A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH)

Protocol Number: UX023-CL203

Original Protocol: 05 September 2014

Amendment 1: 09 May 2016

Amendment 2: 29 September 2017

Investigational Product: KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])

Indication: X-Linked Hypophosphatemia (XLH)

IND Number: 076488

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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-CL203 Amendment 1

09 May 2016

Protocol UX023-CL203 (dated 05 September 2014) has been modified by Amendment 1 to add self-administration of study drug; to add reflexive genetic testing to assess additional genes associated with phenotypes overlapping with XLH if initial PHEX mutation analysis is negative or inconclusive; to clarify the procedures for radiographic and ECHO assessments; to clarify analysis of ECG data; to add lipase testing in all subjects; to add reflexive testing for amylase isoenzymes if serum amylase levels are elevated; to remove the 3-minute stair climb test; to add pharmacokinetic assessments; and to add additional study visits after Week 72, and to make other clarifications. The major protocol changes are summarized below:

1. **Drug Administration**: Section 7.4.2 (Identity of Investigational Product(s)) has been updated to state that "At the discretion of the investigator and after proper training by study personnel in subcutaneous injection technique, the subject or a non-healthcare professional may administer KRN23 to the subject under the supervision of a home health nurse where local regulations permit and where logistically feasible. Subjects or caregivers will be instructed to follow the directions provided in the Instructions for Use."

   Rationale: The study will assess the feasibility and safety of allowing subjects or non-healthcare professionals to administer KRN23 in the home setting. Instructions for Use, developed with input from XLH patients, will be used to guide parents and non-healthcare professionals through the injection process. Self-administration will only begin after Institutional Review Board approval of the Instructions for Use.

2. **Dose titration:** Section 7.1 (Overall Study Design and Plan) has been updated to clarify that, if needed, dose titration either up or down will occur using the three doses of study drug being used in this study 0.3 mg/kg, 0.6 mg/kg, and 1.0 mg/kg. In addition, language has been added that the investigator and medical monitor will discuss the need for dose titration.

   Rationale: These changes were made to clarify the procedures for dose titration if needed during the study.

3. **Reflexive genetic testing**: Section 7.1 (Overall Study Design and Plan) has been modified to add, "If the Baseline result for PHEX mutation analysis is negative or inconclusive (i.e., No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic) and the subject provides informed consent, reflexive genetic

testing will be performed to assess additional genes associated with phenotypes overlapping with XLH."

Rationale: In subjects without a family history of XLH and with a clinical diagnosis of XLH based on phenotypic presentation, *PHEX* mutation analysis results may be negative or inconclusive. For any subject with a *PHEX* mutation analysis result of No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic, reflexive genetic testing will be performed to assess additional genes associated with clinical and biochemical phenotypes overlapping with XLH. In addition, Sanger sequencing for the functional 3'UTR variant in *PHEX* will be performed.

4. **Study population.** Inclusion criterion #2 has been updated to state that subjects with a Screening estimated glomerular filtration rate (eGFR) ≥ 60 mL/min or 45 to <60 mL/min will be eligible with confirmation that the renal insufficiency is not due to nephrocalcinosis. Previously it stated that subjects with eGFR ≥ 60 mL/min were eligible.

Rationale: Many older adults have an eGFR in the range of 45 to <60 mL/min, which is considered a mild to moderate decrease in kidney function that is generally benign. Therefore, the inclusion criterion was expanded to include subjects with this lower eGFR range with confirmation that the reduced renal function is not due to nephrocalcinosis.

5. **Additional sites for radiographic assessments.** Section 7.5.1.2.1 (Bone Health Measurements) has been updated to clarify the possible sites where standard radiographs will be obtained.

Rationale: The original protocol specified that standard radiographs would be obtained at "the legs, feet and lateral spine as well as well as any location(s) where the subject is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (<3 months) fracture." The study reference manual that was developed after completion of the original protocol included additional details about possible sites for standard radiographs. For consistency, those changes have been implemented in this amendment as follows: "Standard radiographs will be obtained of the chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot as well as any location(s) where the subject is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (<3 months) fracture, or in bones where radiographs suggest the presence of a fracture or pseudo-fracture."

6. **Central reads of echocardiograms**. Section 7.5.3.9 (Echocardiogram) has been updated to state that ECHOs will be read centrally rather than locally.

Rationale: ECHOs were included in the UX023-CL203 study to assess two key parameters among other measures of cardiac structure and function: 1) ectopic mineralization in the heart valves and aorta; and 2) left ventricular hypertrophy.

Although assessment of the latter is more straightforward and routinely done at all centers, the assessment of the former is more challenging and subjective and therefore requires efforts to both standardize ECHO acquisition parameters and also the ECHO readers approach. Thus, the reading process for ECHOs has been centralized in this study in an effort to minimize inter-reader variability and improve the utility of the reads for their intended purpose in this study, particularly in the assessment of ectopic mineralization.

7. **Safety Analyses:** In Section 7.6.2.8, electrocardiogram (ECG) is now listed as a general safety assessment. Previously it was listed within the safety assessments for ectopic mineralization.

   Rationale: ECG is performed to evaluate for changes associated with left ventricular hypertrophy. Ectopic mineralization is not expected to affect ECG parameters and ECG was inadvertently listed in that section in the original protocol. Ectopic mineralization in the heart will be assessed by centrally read echocardiographs.

8. **Safety Testing:** Section 7.5.3.6 (Clinical Laboratory Tests) has been updated to add assessment of lipase in all subjects and specify additional laboratory analyses will be performed reflexively if serum amylase levels are elevated to ≥1.5 the upper limit of the reference range (ULRR).

   Rationale: Several organs including the pancreas and salivary gland produce amylase; thus, elevated amylase levels are not diagnostic in the absence of other information. In ongoing and completed KRN23 studies at baseline mild elevations of amylase (<2x ULRR) have been noted. Post-treatment mild shifts in amylase elevation (<2xULRR) have been noted without association with gastrointestinal symptoms. No adverse events of pancreatitis have been observed. The testing for serum lipase and reflexive testing for amylase isoenzymes when serum amylase levels are elevated will allow a determination of whether the amylase elevations are from pancreatic or salivary gland sources.

9. **Removal of 3-Minute Stair Climb Test:** Section 7.5.1.2.3 (Clinical Outcomes Measurements) has been updated to remove the 3-minute stair climb test.

   Rationale: This measurement was removed from the study protocol in the Note to File dated 31 March 2015 because it was not expected to provide sufficient information about subject function to justify the additional burden to the site and to the subject.

10. **Addition of Pharmacokinetic Assessments:** Section 7.5.2 has been added with pre-dose pharmacokinetic (PK) assessments of KRN23 concentration.

    Rationale: To assess KRN23 concentration and possible accumulation, serum pre-dose levels will be evaluated as a PK parameter in this study.

11. **Additional study visits after Week 72:** Changes have been made throughout the document, particularly in Table 2.1 and in Section 7 (Investigational Plan), to add study visits after Week 72 until the new End-of-Treatment (EoT) visit at Week 144 and a follow-up telephone call at Week 152, approximately 12 weeks after the last dose of KRN23. Clinic visits will occur at Weeks 96, 120, and 144/EoT; subjects may be seen at home by home health personnel between the clinic visits.

    Rationale: The study will continue beyond the originally planned completion date. Addition of study visits beyond Week 72 will provide study participants with continued access to long-term treatment with KRN23. The follow up phone call 12 weeks after the last dose corresponds to approximately 5 times the elimination half-life of KRN23.

12. **Schedule of Events:** A footnote has been added to Table 2.1 (Schedule of Events) to state that if there is a technical or operational issue obtaining results for HAHA, FGF23, or KRN23, then an additional blood sample may be obtained at the next suitable clinic visit.

    Rationale: This change was made to clarify procedures and to align with other clinical study protocols in the KRN23 development program.

13. **Record Retention**: Section 8.4.3 has been updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law.

    Rationale: This administrative change has been made to reflect changes to EU clinical trial regulations and current regulations by other health authorities.

14. **Safety Contact Information:** In Section 8.5.8, the safety contact information has been updated.

    Rationale: Administrative change.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX023-CL203 Amendment 2

23 June 2017

Protocol UX023-CL203 Amendment 1 (dated 09 May 2016) has been modified by Amendment 2 to include an extension of treatment up to 30 September 2018. Also, contraception and physical exam requirements were updated, the role of Coordinating Investigator designated for this study was added, and the location of drug administration was further clarified. Additionally, the protocol was updated to reflect that KRN23 administration by the subject or their caregiver may occur without the supervision of a home health (HH) nurse after proper training and that HH visits may occur without the presence of a HH nurse. Therefore, the schedule of events was updated to require the presence of a home health (HH) nurse only for HH visits occurring every 12 weeks after week 96 of the initial extension period to continue assessments after subjects or their caregivers are trained to administer drug. Certain patient-reported outcome assessments will not be required through the extended treatment period. Endpoint descriptions were also updated for clarity. Minor edits and typographical corrections have also been made. Important protocol changes are summarized below:

1. **Study Drug Administration:** Sections 7.4.3 and other relevant sections have been updated to indicate that after proper training by study site personnel in the handling of study drug and subcutaneous injection technique, the subject may self-administer KRN23, or a caregiver may administer KRN23 to the subject, in the home setting without supervision of a HH nurse where local regulations permit and where logistically feasible. Subjects or caregivers will be instructed to follow the directions provided in the Instructions for Use. The dosing schedule will remain the same. Additional instructions regarding the timing of the training and implementation of the subject/caregiver administration have been added as well. Additional language regarding drug administration by the subject or caregiver and the rotation of the injection site has also been provided in Sections 7.4.1, 7.4.2, and 7.4.3.

   Rationale: Currently, some subjects are self-administering or having their caregiver administer KRN23 in the home setting with HH nurse supervision. The requirement for HH nurse supervision of KRN23 administration by subject is being removed to provide increased flexibility for the subjects. Instructions for Use have been developed with input from healthy volunteers and patients with XLH. These instructions will be used to guide subjects and caregivers through the injection process. The Instructions for Use will be approved by sites and IRBs before subject/caregiver administration begins.

2. **Schedule of Events:** The Schedule of Events has been updated to have a HH nurse required only on HH visits occurring every 12 weeks after week 96 to ensure

collection of vital signs, pregnancy testing, and documentation of concomitant medications and AEs. A HH nurse is no longer required at all other HH visits as long as the subject or caregiver has been properly trained and instructed to handle and administer study drug. Assessments collected by the HH nurse at HH visits occurring every 4 weeks will now be collected every 12 weeks at a HH visit or a clinic visit. Language was added to clarify that subjects will not be required to complete two patient-reported outcomes – the Brief Pain Inventory (BPI) and Short Form Health Survey (SF-36) – past Week 144. Additionally, language describing the visit window in the Schedule of Events was corrected to reflect all visits prior to the End of Treatment (EoT) visit.

Rationale: Since supervision is no longer required in the event that drug is administered by the subject or caregiver, assessments previously made by the HH nurse, including pregnancy testing and vital signs, will no longer be collected during every HH visit. However, a HH nurse must be present at HH visits occurring every 12 weeks to ensure accurate safety assessments. The patient-reported outcomes, BPI and SF-36, are not required past Week 144. Extending the visits from 25 to 43 was intended to be made in the Protocol Amendment 1. The additional visits and visit windows were noted in the Protocol Amendment 1, Section 7.5 Study Procedures and Assessments, page 40, but not included in the Schedule of Events footnote section.

3. **Study Duration:** In Sections 7.1 and 7.4.3 and other relevant sections, the study has been extended to include up to approximately 40 weeks of additional KRN23 treatment, until 30 September 2018. (The duration of this extension will vary for individual subjects depending on when study treatment was initiated through 30 September 2018.) In addition, in these sections, the Safety Follow-up telephone call (TC) that occurs over an interval of up to 8 weeks (+5 days) following the EoT or Early Termination Visit has been updated. An initial Safety Follow-up TC will occur 4 weeks (+ 5 days) after the EoT Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, serious adverse events (SAEs), or concomitant medications. If the subject is not continuing KRN23 therapy under commercial use or another mechanism at that time, then site personnel will initiate a subsequent Safety Follow-up TC at 8 weeks (+ 5 days) after the EoT Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications. The maximum study duration has consequently been changed to up to approximately 192 weeks, with up to 184 (+5 days) weeks of treatment. The end of study is defined as the last day that protocol-specified assessments (including telephone contact) are conducted for the last subject in the study.

   Rationale: An additional Treatment Extension of up to 40 weeks has been added to provide KRN23 treatment to subjects until a time when KRN23 is expected to be commercially available in the US. Safety and efficacy parameters will continue to be assessed while the subjects remain on study drug. Safety Follow-up TCs have been

updated after the extension periods to collect information as appropriate on ongoing or new AEs, SAEs, and concomitant medications after subjects discontinue study drug but before KRN23 treatment under commercial use or another mechanism begins.

4. **Pregnancy Testing and Contraception:** In Section 7.5.3.11, the list of examples of highly effective contraception methods was updated and text was updated to further specify potential risks regarding pregnancy.

   Rationale: This change was made to align with the Clinical Trial Facilitation Group (CTFG) guideline, "Recommendations related to contraception and pregnancy testing in clinical trials."

5. **Coordinating Investigator:** Section 8.2 was updated to include the following text "A Coordinating Investigator was identified for multicenter trials. The Coordinating Investigator was 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."

   *Rationale***:** Regulatory guidance in the EU requires selection of a Coordinating Investigator for a multi-center clinical trial.

6. **Anti-KRN23 Antibodies:** In Sections 5.3, 6, 7.5.3.7, and the Schedule of Events, the term HAHA (human anti-human antibody) in reference to anti-KRN23 antibody testing, has been replaced with the term ADA (anti-drug antibody).

   Rationale: This change is a clarification. The immunogenicity of KRN23 is evaluated by quantifying total anti-drug antibodies (ADA), independent of isotype, in human serum. While the study protocol previously used the term "HAHA" for this assessment, it has been replaced with the more correct and specific term, ADA.

7. **Physical Examination**: Section 7.5.3.5 was updated to include "The genitourinary exam scope should be non-invasive and as per age-appropriate standard of care, at the investigator's discretion based on clinical judgement and/or safety need. If the PI determines there is no clinical indication for a genitourinary exam, it is not necessary to perform."

   Rationale: Language was added to section 7.5.3.5 to clarify the scope and necessity of a genitourinary exam.

8. **Safety Language**: Sections 5.2 and 5.3 have been updated to summarize the safety of KRN23 from completed and ongoing clinical trials.

   Rationale: Language updates regarding safety were based on findings from ongoing and completed clinical trials examining the efficacy and safety of KRN23.

9. **Number of Subjects**: Sections 7.1, 7.3, and 7.6.4 have been updated to reflect the final number of subjects enrolled in the study.

   Rationale: Safety and efficacy data is only being assessed for 20 enrolled subjects.

10. **Endpoints**: In Section 7.6.1, endpoint descriptions were updated for clarity. Section 7.6.2.2 was updated to further specify that the PD analysis set consists of subjects that also have evaluable serum data and the term "Intent to Treat analysis set" was replaced with "efficacy analysis set." Additionally, the change from baseline in fractional excretion of phosphorus (FEP) was added as a pharmacodynamic endpoint. The exploratory endpoints in Section 7.6.1 have also been updated to include the long-term assessment of the pharmacokinetics of KRN23, which was previously only included as an exploratory endpoint in the synopsis. The exploratory endpoint of healing of pre-existing pseudofractures and/or Looser zones, as defined by skeletal survey at baseline and subsequent targeted radiography has been updated to clarify that it comprises the following components: the number of active pseudofractures and/or fractures as defined by skeletal survey at baseline and the numbers and percentages of the baseline active pseudofractures/fractures that were healed, partially healed, unchanged, and worsened at post-baseline visits.

    Rationale: The section was updated to clarify current and additional endpoints planned for analysis in this study. Assessment of KRN23 concentrations was listed as an exploratory endpoint in the synopsis and is now included in Section 7.6.1.

2 SYNOPSIS

TITLE OF STUDY: A Phase 2b, Open-Label, Long-Term, Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH)
PROTOCOL NUMBER: UX023-CL203
STUDY SITES: Up to 5 sites in the United States (US)
PHASE OF DEVELOPMENT: Phase 2b long-term extension study
RATIONALE FOR THIS STUDY: X-linked hypophosphatemia (XLH) is a disorder of renal phosphate wasting caused by high circulating levels of fibroblast growth factor 23 (FGF23) that impairs normal phosphate reabsorption in the kidney. Hypophosphatemia and low-normal circulating 1,25-dihydroxy vitamin D (1,25$[OH]_2$D) levels are typical biochemical findings. Adults with XLH typically present with fractures, osteoarthritis, joint pain and stiffness, bone pain, gait abnormalities, and/or dental abscesses; bowing of the lower extremities and short stature remain from childhood. Although treatment with oral phosphate and vitamin D metabolites typically stops in adolescence, many adults experience long-term complications from the treatment, such as hyperparathyroidism and nephrocalcinosis. Physicians may consider treating adults with oral phosphate and/or vitamin D metabolites in select cases where an adult has chronic non-traumatic fractures, pending orthopedic surgery, severe osteomalacia, or disabling skeletal pain. More efficacious, safer, and convenient therapies clearly are needed for adults who continue to experience XLH related complications. KRN23 is a recombinant fully human monoclonal IgG_1 antibody being developed to treat XLH by binding to and inhibiting FGF23 activity, thereby restoring normal phosphate homeostasis. Three clinical studies have been conducted in adults with XLH. A Phase 1 study (KRN-US-02) established the pharmacokinetic (PK) profile of KRN23. A Phase 1/2 study (KRN-INT-001) and an associated extension study (KRN-INT-002) evaluated the PK and pharmacodynamics (PD) of KRN23 on phosphate metabolism and assessed phosphate homeostasis and mineral metabolism. The safety data from these studies suggest that KRN23 in single and repeated monthly doses up to 1.0 mg/kg for as many as 16 doses over a period of 17 months has a favorable safety profile in adult subjects with XLH. This study, an extension of the KRN-INT-001/KRN-INT-002 studies, aims to collect additional information on the safety, immunogenicity, pharmacodynamics (PD), and efficacy response with long-term administration of KRN23.

OBJECTIVES:

Primary Objectives

The primary objectives of this study are to:

- Assess the long-term safety of subcutaneous (SC) KRN23 administration in adult subjects with XLH
- Assess the proportion of subjects achieving serum phosphorus levels in the normal range (2.5-4.5 mg/dL) with long-term administration of KRN23
- Assess long-term PD of KRN23 as measured by changes in the following:
  - Serum and urinary phosphorus
  - Serum intact parathyroid hormone (iPTH)
  - Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) and tubular reabsorption of phosphate (TRP)
  - Serum $1,25(OH)_2D$
  - Serum FGF23
  - Bone biomarkers: serum alkaline phosphatase (ALP), bone-specific ALP (BALP), carboxy terminal cross-linked telopeptide of type I collagen (CTx), and procollagen type 1 N-terminal propeptide (P1NP)
- Assess long-term immunogenicity of KRN23 as measured by presence of anti-KRN23 antibody (anti-drug antibody [ADA])

Exploratory Efficacy Objectives

Exploratory efficacy objectives of this study are to:

- Evaluate changes in underlying skeletal disease as assessed by standard radiographs of the chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot as well as any location(s) where the subject is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (<3 months) fracture(s)
- Evaluate changes in patient-reported outcomes (PROs) and physical function including:
  - Patient reported pain - Brief Pain Inventory (BPI)
  - Disability - Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
  - Quality of life (QOL) scores – 36-item Short Form Health Survey (SF-36)
  - Walking ability - 6-Minute Walk Test (6MWT)
  - Balance and agility - Timed Up and Go (TUG) Test
- Assess the long-term pharmacokinetic (PK) profile of KRN23

STUDY DESIGN AND METHODOLOGY:

***Summary*:**

This study is a Phase 2b, open-label, long-term extension of study KRN23-INT-001/KRN23-INT-002 in adult subjects with XLH. The study population will consist of approximately 25 eligible subjects who participated in Kyowa Hakko Kirin Pharma, Inc.'s (KHK's) study KRN23-INT-001 or KRN23-INT-002 (received at least 2 doses of KRN23). Subjects who were discontinued from KRN23-INT-001 or KRN23-INT-002 due to a treatment-emergent adverse event (TEAE) classified as possibly or probably related to treatment may be eligible for participation in this study based on the clinical judgment of the investigator with agreement from the sponsor. Study treatment will continue over a maximum of 184 weeks (+5 days) to assess long-term safety, immunogenicity, PD response, and efficacy of KRN23

The Screening Visit will include a full medical history, blood tests, urine collections (of 2- and 24-hour duration), and urinalysis to confirm eligibility. A renal ultrasound will also be taken at Screening. A physical examination, assessments of walking ability, balance, and agility; self-reported pain and disability; and quality of life will be done at Baseline. Fasting blood samples and baseline imaging and functional testing will be obtained prior to the initial dose.

Subjects will receive the initial SC injection of KRN23 at the clinic. Starting doses will be individual for each subject, i.e., the subject's last dose in study KRN23-INT-001 or KRN23-INT-002, either 0.3, 0.6, or 1.0 mg/kg. Up to Week 12, individual subjects who have not reached serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL) at the end of the dose interval may have their doses titrated upward every 4 weeks to a maximum dose of 1.0 mg/kg based on fasting trough serum phosphorus levels. Doses may be titrated downward if at any point the serum phosphorus level increases above the upper limit of normal (ULN; 4.5 mg/dL). KRN23 will be administered monthly (every 4 weeks), either at home or in the clinic. Subjects will return to the clinic monthly at Weeks 4, 8, and 12; then every 12 weeks at Weeks 24, 36, and 48; and then every 24 weeks at weeks 72, 96, 120, 144 and as applicable up until the End-of-Treatment (EoT) Visit, which will occur by 30 September 2018. Subjects may be seen at home by Home Health (HH) personnel between the clinic visits, or the HH visits may be completed in the clinic, depending on the proximity of the subjects to the investigational site and the location and availability of HH resources. After proper training, subjects may self-administer KRN23 or be administered KRN23 by caregivers without the supervision of HH nurse; in such cases, the HH visit would become a telephone visit.

Safety, immunogenicity, PK, PD, and efficacy assessments will be performed during the treatment period as outlined in the Schedule of Events. All assessments, with the exception of weight, will be repeated at the EoT Visit. Subjects may choose to withdraw from the study at any time.

NUMBER OF SUBJECTS PLANNED:

Twenty subjects will be enrolled in this study.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

INCLUSION CRITERIA:

Subjects eligible for enrollment in the study must meet all of the following criteria at Screening:

1. Have participated in KHK's KRN23-INT-001 or KRN23-INT-002 studies (received at least 2 doses of KRN23)
2. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) or eGFR of 45 to <60 mL/min at Screening

with confirmation that the renal insufficiency is not due to nephrocalcinosis

3. Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years, or have had tubal ligation at least one year prior to Screening, or have had total hysterectomy.
4. Sexually active subjects must be willing to use two effective methods of contraception while participating in the study and for 12 weeks after receiving the last dose of KRN23.
5. 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.
6. Willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures.

EXCLUSION CRITERIA:

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subject experienced a safety-related event in the KRN23-INT-001 or KRN23-INT-002 study that, in the opinion of the investigator and sponsor, precludes resuming KRN23 treatment.
2. Presence of nephrocalcinosis on renal ultrasound that, in the opinion of the investigator and sponsor, precludes resuming KRN23 treatment.
3. Prior history of positive test results for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, and/or hepatitis C antibody (no additional screening required).
4. Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study.
5. Participation in an investigational drug or device trial within 30 days of enrollment (other than KRN23-INT-001 or KRN23-INT-002).
6. 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.
7. Use of a pharmacologic vitamin D metabolite or analog (e.g., calcitriol, doxercalciferol, and paricalcitol), phosphate, or aluminum hydroxide antacids (e.g., Maalox® and Mylanta®) within 21 days prior to Screening or during the study.
8. Use of medication to suppress PTH (e.g., Sensipar®, cinacalcet, calcimimetics) within 2 months prior to Screening.
9. Have any condition, which in the opinion of the investigator, could present a concern for either subject safety or difficulty with data interpretation, or that places the subject at high risk of poor treatment compliance or of not completing the study.

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. KRN23 will be administered SC without dilution. Subjects will receive study drug via SC injection to the abdomen, upper arms, and thighs; the injection site will be rotated for each visit, with the option to include a different quadrant of the abdomen. No more than 1.5 mL may be administered in a single injection. If a subject needs more than 1.5 mL per administration, multiple injections must be administered. During a visit with multiple injections, the injection site must be different for each administration, but may be in the same general location (eg arm, thigh). After proper training by study personnel in SC injection technique, the subject may self-administer KRN23 or the subject's caregiver may self-administer KRN23 to the subject without supervision of a home health nurse. Starting doses will be individual for each subject, i.e., the

subject's last dose in study KRN23-INT-001 or KRN23-INT-002 (0.3, 0.6, or 1.0 mg/kg). Up to Week 12, individual subjects who have not reached serum phosphorus levels above the LLN (2.5 mg/dL) at the end of the dose interval may have their doses titrated every 4 weeks (i.e., from 0.3 to 0.6 mg/kg or from 0.6 to 1.0 mg/kg) to a maximum dose of 1.0 mg/kg based on fasting trough serum phosphorus levels. Doses may be titrated downward (i.e., from 1.0 to 0.6 mg/kg or from 0.6 to 0.3 mg/kg) if at any point serum phosphorus increases above the ULN (4.5 mg/dL). The investigator will discuss with the medical monitor the need for dose titration.

REFERENCE THERAPY(IES), DOSE AND MODE OF ADMINISTRATION:

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

DURATION OF TREATMENT:

The treatment duration will be a maximum of 184weeks (+ 5 days) with a maximum total of 46 doses administered.

CRITERIA FOR EVALUATION:

Safety and Immunogenicity:

Safety assessments will be summarized at Baseline and at each observed time that they are collected.

Safety variables include:

- Incidence, frequency, and severity of adverse events (AEs), treatment-related AEs, and serious adverse events (SAEs)
- Vital signs and weight
- Physical examinations
- Estimated glomerular filtration rate (eGFR)
- Laboratory tests including chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (amylase, lipase, creatinine, and FGF23)
- Anti-KRN23 antibody testing and dose-limiting toxicities (DLTs)
- Concomitant medications
- Electrocardiogram (ECG)

Ectopic Mineralization Safety Assessments include:

- Serum total calcium and iPTH
- 24-hr urinary calcium excretion
- Fasting 2-hr urinary calcium/creatinine
- Echocardiogram (ECHO)
- Renal ultrasound

Pharmacokinetic:

- Serum KRN23 (pre-dose)

Pharmacodynamic:

- Serum phosphorus, urinary phosphorus, and fractional excretion of phosphorus (FEP)
- Serum iPTH
- TmP/GFR and TRP
- Serum $1,25(OH)_2D$
- Serum FGF23
- Bone biomarkers: ALP, BALP, CTx, P1NP

Exploratory Assessments:

Skeletal:

- Standard radiographs to assess the number of active pseudofractures and/or fractures as defined by skeletal survey at baseline and the numbers and percentages of the baseline active pseudofractures/fractures that were healed, partially healed, unchanged, and worsened at post-baseline visits

PROs and Physical Function:

- Brief Pain Inventory (BPI): Measures the severity of pain and the impact of pain on daily functions
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): Assesses pain, stiffness, and physical function, as measured by subject report
- 36-item Short Form Health Survey (SF-36): Physical and mental health measured by subject report and based on summary and subscale scores in in following sections: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health
- Six Minute Walk Test (6MWT): Measures the total distance walked (meters) in a six minute period. The percent of predicted normal distance walked based on published normative data will also be determined
- Timed up and go (TUG): Tests transition during ambulatory activity, incorporating strength, agility, and dynamic balance

STATISTICAL METHODS:

Safety Analysis:

All subjects who receive any amount of study drug will be included in the safety analysis.

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 (SOC), Preferred Term (PT), severity, and relationship to KRN23 treatment. A by-subject listing will be provided for those subjects who experience an SAE, including death, or who experience an AE associated with early withdrawal from the study or from study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

Pharmacodynamics and Efficacy Analysis:

Pharmacodynamic and exploratory efficacy endpoints will be summarized with descriptive statistics. For continuous variables, the mean, standard deviation, median, minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Changes over time and the association of the efficacy with the PD variables will also be summarized and evaluated.

Table 2.1: Schedule of Events

VISIT TYPE / NUMBER	Scr[1] 1	BL[2] 2	HH[3] 3	4	HH[3] 5	6	HH[3] 7	8	HH[3] 9	HH[3] 10	11	HH[3] 12	HH[3] 13	HH[3] 14	15	HH[3] 16	HH[3] 17
WEEK[4]	**D-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**38**	**40**
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical History & Demographics[5]	X																
Renal Ultrasound	X										X						
Chemistry[6], Hematology[7], Urinalysis	X							X			X				X		
2-hr and 24-hr Urine	X							X			X				X		
Urine Pregnancy Test[8]	X	X		X		X		X	X	X	X		X	X	X		X
Vital Signs[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X									X				X		
Physical Examination		X						X			X				X		
PHEX mutation analysis[10]		X															
Anti-KRN23 antibody (ADA)[11,12]		X		X				X			X				X		
Serum Phosphorus[13]	X	X	X	X[13]	X	X[13]	X	X[13]			X	X	X		X	X	X
Serum Calcium	X	X	X	X	X	X	X	X			X	X	X		X	X	X
Serum Creatinine	X							X			X				X		
Serum iPTH		X						X			X				X		
Serum FGF23[12]		X		X		X		X			X		X		X		X

VISIT TYPE / NUMBER	Scr[1] 1	BL[2] 2	HH[3] 3	4	HH[3] 5	6	HH[3] 7	8	HH[3] 9	HH[3] 10	11	HH[3] 12	HH[3] 13	HH[3] 14	15	HH[3] 16	HH[3] 17
WEEK[4]	**D-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**38**	**40**
Serum $1,25(OH)_2D$		X						X			X				X		
Bone Biomarkers[14]		X									X						
ECHO, ECG		X									X						
BPI, SF36[15]		X						X			X				X		
WOMAC[16]		X						X			X				X		
6MWT, TUG		X									X				X		
X-Ray[17]		X						X			X				X		
Interval History								X			X				X		
Serum KRN23[12,18]											X				X		
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X		X		X		X			X				X		
Drug Administration[19]		X		X		X		X	X	X	X		X	X	X		X

VISIT TYPE / NUMBER	HH[3] 18	19	HH[3] 20	HH[3] 21	HH[3] 22	HH[3] 23	HH[3] 24	HH[3] 25	26[20]
WEEK[4]	**44**	**48**	**50**	**52**	**56**	**60**	**64**	**68**	**72**
Informed Consent									
Inclusion/Exclusion Criteria									
Medical History & Demographics[5]									
Renal Ultrasound		X							X
Chemistry[6], Hematology[7], Urinalysis		X							X
2-hr and 24-hr Urine		X							X
Urine Pregnancy Test[8]	X	X		X	X	X	X	X	X
Vital Signs[9]	X	X	X	X	X	X	X	X	X
Height		X							X
Physical Examination		X							X
PHEX mutation analysis[10]									
Anti-KRN23 antibody (ADA)[11,12]		X							X
Serum Phosphorus		X	X	X		X			X
Serum Calcium		X	X	X		X			X
Serum Creatinine		X							X
Serum iPTH		X							X
Serum FGF23[12]		X							X
Serum $1,25(OH)_2D$		X							X
Bone Biomarkers[14]		X							X
ECHO, ECG		X							X

VISIT TYPE / NUMBER	HH[3] 18	19	HH[3] 20	HH[3] 21	HH[3] 22	HH[3] 23	HH[3] 24	HH[3] 25	26[20]
WEEK[4]	**44**	**48**	**50**	**52**	**56**	**60**	**64**	**68**	**72**
BPI, SF36[15]		X							X
WOMAC[16]		X							X
6MWT, TUG		X							X
X-Ray[17]		X							X
Interval History		X							X
Serum KRN23[12,18]		X							X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Weight		X							X
Drug Administration[19]	X	X		X	X	X	X	X	X

Table 2.2: Schedule of Events Past Week 72

VISIT TYPE / NUMBER	HH[3] or TC[19] 27, 28, 29, 30, 31, 33, 34, 36, 37, 39, 40, 42, 43, 45, 46, and as applicable thereafter until 30 September 2018	HH[20] 35, 41, and as applicable thereafter until 30 September 2018	32, 38, 44, and as applicable thereafter until 30 September 2018	EoT[21] visit number will vary for each subject	Safety Follow-up TC[22]
WEEK[4]	**Every 4 Weeks: 76, 80, 84, 88, 92, 100, 104, 112, 116, 124, 128, 136, 140, 148, 152, and as applicable thereafter until 30 September 2018**	**Every 12 Weeks: 108, 132 and as applicable thereafter until 30 September 2018**	**Every 24 Weeks: 96, 120, 144, and as applicable thereafter until 30 September 2018**	**Last visit occurring by 30 September 2018[21]**	**4 weeks (and. if applicable, 8 weeks) after EoT Visit[22]**
Informed Consent					
Inclusion/Exclusion Criteria					
Medical History & Demographics[5]					
Renal Ultrasound			X	X	
Chemistry[6], Hematology[7], Urinalysis			X	X	
2-hr and 24-hr Urine			X	X	
Urine Pregnancy Test[8]		X	X	X	
Vital Signs[9]		X	X	X	
Height			X	X	
Physical Examination			X	X	
PHEX mutation analysis[10]					
Anti-KRN23 antibody (ADA)[11,12]			X	X	

VISIT TYPE / NUMBER	HH[3] or TC[19] 27, 28, 29, 30, 31, 33, 34, 36, 37, 39, 40, 42, 43, 45, 46, and as applicable thereafter until 30 September 2018	HH[20] 35, 41, and as applicable thereafter until 30 September 2018	32, 38, 44, and as applicable thereafter until 30 September 2018	EoT[21] visit number will vary for each subject	Safety Follow-up TC[22]
WEEK[4]	**Every 4 Weeks: 76, 80, 84, 88, 92, 100, 104, 112, 116, 124, 128, 136, 140, 148, 152, and as applicable thereafter until 30 September 2018**	**Every 12 Weeks: 108, 132 and as applicable thereafter until 30 September 2018**	**Every 24 Weeks: 96, 120, 144, and as applicable thereafter until 30 September 2018**	**Last visit occurring by 30 September 2018[21]**	**4 weeks (and. if applicable, 8 weeks) after EoT Visit[22]**
Serum Phosphorus			X	X	
Serum Calcium			X	X	
Serum Creatinine			X	X	
Serum iPTH			X	X	
Serum FGF23[12]			X	X	
Serum $1,25(OH)_2D$			X	X	
Bone Biomarkers[14]			X	X	
ECHO, ECG			X	X	
BPI, SF-36[15]			X[15]	X[15]	
WOMAC[16]					
6MWT, TUG					
X-Ray[17]			X	X	
Interval History			X	X	
Serum KRN23[12,18]			X	X	
Prior and Concomitant Medications	X	X	X	X	X

VISIT TYPE / NUMBER	HH[3] or TC[19] 27, 28, 29, 30, 31, 33, 34, 36, 37, 39, 40, 42, 43, 45, 46, and as applicable thereafter until 30 September 2018	HH[20] 35, 41, and as applicable thereafter until 30 September 2018	32, 38, 44, and as applicable thereafter until 30 September 2018	EoT[21] visit number will vary for each subject	Safety Follow-up TC[22]
WEEK[4]	**Every 4 Weeks: 76, 80, 84, 88, 92, 100, 104, 112, 116, 124, 128, 136, 140, 148, 152, and as applicable thereafter until 30 September 2018**	**Every 12 Weeks: 108, 132 and as applicable thereafter until 30 September 2018**	**Every 24 Weeks: 96, 120, 144, and as applicable thereafter until 30 September 2018**	**Last visit occurring by 30 September 2018[21]**	**4 weeks (and. if applicable, 8 weeks) after EoT Visit[22]**
Adverse Events	X	X	X	X	X
Weight			X	X	
Drug Administration[19]	X	X	X		

Footnotes for Table 2.1 and Table 2.2

1,25(OH)$_2$D= 1,25-dihydroxy vitamin D; 6MWT = 6-minute walk test; ADA = anti-drug antibodies; BL = Baseline; ECG = electrocardiogram; ECHO = echocardiogram; EoT = end of treatment; FGF23 = fibroblast growth factor 23; HH = home health; HIV = human immunodeficiency virus; hr = hour; iPTH = intact parathyroid hormone; PHEX = phosphate regulating gene with homology to endopeptidases located on the X chromosome; Scr = Screening; TUG = timed up and go (test)

1 Screening tests may be spread out over Screening and Baseline assessments, but have to be performed before drug administration. Screening and Baseline visits may be conducted on consecutive days but may be conducted up to 7 days apart.

2 Baseline Visit tests and assessments may be spread out over 2 consecutive days to accommodate considerable number of assessments.

3 Home Health (HH) visits may also be conducted at the clinic depending on proximity of the subjects to the investigational site and local availability of home health resources.

4 The visit window for all visits after visit 3 and before EoT visit is is ± 3 days. The visit window for the EoT visit is + 5 days.

5 Medical history to include review of previous test results for HIV antibody, hepatitis B surface antigen, and/or hepatitis C antibody. Viral testing will not be repeated in this study.

6 This comprehensive metabolic profile will include the standard Chem-20 serum panel (Na, K, Cl, bicarbonate, blood urea nitrogen [BUN], creatinine and creatinine clearance, glucose, alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], lactate dehydrogenase, phosphorus, uric acid, calcium, total protein, albumin, cholesterol and triglycerides, total bilirubin, and indirect bilirubin) as well as amylase and lipase.

7 Complete blood count, differential, and platelet count.

8 For women of childbearing potential only. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy result.

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

[10] If the Baseline result for PHEX mutation analysis is negative or inconclusive (i.e., No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic), reflexive genetic testing will be performed (another blood draw may be needed) to assess additional genes associated with phenotypes overlapping with XLH.

[11] 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.

[12] If there is a technical or operational issue obtaining results for ADA, FGF23, or KRN23, then an additional blood sample may be obtained at the next suitable clinic visit.

[13] Two serum samples should be collected at indicated clinic visits for serum phosphorus measurements. One sample will be read locally for determination of dosing decision; the other will be sent for analysis by the central laboratory.

[14] Bone biomarkers will include serum measures of total serum ALP, bone-specific ALP (BALP), CTx, and P1NP.

[15] Brief Pain Inventory (BPI) and SF-36 self-reported patient-reported outcomes (PROs) tools. These evaluations are not required past Week 144.

[16] Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) self-reported PRO tool.

[17] Standard radiographs will be customized by patient and will be repeated every 3 months or until specified fractures/psuedofractures are healed.

[18] Sample collection for KRN23 assessment will begin at the earliest indicated study visit once necessary approvals have been obtained.

[19] After proper training, subjects or their caregiver will administer study drug under the supervision of a healthcare provider. If the subject or caregiver demonstrates competency in administration of SC injections at that time, they will be instructed to perform future study drug administrations at home without supervision for HH visits occurring after week 96 or later (with the exception of site visits, during which subject/caregiver administration is preferable to demonstrate continued competency in technique, but not required). Drug administration by a HH nurse may continue at the discretion of the investigator, subject and/or caregiver. If the healthcare provider determines that the subject/caregiver requires additional training on SC injection technique, study drug will again be administered under the supervision of a healthcare provider at the next study visit. Once a subject or their caregiver has received appropriate SC injection technique training and begins administering study drug at home without supervision, they will be contacted via telephone by the study site every 28 days (+ 5 days), with the exception of site visits, to confirm administration of study drug and to record concomitant medications and AEs. Telephone visits may also be conducted at the clinical site depending on proximity of the subject to the site.

[20] For subjects that are self-administering or having a caregiver administer study drug, a healthcare provider will return for HH visits occurring every 12 weeks after week 96 or visit 32 to assess vital signs, pregnancy, and record concomitant medications and AEs.

[21] If a subject will be continuing KRN23 treatment under commercial use or another mechanism, the first dose of that treatment should not be administered until after completion of all of the EoT Visit assessments. Those subjects who terminate the study early will be asked to come back to the clinic for a final assessment. If the subject terminates the study early before Week 72, then the Week 72 assessments will be conducted. If the subject terminates the study early between Weeks 72 and EoT Visit (up until 30 September 2018, occurring within 4 weeks of last dose administration), then the EoT assessments will be conducted. Every reasonable effort should be made to have subjects return to the clinic for the final assessment.

[22] To be completed for all subjects who complete the EoT Visit and are not immediately continuing KRN23 treatment under commercial use or another mechanism. The site personnel will initiate a Safety Follow-up telephone call (TC) 4 weeks (+ 5 days) after the EoT Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, serious adverse events (SAEs), or concomitant medications. Appropriate follow-up of AEs/SAEs should continue until all safety concerns, in the Investigator's opinion, are resolved. If the subject is not continuing KRN23 therapy under commercial use or another mechanism at that time, then site personnel will initiate a subsequent

Safety Follow-up TC at 8 weeks (+ 5 days) after the EoT Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications.

3 TABLE OF CONTENTS

List of Tables

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

$1,25(OH)_2D$	1,25-dihydroxy vitamin D
6MWT	6-Minute Walk Test
ADA	Anti-drug antibodies
AE	Adverse Event
AFO	Ankle foot orthoses
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BALP	Bone-specific alkaline phosphatase
BPI	Brief pain inventory
BUN	Blood urea nitrogen
CFB	Change from Baseline
CFR	Code of Federal Regulations
CO_2	Carbon dioxide
CS	Clinically significant
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Carboxy terminal cross-linked telopeptide of type I collagen
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EoT	End-of-treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FGF23	Fibroblast growth factor 23
GCP	Good Clinical Practice
GEE	General estimating equation
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HH	Home health
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
IP	Investigational product
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
KHK	Kyowa Hakko Kirin Pharma, Inc. (the Sponsor's development partner for KRN23)
KRN23	Investigational product, an anti-FGF23 antibody
LDH	Lactate dehydrogenase
LVH	Left ventricular hypertrophy
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NaPiIIa	Type IIa sodium-phosphate co-transporter
NaPiIIc	Type IIc sodium-phosphate co-transporter
NCI	National Cancer Institute
NCS	Not clinically significant
P1NP	Procollagen type N-propeptide
PD	Pharmacodynamics
PHEX	Phosphate-regulating gene with Homologies to Endopeptidases on the X-chromosome
PK	Pharmacokinetics
PRO	Patient-reported outcome
PT	Preferred term
PTH	Parathyroid hormone
QoL	Quality of life
QTc	Corrected QT interval
RBC	Red blood cell
RLS	Restless Legs Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item Short Form Health Survey
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum concentration

TmP/GFR	Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate
TRP	Tubular reabsorption of phosphate
TUG	Timed up and go (test)
US	United States
VS	Vital signs
WBC	White blood cell
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities osteoarthritis index
XLH	X-Linked Hypophosphatemia

Definition of Terms

°C	Degrees Celsius
dL	Deciliter
kDa	Kilodalton
kg	Kilogram
L	Liter
mg	Milligram
mL	Milliliter
mmHG	Millimeters of Mercury
mmol	Millimole

5 INTRODUCTION

5.1 Overview of the Disease

5.1.1 X-linked Hypophosphatemia

X-linked hypophosphatemia (XLH) is a rare genetic metabolic disorder and the most common inherited form of rickets. XLH was originally called vitamin D-resistant rickets, because doses of vitamin D, usually effective for the treatment of vitamin D-deficient nutritional rickets, did not have an impact on phosphate levels in these patients (Albright et al. 1937); (Baroncelli et al. 2012). The incidence of XLH is 3.9 to 5 per 100,000 live births (Davies et al. 1981); (Beck-Nielsen et al. 2009). XLH is also the most common inherited defect in renal tubular phosphate transport; it is characterized by renal phosphate wasting leading to hypophosphatemia and low or normal concentrations of 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), an inappropriate response to hypophosphatemia (Holm et al. 2012). In XLH patients, high levels of fibroblast growth factor 23 (FGF23) reduce normal phosphate reabsorption in the kidney and cause a phosphate-wasting condition, which is the major manifestation of XLH (Imel et al. 2005); (Liu et al. 2007).

XLH is transmitted as an X-linked dominant disorder, although autosomal recessive and dominant forms of hypophosphatemia have also been observed (Dixon et al. 1998). Mutations resulting in the loss of function of the Phosphate-regulating gene with Homology to Endopeptidases located on the X chromosome (PHEX) form the genetic basis for XLH (Carpenter et al. 2011); PHEX is the only gene in which mutations are known to cause XLH; however, because of the great intrafamilial variation, severity cannot be predicted (Ruppe 2012). Approximately 20% of PHEX mutations are de novo (i.e., not inherited from a parent) based on genetic testing and clinical observations in non-familial XLH patients (Dixon et al. 1998); (Whyte et al. 1996). The phenotypic spectrum of Xlinked- hypophosphatemia (XLH) ranges from isolated hypophosphatemia to severe lower extremity bowing.

Skeletal abnormalities of osteomalacia (rickets) often manifest in the first 2 years of childhood (e.g., bowed legs) when lower extremity bowing becomes evident with the onset of weight bearing; however, the disorder may go undiagnosed until adulthood. The initial presenting complaint in adults may be enthesopathy (calcification of the tendons, ligaments, and joint capsules) (Ruppe 2012). There is a great deal of variability in the manifestations of XLH. In the mildest cases, only hypophosphatemia is evident (Holm et al. 2012). In more severe cases, adult patients with XLH may suffer from bone pain and osteomalacia; increased risk of bone fractures; joint abnormalities and joint pain; osteoarthritis, and enthesopathy (Ruppe 2012); (Tenenhouse et al. 2001); (Reid et al. 1989). Diagnostic testing characteristically reveals low serum phosphate concentration and reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR). Additionally in adults, the normal physiologic response to hypophosphatemia of an elevation of $1,25(OH)_2D$ is absent; serum calcium and alkaline phosphatase (ALP) are within the normal range; and parathyroid hormone (PTH) is normal to slightly elevated. (Ruppe 2012) For definitive evidence of renal phosphate wasting, a 2-hour fasting urine specimen as well as a blood sample collected at the

midpoint of the urine collection period are used to calculate the percent tubular reabsorption of phosphate (TRP) and to determine the tubular threshold maximum for phosphate (Carpenter et al. 2011).

Treatments for XLH to date have been directed at replacing lost phosphorus and correcting osteomalacia by giving phosphorus supplements and an active vitamin D metabolite (e.g., calcitriol). Adult patients with XLH are often not treated with standard of care because of the risk of hyperparathyroidism and nephrocalcinosis and other side effects (i.e., hyperphosphatemia, hypercalcemia, hypercalciuria, nephrocalcinosis, hypoparathyroidism, and secondary hyperparathyroidism) and the lack of evidence that such therapy improves long-term skeletal complications of XLH. Physicians may consider oral phosphate and/or active vitamin D treatment if adult patients suffer from chronic non-traumatic fractures, pending orthopedic surgery, severe osteomalacia, or disabling skeletal pain/stiffness, and treatment requires frequent monitoring of urine and serum chemistries. Routine lower extremity x-rays and annual renal ultrasound examinations are typically included in the standard of care to assess skeletal response to these therapies and to assess for nephrocalcinosis (Ruppe 2012). However, these replacement therapies do not address the main manifestation of the disorder - namely, excess FGF23 (Carpenter et al. 2011).

5.1.2 FGF23

The exact mechanisms by which PHEX mutations lead to FGF23 overexpression are not fully understood (Rowe 2012). Through a series of complex steps, the defect in PHEX leads to an erroneous signal that phosphate levels are high, In response, the osteocytes inappropriately secrete high levels of FGF23 that lead to phosphate wasting in the urine, severe hypophosphatemia and the bone deformities associated with rickets (Rowe 2012); (Gattineni et al. 2012); (Baroncelli et al. 2012). FGF23 is composed of 251 amino acids synthesized primarily by osteocytes and osteoblast. FGF23 principally acts on the kidneys to increase phosphate urinary excretion and suppress $1,25(OH)_2D$ synthesis. Also, FGF23 has a direct effect on the parathyroid glands to decrease PTH formation and secretion. The main mechanism by which FGF23 reduces serum phosphorus is through inhibition of renal proximal tubular phosphate reabsorption via down-regulation of type IIa and type IIc sodium-phosphate (NaPiIIa and NaPiIIc) co-transporters in the renal proximal tubule. (Razzaque et al. 2007); (Fukumoto 2008) FGF23 also decreases serum $1,25(OH)_2D$ levels by inhibiting 25-hydroxy vitamin D-1-alpha-hydroxylase activity and by increasing 25-hydroxy vitamin D 24-hydroxylase activity in the kidney. These actions by FGF23 lead to increased urinary phosphate excretion and decreased intestinal phosphate absorption and result in hypophosphatemia; FGF23 thus has a key adaptive role in maintaining normal serum phosphate levels (Fukumoto 2008); (Juppner 2011).

FGF23 signaling in the kidney is dependent on the presence of fibroblast growth factor receptor 1 (FGFR1) and the obligate co-receptor Klotho, a transmembrane protein required for signaling (Urakawa et al. 2006). FGF23 binds to the FGFR1 and Klotho co-receptor, with both binding events needed for signaling.

5.2 Brief Overview of the Development of the Product

A brief overview of existing information on KRN23 is provided in the following sections. Comprehensive information on KRN23 is contained in the IB provided by Ultragenyx, which should be reviewed prior to initiating the study.

5.2.1 Brief Description of the Investigational Product

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

5.2.2 Mechanism of Action in XLH

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

5.2.3 Nonclinical Studies

The results of initial *in vitro* studies established that KRN23 bound with similar high affinity to human, rabbit, and cynomolgus monkey FGF23 and that this binding was associated with inhibition of receptor-mediated signal transduction, defining a putative mode of action for this human anti-FGF23 mAb. These results further established that rabbit and cynomolgus monkey were pharmacologically relevant animal models for the investigation of the pharmacodynamics (PD) and toxicologic properties of KRN23.

In vivo studies in rabbits and adult and juvenile cynomolgus monkeys demonstrated dosedependent- elevations of serum phosphorus and $1,25(OH)_2D$, confirming the pharmacologic actions of KRN23 in these species. While these studies confirmed the predicted mode of action and pharmacological actions in rabbits and cynomolgus monkeys, they did not provide evidence of reversal of disease-associated changes. To provide the proof of concept that an anti-FGF23 mAb could reverse the characteristic disease-associated effects

seen in XLH, the actions of an anti-FGF23 mAb in the Hyp mouse model for XLH were investigated. Experiments in both juvenile and adult Hyp mice provided evidence that blocking the FGF23 receptor with an anti-FGF23 mAb normalized or ameliorated many of the characteristic abnormalities associated with this disease (e.g., growth, muscle strength, and pain) in the Hyp mouse.

The major toxicological findings of KRN23, such as mineralization, were related to an excessive pharmacological effect (excessive elevation of serum phosphorus above the normal ranges). Except for the pharmacologically-related toxicities, there were no unexpected severe toxicities. In addition, no gross and histopathological abnormalities were observed at the intravenous (IV) infusion sites or subcutaneous (SC) injection sites in the 40-week repeatdose- toxicity studies in adult cynomolgus monkeys.

5.2.4 Clinical Studies

Four clinical studies have been completed 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 associated treatment extension study (KRN23-INT-002). Additional studies in adult and pediatric XLH patients are ongoing. Details of study parameters and current PK, PD, clinical efficacy and safety results are provided in the IB.

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

Repeated doses of KRN23 up to 1.0 mg/kg were well tolerated by adult XLH subjects throughout the Phase 1/2 dose escalation and associated treatment extension study.
No treatment-related deaths have been reported. A drug-related serious, life-threatening event of angioedema was reported in a subject enrolled in this study but this case was more likely caused by a co-suspect concomitant medication, lisinopril. The subject discontinued lisinopril and continued on study medication without a recurrent hypersensitivity reaction. Across multiple-dose studies in adults with XLH, the most common TEAEs were nasopharyngitis, arthralgia, back pain, and pain in extremity. The most common treatment-related TEAEs were Injection site reaction and arthralgia. No discernible clinically significant trends of lab abnormalities suggestive of a treatment-related adverse effect were noted. Overall, no immunogenicity or patterns of dose-limiting toxicity have been associated with KRN23 treatment.

5.3 Summary of Overall Risks and Potential Benefits

KRN23, a fully human mAb that binds and inhibits FGF23, is being developed as a potential therapeutic candidate for XLH, a rare genetic disease associated with hypophosphatemia and elevated levels of FGF23. By blocking the activity of FGF23, KRN23 has the potential to restore phosphate, vitamin D, and bone metabolism homeostasis in patients with XLH, thereby improving osteomalacia, the pathologic hallmark of XLH in adults. This therapeutic approach directly targets the inherent dysregulation in XLH (ie, excess FGF23). In contrast, supplementation therapy with phosphate and/or $1,25(OH)_2D$, is only partially effective and may increase the 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. 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 echocardiogram (ECHO) or 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 the current standard of care consisting of oral phosphate and/or $1,25(OH)_2D$ supplementation, KRN23 does not appear to be associated with progression of cardiac or renal ectopic mineralization beyond the natural course of pre-existing disease.

SC doses of KRN23 in the range from 0.3 to 1.0 mg/kg were able to achieve the desired PD effect in adults, which lasted approximately one month, positioning KRN23 as a drug that could be administered every 4 weeks 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. By positively modulating serum phosphorus, it is expected that the underlying osteomalacia will be treated, leading to improved clinical outcomes including a potential reduction in pain, stiffness, and fracture risk as well as the impact of these factors on the quality of life of adult patients 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

Ultragenyx is evaluating the therapeutic potential of KRN23, a recombinant human IgG1 mAb targeting FGF23 in adult patients with XLH. Many adults who received treatment with oral phosphate and vitamin D metabolites experience long-term complications from the treatment, such as hyperparathyroidism and nephrocalcinosis. Physicians may consider treating adult patients with oral phosphate and/or vitamin D metabolites in select cases where

an adult has chronic non-traumatic fractures, pending orthopedic surgery, severe osteomalacia, or disabling skeletal pain. More efficacious, safer, and more convenient therapies are clearly needed for adults who continue to experience XLH-related complications.

The safety data from the completed Phase 1 and Phase 1/2 studies suggest that KRN23 in single and repeated monthly doses up to 1.0 mg/kg for as many as 16 doses over a period of 17 months has a favorable safety profile in adult subjects with XLH. This study aims to collect additional information on the safety, immunogenicity, and PD response with longterm- administration of KRN23. The scientific rationale, unmet medical needs, and results of nonclinical studies support the proposition that KRN23 has the potential to offer an important new therapeutic option to this patient population.

6 STUDY OBJECTIVES

Primary Objectives

The primary objectives of this study are to:

- Assess the long-term safety of KRN23 SC administration in adult subjects with XLH
- Assess the proportion of subjects achieving serum phosphorus levels in the normal range (2.5-4.5 mg/dL) with long-term administration of KRN23
- Assess long-term PD of KRN23 as measured by changes in the following:
  - Serum and urinary phosphorus
  - TmP/GFR and TRP
  - Serum $1,25(OH)_2D$
  - Serum FGF23
  - Bone biomarkers: serum ALP, bone-specific ALP (BALP), carboxy terminal cross-linked telopeptide of type I collagen (CTx), and procollagen type 1 N-terminal propeptide (P1NP)
- Assess long-term immunogenicity of KRN23 as measured by presence of anti-KRN23 antibody (ADA)

Exploratory Efficacy Objectives

Exploratory efficacy objectives of this study are to:

- Evaluate changes in underlying skeletal disease by standard radiographs of the chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot as well as any location(s) where the subject is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (<3 months) fracture
- Evaluate changes in patient-reported outcomes (PROs) and physical function including:
  - Patient-reported pain – Brief Pain Inventory (BPI)
  - Disability – Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
  - Quality of life (QoL) scores – 36-item Short Form Health Survey (SF-36)
  - Walking ability – 6-Minute Walk Test (6MWT)
  - Balance and agility – Timed Up and Go (TUG) Test
- Assess the long-term PK profile of KRN23

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This study is a Phase 2b, open-label, long-term extension study of the completed studies KRN23-INT-001 and KRN23-INT-002 in adult subjects with XLH. The study population will consist of approximately 20 eligible subjects who participated in KHK's study KRN23-INT-001 or study KRN23-INT-002 (received at least 2 doses of KRN23). Subjects who were discontinued from KRN23-INT-001 or KRN23-INT-002 due to a TEAE classified as possibly or probably related to treatment may be eligible for participation in this study based on the clinical judgment of the investigator with agreement from the sponsor. The study will be conducted over a minimum of 164 weeks and a maximum of 192 weeks, depending on the date of subject entry, to assess the long-term safety, immunogenicity, PD, and clinical efficacy of KRN23.

Subjects will discontinue oral phosphate and active vitamin D metabolite or analog therapy at least 21 days prior to the Screening Visit, will discontinue use of any medication to suppress PTH within 2 months prior to the Screening Visit, and may not resume any of those medications for the duration of the study. Subjects will be brought in for a Screening Visit and asked to provide written informed consent (Section 8.1.3). The Screening Visit will include full medical history and demographic assessments, clinical laboratory testing (blood and urine), a renal ultrasound, and review of all inclusion and exclusion criteria to confirm eligibility.

After eligibility is confirmed, Baseline assessments can occur within 1 day and up to 7 days of the Screening Visit and the tests may be spread out over 2 days. Baseline assessments will include a PHEX mutation analysis for genotype/phenotype correlations, clinical laboratory testing (blood and urine), a physical examination, height and weight, functional and PRO assessments, ECHO and ECG, and Baseline imaging (X-rays). If the Baseline result for PHEX mutation analysis is negative or inconclusive (i.e., No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic) and the subject provides informed consent, reflexive genetic testing will be performed to assess additional genes associated with phenotypes overlapping with XLH.

Any of the baseline tests may be performed at the Screening Visit. The baseline physical examination and PRO assessments may be performed at the Screening Visit as long as the PRO assessments are completed prior to the physical examination and on the same day.

After all Screening and Baseline assessments have been completed, study drug administration will begin at Baseline (Week 0), with open-label, SC injection of undiluted KRN23.

The starting dose of KRN23 at Baseline (Week 0) in this study will be individual for each subject, i.e., the same as a subject's last dose in studies KRN23-INT-001 or KRN23-INT-002

(0.30, 0.60, or 1.0 mg/kg). Dosing will occur at the clinic and the volume will be based on the weight obtained on Day 0.

Up to Week 12, individual subjects who have not reached serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL) at the end of the dose interval may have their doses titrated upward every 4 weeks (i.e., from 0.3 to 0.6 mg/kg or from 0.6 to 1.0 mg/kg) to a maximum dose of 1.0 mg/kg based on fasting trough serum phosphorus levels. Doses may be titrated downward (i.e., from 1.0 to 0.6 mg/kg or from 0.6 to 0.3 mg/kg) if at any point the serum phosphorus level increases above the upper limit of normal (ULN; 4.5 mg/dL). The investigator will discuss with the medical monitor the need for dose titration. KRN23 injections will be repeated every 4 weeks for the duration of the study (from Week 0 until the visit prior to EoT Visit, which will occur prior to 30 September 2018), and weight will be reassessed periodically for dose volume adjustments as needed (Table 2.1 and Table 2.2). The End-of-Treatment (EoT) Visit will be the subject's last visit occurring by 30 September 2018. . A Safety Follow-up TC will occur 4 weeks (+ 5 days) after the EoT Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, serious adverse events (SAEs), or concomitant medications. If the subject is not continuing KRN23 therapy under commercial use or another mechanism at that time, then site personnel will initiate a subsequent Safety Follow-up TC at 8 weeks (+ 5 days) after the EoT Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications. The end of the study is defined as the last day that protocol-specified assessments are conducted for the last subject.

Safety, immunogenicity, PD, and efficacy assessments will be performed throughout the study, as outlined in Table 2.1 and Table 2.2. Subjects may choose to withdraw from the study at any time.

7.2 Discussion of Study Design, Including Choice of Control Group

This is an open-label study with the primary objectives of further characterizing the longterm- safety, immunogenicity, PK, PD, and efficacy profile of SC dosing of KRN23 every 4 weeks in adults with XLH. Efficacy assessments are included only as exploratory objectives; therefore, no control group is included. In a single-dose pharmacokinetic (PK) study of KRN23 administered SC, the time of maximum concentration (t_{max}) of KRN23 in serum ranged from 192 to 272 hours (8 to 11 days) after a single dose. KRN23 was eliminated with a half-life ($t_{1/2}$) of 322 to 448 hours (13 to 19 days). Exposure to KRN23 increased in a dose proportional manner up to 1.0 mg/kg following SC administration. Similar results in multiple-dose PK studies indicated that absorption of KRN23 following SC administration was consistent using a 4-week dosing schedule.

The design, dose, and dosing frequency of KRN23 in this open-label study were selected based on nonclinical data and data from completed clinical studies in which repeated doses of KRN23 up to 1.0 mg/kg were well tolerated by adult XLH subjects over a 48-week treatment period. The safety events to date have been mild to moderate in general, and only one drug-

related, life-threatening event of angioedema occurred in this study as described in Section 5.2.4.No immune response to KRN23 has been identified. While the safety is still under evaluation at this stage of development, the events to date suggest that KRN23 is well tolerated and that potential safety issues can be monitored.

Eligible subjects must have participated in KHK's study KRN23-INT-001 or study KRN23-INT-002 (received at least 2 doses of KRN23) to be eligible for this long-term (up to 192 weeks) extension study. Given the known safety profile of KRN23 to date, the inclusion/exclusion criteria are designed to exclude subjects with known kidney dysfunction (i.e., an eGFR <45 mL/min or nephrocalcinosis serious enough to preclude study participation), and subjects will be monitored throughout the study for changes in phosphate homeostasis and other relevant renal biochemistry parameters. Subjects who were reported to have safety-related events in KRN23-INT-001 or KRN23-INT-002 that, in the opinion of the investigator and sponsor, preclude resuming KRN23 treatment will also be excluded. Subjects will be carefully monitored for other possible risks during the study (i.e., immunogenicity and injection site reactions, ectopic mineralization, renal failure secondary to nephrocalcinosis, and pregnancy). Also, since elevated free FGF23 has been associated with LVH in patients with advanced kidney disease, ECHOs and ECGs are included to mitigate that risk.

7.3 Selection of Study Population

The study will be conducted in approximately 20 male and female adult subjects who are ≥18 years of age with a diagnosis of XLH and who participated in KHK's study KRN23-INT-001 or study KRN23-INT-002 (received at least 2 doses of KRN23).
The inclusion criteria are structured to enroll subjects with similar biochemical and clinical characteristics, including eGFR ≥60 mL/min or 45 to <60 mL/min at Screening with confirmation that the renal insufficiency is not due to nephrocalcinosis. Sites throughout the United States (US) will be participating in this study.

7.3.1 Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria at Screening:

1. Have participated in KHK's KRN23-INT-001 or KRN23-INT-002 studies (received at least 2 doses of KRN23).
2. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) or eGFR of 45 to <60 mL/min at Screening with confirmation that the renal insufficiency is not due to nephrocalcinosis.
3. Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years,

or have had tubal ligation at least one year prior to Screening, or have had total hysterectomy.

4. Sexually active subjects must be willing to use two effective methods of contraception (Section 7.5.3.11) while participating in the study and for 12 weeks after receiving the last dose of KRN23.
5. 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.
6. Willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures.

7.3.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subject experienced a safety-related event in the KRN23-INT-001 or KRN23-INT-002 study that, in the opinion of the investigator and sponsor precludes resuming KRN23 treatment.
2. Presence of nephrocalcinosis on renal ultrasound that in the opinion of the investigator and sponsor precludes resuming KRN23 treatment.
3. Prior history of testing positive for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, and/or hepatitis C antibody.
4. Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study.
5. Participation in an investigational drug or device trial within 30 days of enrollment (other than KRN23-INT-001 or KRN23-INT-002).
6. Presence or history of any hypersensitivity to KRN23 excipients (see Section 7.4.2) that, in the judgment of the investigator, places the subject at increased risk for adverse effects.
7. Use of a pharmacologic vitamin D metabolite or analog (e.g., calcitriol, doxercalciferol, and paricalcitol), phosphate, or aluminum hydroxide antacids (e.g., Maalox® and Mylanta®) within 21 days prior to Screening or during the study.
8. Use of medication to suppress PTH (e.g., Sensipar®, cinacalcet, calcimimetics) within 2 months prior to Screening.
9. Have any condition, which in the opinion of the investigator, could present a concern for either subject safety or difficulty with data interpretation, or that places the subject at high risk of poor treatment compliance or of not completing the study.

7.3.3 Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The investigator may withdraw a subject at any time at their discretion. Ultragenyx must be notified of all subject withdrawals as soon as possible.

Ultragenyx also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual subject or investigator due to poor enrollment or noncompliance, as applicable.

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

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

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 electronic Case Report Form (eCRF). AEs should be followed until the abnormality stabilizes, resolves, or until a decision is made that it is not likely to resolve. If AEs of abnormal clinical laboratory test results do not return to Baseline within 30 days after the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the EoT Visit procedures within four weeks of discontinuation. If the subjects will be continuing KRN23 treatment under commercial use or another mechanism, all EoT assessments should be performed before beginning that treatment. For subjects not immediately continuing KRN23 treatment under commercial use or another mechanism, a Safety Follow-up TC will occur 4 weeks (+ 5 days) after the EoT visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications. If the subject is not continuing KRN23 therapy under commercial use or another mechanism at that time, then site personnel will initiate a subsequent Safety Follow-up TC 8 weeks (+ 5 days) after the ET Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications.

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

7.3.3.1 Stopping Rules

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. Likewise, if a subject experiences DLT (Section 7.5.3.13) or positive immunogenicity result(s), the case will be evaluated by the

investigator, medical monitor, and sponsor to determine the subject's continuation or withdrawal from the study.

Individual subjects will be monitored for ectopic mineralization by renal ultrasounds and ECHOs. 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.

The Institutional Review Board (IRB) will be informed should unexpected and possibly, probably, or definitely drug-related SAEs occur. A full clinical evaluation of the event will be performed as described previously in order to make a decision regarding what actions to take, including whether to recommend stopping the study.

7.4 Treatments

7.4.1 Treatments Administered

The study design is open-label and all subjects will receive KRN23; no placebo or reference therapy will be administered in this study. All subjects will receive SC injections of KRN23 every 4 weeks, from Week 0 until the visit prior to the EoT Visit, which will occur prior to the end of September 2018, when KRN23 is expected to be commercially available in the US. Dose levels to be administered are described in Section 7.1.

KRN23 will be administered SC without dilution. Subjects will receive study drug via SC injection to the abdomen, upper arms, and thighs; the injection site will be rotated for each visit, with the option to include a different quadrant of the abdomen. No more than 1.5 mL may be administered in a single injection. If a subject needs more than 1.5 mL per administration, multiple injections must be administered. During a visit with multiple injections, the injection site must be different for each administration, but may be in the same general location (eg arm, thigh). After proper training by study personnel in SC injection technique, the subject may self-administer KRN23 or the subject's caregiver may self-administer KRN23 to the subject without supervision of a home health nurse.

7.4.2 Identity of Investigational Product(s)

KRN23 is supplied as a sterile, clear, colorless and preservative-free solution in single-use 5 mL vials containing 1 mL of KRN23 at a concentration of 10 mg/mL or 30 mg/mL. Subjects will receive study drug via SC injection to the abdomen, upper arms and thighs; the injection site will be rotated with each study visit, with an option to include a different quadrant of the abdomen. If the dose level exceeds 1.5 mL in volume, the dose may be administered at 2 injection sites. During a visit with multiple injections, the injection site must be different for each administration, but may be in the same general location (eg arm, thigh). At the discretion of the investigator and after proper training by study personnel in subcutaneous injection technique, the subject or a non-healthcare professional may administer KRN23 to the subject under without supervision of a home health nurse where

local regulations permit and where logistically feasible. Subjects or caregivers will be instructed to follow the directions provided in the Instructions for Use.

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

7.4.3 Storage, Handling, and Administration

KRN23 should be securely stored in a refrigerator at 2°C to 8°C and protected from light. It should not be frozen. A log to document the daily temperature of the refrigerator must be maintained as a Good Clinical Practice (GCP) requirement. Access to and administration of KRN23 will be limited to the investigator and authorized site staff. KRN23 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Subjects will receive study drug via SC injection to the abdomen, upper arms, and thighs. The injection site will be rotated with each visit, with the option to include a different quadrant of the abdomen. If the dose level exceeds 1.5 mL in volume, the dose must be administered at 2 injection sites. During a visit with multiple injections, the injection site must be different for each administration, but may be in the same general location (eg arm, thigh).

Subjects or their caregiver will receive training from study personnel in SC injection technique and will administer study drug under the supervision of the site personnel. After proper training by study personnel in SC injection technique, a subject's caregiver may administer KRN23 to the subject. Subjects or caregivers will be instructed to follow the directions provided in the Instructions for Use. If the subject or caregiver demonstrates competency in administration of SC injections at that time, this will be documented, and they will be instructed to perform future study drug administrations at home without supervision (with the exception of site visits, during which subject/caregiver administration is preferable to demonstrate continued competency in technique, but not required). The dosing schedule will remain the same.

If at any time a subject/caregiver has questions pertaining to home study drug administration, they may call the study site for additional training/support. If the healthcare provider determines the subject/caregiver require additional training or if a subject/caregiver fails proper administration at any time, the investigator has discretion, in consultation with the Sponsor, to have the subject return to the site for subsequent study drug administration or reinstate home health nursing visits for home administration. Study personnel should periodically review the method of administration with the subject/caregiver to ensure they are using proper technique.

Each administration of study drug will be recorded on the CRF. Once a subject or their caregiver has received appropriate SC injection technique training and begins administering study drug at home without supervision, they will be contacted via telephone by the study

site every 28 days (+ 5 days), with the exception of site visits, to confirm administration of study drug and to record related information about each administration of study drug on the CRF. Telephone visits may also be conducted at the clinical site depending on proximity of the subject to the site. Empty vials will be returned to the study site for drug accountability records by a HH nurse or the subject.

7.4.4 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. All subjects will receive open-label SC injections of KRN23.

7.4.5 Selection of Doses in the Study

A multiple-dose, dose escalation Phase 1/2 study (KRN23-INT-001) was conducted in adult XLH subjects. KRN23 was well tolerated following SC administration of 4 intra-subject escalating doses (0.05 mg/kg → 0.1 mg/kg → 0.3 mg/kg → 0.6 mg/kg) administered once per 28 days. The proportion of KRN23-treated subjects with serum phosphorus levels in the target range (>2.5 to ≤3.5 mg/dL) increased with KRN23 dose level but did not exceed the ULN (4.5 mg/dL) in any subject at any time point. A direct PK-PD relationship between serum KRN23 concentrations and serum phosphorus levels was noted in the study. In an associated extension study (KRN23-INT-002), doses up to 1.0 mg/kg KRN23 administered monthly were well tolerated by adult XLH subjects over a period of 48 weeks.

Previous studies with KRN23 in adult XLH patients did not show any "off target" effects; therefore, the safety profile is expected to be related solely to the PD effect (i.e., increased serum phosphorus). Since the defined serum phosphorus target range in this study is well below the ULN, the likelihood of a dose-related safety issue is low (the target fasting peak serum phosphorus range for this study is ≥2.5 to ≤3.5 mg/dL [0.81 to 1.13 mmol/L]). The efficacy data on phosphate control from these previous studies also suggest there is a plateau in effect with KRN23 administered at dose levels between 0.60 mg/kg and 1.0 mg/kg. Dose adjustments will be individually titrated based on PD effects on serum phosphorus, safety, and tolerability.

The planned duration of treatment in this study is until the end of September 2018, ranging from 156-184 weeks (+5 days) depending on subject entry date.

7.4.6 Selection and Timing of Dose for Each Subject

All subjects will receive open-label SC injections of KRN23. The starting dose of KRN23 at Baseline (Week 0) in this study will be individual for each subject (i.e., the same as a subject's last dose in studies KRN23-INT-001 or KRN23-INT-002). Dosing will occur at the clinic and the volume will be based on the weight obtained on Day 0.

Up to Week 12, individual subjects who have not reached serum phosphorus levels above the LLN (2.5 mg/dL) at the end of the dose interval may have their doses titrated upward every 4 weeks (i.e., from 0.3 to 0.6 mg/kg or from 0.6 to 1.0 mg/kg) to a maximum dose of

1.0 mg/kg based on fasting trough serum phosphorus levels. Doses may be titrated downward (i.e., from 1.0 to 0.6 mg/kg or from 0.6 to 0.3 mg/kg) if at any point the serum phosphorus level increases above the ULN (4.5 mg/dL). The investigator will discuss with the medical monitor the need for dose titration. KRN23 injections will be repeated every 4 weeks for the duration of the study (from Week 0 through 30 September 2018), and weight will be reassessed periodically for dose volume adjustments as needed (Table 2.1 and Table 2.2).

The investigator must evaluate the subject's safety assessments to determine the need for dose adjustments. If a TEAE should occur, the investigator will confer with the medical monitor and sponsor to determine acceptable conditions for dose increases or decreases. Weight will also be monitored periodically throughout the study to determine whether dose volumes need to be adjusted (see Table 2.1 and Table 2.2).

Dosing may be delayed should a subject experience clinically significant findings, including (but not limited to) AEs, clinical laboratory abnormalities, or physical examination findings. Dosing may be resumed, based on the outcome of the investigation (with or without dose adjustment), as deemed medically appropriate by the investigator after consultation with the medical monitor and sponsor.

7.4.7 Blinding

Since all subjects will receive the same investigational product, blinding is unnecessary; study drug will be provided to investigators and subjects open-label.

7.4.8 Treatment Compliance

Trained personnel, subjects, or non-healthcare professionals will administer study drug by SC injection at the investigational site or during home health visits as indicated in Table 2.1 and Table 2.2. Each administration of study drug will be recorded on the eCRF.

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

7.5 Study Procedures and Assessments

Subjects will be brought in for a Screening Visit and asked to provide written informed consent. At the Screening Visit, inclusion/exclusion criteria will be reviewed, medical/surgical history and demographic data will be collected, clinical laboratory test samples will be collected (blood and urine), and a renal ultrasound will be performed to confirm subject eligibility.

Each subject who successfully meets the eligibility criteria and is enrolled in the study will undergo PHEX mutation analysis for genotype/phenotype correlations as well as the safety, immunogenicity, PD, and efficacy assessments as outlined in Table 2.1 and Table 2.2, which lists the study assessments, the expected visit type/number, and the Week numbers. The Baseline Visit (Week 0) may be completed over 2 days if needed, to accommodate the

number of required procedures. Overall the study will include at least 47 protocol-defined visits (2 visits to complete Screening and Baseline assessments, 41 visits during the On-Treatment Period, and 1 EoT Visit).

All of the visits should be conducted in a fasted state (i.e., refrain from eating and drinking, other than water) for at least 8 hours prior to the study visit. If the subject is not in a fasted state, specimens for laboratory assessments are not to be collected, and the visit should be rescheduled for the subject to return in a fasted state. Subjects should be instructed to take all other prescribed medications as usual on the morning of study visits, unless medications are taken with food, in which case they should be delayed until after study tests are performed.

The first dose of study drug will be administered when the subject has successfully completed all Baseline assessments. For the On-Treatment Period, the study visits should be scheduled based on the Baseline Visit (Week 0), i.e., the first administration of open-label KRN23 defines Baseline. For Visits 3 through the remainder of the study, the visits should be scheduled on the designated visit day ±3 days. The permitted visit window may be expanded to accommodate special circumstances for all study visits.

Subjects will report to the clinic for Screening and Baseline Visits, and for Visits 4, 6, 8, 11, 15, 19, 26, 32, 35, 38, 41, and 44 and every 24 weeks as applicable until EoT (Weeks 4, 8, 12, 24, 36, 48, 72, 84, 96, 108, 120, 132, and 144 and every 24 weeks as applicable respectively). All other study assessments will be performed in the subject's home, or at the clinic, depending on the subject's proximity to the clinic and local availability of HH resources. The EoT Visit will occur by 30 September 2018 . For subjects not immediately continuing KRN23 treatment under commercial use or another mechanism upon completion of study drug treatment or early withdrawal from this study, a Safety Follow-up TC will occur 4 weeks (+5 days) after their EoT visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications. If the subject is not continuing KRN23 therapy under commercial use or another mechanism at that time, then site personnel will initiate a subsequent Safety Follow-up TC 8 weeks (+ 5 days) after the subject's final study site visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications.

7.5.1 Pharmacodynamic and Efficacy Measurements

Pharmacokinetic, PD, and efficacy endpoints will be evaluated in all subjects. All PK and PD samples should be taken in the morning. The subject must be in a fasted state (at least 8 hours without food and drink, except water) and blood should be collected before being dosed with KRN23 and/or as one of the early procedures during study visits, as appropriate. The usual precaution for venipuncture should be observed. It is important to avoid hemolysis.

7.5.1.1 Primary Pharmacodynamic Measurements

The PD effect of KRN23 will be assessed in adults with XLH by measuring the following before KRN23 administration in a fasted state:

- Serum phosphorus (pre-dose at Weeks 0, 2, 4, 6, 8, 10, 12, 24, 26, 28, 36, 38, 40, 48, 50, 52, 60, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)
- TRP (pre-dose at Week 0)
- TmP/GFR (fasting 2-hour urine; pre-dose at Weeks 0, 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)
- Serum intact parathyroid hormone (iPTH; pre-dose at Weeks 0, 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)
- Serum FGF23 (pre-dose at Weeks 0, 4, 8, 12, 24, 28, 36, 40, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)
- Serum $1,25(OH)_2D$ (pre-dose at Weeks 0, 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)
- Bone biomarkers: ALP, BALP, CTx, and P1NP (pre-dose at Weeks 0, 24, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)
- 2-hour (fasting) and 24-hour urine (urinary phosphorus, creatinine, and calcium; Weeks 0, 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit)

7.5.1.2 Exploratory Efficacy Measurements

Exploratory clinical efficacy measures will evaluate the effect of KRN23 on bone health (Section 7.5.1.2.1), PROs (Section 7.5.1.2.2), and clinical outcomes (Section 7.5.1.2.3), in adults with XLH. Refer to the study reference manual for additional details on clinical efficacy measures.

7.5.1.2.1 Bone Health Measurements

Standard radiographs will be obtained predose- at Week 0 and at Weeks 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit until identified fractures/pseudofractures resolve. Standard radiographs will be obtained of the chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot as well as any location(s) where the subject is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (<3 months) fracture, or in bones where radiographs suggest the presence of a fracture or pseudo-fracture. Radiographs will be interpreted locally for the identification of new abnormalities, and on treatment- radiographs will be compared to Screening radiographs by 3 trained central readers (2 primary and 1 adjudicator) who are blinded to post-treatment time point and subject data. At each

on-treatment time point, the radiograph will be compared to Baseline and rated by the 3 central readers, using a pre-defined list of abnormalities. Central readers will be blinded to other patient data.

7.5.1.2.2 Patient-reported Outcomes Measurements

Pain, physical function, and physical and mental health will also be assessed using validated PRO instruments, including the WOMAC, the BPI, and the SF-36.

WOMAC: The WOMAC will be completed by subjects pre-dose at Weeks 0, 12, 24, 36, 48, and 72 to assess pain, stiffness, and physical function. The WOMAC consists of 24 items divided into 3 subscales:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties

BPI: The BPI will be completed by subjects pre-dose at Weeks 0, 12, 24, 36, 48, 72, 96, 120, and 144 to assess pain severity and the impact of pain on daily functioning. On the BPI, mild pain is defined as a worst pain score of 1 to 4, moderate pain is defined as a worst pain score of 5 to 6, and severe pain is defined as a worst pain score of 7 to 10.

SF-36: The SF36 will be completed by subjects- pre-dose at Weeks 0, 12, 24, 36, 48, 72, 96, 120, and 144 to assess physical and mental health based on 8 scaled scores that are the weighted sums of the questions in their section: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. Lower scores indicate more disability and higher scores indicate less disability, i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

7.5.1.2.3 Clinical Outcomes Measurements

Gross motor impairment, including diminished walking ability, pain, and muscle weakness are potential complications associated with XLH-related skeletal deformities. Changes in walking ability, lower extremity strength, and agility will be measured by 6MWT and the TUG test pre-dose at Week 0 and while on treatment at Weeks 24, 36, 48, and 72. A trained clinician will administer this assessment following participation in a formal training protocol conducted by the sponsor.

6MWT: The 6MWT assesses walking ability and will be administered in accordance with general principles set forth in the American Thoracic Society (ATS) guidelines (ATS/ERS 2002). 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. The percent of predicted normal values will be calculated using published normative data based on age, and gender (Gibbons et al. 2001).

TUG: The TUG assesses transitions during ambulatory activity incorporating strength, agility, and dynamic balance assessments. The TUG score will be reported as the time (in seconds) that a person takes to rise from a chair, walk three meters (approximately 10 feet), turn around, walk back to the chair, and sit down.

7.5.2 Drug Concentration Measurements

To assess KRN23 concentration and possible accumulation, serum pre-dose levels will be evaluated as a PK parameter in this study. A pre-dose blood sample will be obtained at Weeks 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit or at the earliest indicated visit once the necessary approvals have been obtained. For each sample collection, the time elapsed since last study drug administration will be recorded on the eCRF.

7.5.3 Safety Measurements

7.5.3.1 Adverse Events

The investigator will inquire about AEs at all subject visits by asking the subject a question such as: "How have you been feeling since your last visit?" All AEs, whether observed by the investigator or reported by the subject, will be recorded on the appropriate AE page of the eCRF and as appropriate on the SAE form, from the time the subject signs the informed consent through their EoT Visit or final Safety Follow-up TC as outlined in Section 7.1. The Safety Follow-up telephone call (TC) that occurs 4 weeks (+5 days) after a subject's EoT Visit, will collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications. If the subject is not continuing KRN23 therapy under commercial use or another mechanism at that time, then site personnel will initiate a subsequent Safety Follow-up TC 8 weeks (+ 5 days) after the ET Visit to collect information on whether KRN23 treatment has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit and the follow-up telephone call, 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, all HH visits, and the follow-up telephone call as outlined in Section 7.1. All AEs will be evaluated to determine whether they meet the criteria of being a DLT (Section 7.5.3.13).

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

Any laboratory test results that fall outside the laboratory normal range will be considered abnormal. The investigator will indicate if such values are clinically significant (CS) or not (NCS). All laboratory tests with clinically abnormal values (i.e., beyond those expected for subjects with XLH of this age group) should only be recorded as an AE if symptomatic, if potentially life-threatening without symptoms, or if deemed appropriate by the investigator.

If a subject experiences an AE, the subject will receive appropriate treatment and supportive care as necessary, and the investigator will continue to follow up on the AE until there is a return to the subject's Baseline condition or until a clinically satisfactory resolution is achieved.

7.5.3.2 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 standard of care treatment.

Subjects must be willing to provide access to prior medical records for the collection of historical biochemical and radiographic data, as well as disease history. The specific diagnosis of XLH will be recorded, along with date of onset, clinical presentation, and date and method of diagnosis. A disease-specific list of signs, symptoms, and conditions associated with XLH in adults, as well as any medications administered to manage these conditions, will be completed as part of the medical history.

7.5.3.3 Prior and Concomitant Medications/Therapies

Subjects will be asked whether medication to suppress PTH (e.g., Sensipar®, cinacalcet, calcimimetics) has been taken within 2 months before the Screening Visit; subjects who must continue to take PTH suppressors will be excluded from the study, or, if medically able to discontinue PTH suppressors, the subject may be enrolled after a 2-month washout period. Likewise, a 21-day washout of any active pharmacologic vitamin D metabolite or its analog (e.g., calcitriol, doxercalciferol, and paricalcitol), phosphate, and aluminum hydroxide antacids (e.g., Maalox® and Mylanta®) is required for inclusion if medically able to discontinue those medications. Live (attenuated) vaccines (except influenza vaccines) are prohibited within 3 months prior to Screening through the EoT Visit.

All other medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken within 30 days before the Screening Visit will be reviewed and recorded. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except those listed in Section 7.5.3.3.1. Therapies (physical therapy, occupational therapy as well as mobility and walking devices, including ankle foot orthoses (AFOs), braces, cane, crutches, walker, wheelchair etc.) used within 30 days before the Screening Visit and at Baseline will also be reviewed and recorded.

Concomitant medications and therapies while on treatment will be reviewed and recorded in the subject's eCRF beginning on the day of initial dosing (Baseline, Week 0) (indication, start date, stop date, dose, dose regimen), at all clinic and HH visits, and at the follow-up telephone call. At each subsequent visit, change in medications and therapies since the previous visit will be recorded on the concomitant medication pages in the subject's eCRF. 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 7.5.3.3.1.

7.5.3.3.1 Prohibited Medications

To be eligible for the study, subjects must agree to discontinue use of certain medications for the indicated timeframe prior to enrollment. These medications will remain prohibited throughout the conduct of the study. Any subject who resumes or requires the use of any of these medications during the 144-week treatment period will be discontinued from the study.

- PTH suppressors (e.g., Sensipar®, cinacalcet, calcimimetics) within 2 months before Screening and during the study
- Active pharmacologic vitamin D metabolites or analogs (e.g., calcitriol, doxercalciferol, and paricalcitol), phosphate, or aluminum hydroxide antacids (e.g., Maalox® and Mylanta®) within 21 days before Screening or during the study
- Any mAb therapy (other than study drug)

7.5.3.3.2 Permitted Medications

Other than the medications specifically prohibited in this protocol, subjects may receive concomitant medications as required.

7.5.3.3.3 Constraints during the Course of the Study

Subjects are not permitted to change current diet or activity/exercise regimen from 1 week before dosing to the EoT evaluation. Alcohol intake will be permitted (up to 3 drinks per day) during the study duration.

7.5.3.4 Vital Signs

Vital signs (VS) will include seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in millimeters of mercury (mmHg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital sign measurements will be performed pre-dose at Week 0 and at the time points indicated in Table 2.1 and Table 2.2 before any additional assessments are completed. At each site visit, weight (in kilograms) will be obtained using a scale. Weight measurements will be used to calculate the appropriate KRN23 volume to be administered on a mg/kg basis.

All BP measurements will be made on the subject's non-dominant arm supported at heart level. If possible, vital signs should be taken by the same staff member, at the same time of day and by the same instrument at each visit.

7.5.3.5 Physical Examination

Physical examinations are to be performed by a qualified, licensed medical professional (i.e., MD, physician's assistant, or nurse practitioner), as designated by the investigator. Complete physical examinations will be performed pre-dose at Week 0 and at the time points indicated in Table 2.1 and Table 2.2. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; and the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

The genitourinary exam scope should be non-invasive and as per age-appropriate standard of care, at the investigator's discretion based on clinical judgement and/or safety need. If the PI determines there is no clinical indication for a genitourinary exam, it is not necessary to perform.

7.5.3.6 Clinical Laboratory Tests

Fasting for a minimum of 8 hours (overnight) is required prior to each blood draw; the duration of fasting will be recorded on the eCRF. Blood and urine samples will be collected at Screening, pre-dose at Baseline, and at regular intervals throughout the study, as indicated in Table 2.1 and Table 2.2. The local lab at the investigational sites will be used to assess safety parameters required for study eligibility (except FGF23). For the laboratory assessments collected at Screening, any results that fall outside the laboratory normal range will be considered abnormal and will be recorded in the medical history. The investigator will indicate whether laboratory test results are CS or NCS.

A comprehensive serum metabolic panel (Chem-20), complete blood count, and urinalysis will be used as routine screens to assess KRN23 safety. Certain analytes (i.e., ALP and serum phosphorus) in the routine Chem-20 panel are also designated as PD/efficacy parameters in this study (Section 7.5.1). KRN23/XLH biochemical parameters of interest include serum amylase, lipase, total calcium, creatinine, FGF23, and iPTH; and urinary calcium and creatinine. Reflexive testing for amylase isoenzymes will be performed if serum amylase levels are elevated by ≥1.5 the upper limit of the reference range. FGF23 concentrations will be measured using validated assays.

Twenty-four hour urine collection is required to assess urinary phosphorus:creatinine and calcium:creatinine ratios; urinary phosphorus (a PD parameter, Section 7.5.1.1) will also be obtained from 24-hour urine samples. The fasting 2-hour urine collection (collected in conjunction with the 24-hour urine collection) is also required, to determine TmP/GFR levels. The 2-hour and 24-hour urine collection will be performed at Screening for TmP/GFR eligibility and at Weeks 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable

through the EoT Visit as indicated in Table 2.1 and Table 2.2. Results obtained at Screening will serve as Baseline data.

Clinical laboratory parameters to be assessed for safety are provided in Table 7.5.3.6.1. See the Study Reference Manual for details on sample collection and processing.

Table 7.5.3.6.1: Clinical Laboratory Assessments

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
Amylase isoenzymes†	White blood cell (WBC) count	Ketones
Aspartate aminotransferase (AST)	Mean corpuscular volume (MCV)	Protein
Bone-specific ALP (BALP)*	Mean corpuscular hemoglobin (MCH)	Glucose
Bilirubin (direct and total)	MCH concentration	
Blood urea nitrogen (BUN)		**24-hour Urine**
Calcium (total)		Calcium
Chloride		Calcium/creatinine ratio
Carbon dioxide (CO_2)		Creatinine
Cholesterol (total) and triglycerides		Phosphorus
Creatinine		Phosphorus/creatinine ratio
Carboxy terminal cross-linked telopeptide of type I collagen (CTx)		
Gamma-glutamyl transpeptidase (GGT)		**2-hour Urine**
Glucose		Calcium
FGF23		Creatinine
Intact parathyroid hormone (iPTH)*		Calcium/creatinine ratio
Lactate dehydrogenase (LDH)		Phosphorus
Lipase		TmP/GFR
Phosphorus*		Pregnancy Test (if applicable)
Potassium		
Procollagen type 1 N-terminal propeptide (P1NP)*		
Protein (albumin and total)		
Sodium		
Uric acid		

*Also designated as PD/efficacy parameter
† Will be assessed reflexively if amylase levels are ≥1.5 times the upper limit of the reference range

The following laboratory abnormalities should be captured on the SAE form and/or eCRF, as appropriate:

- Any laboratory test result that meets the criteria for an SAE
- Any laboratory abnormality that requires the subject to have study medication discontinued or interrupted
- Any laboratory abnormality that requires the subject to receive specific corrective therapy

Any clinically significant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until 1 or more of the following occur:

- The value returns to Baseline
- The value is judged to be clinically acceptable by the investigator and the sponsor
- A diagnosis is reached that explains the abnormal laboratory value

Whenever possible, the investigator should report the clinical rather than the laboratory term (e.g., anemia, vs. low hemoglobin [Hb]).

Subjects who experience an 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.

7.5.3.7 Anti-KRN23 Antibody Screening

To determine the immunogenicity profile of KRN23, blood samples will be obtained for analysis of ADA pre-dose at Weeks 0, 4, 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit as indicated in Table 2.1 and Table 2.2. The concentration of anti-KRN23 antibodies in human serum will be determined using a validated sandwich enzyme-linked immunosorbent assay (ELISA) and a 2-tiered strategy: screening assay and specificity confirmation assay. If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points on a case-by-case basis, if warranted.

7.5.3.8 Renal Ultrasound

Renal ultrasounds will be conducted at Screening and at Weeks 24, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit as indicated in Table 2.1 and Table 2.2. The ultrasound may be performed either before or after administration of KRN23 while on treatment. The screening ultrasound will be interpreted by qualified personnel at the investigational site to determine eligibility and to serve as Baseline data. However, central readings will be performed for all on-treatment renal ultrasounds to evaluate changes in calcifications and all other renal abnormalities from Baseline. Ratings will be performed by a single central reader.

7.5.3.9 Echocardiogram

ECHO will be performed pre-dose at Week 0 and either before or after administration of KRN23 at Weeks 24, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit. The goal is twofold: 1) assess for evidence of ectopic mineralization in the heart and aorta, and 2) evaluate for signs of LVH or cardiac dysfunction. Additional tests may be performed if any abnormalities are detected or if medically indicated. ECHO administration procedures will be standardized and results will be read centrally by trained personnel who are blinded to the dose and dose regimen of the subjects. ECHOs will be assessed for any clinically significant abnormality or relevant changes from Baseline (CFB), and new evidence of cardiac calcifications, LVH, or other new abnormalities will be recorded as TEAEs.

7.5.3.10 Electrocardiogram

A standardized 12-lead ECG will measure PR, QRS, QT, and corrected QT (QTc) intervals pre-dose at Week 0 and either before or after administration of KRN23 at Weeks 24, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit. The goal is to evaluate for changes associated with LVH, as well as for changes in conductivity and intervals. ECG administration procedures will be standardized and results will be read locally by trained site personnel. A medically qualified person will assess the ECG results for any clinically significant abnormality that would exclude a subject from eligibility in the study and for clinically relevant changes between examinations. Copies of the ECGs should be kept with the subject's source documents. New evidence of LVH or other new abnormalities will be recorded as TEAEs.

7.5.3.11 Pregnancy Testing

Female subjects of child-bearing potential must be non-pregnant and non-nursing and will have urine pregnancy tests pre-dose at all dosing visits and at EoT, as indicated in Table 2.1 and Table 2.2. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result. In the event of a positive urine pregnancy test at an HH visit, KRN23 will not be administered and a serum sample will be drawn for confirmation of pregnancy. Female subjects with a positive serum pregnancy test at Screening will not be enrolled in the study. Female subjects with a positive serum pregnancy test at Baseline or any subsequent visit will be discontinued from the study.

Experience with KRN23 in pregnant women is limited. The study drug may involve risks to a pregnant female or unborn baby that are currently unknown. Female participants of child-bearing potential who have not undergone a total hysterectomy or bilateral salpingo-oophorectomy and are sexually active must consent to use a highly effective method of contraception as listed below from the period following the signing of the informed consent through 12 weeks (approximately 5 times the elimination half-life) after stopping the study drug. Sexually active male participants with female partners of childbearing potential must consent to use a condom with spermicide or a highly effective method of contraception

listed below from the period following the signing of informed consent through 12 weeks after stopping the study drug. Examples of highly effective methods include:

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

7.5.3.12 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The reporting period for pregnancies is the period from the signing of the ICF through the EoT Visit or final Safety Follow-up TC, as defined in Section 7.1. 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. Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy.

7.5.3.13 Dose-limiting Toxicity

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

- A Grade 3 or higher toxicity (based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events [CTCAE] Version 4 (NCI 2010) that occurs during treatment and is considered to be either possibly, probably, or definitely related to study drug
- 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.

7.5.3.14 Other Safety Considerations

Any clinically significant changes in safety assessments noted during the study, whether or not these assessments are required by the protocol, must also be recorded on the appropriate AE page of the eCRF and the SAE form, as appropriate, in order for the sponsor to collect additional information about that abnormality, including information regarding relationship to Investigational Product (IP), any action taken, and resolution.

7.5.4 Appropriateness of Measurements

As described in Section 5, XLH is characterized by renal phosphate wasting leading to hypophosphatemia and low or normal concentrations of $1,25(OH)_2D$, leading to signs/symptoms of bone pain and osteomalacia; increased risk of bone fractures; joint abnormalities and joint pain; enthesopathy; and osteoarthritis (Tenenhouse et al. 2001); (Reid et al. 1989). Measurements chosen for this study are therefore appropriate to assess the PD impact and safety profile of KRN23 on the disease characteristics over time, as well as to explore the efficacy of KRN23 in improving bone mineralization; strength, balance, and agility; and overall QoL.

7.6 Statistical Methods and Determination of Sample Size

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

7.6.1 Study Endpoints

7.6.1.1 Primary Safety Endpoints

Safety assessments will be summarized at Baseline and at each observed time that they are collected. The following endpoints will be examined:

- Incidence and frequency of AEs
- Number of clinically significant changes in vital signs
- Change from baseline in vital signs, laboratory tests, physical examinations, ECHO and ECG, and renal ultrasounds
- Number of subjects who develop anti-KRN23 antibodies

7.6.1.2 Primary Pharmacodynamic Endpoints

Pharmacodynamic parameters will be summarized at Baseline and at each observed time that they are collected. The following endpoints will be examined:

- Number and percentage of subjects who have serum phosphorus levels which, at any time after dosing are in the normal range: ≥ 2.5 and ≤ 4.5 mg/dL
- Change from baseline in serum biochemistry parameters associated with XLH, as measured by serum phosphorus, iPTH, FGF23, and $1,25(OH)_2D$
- Change from baseline in urinalysis parameters associated with XLH, as measured by 2-hour urine TmP/GFR and TRP, i.e., calcium, creatinine, and phosphorus
- Change from baseline in urine parameters associated with XLH, as measured by 24-hour urine, i.e., urinary phosphate, calcium, creatinine, and urine calcium/creatinine ratio
- Change from baseline in bone biomarkers associated with XLH, as measured by total ALP and BALP, CTx, and P1NP
- Change from baseline in fractional excretion of phosphorus (FEP), defined as 100%*(2-hour urine phosphorus*serum creatinine)/(2-hour urine creatinine * serum phosphorus)

7.6.1.3 Exploratory Endpoints

Exploratory efficacy and pharmacokinetic parameters will be summarized at Baseline and at each observed time that they are collected. The following endpoints will be examined:

- Change from baseline in pain and health-related QoL as measured by changes in the WOMAC, BPI, and SF-36 scores
- The number of active pseudofractures and/or fractures as defined by skeletal survey at baseline and the numbers and percentages of the baseline active pseudofractures/fractures that were healed, partially healed, unchanged, and worsened at post-baseline visits
- Change from baseline in walking ability as measured by change in the distance walked on the 6MWT in meters and percent predicted normal values.
- Change from baseline in transitions during ambulatory activity that incorporates strength, agility, and dynamic balance as measured by the TUG test
- Long-term pharmacokinetics of KRN23, as measured by KRN23 concentration

7.6.2 Statistical and Analytical Plans

7.6.2.1 Key Elements of Analysis Plan

The analyses planned in this protocol will be expanded in the UX023-CL203 SAP, which will be 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 (CSR).

7.6.2.2 Analysis Populations

Safety Analysis Set: All safety analyses will be performed on the safety analysis set, which will consist of all subjects who receive at least one dose of investigational product.

PD Analysis Set: PD analyses will be performed using this analysis set, which will consist of all subjects who receive at least 1 dose of investigational product and who have evaluable plasma/serum data.

Efficacy Analysis Set: All efficacy analyses will be performed on the efficacy analysis set. The efficacy analysis set will consist of all subjects who receive at least 1 dose of investigational product and who have at least one pre- and post-treatment measurement.

7.6.2.3 Statistical Principles

Descriptive statistics (mean, standard deviation [SD], median, and range) will be used to summarize continuous variables. For discrete data, the frequency and percent distributions will be provided. Statistical tests will use 2-sided alpha at a 0.05 significance level. Two sided- 95% confidence intervals will also be presented.

Safety, immunogenicity, PD, and efficacy results will be summarized using all available data. Missing data will not be imputed and will be treated as missing in all analyses.

7.6.2.4 Demography, Baseline Characteristics, and Disposition

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

The number of subjects screened, enrolled, treated, and completed will be summarized. Subject discontinuation from the study, and from treatment, will each be summarized including reason for discontinuation.

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

7.6.2.5 Pharmacodynamic Analyses

Pharmacodynamic parameters will be summarized at Baseline and at each observed time that they are collected. Correlations among PD parameters may also be assessed.

The number and percent of subjects who achieved the normal target range of serum phosphorus (≥2.5 and ≤4.5 mg/dL).

Individual PD-time plots may be presented for each subject as well as mean PD-time plots. Additional analyses using statistical models may be performed. The relationship between various PD parameters as well as KRN23 concentrations may be examined.

7.6.2.6 Exploratory Efficacy Analysis

X-rays will be obtained at Baseline and Weeks 12, 24, 36, 48, 72, 96, 120, 144, and every 24 weeks as applicable through the EoT Visit, or until fractures/pseudofractures are healed. The last assessment for each subject prior to receiving KRN23 will be used as Baseline.

Assessments of PROs will be measured at Baseline and Weeks 12, 24, 36, 48, 72, 96, 120, and 144. Subjects will not be required to complete the BPI and SF-36 past Week 144. The last assessment for each subject prior to taking KRN23 will be used as Baseline.

Assessments of physical function will be measured at Baseline, Weeks, 24, 36, 48, and 72. The last assessment for each subject prior to taking KRN23 will be used as Baseline.

The mean CFB will be described across subjects in terms of the mean and SD and will be tested using the generalized estimating equation (GEE) method. The model for change from Baseline will include Baseline and time as a categorical variable.

7.6.2.7 Pharmacokinetic Analyses

Summary statistics will be generated for pre-dose PK parameters.

7.6.2.8 Safety Analyses

All subjects in the Safety Analysis Data Set will be included in all summaries of safety endpoints.

General safety endpoints will include:

- Incidence and frequency of AEs, treatment-related AEs, SAEs, and DLTs (see Section 7.5.3.13)
- Clinically significant CFB in vital signs, weight, physical examination findings, and clinical laboratory tests (eGFR, chemistry, hematology, and urinalysis), including additional KRN23/XLH biochemical parameters of interest (amylase, lipase, creatinine, and FGF23)

- Anti-KRN23 antibody testing
- Concomitant medications
- ECG

Ectopic mineralization safety endpoints will include CFB in:

- Serum total calcium and iPTH
- 24-hr urinary calcium excretion
- Fasting 2-hr urinary calcium/creatinine
- ECHO
- Renal Ultrasound

7.6.2.8.1 Adverse Events

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 (SOC), Preferred Term (PT), relationship to study drug, and severity. All reported AEs with onset during the treatment (i.e., TEAEs) 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. The numbers (frequency) and incidence rates of AEs and SAEs will be summarized. Special attention will be given to those subjects who died, discontinued treatment due to an AE, or experienced an SAE (e.g., summaries, listings, and narrative preparation may be provided, as appropriate).

7.6.2.8.2 Clinical Laboratory Evaluations

Clinical laboratory data will be summarized by the type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at Baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any markedly abnormal laboratory results will be provided. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement. A list of reference ranges standardized across clinical laboratories will be provided.

7.6.2.8.3 Vital Signs

Vital signs will be summarized and listed by individual subject. Summaries of vital signs data over time and CFB over time will be provided.

7.6.2.8.4 Echocardiograms and Electrocardiograms

Echocardiogram and ECG data will be listed and summarized by individual subject and study population. Individual subject results will be examined in relation to Baseline recordings. Summaries of PR, QRS, QT and QTc intervals over time and CFB over time will be provided.

7.6.2.8.5 Renal Ultrasound

Renal ultrasound data will be listed and summarized for each subject and study population. Individual subject ultrasound results will be examined in relation to the subjects' Screening ultrasound, and the overall renal ultrasound results will be summarized.

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

7.6.2.8.6 Prior and Concomitant Medications

The World Health Organization (WHO) drug dictionary will be used to classify prior and concomitant medications by therapeutic class and PT. Prior medications include medications that were taken before the first administration of study drug, including those reported before dosing at the Baseline Visit (Week 0). Concomitant medications include medications that were taken at any time after the start of treatment within this study until the follow-up TC as defined in Section 7.1).

7.6.2.9 Exposure

Exposure to KRN23 will be summarized using the total amount of KRN23 administered to each subject during the study. Subject exposure will also be categorized and the number and percentage of subjects in each category will be presented.

7.6.2.10 Anti-KRN23 Antibody Assessment

The anti-KRN23 antibody data, including neutralizing and non-neutralizing antibody titers, will be listed and summarized by individual subject and study population.

7.6.3 Interim Analyses

No interim analyses are planned for this study.

7.6.4 Determination of Sample Size

The rationale for the sample size for this open-label extension study is based on practical considerations to obtain the needed information to meet study objectives. The sample size of this study is based on the number of subjects who have satisfactorily completed studies KRN23-INT-001 and/or KRN23-INT-002, along with the other eligibility criteria, and have agreed to participate in this long-term extension study. Approximately 20 subjects may be

enrolled in this study. Subjects who were enrolled in the KRN23-INT002 bone substudy- and who received KRN23 are also eligible. Since this is an exploratory study, no formal statistical power and sample size estimation methods were used to determine the sample size; therefore, the current study design is not powered to assess a pre-defined statistical difference in any endpoint.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board (IRB)

The IRB must be a properly constituted board or committee operating in accordance with 21 Code of Federal Regulations (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 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 for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB and Ultragenyx or its designee for review and approval prior to implementation. IRB 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 should be notified immediately and the amendment forwarded to the IRB 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 investigator will make every effort that the study described in this protocol is conducted in full conformance with those principles, current US Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) GCP guidelines, and local ethical and regulatory requirements. Should a conflict arise, the 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 IP, as described in this protocol and the IB, prior to the initiation of the study.

8.1.3 Subject Information and Consent

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

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 eCRF. 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

A Coordinating Investigator was identified for multicenter trials. The Coordinating Investigator was 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.

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

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

8.3 Investigational Product Accountability

The investigator, institution, or head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance through the course of the study. While at the clinical site, IP must be stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study. Subjects will be given instructions on the proper storage of IP when initially

dispensed and reminded of storage requirements at all subsequent visits (see also Section 7.4.3).

A drug accountability record must be maintained for all Investigational Product 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 IP must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the investigational product.

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 eCRFs. Data must be recorded on eCRFs approved by Ultragenyx or its designee. All information recorded on eCRFs 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 Ultragenyxauthorized 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 eCRF. All data entered in to the eCRF- must be verifiable; therefore, eCRFs 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 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 eCRFs and source documents, and ensuring the integrity of the data. eCRFs 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, and/or Ultragenyx or its designees have the right to access all eCRFs, 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 AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

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

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

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

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

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.

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

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the NCI CTCAE version 4.0. 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 disabling.

- ***Death (Grade 5):*** Events that result in death.

To ensure that there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific

event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

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

Categories of attributions for "Not Related" events:

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

Categories of attributions for "Related" events:

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

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

8.5.4 Adverse Event Reporting to Ultragenyx

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

All AEs will be collected from the time the subject signs informed consent through their EoT Visit or final Safety Follow-up TC as outlined in Section 7.1. In addition, the investigator may report any AE that occurs after this time period that is believed to have a reasonable possibility of being associated with study drug. For AEs that are ongoing beyond the follow-up telephone call (Week 152), the investigator should comment in the source document whether the event has recovered, recovered with sequelae, or stabilized.

8.5.5 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's, designee's, or site personnel's knowledge of the event. SAEs will be reported by completing and submitting an SAE report from the investigator to Ultragenyx or its 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, that occur from signing of the informed consent through EoT Visit or final Safety Follow-up TC (Section 7.1) must be reported as SAEs as described previously.

8.5.6 Pregnancy Reporting

Any pregnancy of a subject or a subject's partner that is reported while participating in the study will be monitored for the full term and or followed until the outcome of the pregnancy is known. Pregnancy-associated SAEs will be processed and submitted as necessary, as per the suspected unexpected serious adverse reactions (SUSAR) reporting process described in the following section.

8.5.7 Communication Plan

Ultragenyx or its designee will submit SUSAR reports to appropriate regulatory authorities 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 will be submitted within an additional eight (8) days. All other SUSARs will be submitted within 15 calendar days of first knowledge of the event.

Principal Investigators are required to report any urgent safety matters to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the regulatory authorities and investigators of any events (e.g., change to the safety profile of KRN23, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from signing the informed consent through 12 weeks following the last dose of study drug.

The investigator is responsible for notifying the IRBs of SAEs and any urgent safety matters, in accordance with IRB 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, as required

8.5.8 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: PPD email: PPD	PPD Telephone: PPD Cell: 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.

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10 SIGNATURE PAGE

Protocol Title: A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH)

Protocol Number: UX023-CL203 Amendment 2

I have read Protocol UX023-CL203 Amendment 2. 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 study.

PPD

PPD

Javier San Martin, MD
Vice President, Clinical Development
Ultragenyx Pharmaceuticals Inc.

Date