with 1 or 2 mcg/ml of drug
1a- hydroxyvitamin D (alfacalcidol)	0.25, 0.5, and 1 mcg capsules Oral solution (drops): 2 mcg/ml Solution for IV use: 2 mcg/ml
Vitamin D analogues:	
paricalcitol (Zemplar®)	1, 2, and 4 mcg capsules
doxercalciferol (Hectoral®)	0.5, 1, and 2.5 mcg capsules

(Carpenter et al. 2011)

Table 7.1.2: Recommended Ranges of Doses for Phosphate and Active Vitamin D for Treatment of XLH

Period	Phosphate supplements	Vitamin D analogs (alfacalcidol only[a])	Surveillance for efficacy and safety	Frequency
Infancy (dose) divided into	55–70 mg/kg per day	1.5–2.0 µg/day once/day	Clinical: height, weight, cranial circumference	Every 3 months
	four times/day		Blood: alkaline phosphatases, total calcium, PTH, creatinine	
			Urines (spot): calcium/creatinine	
Childhood (dose) divided into	45–60 mg/kg per day	1.0–2.0 µg/day	Clinical: height, weight, leg bowing, teeth	Every 6 months
	three times/day	once/day	Blood: alkaline phosphatases, total calcium, PTH, creatinine	Every 6 months
			Urines (24-h): calciuria, phosphaturia	Every 3 months
			Renal ultrasound	Every year
Puberty (dose) divided into	35–50 mg/kg per day	1.5–3.0 µg/day	Clinical: height, weight, leg bowing, teeth	Every 6 months
	three times/day	once/day	Blood: alkaline phosphatases, total calcium, PTH, creatinine	Every 6 months
			Urines (24-h): calciuria, phosphaturia	Every 3 months
			Renal ultrasound	Every year

(Linglart et al. 2014)

For subjects in Japan and Korea, the Week 64 visit at the end of the Treatment Period will be the End of Study (EOS) Visit ("Week 64/EOS I"); subjects in these countries will be enrolled into a separate clinical trial of KRN23 or will receive KRN23 through another mechanism. Post-study safety follow up calls and safety visits will occur only for subjects who are not documented to be continuing on KRN23 at the Week 64/EOS I Visit. A safety follow-up telephone call will occur at 5 weeks (+5 days) after the Week 64/EOS I Visit to determine if KRN23 therapy has been started in another clinical trial, as commercial product, or through another mechanism; if KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue KRN23 therapy, an additional safety visit will occur 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing the blood and urine samples as part of a Home Health visit.

Treatment Extension Period (Weeks 66 – 140) – Subjects in Europe, the US, Canada, and Australia

The purpose of Treatment Extension Period is to continue to provide KRN23 treatment after the Treatment Period to subjects in Europe, the US, Canada, and Australia while also continuing to collect long-term safety and efficacy data. Safety and efficacy parameters will continue to be followed while subjects remain on study and receive treatment. After completion of the 64-week Treatment Period, subjects in Europe, the US, Canada, and Australia who were randomized to KRN23 will continue treatment with KRN23 at their previous dose and regimen in the Treatment Extension Period. Subjects who were randomized to active control will cross over to receive KRN23 at the starting dose and regimen administered to subjects in the KRN23 arm (starting dose of 0.8 mg/kg Q2W; dose may be increased to 1.2 mg/kg Q2W).

Before their first dose of KRN23 at Week 66, subjects who were in the active control arm in the Treatment Period will discontinue treatment with active control the day after the Week 64 visit to allow washout of oral phosphate and active vitamin D treatments. These subjects must have serum phosphorus < 3.2 mg/dL (< 1.03 mmol/L) (ie, below the lower limit of normal) to continue on study and receive KRN23 in the Treatment Extension Period.
If hypophosphatemia is not observed, the subject should be retested for serum phosphorus within a week to ensure that the test result was not due to a technical issue.
If hypophosphatemia is still not observed after test and retest, the subject will be discontinued from the study. The assessment of serum phosphorus to document hypophosphatemia before administration of the first dose of KRN23 in subjects originally assigned to active control will be done at the local laboratory so that KRN23 can be administered the same day. A sample will also be drawn for a serum phosphorus assessment at the central laboratory. For subjects crossing over to KRN23 treatment, the Weeks 66 and 68 visits will be in-clinic visits.

For subjects in Europe and Australia, the Treatment Extension Period will end in September 2018, and subjects will be enrolled into separate clinical trials of KRN23 or will receive KRN23 through another mechanism (Table 7.1.3). For subjects in the US and Canada, the Treatment Extension Period will end in September 2018 and June 2019, respectively, when commercial KRN23 is expected to be available; subjects will receive commercial KRN23 or will receive KRN23 through another mechanism. Subjects leaving the study will have an EOS visit that includes efficacy assessments (EOS II). Post-study safety follow-up calls and safety visits will occur only for subjects who are not documented to be continuing on KRN23 at the EOS II Visit. A safety follow-up telephone call will occur at 5 weeks (+5 days) after the EOS II Visit to determine if KRN23 therapy has been started in another clinical trial, as commercial product, or through another mechanism; if KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue KRN23 therapy, an additional safety visit will occur 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit.

Table 7.1.3: Enrollment in Treatment Extension Period, Study Duration, and Post-study KRN23 Treatment by Country or Region

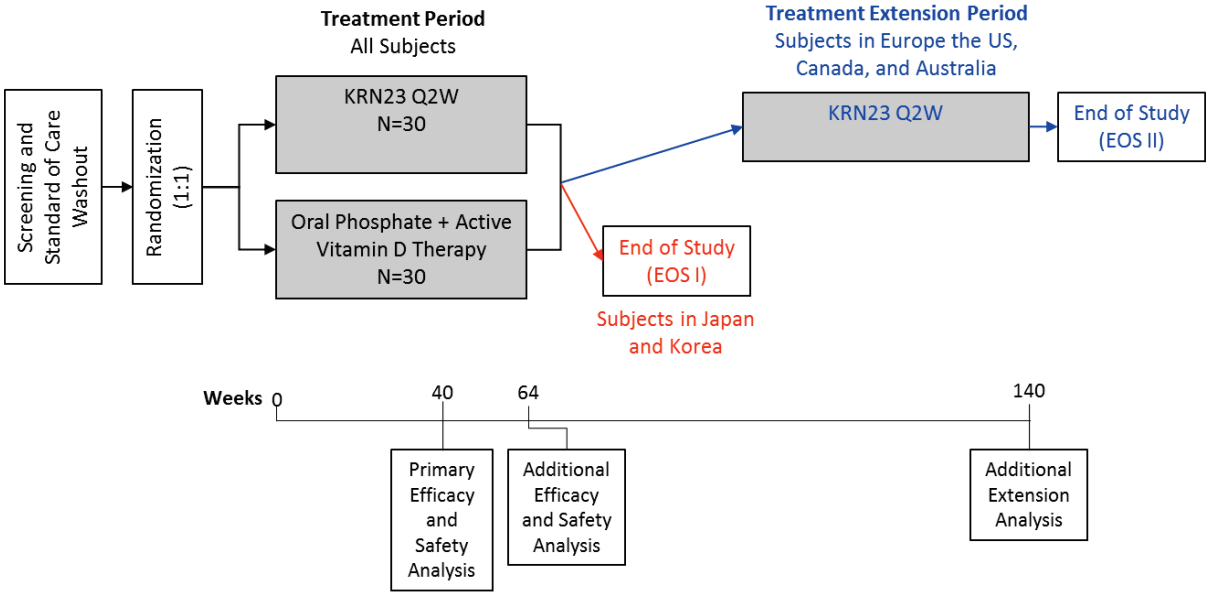
Country/ Region	Enrollment in Treatment Extension Period	Expected End of Study	Study Duration	Post-study KRN23 Treatment
Japan, Korea	No	Week 64/EOS I	64 weeks	Separate clinical trial or other mechanism
Europe, Australia	Yes	September 2018	Varies for individual subjects[a]	Separate clinical trial or other mechanism
US	Yes	September 2018	Varies for individual subjects[a]	Commercial KRN23 or other mechanism
Canada	Yes	June 2019	Varies for individual subjects[a]	Commercial KRN23 or other mechanism

[a] Maximum: 140 weeks

The study will be conducted in a pediatric population; as such, additional measures including an external, independent 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 including the use of home health visits (KRN23 treatment arm only). At every home health visit for subjects in the KRN23 treatment arm, all subjects randomized to the active control arm will receive a phone call to assess adverse events and concomitant medications. Home Health visits are not applicable to subjects in Japan or Korea. Where possible, timing of assessments will be coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing. The primary analysis will be at Week 40; analyses at Week 64/EOS I and Week 140/EOS II will assess the durability of treatment effect, additional efficacy outcomes, and long-term safety. The end of the study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

Figure 7.1.1 provides a schematic of the overall study design.

Figure 7.1.1: UX023-CL301 Study Schema



Pre- and post-prandial serum phosphorus and calcium concentrations will be assessed at a single clinic visit anytime 10 to 14 days after a KRN23 dose; this clinic visit may take the place of a Home Health visit. Approximately 20 subjects, age ≥ 3 years, will fast overnight for a minimum of 8 hours, and fasting serum will be collected prior to a breakfast containing predefined ranges of phosphate, calories, and carbohydrate representative of a typical Western diet for children. Dietary phosphate will be estimated based on the amount of food consumed. Serum samples will be drawn 1 and 2 hours after the completion of the meal.

All radiologic, renal ultrasound, and cardiac (ECG, ECHO) assessments will be administered by personnel trained in the performance of the tests in children, and the results will be interpreted by experts trained in the interpretation of pediatric data. All assessments will be performed and interpreted by staff who are blinded to assigned treatment in the Treatment Period.

7.2 Discussion of Study Design, Including Choice of Control Group

The primary objective of this study is to evaluate the effect of KRN23 therapy on improving rickets in children with XLH compared with an active control (oral phosphate/active vitamin D therapy). Secondary efficacy objectives are to evaluate the effect of KRN23 compared with active control on growth velocity, lower extremity deformity (ie, bowing), changes in serum phosphorus and other PD markers, walking ability and patient-/parent-reported pain, fatigue, and physical function/mobility. Dental outcomes will be evaluated as an exploratory objective. The safety objective will be to establish the safety and tolerability profile of KRN23 in the treatment of pediatric patients with XLH, including AEs (eg, nephrocalcinosis), as compared with active control, and immunogenicity profile.

An open-label study design was chosen since blinding such a study would be problematic due to the different methods of administration and the individualized nature and frequent dose adjustments needed with oral phosphate/active vitamin D therapy.

Data from the ongoing pediatric Phase 2 study (UX023-CL201) helped establish the dose regimen and provided information for the design of this Phase 3 clinical trial in children with XLH. Interim data from the pediatric Phase 2 study suggested KRN23, administered Q2W at approximately 0.8 mg/kg for 40 weeks, increased serum phosphorus by an average of 0.7 mg/dL; increases of > 0.5 mg/dL were seen in 83.3% of subjects. Serum $1,25(OH)_2D$ concentrations and TmP/GFR levels also increased, demonstrating overall improved phosphorus homeostasis. The increases in serum phosphorus and $1,25(OH)_2D$ were sufficient to provide substantial healing of rickets. No subjects have experienced serum phosphorus levels above the upper limit of normal. The Q2W dosing regimen was chosen for this Phase 3 study because it appeared to produce a more stable and consistent increase in serum phosphorus levels with less fluctuation over time than the Q4W dosing regimen, and a safety profile that was not substantially different from the Q4W dosing regimen.

Although there are no approved therapies for children with XLH, the most common treatment consists of multiple daily doses of oral phosphate combined with appropriate doses of active vitamin D analogs, most frequently calcitriol or alfacalcidol. Because of the variability in the doses and dosing frequencies of oral phosphates and active vitamin D therapies in clinical practice, these treatments will be individualized for each subject at the investigator's discretion, but general guidance is provided based on expert recommendations in the US and Europe as described in Table 7.1.1 and Table 7.1.2.

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 primary analysis will be at Week 40; analyses at Week 64/EOS I and Week 140/EOS II will assess the durability of treatment effect, additional efficacy outcomes, and long-term safety.

Change in rickets as measured by the RGI-C is deemed to be an appropriate primary efficacy endpoint in this study since it is the basis for, and correlates with the major morbidities patients with XLH suffer during their lifespan. A disease-specific RGI-C scale can be used to evaluate treatment-related changes in the severity of rickets and bowing in an individual subject. The RGI-C system of evaluating pre- and post- images in a side-by-side comparison is also ideal for the evaluation of healing of rickets as it most closely resembles the approach used by radiologists in the clinical setting to evaluate changes in the appearance of bone. Three pediatric radiologists not affiliated with the conduct of the study and who are blinded to subject number and treatment assignment will be contracted by a central imaging facility to perform RGI-C ratings. The ratings will be performed independently using an EDC system with the raters having no opportunity to discuss images or compare ratings. The mean of the scores assigned by the 3 independent raters is used to calculate an RGI-C wrist score, an RGI-C knee score, and a global RGI-C score.

The primary hypothesis of the primary endpoint is to test whether there is a difference between the KRN23 and active control (oral phosphate/active vitamin D) groups in the mean RGI-C global scores at Week 40. The RSS will serve as a complementary analysis to the RGI-C scale and is the method currently being used in the ongoing pediatric Phase 2 Study.

Additional secondary endpoints are designed to evaluate the beneficial impact of KRN23 in maximizing growth, restoring phosphorus homeostasis, ameliorating defective bone mineralization, reducing the clinical burden of disease, as well as to evaluate the safety of KRN23 in pediatric XLH.

The purpose of Treatment Extension Period is to continue to provide KRN23 treatment after the Treatment Period to subjects in Europe, the US, Canada, and Australia while also continuing to collect long-term safety and efficacy data.

7.3 Selection of Study Population

The proposed patient population for this Phase 3 study is pediatric patients with a diagnosis of XLH and rickets (as documented by bilateral PA hand/wrist radiographs). The proposed key inclusion/exclusion criteria are summarized in Sections 7.3.1 and 7.3.2.

To ensure that appropriate patients are selected, eligibility requirements include demonstrated hypophosphatemia, radiographic evidence of rickets, and genetic evidence consistent with a diagnosis of XLH. *PHEX* sequence variants will be classified consistent with the joint consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al. 2015). Patients with *PHEX* mutations classified as pathogenic, likely pathogenic, and possibly pathogenic will be included. Patients with *PHEX* variants of uncertain significance will also be included, as was recommended by experts in pediatric XLH. There are hundreds of variants of the *PHEX* gene and many of these have not yet been fully characterized. The study also requires patients to receive oral phosphate/active vitamin D therapy for ≥ 12 consecutive months prior to screening (for children ≥ 3 years of age) or ≥ 6 consecutive months (for children < 3 years of age), 7 days prior to the Randomization Visit..

To ensure that the patients enrolled will have open epiphyses for the duration of the study, only patients ≤ 12 years of age will be included and patients with a Tanner stage 4 or higher will be excluded. Limiting the maximum age to 12 years will help to ensure patients' epiphyses will remain open during the course of the study so that changes in rickets and growth can be evaluated. Week 40 results (N=36) from Phase 2 Study (UX023-CL201) indicated that to best demonstrate a treatment effect and maximize the ability to detect change, baseline rickets should be clearly evident radiographically; the minimal threshold of baseline rickets severity to consistently detect change with treatment based on the current UX023-CL201 data is an RSS score of ≥1.5. To ensure that all patients will have significant rickets at baseline, the study will include patients with a baseline total RSS of 2.0 or higher. Patients will be required to have been on oral phosphate/active vitamin D treatment for at least 12 consecutive months (for children ≥3 years of age) or ≥ 6 consecutive months (for

children <3 years of age) and have residual disease despite this in order to show the effect of KRN23 in a relevant population in which the unmet medical need is very clear. A majority of patients with XLH receive treatment within the first 2 years of life. Therefore, the study will not enroll any treatment-naïve patients. To ensure the protection and safety of the study population, the study excludes patients with evidence of hyperparathyroidism, hypocalcemia, and hypercalcemia.

Females are affected more frequently than males, consistent with X-linked dominant inheritance (Ichikawa et al. 2013). However, it is unclear whether the severity of disease is affected by sex or gene dosage. Therefore, no more than 70% female subjects will be enrolled.

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. Published retrospective data suggest that earlier treatment leads to better outcomes for children with XLH (Makitie et al. 2003), (Quinlan et al. 2012). Thus, initiation of therapy at early ages is recommended to achieve improved height outcomes (Carpenter et al. 2011). Consequently, children younger than 5 years of age were included to determine if earlier treatment with KRN23 would confer greater benefits in improving rickets and growth potential, as well as in restoring normal phosphorus homeostasis. At least 20 subjects aged 1 to < 5 years will be included (approximately 10 in each treatment arm).

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.

7.3.1 Inclusion Criteria

Note: All laboratory evaluations required for study eligibility will be determined centrally

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

1) Male or female, aged 1 to ≤12 years with radiographic evidence of rickets with a minimum rickets severity score (RSS) total score of 2.0 as determined by central read
2) *PHEX* mutation or variant of uncertain significance in either the patient or in a directly related family member with appropriate X-linked inheritance
3) Biochemical findings associated with XLH: Serum phosphorus < 3.0 mg/dL (< 0.97 mmol/L)*
4) Serum creatinine below the age-adjusted upper limit of normal *
5) Serum 25(OH)D above the lower limit of normal (≥16 ng/mL) at the Screening Visit**

6) Have received both oral phosphate and active vitamin D therapy for ≥ 12 consecutive months (for children ≥ 3 years of age) or ≥ 6 consecutive months (for children <3 years of age) 7 days prior to the Randomization Visit
7) Willing to provide access to prior medical records for the collection of historical growth and radiographic data and disease history.
8) Provide written or verbal assent (as appropriate for the subject and region) 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. Female subjects of childbearing potential must be willing to use a highly effective method of contraception for the duration of the study plus 12 weeks after stopping the study drug. Sexually active male subjects with female partners of childbearing potential must consent to use a condom with spermicide or a highly effective method of contraception for the duration of the study plus 12 weeks after stopping the study drug.

7.3.2 Exclusion Criteria

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

1) Tanner stage 4 or higher in any of the following: genitals, breast, or pubic hair, based on physical examination
2) Height percentile > 50th based on country-specific norms
3) Use of aluminum hydroxide antacids (eg, Maalox® and Mylanta®), systemic corticosteroids, acetazolamide, and thiazides within 7 days prior to the Screening Visit
4) Current or prior use of leuprorelin (eg, Lupron®, Viadur®, Eligard®), triptorelin (TRELSTAR®), goserelin (Zoladex®), or other drugs known to delay puberty
5) Use of growth hormone therapy within 12 months before the Screening Visit
6) Presence of nephrocalcinosis on renal ultrasound grade 4 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 orthopedic surgery, including osteotomy or implantation or removal of staples, 8-plates, or any other hardware, within the first 40 weeks of the study
8) Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits*
9) Evidence of hyperparathyroidism (PTH levels 2.5X upper limit of normal [ULN])
10) Use of medication to suppress PTH (eg, cinacalcet, calcimimetics) within 2 months prior to the Screening Visit
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) History of recurrent infection or predisposition to infection, or of known immunodeficiency
14) Use of a therapeutic monoclonal antibody within 90 days prior to the Screening Visit or history of allergic or anaphylactic reactions to any monoclonal antibody
15) 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.
16) 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.

    OR, in Japan, use of any investigational product or investigational medical device within 4 months 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 the Screening and/or Baseline Visit

** If 25(OH)D levels are below the normal range, 25(OH)D supplementation will be prescribed. Assuming a subject meets all other eligibility requirements, the subject may be rescreened after a minimum of 7 days of treatment

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 and Ultragenyx also have the right to remove subjects from the study. 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
- Pregnancy in subject
- At the request of the subject, investigator, or Ultragenyx, for administrative or other reasons
- Protocol deviation or noncompliance

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 12 weeks 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 4 weeks of discontinuation. Subjects who discontinue KRN23 due to an SAE will be monitored for safety for a period of 12 weeks after the date of last study drug administration.

7.3.3.1 Stopping Rules

A Data Monitoring Committee (DMC) will be constituted for Study UX023-CL301 and will act in an advisory capacity to monitor the safety of KRN23 on a routine basis throughout the trial (Section 7.6.6). The DMC may provide advice to Ultragenyx to aid in the determination of whether study enrollment should be paused or if the study should be stopped. If the Sponsor deems it appropriate to restart the trial following an internal safety review, this will be done only following approval by Regulatory Authorities.

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 renal ultrasound (Section 7.5.3). 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 Institutional Review Board (IRB)/Ethics Committee (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

The study drug and reference products are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations. The Investigational Product should be securely stored under conditions indicated in the IB.

The amount of investigational product administered will be calculated based on a subject's weight (Section 7.4.1). Treatment with oral phosphates and active vitamin D will be individualized to reflect real-world clinical practice, but general guidance will be provided (Section 7.4.2).

Selection of doses, dose titration, and dose adjustments for the investigational product are described in Section 7.4.4.

7.4.1 Investigational Product (KRN23)

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. The starting dose will be 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) 2 consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by ≤ 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of KRN23 that would account for the decrease in serum phosphorus. The maximum allowable dose of KRN23 per administration is 90 mg.

At any time during the study, if serum phosphorus increases above the upper limit of normal (ULN) for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received (ie, half of either 0.8 mg/kg or 1.2 mg/kg; maximum dose per administration: 40 mg). Serum phosphorus will be followed through unscheduled serum phosphorus assessments (approximately 2 weeks post-dose and assessed by the central laboratory; the assessments may be repeated as necessary). A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

Subjects will receive study drug via SC injection to the abdomen, upper arms, thighs, or buttocks; the injection site should be rotated with each injection. If the dose level exceeds 1.5 mL in volume, the dose should be administered at 2 injection sites.

KRN23 dosing should occur no sooner than 8 days after the last dose administered.

7.4.2 Active Control (Reference) Therapy

The study is designed as an open-label comparison with oral phosphate and active vitamin D therapy, which will be individualized by subject at the investigator's discretion based on published US and European expert guidelines (Carpenter et al. 2011), (Linglart et al. 2014) (in Table 7.1.1 and Table 7.1.2). It should be noted that while commonly used, oral phosphate and active vitamin D therapy are not approved for the treatment of XLH.

Detailed information about the brand, starting dosages, and any changes in oral phosphate and active vitamin D therapy will be determined by the treating Investigator within the expert guidelines and recorded at every site visit. US expert guidelines generally recommend a calcitriol dosage of 20 to 30 ng/kg/day in 2 to 3 divided doses and an elemental phosphorus dose of 20 to 40 mg/kg/day (in 3 to 5 divided doses), acknowledging that some children require more, whereas some do well with less (Carpenter et al. 2011). European expert guidelines recommend an alfacalcidol dosage of 1 to 2 µg/day (once daily) and a phosphate supplemental dose of 45 to 70 mg/kg/day (in 3 to 4 divided doses) (Linglart et al. 2014). Calcitriol and alfacalcidol dosages should be adjusted based on the clinical and laboratory values that guide best possible treatment.

7.4.3 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. Subjects will be randomized 1:1 to receive open-label KRN23 by subcutaneous injection or active control via an Interactive Web Response System (IWRS) based on a randomization schedule developed by an independent third-party vendor. Randomization will be stratified by baseline rickets severity (RSS total score ≤ 2.5 vs > 2.5) and age (< 5 vs ≥ 5 years).

After completion of the 64-week Treatment Period, subjects in Europe, the US, Canada, and Australia who were randomized to KRN23 will continue treatment with KRN23 at their previous dose and regimen in the Treatment Extension Period. Subjects in Europe, the US, Canada, and Australia who were randomized to active control will cross over to receive KRN23 at the starting dose and regimen administered to subjects in the KRN23 arm (starting dose of 0.8 mg/kg Q2W; dose may be increased to 1.2 mg/kg Q2W).

7.4.4 Selection of Doses and Study Duration

The amount of KRN23 administered will be calculated based on the subject's weight.
As discussed earlier, data from the pediatric Phase 2 study suggested KRN23, administered Q2W at approximately 0.8 mg/kg for 40 weeks, increased serum phosphorus by an average of 0.7 mg/dL; increases of > 0.5 mg/dL were seen in 83.3% of subjects. The Q2W dosing regimen was chosen for this Phase 3 study because it appeared to produce a more stable and consistent increase in serum phosphorus levels with less fluctuation over time than the every 4 week (Q4W) dosing regimen, and a safety profile that was not substantially different from the Q4W dosing regimen.

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. A study duration of 40 weeks, similar to the Phase 2 study (UX023-CL201), is considered sufficient to observe treatment effect on rickets; therefore, the primary analysis was established at Week 40. A longer period of 64 weeks will assess the durability of treatment effect, additional efficacy outcomes, and long-term safety. The Treatment Extension Period will provide long-term safety and efficacy data up to 140 weeks.

Treatment duration will vary by region. The study consists of a Treatment Period (64 weeks) for all subjects and a Treatment Extension Period (up to 76 weeks) for subjects in Europe, the US, Canada, and Australia. For subjects in Japan and Korea, the planned duration of treatment in this study is 64 weeks, and the Week 64 visit at the end of the Treatment Period will be the EOS I visit. For subjects in Europe, the US, Canada, and Australia, the planned duration of treatment is up to 140 weeks (64 weeks in the Treatment Period and up to 76 weeks in the Treatment Extension period). In Europe and Australia, treatment in the Treatment Extension Period will end by September 2018, and subjects will be enrolled in separate clinical trials of KRN23 or will receive KRN23 through another mechanism. In the US and Canada, treatment in the Treatment Extension Period will end by September 2018 or June 2019, respectively (expected availability of commercial KRN23); subjects will receive commercial KRN23 or will receive KRN23 through another mechanism. The duration of Treatment Extension Period will vary for individual subjects and will be determined by the time from Week 64 through the EOS II visit.

The end of the study for reporting purposes 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, all subjects will undergo a washout period where they will discontinue treatment with oral phosphates and pharmacologic vitamin D metabolites or analogs (eg, calcitriol, doxercalciferol, alfacalcidol, and paricalcitol) for 7 days prior to randomization. Eligible subjects will then be randomly assigned to receive either KRN23 treatment or oral phosphates/active vitamin D treatment (control). Subjects randomly assigned to KRN23 are prohibited from receiving oral phosphates and active vitamin D for

the duration of the study. Subjects randomly assigned to the active control arm will be permitted to receive oral phosphates/active vitamin D treatment after randomization.

At Week 64 for subjects continuing into the Treatment Extension Period, subjects randomized to active control in the Treatment Period will cross over to receive KRN23 at the dose and regimen administered to subjects in the KRN23 arm. Active control will be discontinued after the Week 64 visit to allow washout of oral phosphate and active vitamin D treatments before the first dose of KRN23 at Week 66.

In addition, subjects must agree to discontinue use of certain medications for the indicated timeframe to qualify for study entry (Section 7.3).

- Growth hormone therapy within 12 months before the Screening Visit
- Aluminum hydroxide antacids (eg, Maalox® and Mylanta®), systemic corticosteroids, acetazolamide, and thiazides within 7 days prior to the Screening Visit
- Current and prior use of leuprorelin (eg, Lupron®, Viadur®, Eligard®), triptorelin (TRELSTAR®), goserelin (Zoladex®), or other drugs known to delay puberty
- PTH suppressors (eg, Sensipar®, cinacalcet, calcimimetics) within 2 months prior to the Screening Visit
- Any therapeutic mAb therapy within 90 days prior to the Screening Visit

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. Subjects randomly assigned to the active control arm may receive oral phosphate/active vitamin D treatment after a 7-day washout and randomization. If serum 25-hydroxyvitamin D (25(OH)D) levels fall below 16 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 KRN23 by SC injection or dispense oral phosphates and active vitamin D treatment at the investigational site or during home health visits (KRN23 treatment arm only) as indicated in the Schedule of Events (Table 2.1 Table 2.2, and Table 2.3). Each administration of study drug or oral phosphate/active vitamin D (including type, dose, and frequency) will be recorded on the CRF. If a subject does not receive a dose within 10 days of a scheduled dose for the Q2W regimen of study drug, that dose should be skipped and the next dose will be administered at the next scheduled Q2W dosing visit.

7.5 Study Procedures and Assessments

7.5.1 Schedule of Events

The schedule of visits and assessments are provided in Table 2.1 and Table 2.2, and Table 2.3. Home Health visits (KRN23 treatment arm only) may 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 subjects will have x-rays (knees and hand/wrist) at the Screening Visit and confirmed by central read prior the Baseline visit to determine if the subject meets the eligibility criteria. If radiographic evidence of rickets is not present (ie, RSS total score ≥2.0), the subject will be considered a screen failure. Patients with confirmed rickets who also have a *PHEX* mutation or variant of uncertain significance in either self or an appropriate directly related family member can start the process of weaning from oral phosphate/active vitamin D therapy (Section 7.4.5.1) and return to the site after 7 days for the Baseline visit if all other inclusion criteria are met. *PHEX* mutation analysis will be performed in all subjects. Potential subjects without a previously confirmed *PHEX* mutation will be notified of *PHEX* mutation results, and if presence of a mutation is confirmed, will have the baseline visit scheduled.

Subjects who successfully pass the requirements at the Screening Visit will discontinue oral phosphate for a minimum of 7 days and active vitamin D therapy for a minimum of 7 days prior to the Baseline visit. The Screening Visit window may be up to 8 weeks for *PHEX* mutation analysis and washout of oral phosphate and active vitamin D therapy. Subjects who have serum 25(OH)D below the lower limit of normal (16 ng/mL) will need to have the levels corrected and, assuming they meet all other eligibility requirements, the subject may be rescreened after a minimum of 7 days. Walking ability (6MWT; for subjects ≥ 5 years of age at the Screening Visit) will be completed at the Screening Visit (for practice) and at the Baseline (Week 0) visit; the Baseline 6MWT must be assessed on the same day that the questionnaires are administered. Pain, fatigue, and physical function (PROMIS [Patient-Reported Outcomes Measurement Information System] Pain Interference, Physical Function Mobility and Fatigue domain scores; for subjects ≥ 5 years of age at the Screening Visit); pain intensity (Faces Pain Scale – Revised [FPS-R] for subjects ≥ 5 years of age at the Screening Visit, and the SF-10 for Children Health Survey (SF-10; for subjects ≥ 5 years of age at the Screening Visit) may be completed at the Baseline visit.

Historical radiographs of the anteroposterior (AP) knee, posteroanterior (PA) hand/wrist, and long leg are of importance and interest to evaluate the presentation and severity of the subject's XLH disease and rickets severity over time. Available AP knee, PA hand/wrist, and standing long leg radiographs taken in the 5 years prior to the Screening Visit will be collected; radiographs of other skeletal locations will not be collected. Approximately 1 set of radiographs per year will be collected; if there are multiple sets within a year, the set

closest to the subject's birthday should be obtained. The wrist and knee radiographs will be used to evaluate rickets severity and to determine how much rickets fluctuate over time in patients who were treated with oral phosphate/active vitamin D prior to study enrollment. The standing long leg radiographs will be used to assess changes in genu varum and/or valgum following prolonged treatment with oral phosphate/active vitamin D prior to study enrollment. The images will be de-identified and rated using the RSS and RGI-C.

Similarly, historical growth data are of importance and interest. All available recumbent length and standing height data assessed prior to the Screening visit will be collected.

All study visits will be scheduled relative to the Baseline visit, with an allowable variance of ± 3 days for each visit (with the exception of the Screening and Safety Follow-up Visits) to accommodate scheduling. All Screening/Baseline assessments and inclusion/exclusion criteria based on central laboratory results must be satisfied prior to randomization and dosing. KRN23 dosing should occur no sooner than 8 days since the last dose administered.

Subjects may be monitored between site visits through a series of Home Health visits (KRN23 treatment arm only) depending on the preference of the subject and the proximity of the subject to the site. Home Health visits are not applicable to subjects in Japan or Korea. The visit window for Home Health visits is ±3 days during the Treatment Period. HH visits are not required for subjects randomized to the active control arm because they do not require their medicine to be administered by a healthcare professional. To more closely mimic clinical practice, subjects randomized to the active control arm will only be seen at the site visits. 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 will not be performed at the Early Termination visit if post-treatment test(s) have been performed within 6 months of Early Termination. Similarly, the 6MWT 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.

Post-study safety follow-up calls and safety visits will occur only for subjects who are not documented to be continuing on KRN23 at the Week 64/EOS I Visit or EOS II Visit, as appropriate. A safety follow-up telephone call will occur for these subjects at 5 weeks (+5 days) after the Week 64/EOS I visit (in Japan and Korea) or after the EOS II visit (in Europe, the US, Canada, and Australia) to determine if the subject is receiving KRN23 therapy in another clinical trial, as commercial product, or through another mechanism. If KRN23 therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue KRN23 therapy, an additional safety visit will occur 12 weeks ±1 week after the last dose of study drug. Every reasonable effort should be made to have required 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 providing blood and urine samples as part of a Home Health visit.

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

7.5.2 Efficacy Measurements

Clinical efficacy measures will evaluate the effect of KRN23 on bone health and functional outcome in children with XLH. Measures of healing of rickets, growth, 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 and patient/parent-reported pain, fatigue, and physical function/mobility will provide insight into the effect of KRN23 on clinical outcomes.

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

7.5.2.1 Primary Efficacy Measurement

XLH causes rickets in the wrists and/or knees and other bone abnormalities and the primary goals of treatment in children with XLH are to prevent and heal rickets and radiographic abnormalities. The primary efficacy endpoint in this study is change in rickets at Week 40 as assessed by the RGI-C global score.

Bilateral AP knee radiographs and bilateral PA hand/wrist radiographs will be taken at the Screening Visit to confirm eligibility and at the Weeks 40, 64, 88, 112, and 140/EOS II (or Early Termination) study visits. Screening radiographs will be read centrally. Standing long-leg radiographs will be taken at Baseline, Weeks 40, 64, 88, 112, and 140/EOS II (or Early Termination). Knee, hand/wrist, and standing long leg radiographs will be taken at Early Termination if post-baseline radiographs have not been obtained within 6 months of termination. Radiographs will be read centrally and will be interpreted. AP knee and PA hand/wrist x-rays will be acquired for all subjects and standing long leg x-rays will be acquired for all qualifying subjects.

The RGI-C utilizes a 7-point ordinal scale to evaluate the extent of healing in pre- vs. post-treatment x-rays with scores ranging from -3 (very much worse or severe worsening of rickets or bowing) to +3 (very much better, indicating complete or near complete healing of rickets or significant improvement in bowing). Three pediatric radiologists not affiliated with the conduct of the study will be contracted by a central imaging facility to perform RGI-C ratings for the wrist, knee, and long leg images. The 3 raters will be blinded to subject number and treatment assignment. To keep the radiologists blinded to group (ie, KRN23 treatment or active control group), x-ray pairs will be presented for review in random order and the radiologists will not be provided access to the protocol, subject identifiers, or information related to KRN23 or oral phosphate/active vitamin D treatment. The ratings will be performed independently using an EDC system with the raters having no opportunity to discuss images or compare ratings. For each rating exercise, radiographs are presented side-by-side with the earlier image (baseline) on the left and the later image on the right.

Radiographs will be taken at the Screening Visit and Weeks 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination).

7.5.2.2 Secondary Efficacy Measurements

7.5.2.2.1 Rickets Severity Score (RSS)

As a complementary measure to the RGI-C, 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, radiographs of the wrist and knee are scored individually by a central rater who is blinded to subject number, characteristics, and treatment assignment. Radiographs of the wrists and knees will be taken at the Screening Visit and Weeks 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination).

7.5.2.2.2 Lower Extremity Deformities

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. 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, as well as other disease-specific lower extremity abnormalities, standing long leg x-rays will be taken at the Baseline Screening Visit and Weeks 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination if post-baseline x-rays have not been obtained within 12 months of termination). Central readings of the standing long leg X-rays will be performed and ratings assigned using a disease-specific qualitative RGI-C scoring system.

7.5.2.2.3 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 prior to and following treatment by changes in standing height and sitting height (and percentiles) for subjects ≥ 2 years old or in recumbent length (and percentiles) for subjects < 2 years old. Recumbent length will be measured in subjects < 2 years old or those unable or unwilling to stand for the measurement. Standing height/recumbent length measurements prior to treatment will be abstracted from medical records. Parents will also be asked to report their final adult height and this information will be recorded in the CRF. To assess growth during KRN23 treatment, standing height/recumbent length and sitting height will be measured by a clinical evaluator at Baseline and Weeks 24, 40, 64, 76, 88, 100, 112, 124, and 140 (or Early Termination).
At each time point, heights or recumbent length will be assessed 3 times and each assessment will be recorded onto the subject chart and eCRF. An average of the 3 measurements will be calculated. All pre-treatment growth historical records will be collected. Change in growth

velocity will be evaluated pre-treatment and post-treatment at Weeks 40, 64/EOS I, 76, 88, 100, 112, 124, and 140/EOS II (or Early Termination).

7.5.2.2.4 Pharmacodynamic Assessments

KRN23 binds to and inhibits FGF23, which is an important regulator of serum phosphorus levels. Serum phosphorus will be measured as a key PD assessment in this study. To assess the spectrum of KRN23 biological activity on phosphorus homeostasis and markers of bone health, and optimize dose level and regimen, a panel of PD markers will be assessed as indicated in the Schedule of Events, including serum PD markers (phosphorus and $1,25(OH)_2D$), markers of phosphate reabsorption (TmP/GFR and TRP), and a bone biomarker (ALP).

PD parameters will be assessed by central laboratory to determine study eligibility. Where possible, PD parameters (serum phosphorus and ALP) will be assessed as part of the standard clinical laboratory tests for safety (Section 7.5.3.8).

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 (Payne 1998). For subjects < 5 years of age, spot urine may be collected in place of the 2-hr urine samples for measurements of urinary calcium, phosphorus, and creatinine. 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.

7.5.2.2.5 Walking Ability and Patient-reported Outcomes

Gross motor impairment, including diminished walking ability, pain and muscle weakness are potential complications associated with XLH-related skeletal deformities.

The Six Minute Walk Test (6MWT) will be administered in subjects ≥ 5 years of age at the Screening Visit at the following study visits: at the Screening Visit (for practice), Baseline (Week 0), and Weeks 24, 40, 64, 88, 112, and 140 (or Early Termination if post-baseline 6MWT has not been obtained within 3 months of termination and Early Termination occurs at or before Week 140). If a subject is < 5 years of age at the Screening Visit, the 6MWT will not be assessed when the subject is over 5 years of age during the post-baseline visits. The 6MWT will be administered by a trained clinician. Subjects will be instructed to walk the length of a pre-measured course for 6 consecutive minutes. The total distance walked at the end of 6 minutes will be recorded in meters (Geiger et al. 2007).

The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). The domain-specific approach is based on the idea that health attributes, such as pain and physical function are not unique to a specific disease. The PROMIS contains a bank of questions from which relevant items can be

extracted and used to create a custom form. The PROMIS Pain Interference, Physical Function Mobility, and Fatigue domain scores will be administered to subjects ≥ 5 years of age at the Screening Visit. To assess these health domains, items from the Pediatric Pain Interference, Physical Function Mobility, and Fatigue item banks (Version 2.0) were extracted to develop a self-report form that will be completed by children 8 years of age and older at the Screening Visit. For children ages 5 to < 8 years at the Screening Visit, the same items were extracted from the Parent Proxy item banks (Version 2.0) that will be completed by the parent or legal guardian. The Parent/Legal Guardian form will be used for the duration of the study for subjects < 8 years of age at the Screening Visit, even when a subject turns 8 years old during the study. If a subject who is > 8 years of age at Screening has difficulty completing the PROMIS self-report, the investigator may allow the PROMIS interview to be administered by a trained clinic staff or allow the parent to complete the PROMIS Parent Proxy version. The reason should be carefully documented and consistent practice of administration should be maintained for every visit from Baseline. The PROMIS Pain Interference, Physical Function Mobility, and Fatigue measurements will be administered at Baseline (Week 0) and Weeks 24, 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination).

Pain intensity will be self-reported by subjects using the Faces Pain Scale – Revised (FPS-R) for subjects ≥ 5 years of age at the Screening Visit. The FPS-R is a self-reported measure of pain intensity developed for children (Hicks et al. 2001). It was adapted from the Faces Pain Scale (Bieri et al. 1990) to make it possible to score the sensation of pain on the widely accepted 0-to-10 metric. The FPS-R has been validated for use in children 5 to 16 years of age. The FPS-R graphically depicts pain intensity using faces with scores chosen from 0, 2, 4, 6, 8, and 10 (0=no hurt; 10=hurts worst). The FPS-R will be administered at Baseline (Week 0) and Weeks 24, 40, 64, 88, 112, and 140 (or Early Termination).

7.5.2.2.6 Pharmacokinetic Assessment

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 Weeks 1, 2, 4, 8, 16, 24, 33, 40, 64/EOS I during the Treatment Period. For each sample collection, the time elapsed since last study drug administration will be recorded on the CRF. Subjects randomized to active control will not have blood samples drawn for this assessment during the Treatment Period; during the Treatment Extension Period, blood samples for KRN23 concentrations will be drawn on the same schedule as subjects originally randomized to KRN23, ie, Weeks 88, 112, and 140/EOS II (or Early Termination). In addition, for subjects crossing over to KRN23 during the Treatment Extension Period, a sample for KRN23 serum concentration will be drawn at Week 68.

7.5.3 Safety Measurements

General assessments include Tanner staging for breast and testicular development, *PHEX* mutation analysis, medical history, and demographics. 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 in vital signs, weight, interval history and physical examination, eGFR, clinical laboratory evaluations (including additional KRN23/XLH biochemical parameters of interest), and concomitant medications. Ectopic mineralization safety assessments include renal ultrasound, echocardiogram (ECHO) and ECG, serum calcium 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.

7.5.3.1 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 previous treatments (eg, oral phosphate/active vitamin D).

Subjects must be willing to provide access to prior medical records for the collection of 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, including any available previous *PHEX* mutation analysis results for the subject or relevant family members with appropriate X-linked inheritance pattern. The height of both parents will also be recorded.

XLH treatment history and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Previous treatments may include calcitriol and oral phosphate, calcimimetics, and 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.

7.5.3.2 Vital Signs Including Standardized Blood Pressure Measurement Procedure

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). Blood pressure (BP) measurements will only be obtained at clinic visits and only in children ≥3 years of age at the Screening Visit. Children who turn 3 years of age during the study will start BP assessments at the next scheduled clinic visit and continue with subsequent scheduled BP assessments for the duration of the study. The guidance provided by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (NIH 2005) will be used as a reference.

Vital signs measurements will be obtained at each indicated visit (Table 2.1, Table 2.2, and Table 2.3). On the Screening and Baseline Visit, 2 sets of 3 BP measurements will be obtained - the first set will be done at the beginning of the visit and the second set at end of the visit after all site procedures are completed. BP measurements should be done after the

subject has rested for 5 minutes and a second and third BP measurement should be obtained, each performed 30 seconds apart. Thus there will be a total of 6 BP measurements on these 2 visits. As part of the site initiation visit, standardized BP measurement training will be provided to all study personnel responsible for BP measurement and appropriate documentation in monitoring report. In addition, evidence of annual calibration of BP measurement device will be documented.

Participants are instructed to refrain from exercise at least 30 minutes before and until completion of BP measurement. They are also instructed to refrain from playing video games, or other activities that may affect BP until all measurements are obtained. Clinic BP measurements are obtained in the right arm of the study participant. At each study visit, before BP determination, arm circumference is measured (in centimeters) with a plastic measuring tape at the midpoint of the upper arm between the acromium (tip of shoulder) and olecranon (tip of elbow) and a cuff is then selected so that the length of the cuff bladder is equal to 80% to 100% of the arm circumference. Effort should be made to use the same BP measuring device for BP measurements during subsequent visits.

After 5 minutes of rest, pulse and BP measurements begin. The cuff is inflated approximately 30 mm Hg above the pressure when the radial pulse is no longer felt. The BP measurements are obtained by auscultation (ie, manually and without using an automated device) of the brachial artery using the first Korotkoff sound for systolic BP (SBP) and the fifth Korotkoff sound for diastolic BP (DBP). Three BP measurements are obtained at a sitting and recorded in the participant's BP records for the study visit. For the subsequent site visits post-baseline, 3 BP measurements is recorded during the site visit.

7.5.3.3 Echocardiogram

ECHO will be performed at Baseline and Weeks 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination if not performed within 3 months of termination) in subjects ≥ 5 years of age at the Screening Visit. Children who turn 5 years of age during the study will start ECHO assessments at the next scheduled clinic visit and continue with subsequent scheduled ECHO assessments for the duration of the study. The goal is to assess for evidence of ectopic mineralization in the heart and aorta. 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 site personnel.

7.5.3.4 Weight

Weight will be obtained using a scale and recorded in kilograms at the Screening Visit, Baseline, and at study visits at Weeks 1, 4, 8, 16, 24, 32, 40, 52, 64/EOS I, 76, 88, 100, 112, 124, and 140/EOS II (or Early Termination) (Table 2.1, Table 2.2, and Table 2.3).
In addition, for subjects crossing over to KRN23 during the Treatment Extension Period, weight will be obtained at Week 68. The subject's weight collected at in-clinic visits will be the basis of the KRN23 dose calculation until the next in-clinic weight collection.

7.5.3.5 Physical Examination

Complete physical examinations will be performed at the Screening Visit, Baseline, and at the study visits at Weeks 8, 16, 24, 32, 40, 52, 64, 76, 88, 100, 112, 124, and 140 (or Early Termination) and at the Safety Visit (if applicable). In addition, for subjects crossing over to KRN23 during the Treatment Extension Period, a complete physical exam will be performed at Week 68. 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. The genitourinary exam should be non-invasive, age-appropriate and consistent with the standard of care principles of the Investigator. The primary purpose of the genitourinary exam is to establish and monitor Tanner staging over the course of the study.

7.5.3.6 Renal Ultrasound and Glomerular Filtration Rate

Renal ultrasounds will be conducted at the Screening Visit, and Weeks 24, 40, 64/EOS I, 88, 112, and 140/EOS II visits (or Early Termination). The ultrasound will be interpreted by qualified personnel at the central laboratory for purposes of inclusion criteria.

Baseline and all post-treatment renal ultrasounds will be evaluated by a trained central reader blinded to treatment assignment and subject data to evaluate changes in calcifications and all other renal abnormalities from baseline (.e, screening assessment). Ultrasonographic findings of nephrocalcinosis will be graded on a 5-point scale (Verge et al. 1991).

The eGFR will be calculated using the Bedside Schwartz equation (Schwartz et al. 1976) for determining creatinine clearance.

7.5.3.7 Electrocardiogram

A standardized 12-lead ECG will measure PR, QRS, QT, and QTc at Baseline and Weeks 24, 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination). The goal is to evaluate both for left ventricular hypertrophy (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 blinded to treatment assignment and subject data. The ECG results will be assessed for any clinically significant abnormality or relevant changes from baseline.

7.5.3.8 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 safety. Certain analytes (eg, serum phosphorus) in the routine Chem-20 panel are also designated as PD/efficacy parameters in this study. Additional KRN23/XLH biochemical parameters of interest include serum $1,25(OH)_2D$, calcium, creatinine, and iPTH; and urinary phosphorus, calcium, and creatinine.

Blood and urine samples will be collected at Screening, Baseline, and regular intervals throughout the study as indicated in the Schedule of Events (Table 2.1, Table 2.2, and Table 2.3).

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 for subjects ≥ 5 years of age is required to assess urinary phosphorus:creatinine and calcium:creatinine ratios; urinary phosphorus, a PD parameter will also be obtained from 24-hour urine samples. Details for blood and urine collection can be found in the central laboratory manual.

Pre- and post-prandial serum phosphorus and calcium concentrations will be assessed at a single visit in approximately 20 subjects (Section 7.5.4.3).

Clinical laboratory parameters to be assessed for safety are provided in Table 7.5.3.8.1. See the Study Reference Manual for details on sample collection and processing.

Table 7.5.3.8.1: Clinical Laboratory Assessments for Safety

Chemistry	**Hematology**	**Urinalysis**
$1,25(OH)_2D$	Hematocrit	Appearance
Alanine aminotransferase (ALT)	Hemoglobin	Color
Alkaline phosphatase (ALP)	Platelet count	pH
Amylase	Red blood cell (RBC) count	Specific gravity
Aspartate aminotransferase (AST)	White blood cell (WBC) count	Ketones
Bilirubin (direct and total)	Mean corpuscular volume (MCV)	Protein
Blood urea nitrogen (BUN)	Mean corpuscular hemoglobin (MCH)	Glucose
Calcium (total)	MCH concentration	
Chloride		
Cholesterol (total)		**24-hour Urine**
Creatinine		Calcium
Gamma-glutamyl transpeptidase (GGT)		Calcium/creatinine ratio
Glucose		Creatinine
Intact parathyroid hormone (iPTH)		Phosphorus
Lactate dehydrogenase (LDH)		Phosphorus/creatinine ratio
Lipase		
Phosphorus		**2-hour Urine**
Potassium		Calcium
Protein (albumin and total)		Creatinine
Sodium		Phosphorus
Uric acid		Pregnancy test (if applicable)

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.

7.5.3.8.1 Intact Fibroblast Growth Factor 23

Intact FGF23 (iFGF23) concentrations will be measured at Baseline and Weeks 24, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination) using a validated electrochemiluminescent assay (ECLA) developed by the Sponsor's development partner KHK, and transferred to and run by a central laboratory.

7.5.3.8.2 Anti-KRN23 Antibody Testing

To determine the immunogenicity profile of KRN23 in children with XLH, blood samples will be obtained for anti-KRN23 antibody (anti-drug antibodies [ADA]) testing at Baseline, and at Weeks 4, 8, 16, 24, 40, 64/EOS I, 88, 112, and 140/EOS II (or Early Termination). The formation of anti-KRN23 antibodies in human serum will be determined using a validated ECLA 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. Subjects randomized to active control will not have blood samples drawn for this assessment during the Treatment Period; during the Treatment Extension Period, blood samples for ADA will be drawn on the same schedule as subjects originally randomized to KRN23, ie, Weeks 88, 112, and 140/EOS II.

7.5.3.9 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests throughout the study as indicated in Table 2.1, Table 2.2, and Table 2.3. Females not of childbearing potential are not required to undergo pregnancy testing, including those who have not experienced menarche or are permanently sterile.

Female subjects of childbearing potential with a positive pregnancy test at Screening will not be enrolled in the study.

Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result, or can be performed if pregnancy test by urine is not feasible.

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 listed below from the period following the signing of the informed consent through 12 weeks after stopping the study drug. Sexually active male subjects 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 (eg, oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (eg, oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)

- Bilateral tubal occlusion
- Male sterilization, also called vasectomy
- Sexual abstinence (ie, 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)

Refer to Section 8.5.4.3 for Pregnancy Reporting requirements.

7.5.3.10 Pregnancy of 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.

7.5.3.11 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 and during Home Health visits (KNR23 treatment arm only during the Treatment Period). 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 ankle-foot orthosis, braces, cane, crutches, walker, wheelchair etc.) utilized during the 30 days prior to Screening will also be reviewed and recorded. At each subsequent visit, 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.

7.5.3.12 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 or the active control
- 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.

7.5.3.13 Adverse Events

All AEs will be recorded from the time the informed consent is signed through 12 weeks following the last dose of study drug, unless the subject enrolls in another clinical study of KRN23, is treated with commercially available KRN23, or is treated with KRN23 through another mechanism, at which point the collection of AEs within this study is no longer applicable. However, AEs will continue to be reported either under another KRN23 protocol or per post-approval requirements for safety monitoring, as applicable.

For subjects not continuing KRN23 treatment under commercial use or another mechanism upon completion of study drug treatment or early withdrawal from this study, a Safety Visit will be conducted 12 weeks ±1 week after the last dose of KRN23 in this protocol.

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 and at Home Health Visits (KNR23 treatment arm only).

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

7.5.4 Exploratory Assessments

7.5.4.1 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 in subjects ≥ 5 years of age at the Screening Visit during the Baseline visit (Week 0), and Weeks 24, 40, 64/EOS II, 88, 112, and 140/EOS II (or Early Termination). If a subject is < 5 years of age at the Screening Visit and therefore has no baseline data, SF-10 will not be administered even when the subject turns 5 during the study. Every attempt should be made to ensure that the responder completing the first administration completes subsequent administrations to minimize variability.

7.5.4.2 Dental Evaluation

Some children with XLH may present with severe dental defects, which typically manifest as spontaneous infections leading in dental abscesses (Carpenter et al. 2011). These infections

are a result of defective dentin and enamel hypoplasia that diminishes the layer surrounding the pulp chamber, enabling oral bacteria to enter the pulp chamber and form abscesses.

Dental evaluations will be conducted to assess the number of dental events from dental caries, delay in eruption of the dentition, enamel hypoplasia, dental abscesses, and gingivitis. At each clinic visit, an oral examination will be conducted by the investigator and subjects will be proactively asked if they had any dental events such as dental caries, tooth extraction, root canal, dental abscesses, and gingivitis.

7.5.4.3 Pre- and Post-prandial Serum Phosphorus and Calcium Concentrations Substudy

Pre- and post-prandial serum phosphorus and calcium concentrations will be assessed at a single clinic visit anytime 10 to 14 days after a KRN23 dose. The substudy will be conducted at sites in the US, Canada, and Australia that are able to provide and observe a nutritionally defined meal in their clinic. The substudy will be conducted in approximately 20 subjects, age ≥ 3 years.

The Investigators or Study Coordinators at the sites chosen will contact the subject/caregiver asking for participation in the substudy. If agreed, a clinic visit will be scheduled and the subject will be consented at that time and prior to any substudy assessments being conducted. The clinic visit may take the place of a Home Health visit or be at a regularly scheduled clinic visit. Before the visit at which the substudy assessments are conducted, subjects must have received at least 4 doses of KRN23 (≥ 8 weeks of treatment) with at least 80% compliance and did not miss the previous dose of KRN23.

Subjects will fast overnight for a minimum of 8 hours, and fasting serum will be collected prior to breakfast (Table 7.5.4.3.1). Meals will contain predefined ranges of phosphate, calories, and carbohydrate and will be representative of a typical Western diet for children. Subjects will have the option of 2 to 3 nutritionally defined meals (depending on the clinical site). Subjects will be given a 1-hour window to consume the meal. Dietary phosphate will be estimated based on the amount of food consumed. Serum samples will be drawn 1 and 2 hours after the completion of the meal.

Table 7.5.4.3.1: Schedule of Events for the Pre- and Post-prandial Serum Phosphorus Concentrations Substudy

	Prior to Substudy Assessments	Hour 0	Hour 1	Hour 2	Hour 3
Informed consent	X				
Serum phosphorus and calcium[1]		X			
Begin meal[2]		X			
End meal[3]			X		
Serum phosphorus and calcium[4]				X	X

1. Serum collected after at least 8 hours of fasting and before meal.
2. Nutritionally defined meal typical of a Western diet for children with a known phosphate content (approximately 200 to 500 mg).
3. Meal should be completed within 1 hour. If the meal cannot be completely consumed, record the quantity consumed.
4. Serum collected 1 and 2 hours after completion of the meal.

7.5.5 Appropriateness of Measurements

The assessments and timing of assessments used in this study, and the variables analyzed, are typical of those used to evaluate healing and severity of rickets, as well hypophosphatemia, renal reabsorption, and vitamin D metabolism in subjects with XLH. The primary goals of treatment in pediatric XLH patients are to correct or minimize rickets/osteomalacia, radiographic abnormalities, and skeletal deformities and improve growth outcomes (Carpenter et al. 2011). KRN23 binds to and inhibits FGF23. FGF23-mediated hypophosphatemia plays leads to rickets in children with XLH. Therefore, change in rickets in the KRN23 group will be the primary endpoint in this study.

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 (≥ 5 years old at the Screening Visit) in subjects have been successfully used in other clinical development programs. Additionally, age-appropriate, patient-reported outcome were included to assess functional disability, pain, and health-related quality of life (ie, PROMIS Pediatric Pain Interference, Fatigue and Physical Function Mobility; FPS-R; and SF-10 in subjects ≥ 5 years old at the Screening Visit).

Additional assessments are included both as PD measures and safety indicators of potential secondary complications associated with treatment, including serum phosphorus, 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 oral phosphate/active vitamin D therapy in XLH, as secondary hyperparathyroidism is common. Biochemical markers of bone turnover that reflect rickets severity (eg, alkaline phosphatase

[ALP]) may provide an indication of treatment effect. The relatively extensive panel of biomarkers has been included in this Phase 3 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.

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 will be used to detect any calcinosis in susceptible organs. Since elevated free FGF23 has been associated with left ventricular hypertrophy (LVH) in patients with chronic kidney disease, ECGs will examine the potential risk in XLH subjects.

The study will be conducted in a pediatric population, as such additional safety measures including Home Health care visits (KRN23 treatment arm only) 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.

7.6 Statistical Methods and Determination of Sample Size

A full description of the analysis details will be provided in the Statistical Analysis Plan (SAP).

7.6.1 Determination of Sample Size

This Phase 3 study is adequately powered to test the effect of KRN23 on improvement of rickets using RGI-C global score at Week 40 against the active control (oral phosphate and active vitamin D) based on the assumption of a mean RGI-C global score of 1.80 in the KRN23 group, 1.40 in the active control group, and a common standard deviation of 0.50. Given these assumption, a total sample size of 60 (30 per group) will provide approximately 80% power to detect such a difference in the mean RGI-C global score at Week 40 between treatment groups using a 2-sample t-test with a 2-sided alpha level of 0.05. A 10% drop-out rate is incorporated in the sample size calculation.

7.6.2 Primary and Secondary Efficacy Endpoints

7.6.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in rickets at Week 40 as assessed by the RGI-C global score. The primary endpoint will be compared between the KRN23 and active control (oral phosphate/active vitamin D) groups.

7.6.2.2 Secondary Efficacy Endpoint(s)

The following secondary endpoints will be compared between the KRN23 and active control groups:

- Proportion of subjects with a mean RGI-C global score ≥+2.0 (substantial healing) at Week 40 and Week 64
- Change in rickets at Week 64 as assessed by the RGI-C global score
- Change from baseline in RSS total score at Weeks 40 and 64
- Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as assessed by the RGI-C long leg score at Weeks 40 and 64
- Change in standing height (or recumbent length in children <2 years) from baseline to Weeks 24, 40, and 64 in cm
- Change in height-for-age z-scores from baseline to Weeks 24, 40, 64
- Change in growth velocity from pre-treatment and post-treatment at Weeks 40 and 64 in cm/yr
- Pharmacodynamic* assessments including
    - Change from baseline over time in serum phosphorus
    - Change from baseline over time in serum $1,25(OH)_2D$, urinary phosphorus, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and tubular reabsorption of phosphate (TRP)
    - Change and percent change from baseline over time in biochemical markers of bone turnover that reflect rickets severity (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
- Pain, fatigue and physical function: Change from baseline in the PROMIS (Patient-Reported Outcomes Measurement Information System) Pain Interference, Physical Function Mobility and Fatigue domain scores (for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40 and 64
- Pain intensity: Change from baseline in the Faces Pain Scale – Revised (FPS-R) (for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40 and 64
- Walking ability: Change from baseline in the Six Minute Walk Test (6MWT) total distance and percent of predicted normal (for subjects ≥ 5 years of age at the Screening Visit) at Weeks 24, 40, and 64

7.6.3 General Principles

A general description of the statistical methods to be used to analyze the efficacy and safety of KRN23 is outlined below. The analyses planned in this protocol will be expanded in the SAP to include detailed description of the analyses. The SAP will be finalized and approved prior to the database lock. Any deviations from the analyses described in the protocol and SAP will be noted in the final clinical study report.

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, unused, or spurious data, along with the detailed method for analyses will be presented in the SAP.

The statistical analyses will be reported using summary tables, figures, and data listings. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, quartile, minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided.

Full analysis set will include all randomized subjects who received at least 1 dose of assigned medication, and full analysis set will be used for both efficacy and safety analyses.

7.6.3.1 Subject Accountability

The number of subjects randomized, who complete the study, and discontinue the study will be summarized. The reason for study treatment discontinuation and study discontinuation will also be summarized.

7.6.3.2 Demographic and Baseline Characteristics

Demographics (age, gender, race, and ethnicity) and other baseline disease characteristics will be summarized using descriptive statistics.

7.6.4 Efficacy Endpoints and Analyses

The full analysis set will be used for efficacy analyses, and subjects will be analyzed by the randomized treatment group.

The primary efficacy endpoint will be tested to compare the mean RGI-C global score between the KRN23 and active control groups.

At the Week 40 Analysis (the primary efficacy analysis time point), the primary hypothesis of the primary endpoint is to test whether there is a difference between the KRN23 and active control groups in the mean RGI-C global scores at Week 40. An Analysis of Covariance (ANCOVA) model with treatment group adjusting for baseline rickets severity and age will be used to test this hypothesis at a 2-sided alpha level of 0.05. The proportion of RGI-C responder will be summarized for each treatment group.

At the Week 64 Analysis (secondary analysis), RGI-C global score over time will be analyzed using the repeat measurement model that includes treatment group, visit, treatment group by visit interaction, and adjusted for baseline rickets severity and age.

The change from baseline in RSS total score over time will be analyzed using the same method as that of the RGI-C score.

Analyses of other efficacy and PD measures will be performed at Week 40,Week 64/EOS I, and Week 140/EOS II. Endpoints will be summarized descriptively by each treatment group. Treatment comparison will be performed using the repeat measurement model including treatment group, visit, treatment group by visit interaction, adjusting for baseline age, rickets severity. Other baseline covariate may be considered for adjustment.

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

7.6.5 Safety Analyses

Full Analysis Set will be used for the safety analysis. Subjects will be analyzed based on the actual treatment received. Safety variables including AEs, SAEs, safety laboratory assessments, vital signs, renal ultrasound, ECG, ECHO, and anti-KRN23 antibody will be summarized descriptively by treatment group.

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, relationship to study drug, and severity. All reported AEs with onset during the treatment (ie, 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. Special attention will be given to those subjects who died, discontinued treatment due to an AE, or experienced a SAE.

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. The frequency and percentage of subjects who experience abnormal clinical laboratory results (ie, outside of reference ranges) and/or clinically significant abnormalities (as determined by the Investigator) will be presented for each clinical laboratory measurement. The SAP will provide additional details on the planned safety analyses.

7.6.6 Data Monitoring Committee

An independent DMC that includes members with expertise in metabolic bone disease, cardiology, and nephrology, and the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial. The DMC will meet at least twice a year during the active-controlled period. The roles and responsibilities of the DMC will be defined in the DMC Charter.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

The IRB/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, the associated informed consent forms (ICFs), and the informed consent procedures must be submitted to the IRB/EC for review and must be approved before the enrollment of any subject into the study. Investigational Product 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 Assembly General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The sponsor and investigator will make every effort that 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 Investigational Product, as described in this protocol and the Investigator's Brochure for KRN23 or the appropriate product labels for oral phosphate and active vitamin D (Appendix 1), 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 or acknowledgement of the IRB/EC's approval of the ICF before the shipment of Investigational Product 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 who are not of legal age (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 or equivalent.

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 (SDV). The monitor will verify the investigator's ongoing qualifications, to inspect clinical site facilities, and to inspect study records, including proof of EC/IRB review, with the stipulation that patient 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, KRN23 must be stored in a secure limited access location at controlled temperature as described in the Investigator's Brochure and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study.

A drug accountability record must be maintained for all KRN23 received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. Following the close-out of the study, all unused KRN23 must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the 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 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 2 years after the last approval of a marketing application or for at least 2 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 Adverse Event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event 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.

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

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

Serious adverse event (SAE) or serious suspected adverse reaction is an adverse event or suspected adverse reaction that at any dose, in the view of either the investigator or sponsor, results in any of the following outcomes:

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

Note that hospitalizations planned prior to study enrollment (eg, 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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (NCI 2010). 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 are 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. During the Treatment Period, the relationship of the AE to KRN23 will be assessed for subjects in the KRN23 arm, and the relationship of the AE to oral phosphate and to active vitamin D will be assessed for subjects in the active control arm. During the Treatment Extension Period, the relationship of the AE to KRN23 will be assessed.

Categories of attributions for "Unrelated" events:

- ***Unrelated:*** This category applies to an AE that ***is clearly not related*** to the investigational agent/procedure.
- ***Unlikely Related:*** This category applied to an AE that ***is doubtfully related*** to the investigational agent/procedure.

Categories of attributions for "Related" events:

- ***Possibly Related:*** This category applies to an AE that ***may be related*** to the investigational agent/procedure.
- ***Probably Related:*** This category applies to an AE that ***is likely related*** to the investigational agent/procedure.
- ***Definitely Related:*** This category applies to an AE that ***is clearly related*** to the investigational agent/procedure.

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Unrelated or Unlikely Related will be considered Unrelated.

8.5.4 Adverse Event Reporting

8.5.4.1 General

All AEs (ie, 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 CRF. The 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.

For subjects not continuing KRN23 treatment under commercial use or another mechanism upon completion of study drug treatment or early withdrawal from this study, a Safety Visit will be conducted 12 weeks ±1 week after the last dose of study drug in this protocol. All AEs will be recorded from the time the informed consent is signed through 12 weeks following the last dose of study drug, unless the subject enrolls in another clinical study of KRN23, is treated with commercially available KRN23, or is treated with KRN23 through another mechanism, at which point the collection of AEs within this study is no longer applicable. 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 will continue to be reported either under another KRN23 protocol or per post-approval requirements for safety monitoring, as applicable.

AEs ongoing at 12 weeks following the last dose of study drug 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 12 weeks following the last dose of study drug are to be reported as SAEs to Ultragenyx or its designee within 24 hours of knowledge.

8.5.4.3 Pregnancy in Subject or Partner, and Requirements for Immediate Reporting

Ultragenyx or its designee must be notified of the occurrence of any pregnancy in a subject or subject's partner that occurs during the reporting period within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. Pregnancies will be reported by completing and submitting Pregnancy Notification forms to Ultragenyx or designee. 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. 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.

Ultragenyx or its designee must be notified of the outcome of the pregnancy within 24 hours of the Investigator, designee, or site personnel's knowledge of the outcome. Pregnancy outcomes will be reported by completing and submitting Pregnancy Outcome forms to Ultragenyx or designee.

Any pregnancy-associated SAEs must be reported as per the SAE reporting process indicated in Section 8.5.4.2.

8.5.5 Communication Plan

8.5.5.1 Serious Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), ECs, 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 8 days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event. Ultragenyx will use the current KRN23 Investigator's Brochure to evaluate expectedness for SAEs occurring in the KRN23 treatment group. Ultragenyx will use applicable product labels (Appendix 1) to evaluate expectedness for SAEs occurring in the active control treatment group (oral phosphate and active vitamin D).

The Investigator will notify the IRBs/Research Ethics Boards (REB)/ECs of SAEs, 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.

8.5.5.2 Urgent Safety Matters and Non-SUSAR Reporting

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, ECs, and Investigators of any events (eg, 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 12 weeks following the last dose of study drug.

The Investigator will notify the IRBs/ REB/ECs of 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 ECs, as per local laws and regulations.

8.5.6 Review of Safety Data

An independent DMC will act in an advisory capacity to monitor subject safety on a routine basis throughout the course of the study. The DMC may meet approximately twice a year, 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.

Potential safety signals identified during the DMC 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, eg, Regulatory Authorities, ECs, IRBs, and Investigators.

8.5.7 Safety Contact Information

Drug Safety – SAE and Pregnancy Reporting	Medical Monitor
PrimeVigilance Fax: PPD e-mail: PPD	PPD Telephone: PPD Mobile: PPD Email: 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.

9 REFERENCES

Aono, Y, Hasegawa, H, Yamazaki, Y, Shimada, T, Fujita, T, Yamashita, T, and Fukumoto, S. 2011. "Anti-FGF-23 neutralizing antibodies ameliorate muscle weakness and decreased spontaneous movement of Hyp mice." *J Bone Miner Res* 26 (4):803-10.

Aono, Y, Yamazaki, Y, Yasutake, J, Kawata, T, Hasegawa, H, Urakawa, I, Fujita, T, Wada, M, Yamashita, T, Fukumoto, S, and Shimada, T. 2009. "Therapeutic effects of anti-FGF23 antibodies in hypophosphatemic rickets/osteomalacia." *J Bone Miner Res* 24 (11):1879-88.

Beck-Nielsen, SS, Brock-Jacobsen, B, Gram, J, Brixen, K, and Jensen, TK. 2009. "Incidence and prevalence of nutritional and hereditary rickets in southern Denmark." *Eur J Endocrinol* 160 (3):491-7.

Bieri, D, Reeve, RA, Champion, GD, Addicoat, L, and Ziegler, JB. 1990. "The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties." *Pain* 41 (2):139-50.

Broderick, JE, DeWitt, EM, Rothrock, N, Crane, PK, and Forrest, CB. 2013. "Advances in Patient-Reported Outcomes: The NIH PROMIS((R)) Measures." *EGEMS (Wash DC)* 1 (1):1015.

Burnett, CH, Dent, CE, Harper, C, and Warland, BJ. 1964. "Vitamin D-Resistant Rickets. Analysis of Twenty-Four Pedigrees with Hereditary and Sporadic Cases." *Am J Med* 36:222-32.

Carpenter, TO, Imel, EA, Holm, IA, Jan de Beur, SM, and Insogna, KL. 2011. "A clinician's guide to X-linked hypophosphatemia." *J Bone Miner Res* 26 (7):1381-8.

Carpenter, TO, Imel, EA, Ruppe, MD, Weber, TJ, Klausner, MA, Wooddell, MM, Kawakami, T, Ito, T, Zhang, X, Humphrey, J, Insogna, KL, and Peacock, M. 2014. "Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia." *J Clin Invest* 124 (4):1587-97.

CTFG. 2014. Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

Dixon, PH, Christie, PT, Wooding, C, Trump, D, Grieff, M, Holm, I, Gertner, JM, Schmidtke, J, Shah, B, Shaw, N, Smith, C, Tau, C, Schlessinger, D, Whyte, MP, and Thakker, RV. 1998. "Mutational analysis of PHEX gene in X-linked hypophosphatemia." *J Clin Endocrinol Metab* 83 (10):3615-23.

Fukumoto, S. 2008. "Physiological regulation and disorders of phosphate metabolism--pivotal role of fibroblast growth factor 23." *Intern Med* 47 (5):337-43.

Geiger, R, Strasak, A, Treml, B, Gasser, K, Kleinsasser, A, Fischer, V, Geiger, H, Loeckinger, A, and Stein, JI. 2007. "Six-minute walk test in children and adolescents." *J Pediatr* 150 (4):395-9.

Hicks, CL, von Baeyer, CL, Spafford, PA, van Korlaar, I, and Goodenough, B. 2001. "The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement." *Pain* 93 (2):173-83.

Ichikawa, S, Gray, AK, Bikorimana, E, and Econs, MJ. 2013. "Dosage effect of a Phex mutation in a murine model of X-linked hypophosphatemia." *Calcif Tissue Int* 93 (2):155-62.

Imel, EA, and Econs, MJ. 2005. "Fibroblast growth factor 23: roles in health and disease." *J Am Soc Nephrol* 16 (9):2565-75.

Imel, EA, Zhang, X, Ruppe, MD, Weber, TJ, Klausner, MA, Ito, T, Vergeire, M, Humphrey, JS, Glorieux, FH, Portale, AA, Insogna, K, Peacock, M, and Carpenter, TO. 2015. "Prolonged Correction of Serum Phosphorus in Adults With X-Linked Hypophosphatemia Using Monthly Doses of KRN23." *J Clin Endocrinol Metab* 100 (7):2565-73.

Jonsson, KB, Zahradnik, R, Larsson, T, White, KE, Sugimoto, T, Imanishi, Y, Yamamoto, T, Hampson, G, Koshiyama, H, Ljunggren, O, Oba, K, Yang, IM, Miyauchi, A, Econs, MJ, Lavigne, J, and Juppner, H. 2003. "Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia." *N Engl J Med* 348 (17):1656-63.

Linglart, A, Biosse-Duplan, M, Briot, K, Chaussain, C, Esterle, L, Guillaume-Czitrom, S, Kamenicky, P, Nevoux, J, Prie, D, Rothenbuhler, A, Wicart, P, and Harvengt, P. 2014. "Therapeutic management of hypophosphatemic rickets from infancy to adulthood." *Endocr Connect* 3 (1).

Liu, S, Tang, W, Zhou, J, Vierthaler, L, and Quarles, LD. 2007. "Distinct roles for intrinsic osteocyte abnormalities and systemic factors in regulation of FGF23 and bone mineralization in Hyp mice." *Am J Physiol Endocrinol Metab* 293 (6):E1636-E1644.

Makitie, O, Doria, A, Kooh, SW, Cole, WG, Daneman, A, and Sochett, E. 2003. "Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets." *J Clin Endocrinol Metab* 88 (8):3591-97.

NCI. *National Cancer Institute Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS). Common Terminology Criteria for Adverse Events V4.3 (CTCAE). Published: June14, 2010. Available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.* 2010.

NIH. *US National Heart, Lung, and Blood Institute. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* 2005. Available from https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf.

NIH. 2015. *PROMIS* 2015 [cited January 2015]. Available from http://www.nihpromis.org/default.aspx#6.

Payne, RB. 1998. "Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation." *Ann Clin Biochem* 35 (Pt 2):201-6.

Perwad, F, Azam, N, Zhang, MY, Yamashita, T, Tenenhouse, HS, and Portale, AA. 2005. "Dietary and serum phosphorus regulate fibroblast growth factor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice." *Endocrinology* 146 (12):5358-64.

PHEXdb. *PHEX Locus Database, Search Engine Site* [cited November 2014. Available from http://www.phexdb.mcgill.ca/.

Quinlan, C, Guegan, K, Offiah, A, Neill, RO, Hiorns, MP, Ellard, S, Bockenhauer, D, Hoff, WV, and Waters, AM. 2012. "Growth in PHEX-associated X-linked hypophosphatemic rickets: the importance of early treatment." *Pediatr Nephrol* 27 (4):581-8.

Razzaque, MS, and Lanske, B. 2007. "The emerging role of the fibroblast growth factor-23-klotho axis in renal regulation of phosphate homeostasis." *J Endocrinol* 194 (1):1-10.

Richards, S, Aziz, N, Bale, S, Bick, D, Das, S, Gastier-Foster, J, Grody, WW, Hegde, M, Lyon, E, Spector, E, Voelkerding, K, Rehm, HL, and Committee, ALQA. 2015. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genet Med* 17 (5):405-24.

Rowe, PS. 2012. "Regulation of bone-renal mineral and energy metabolism: the PHEX, FGF23, DMP1, MEPE ASARM pathway." *Crit Rev Eukaryot Gene Expr* 22 (1):61-86.

Santos, F, Fuente, R, Mejia, N, Mantecon, L, Gil-Pena, H, and Ordonez, FA. 2013. "Hypophosphatemia and growth." *Pediatr Nephrol* 28 (4):595-603.

Saris-Baglama, RN, DeRosa, MA, Raczek, AE, Bjorner, JB, and Ware, JE. 2006. "Development, validation, and norming of the SF-10 for Children Health Survey." *Quality of Life Research* 15 (S1):A-145.

Schwartz, GJ, Haycock, GB, Edelmann, CM, Jr., and Spitzer, A. 1976. "A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine." *Pediatrics* 58 (2):259-63.

Shore, RM, and Chesney, RW. 2013. "Rickets: Part I." *Pediatr Radiol* 43 (2):140-51.

Sullivan, W, Carpenter, T, Glorieux, F, Travers, R, and Insogna, K. 1992. "A prospective trial of phosphate and 1,25-dihydroxyvitamin D3 therapy in symptomatic adults with X-linked hypophosphatemic rickets." *J Clin Endocrinol Metab* 75 (3):879-85.

Tenenhouse, H, and Econs, M. 2001. "Mendelian Hypophosphatemias." In *The metabolic and molecular basis of inherited disease, 8th ed.*, edited by CR; Beaudet Scriver, AL; Sly, WS; Valle, D, 5039–5067. New York: McGraw-Hill.

Thacher, TD, Fischer, PR, Pettifor, JM, Lawson, JO, Manaster, BJ, and Reading, JC. 2000. "Radiographic scoring method for the assessment of the severity of nutritional rickets." *J Trop Pediatr* 46 (3):132-9.

Verge, CF, Lam, A, Simpson, JM, Cowell, CT, Howard, NJ, and Silink, M. 1991. "Effects of therapy in X-linked hypophosphatemic rickets." *N Engl J Med* 325 (26):1843-8.

Yamazaki, Y, Okazaki, R, Shibata, M, Hasegawa, Y, Satoh, K, Tajima, T, Takeuchi, Y, Fujita, T, Nakahara, K, Yamashita, T, and Fukumoto, S. 2002. "Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia." *J Clin Endocrinol Metab* 87 (11):4957-60.

Yamazaki, Y, Tamada, T, Kasai, N, Urakawa, I, Aono, Y, Hasegawa, H, Fujita, T, Kuroki, R, Yamashita, T, Fukumoto, S, and Shimada, T. 2008. "Anti-FGF23 neutralizing antibodies show the physiological role and structural features of FGF23." *J Bone Miner.Res* 23 (9):1509-1518.

Zivicnjak, M, Schnabel, D, Billing, H, Staude, H, Filler, G, Querfeld, U, Schumacher, M, Pyper, A, Schroder, C, Bramswig, J, and Haffner, D. 2011. "Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets." *Pediatr Nephrol* 26 (2):223-31.

10 SIGNATURE PAGE

Protocol Title: A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH)

Protocol Number: UX023-CL301 Amendment 1 (Global)

I have read Protocol UX023-CL301. 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 that the Investigator is informed of all relevant information that becomes available during the conduct of this stud

PPD

PPD

PPD

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

Date

11 APPENDIX 1: REFERENCE SAFETY INFORMATION FOR THE ACTIVE CONTROL ARM

The attached SmPCs serve as RSI for the oral phosphate and active vitamin D products used in the active control arm of this study at clinical sites in Europe. For regulatory reporting purposes, the information located in Section 4.8 of the following SmPCs will be used to determine if a serious adverse event is unexpected for the applicable compound.

Alfacalcidol – One-Alpha®

Calcitriol – Rocaltrol®

Oral Phosphate – Phosphate Sandoz®

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

One-Alpha Capsules 0.5 microgram.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol 0.5 µg

3. PHARMACEUTICAL FORM

Red soft gelatin capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

One-Alpha® is indicated in all conditions where there is a disturbance of calcium metabolism due to impaired 1-ct hydroxylation such as when there is reduced renal function. The main indications are:

a) Renal osteodystrophy
b) Hyperparathyroidism (with bone disease)
c) Hypoparathyroidism
d) Neonatal hypocalcaemia
e) Nutritional and malabsorptive rickets and osteomalacia
f) Pseudo-deficiency (D-dependent) rickets and osteomalacia
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia

4.2 Posology and method of administration

Route of administration: oral

Initial dose for all indications:

Adults: 1 microgram/day

Dosage in the elderly:	0.5 microgram/day
Neonates and premature infants:	0.05 - 0.1 microgram/kg/day
Children under 20 kg bodyweight:	0.05 microgram/kg/day
Children over 20 kg bodyweight:	1 microgram/day

The dose of One-Alpha® should be adjusted thereafter to avoid hypercalcaemia according to the biochemical response. Indices of response include plasma levels of calcium (ideally corrected for protein binding), alkaline phosphatase, parathyroid hormone, as well as radiographic and histological investigations.

Plasma levels should initially be measured at weekly intervals. The daily dose of One-Alpha® may be increased by increments of 0.25 - 0.5 microgram. When the dose is stabilised, measurements may be taken every 2 - 4 weeks.

Most adult patients respond to doses between 1 and 3 micrograms per day. When there is biochemical or radiographic evidence of bone healing, (and in hypoparathyroid patients when normal plasma calcium levels have been attained), the dose generally decreases. Maintenance doses are generally in the range of 0.25 to 1 microgram per day. If hypercalcaemia occurs, One-Alpha® should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

(a) Renal bone disease:

Patients with relatively high initial plasma calcium levels may have autonomous hyperparathyroidism, often unresponsive to One-Alpha®. Other therapeutic measures may be indicated.

Before and during treatment with One-Alpha®, phosphate binding agents should be considered to prevent hyperphosphataemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

(b) Hyperparathyroidism:

In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, preoperative treatment with One-Alpha® for 2-3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia, One-Alpha® should be continued until plasma alkaline phosphatase levels fall to normal or hypercalcaemia occurs.

(c) Hypoparathyroidism:

In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with One-Alpha®. Severe hypocalcaemia is corrected more rapidly with higher doses of One-Alpha® (eg 3-5 micrograms) together with calcium supplements.

(d) Neonatal hypocalcaemia:

Although the normal starting dose of One-Alpha® is 0.05-0.1 microgram/kg/day (followed by careful titration) in severe cases doses of up to 2 microgram/kg/day may be required. Whilst onised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of alkaline phosphatase approximately 7.5 times above the adult range indicates active disease.

A dose of 0.1 microgram/kg/day of One-Alpha® has proven effective as prophylaxis against early neonatal hypocalcaemia in premature infants.

(e) Nutritional and malabsorptive rickets and osteomalacia:

Nutritional rickets and osteomalacia can be cured rapidly with One-Alpha®. Malabsorptive osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of One-Alpha®.

(f) Pseudo-deficiency (D-dependent) rickets and osteomalacia:

Although large doses of parent vitamin D would be required, effective doses of One-Alpha® are similar to those required to heal nutritional vitamin D deficiency rickets and osteomalacia.

(g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia:

Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with One-Alpha® at normal dosage rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

4.3 Contraindications

Hypercalcaemia, metastatic calcification.

Hypersensitivity to alfacalcidol or any of the other ingredients.

4.4 Special warnings and precautions for use

One-Alpha® should be used with caution for:

- patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients
- patients with nephrolithiasis

During treatment with One-Alpha® serum calcium and serum phosphate should be monitored regularly especially in children, patients with renal impairment and patients receiving high doses. To maintain serum phosphate at an acceptable level in patients with renal bone disease a phosphate binding agent may be used.

Hypercalcaemia may appear in patients treated with One-Alpha®, the early symptoms are as follows:

- polyuria
- polydipsia
- weakness, headache, nausea, constipation
- dry mouth
- muscle and bone pain
- metallic taste

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). One-Alpha® treatment may then be restarted at a reduced dose (half the previous dose).

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking barbiturates or anticonvulsants may require larger doses of One-Alpha® to produce the desired effect due to the induction of hepatic detoxification enzymes.

Use with caution in patients being treated with thiazide diuretics as they may have an increased risk of developing hypercalcaemia.

4.6 Pregnancy and lactation

There are no adequate data from the use of alfacalcidol in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risks for humans are unknown. Caution should be taken when prescribing to pregnant women as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.

Although it has not been established, it is likely that increased amounts of 1,25-dihydroxyvitamin D will be found in the milk of lactating mothers treated with One-Alpha®. This may influence calcium metabolism in the infant.

4.7 Effects on ability to drive and use machines

One-Alpha® has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The most frequently reported undesirable effects are hypercalcaemia and various skin reactions. Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). One-Alpha® treatment may then be re-started at half the previous dose.

Based on data from post-market use the total undesirable effect ‘reporting rate’ is rare or very rare being approximately 1:10,000 patients treated.

- Metabolism and Nutrition Disorders

  Hypercalcaemia

  Hyperphosphataemia

- Skin and Subcutaneous Tissue Disorders

  Pruritus

  Rash

Urticaria

- Renal and Urinary Disorders

  Nephrocalcinosis

  Renal impairment

4.9 Overdose

Hypercalcaemia is treated by suspending the administration of One-Alpha®.

In severe cases of hypercalcaemia general supportive measures should be undertaken. Keep the patient well hydrated by i.v. infusion of saline (force diuresis), measure electrolytes, calcium and renal function indices; assess electrocardiographic abnormalities, especially in patients on digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Alfacalcidol (One-Alpha®) is converted rapidly in the liver to 1,25-dihydroxyvitamin D. This is the metabolite of vitamin D which acts as a regulator of calcium and phosphate metabolism. Since this conversion is rapid, the clinical effects of One-Alpha® and 1,25-dihydroxyvitamin D are very similar.

Impaired 1-α hydroxylation by the kidneys reduces endogenous 1,25-dihydroxyvitamin D production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, neonatal hypocalcaemia and vitamin D dependent rickets. These disorders, which require high doses of parent vitamin D for their correction, will respond to small doses of One-Alpha®.

The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse. The major advantage of One-Alpha® is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

5.2 Pharmacokinetic properties

In patients with renal failure, 1-5 μg/day of lα-hydroxyvitamin D (1α-OHD3) increased intestinal calcium and phosphorus absorption in a dose-related manner. This effect was observed within 3 days of starting the drug and conversely, it was reversed within 3 days of its discontinuation.

In patients with nutritional osteomalacia, increases in calcium absorption were noted within 6 hours of giving 1 μg 1α-OHD3 orally and usually peaked at 24

hours. 1α-OHD3 also produced increases in plasma inorganic phosphorus due to increased intestinal absorption and renal tubular re-absorption. This latter effect is a result of PTH suppression by 1α-OHD3. The effect of the drug on calcium was about double its effect on phosphorus absorption.

Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving 1α-OHD3 in a dose of 0.5 - 1.0 μg/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sesame oil, all-*rac*-α-tocopherol, gelatin, glycerol, potassium sorbate, red iron oxide, titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/AL blister of 30 (OP), with polyamide-coated aluminium cover.

6.6 Instructions for use/handling

None.

7 MARKETING AUTHORISATION HOLDER

LEO Laboratories Limited

Horizon

Honey Lane

Hurley

Maidenhead

Berkshire

SL6 6RJ

UK

8. MARKETING AUTHORISATION NUMBER

PL 0043/0206

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 January 1978 / 13 January 1994

10 DATE OF REVISION OF THE TEXT

02/12/2013

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rocaltrol 0.25 microgram Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.25 microgram of calcitriol.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Soft capsules.

One length brown-orange to red-orange opaque and the other white to grey-yellow or grey-orange opaque.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocaltrol is indicated for the correction of the abnormalities of calcium and phosphate metabolism in patients with renal osteodystrophy.
Rocaltrol is also indicated for the treatment of established post-menopausal osteoporosis.

4.2 Posology and method of administration

The dose of Rocaltrol should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcaemia.

The effectiveness of treatment depends in part on an adequate daily intake of calcium, which should be augmented by dietary changes or supplements if necessary. The capsules should be swallowed with a little water.

Adults
Renal Osteodystrophy
The initial daily dose is 0.25 mcg of Rocaltrol. In patients with normal or only slightly reduced calcium levels, doses of 0.25 mcg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within 2 - 4 weeks, the daily dosage may be increased by 0.25 mcg at 2 - 4 week intervals. During this period, serum calcium levels should be

determined at least twice weekly. Should the serum calcium levels rise to 1 mg/100ml (250 µmol/l) above normal (9 to 11 mg/100 ml or 2250 – 2750 µmol/l), or serum creatinine rises to > 120 µmol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues. Most patients respond to between 0.5 mcg and 1.0 mcg daily. See section 4.5 for details of dose adjustments related to drug interactions.

An oral Rocaltrol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal doses given at the end of the dialysis has been shown to be effective in patients with osteodystrophy refractory to continuous therapy. A maximum total cumulative dosage of 12 mcg per week should not be exceeded.

Post-menopausal Osteoporosis
The recommended dose of Rocaltrol is 0.25 mcg twice daily.

Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6 monthly intervals thereafter.

Elderly
Clinical experience with Rocaltrol in elderly patients indicates that the dosage recommended for use in younger adults may be given without apparent ill-consequence.

Paediatric Population
The safety and efficacy of calcitriol capsules in children have not been sufficiently investigated to enable dosing recommendations. Limited data are available for the use of calcitriol capsules in paediatric patients.

Rocaltrol capsules are for oral administration only.

4.3 Contraindications

Rocaltrol is contraindicated:

- in all diseases associated with hypercalcaemia
- in patients with evidence of metastatic calcification
- in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the constituent excipients
- if there is evidence of vitamin D toxicity.

4.4 Special warnings and precautions for use

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia.

All other vitamin D compounds and their derivatives, including proprietary compounds or foodstuffs which may be "fortified" with vitamin D, should be withheld during treatment with Rocaltrol.

An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia.

As soon as the serum calcium levels rise to 1 mg/100 ml (250 µmol/l) above normal (9-11 mg/100 ml or 2250-2750 µmol/l), or serum creatinine rises to >120 µmol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues (see section 4.2).

Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate-binding agents and low phosphate diet.

The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2.

Patients with vitamin D-resistant rickets (familial hypophosphataemia) who are being treated with Rocaltrol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by Rocaltrol should be taken into account since this effect may modify the need for phosphate supplementation.

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with Rocaltrol, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from a long acting vitamin D preparation (e.g. ergocalciferol (vitamin D_2) or colecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcaemia (see section 4.9).

Patients with normal renal function who are taking Rocaltrol should avoid dehydration. Adequate fluid intake should be maintained.

In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine.

Rocaltrol capsules contain sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Rocaltrol capsules.

4.5 Interaction with other medicinal products and other forms of interaction

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcaemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias (see section 4.4).

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

Magnesium-containing drugs (e.g. antacids) may cause hypermagnesaemia and should therefore not be taken during therapy with Rocaltrol by patients on chronic renal dialysis.
Since Rocaltrol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration (normal values: 2-5 mg/100 ml, or 0.65-1.62 mmol/l).

Patients with vitamin D-resistant rickets (familial hypophosphataemia) should continue their oral phosphate therapy. However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Fertility, pregnancy and lactation

The safety of Rocaltrol during pregnancy has not been established.

Supravalvular aortic stenosis has been produced in foetuses by near-fatal oral doses of vitamin D in pregnant rabbits. There is no evidence to suggest that vitamin D is teratogenic in humans even at very high doses. Rocaltrol should be used during pregnancy only if the benefits outweigh the potential risk to the foetus.

It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcaemia in the mother and for adverse reactions from Rocaltrol in nursing infants, mothers may breastfeed while taking Rocaltrol, provided that the serum calcium levels of the mother and infant are monitored.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities.

4.8 Undesirable effects

The adverse reactions listed below reflect the experience from investigational studies of Rocaltrol, and the post-marketing experience.

The most commonly reported adverse reaction was hypercalcaemia.

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Summary of ADRs Occurring in Patients Receiving Rocaltrol® (calcitriol)

System Organ Class	Very common	Common	Uncommon	Not known
Immune System Disorders				Hypersensitivity, Urticaria
Metabolism and Nutrition Disorders	Hypercalcaemia		Decreased appetite	Polydipsia, Dehydration, Weight decreased
Psychiatric Disorders				Apathy, Psychiatric disturbances
Nervous System Disorders		Headache		Muscular weakness, Sensory disturbance, Somnolence
Cardiac Disorders				Cardiac arrhythmias
Gastrointestinal Disorders		Abdominal pain, Nausea	Vomiting	Constipation, Abdominal pain upper, Paralytic ileus

Skin and subcutaneous tissue disorders		Rash		Erythema, Pruritus
Musculoskeletal and Connective Tissue Disorders				Growth retardation
Renal and Urinary Disorders		Urinary tract infection		Polyuria, Nocturia
General disorders and administration site conditions				Calcinosis, Pyrexia, Thirst
Investigations			Blood creatinine increased	

Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcaemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcaemia) (see sections 4.2 and 4.4*)*. Occasional acute symptoms include decreased appetite, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalisation of elevated serum calcium within a few days of treatment withdrawal, i.e. much faster than in treatment with vitamin D_3 preparations.

Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation and urinary tract infections.

In concurrent hypercalcaemia and hyperphosphataemia of > 6 mg/100 ml or > 1.9 mmol/l, calcinosis may occur; this can be seen radiographically.

Hypersensitivity reactions including rash, erythema, pruritus and urticaria may occur in susceptible individuals.

Laboratory Abnormalities
In patients with normal renal function, chronic hypercalcaemia may be associated with a blood creatinine increase.

Post Marketing
The number of adverse effects reported from clinical use of Rocaltrol over a period of 15 years in all indications is very low with each individual effect, including hypercalcaemia, occurring at a rate of 0.001 % or less.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Treatment of asymptomatic hypercalcaemia (see section 4.2).

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with Rocaltrol may give rise to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2 / dl^2. A high calcium level in the dialysate may contribute to the development of hypercalcaemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.
Chronic symptoms: dystrophy (weakness, loss of weight), sensory disturbances, possibly fever with thirst, polyuria, dehydration, apathy, arrested growth and urinary tract infections. Hypercalcaemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote faecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Hypercalcaemia at higher levels (>3.2 mmol/L) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcaemia occur following prolonged treatment, Rocaltrol should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Rocaltrol can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent haemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation. The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to DNA sites to modify the expression of target genes.

Rocaltrol is a synthetic preparation of calcitriol. Oral administration of Rocaltrol to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcaemia are improved, thereby reversing the signs and symptoms of bone disease.

In patients with established post-menopausal osteoporosis, Rocaltrol increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of Rocaltrol are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

5.2 Pharmacokinetic properties

Absorption
Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1µg Rocaltrol in healthy subjects were found within 2-6 hours.

After a single oral dose of 0.5 mcg Rocaltrol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/ml to 60.0 ± 4.4 pg/ml after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/ml after 24 hours.

Distribution
During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to

lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated, and increased binding to lipoproteins and albumin occurs.

Metabolism
Calcitriol is hydroxylated and oxidised in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.

Several metabolites with different degrees of vitamin D activity have been identified.

Elimination
The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 µg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation

5.3 Preclinical safety data

Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to 6 months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcaemia.

Reproductive toxicity studies in rats indicated that oral doses up to 300 ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, multiple foetal abnormalities were observed in two litters at an oral maternally toxic dose of 300 ng/kg/day and one litter at 80 ng/kg/day, but not at 20 ng/kg/day (twice the usual human dose). Although there were no statistically significant differences between treated groups and controls in the numbers of litters or foetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content

Butylhydroxyanisole

Butylhydroxytoluene

Medium–chain triglycerides

Shell

Gelatin

Glycerol

Karion 83 (Sorbitol, Mannitol, Hydrogenated hydrolysed starch)

Titanium dioxide E171

Iron oxide red E172

Iron oxide yellow E172

6.2 Incompatibilities

None.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package and keep the blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

PVC opaque blisters containing 100 capsules (5 strips of 20 capsules).

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00031/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 January 2003

10 DATE OF REVISION OF THE TEXT

24/06/2014

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PHOSPHATE SANDOZ® Effervescent Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PHOSPHATE SANDOZ Effervescent Tablets containing 1.936g of sodium acid phosphate anhydrous.

3. PHARMACEUTICAL FORM

Effervescent Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Hypercalcaemia associated with such conditions as hyperparathyroidism, multiple myelomatosis and malignancy.

Hypophosphataemia associated with vitamin D resistant rickets and vitamin D resistant hypophosphataemic osteomalacia.

4.2. Posology and Method of Administration

PHOSPHATE SANDOZ Effervescent should be dissolved in 1/3 to 1/2 a tumblerful of water and taken orally.

Dosage should be adjusted to suit the requirements of individual patients. Excessive dosage has been reported to produce hypocalcaemia in isolated cases. Particular care should therefore be taken to ensure appropriate dosage in the elderly.

Adults

Hypercalcaemia: up to 6 tablets daily (adjustment being made according to requirements).

Vitamin D resistant hypophosphateaemic osteomalacia: 4-6 tablets daily.

Children under 5 years

Hypercalcaemia: up to 3 tablets daily (adjustment being made according to requirements).

Vitamin D resistant rickets: 2-3 tablets daily.

4.3. Contra-Indications

None.

4.4. Special Warnings and Special Precautions for Use

In cases of impaired renal function associated with hypercalcaemia and in cases where restricted sodium intake is required, eg. congestive cardiac failure, hypertension or pre-eclamptic toxaemia, the sodium (20.4mmol per tablet) and potassium (3.1mmol per tablet) content of PHOSPHATE SANDOZ should be taken into consideration. In cases of hypercalcaemia associated with impaired renal function and hyperphosphataemia, the main effect of oral phosphate is to bind calcium in the gut and thus reduce calcium absorption.

The effect of oral phosphate on serum phosphate is likely to be minimal, but close monitoring of serum levels is recommended.

Soft tissue calcification and nephrocalcinosis have been reported in isolated cases following intravenous therapy with phosphate.

This is thought to be a function of dosage and rapidity of phosphate administration. While such effects appear less likely to occur with oral phosphates, careful surveillance of patients is recommended, especially if on long term therapy.

4.5. Interactions with other Medicinal Products and other Forms of Interaction

Concurrent administrations of antacids, containing agents such as aluminium hydroxide, may result in displacement of calcium from binding to oral phosphate, thus reducing efficacy.

4.6. Pregnancy and Lactation

The safety of PHOSPHATE SANDOZ in human pregnancy has not been formally studied, but the drug has been widely used for many years without ill-consequence.

4.7. Effects on Ability to Drive and Use Machines

None.

4.8 Undesirable effects

Apart from gastro-intestinal upsets, nausea and diarrhoea, very few side effects have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system in the United Kingdom: Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

4.9. Overdose

Excessive dosage has been reported to produce hypocalcaemia in isolated cases. This has proved reversible when dosage has been adjusted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Oral administration of inorganic phosphates produces a fall in serum calcium in patients with hypercalcaemia. PHOSPHATE SANDOZ Effervescent Tablets also contain sodium ions which aid the correction of the dehydration and sodium depletion seen in hypercalcaemia.

5.2. Pharmacokinetic Properties

Approximately two thirds of ingested phosphate is absorbed from the gastro-intestinal tract; most of the absorbed phosphate is then filtered by the glomeruli and subsequently undergoes reabsorption. Parathyroid hormone and vitamin D stimulate absorption of phosphate from the small intestine and its reabsorption from the proximal tubule. Virtually all absorbed phosphate is eventually excreted in the urine, the remainder being excreted in the faeces.

5.3. Pre-clinical Safety Data

PHOSPHATE SANDOZ Effervescent Tablets contain sodium acid phosphate, anhydrous, sodium bicarbonate and potassium bicarbonate (all of which are subject to pharmacopoeial monographs). The physiological, pharmacological and clinical toxicity of potassium salts
are well documented and limited animal data are therefore available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Potassium bicarbonate, sodium bicarbonate, sodium saccharin, orange flavour 52.570 TP, polyethylene glycol 4000, sugar icing CP, citric acid anhydrous, water.

6.2. Incompatibilities

None.

6.3. Shelf-Life

36 months.

6.4. Special Precautions for Storage

Do not store above 25°C. Store in the original container. Keep the container tightly closed.

6.5. Nature and Content of Container

Polypropylene tubes of 20 effervescent tablets in boxes of 5 tubes (100 tablets).

6.6. Instruction for Use and Handling

None.

7 MARKETING AUTHORISATION HOLDER

HK Pharma Ltd
PO BOX 845
BEDFORD,
MK45 9EB

8. MARKETING AUTHORISATION NUMBER(S)

PL 16784/0001

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

28th April 1998

10 DATE OF REVISION OF THE TEXT

27/07/2015