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

Protocol Number:	**UX023-CL205**
Original Protocol:	**22 October 2015**
Amendment 1:	**28 March 2016**
Amendment 2:	**12 June 2017**

Investigational Product:	KRN23 (Recombinant human IgG_1 monoclonal antibody to fibroblast growth factor 23 [FGF23])
Indication:	X-linked Hypophosphatemia (XLH)
IND Number:	76,488
EudraCT Number	Not applicable
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA
Sponsor's Responsible Medical Officer:	Javier San Martin, MD VP, Clinical Sciences Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA PPD
Coordinating Investigator:	Erik Imel, MD Indiana University School of Medicine Indianapolis, IN 46202 USA

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

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX023-CL205 Amendment 2

12 June 2017

Protocol UX023-CL205 Amendment 1 (dated 28 March 2016) has been modified by Amendment 2 to modify the study duration, allow for parent/caregiver administration of study drug, and formally incorporate information communicated to investigators via memoranda (dated 05 Apr 2016, 30 Sept 2016, 20 Oct 2016, and 13 Dec 2016). The major protocol changes that impact study design and conduct are summarized below:

1. **Study Objectives:** The following additional study objective (along with corresponding Section 7.5.4 Pharmacokinetic Assessment) has been modified:

   - *~~Pre-dose~~ KRN23 drug concentration levels **(PK)***

   Rationale: Clarification of language since KRN23 drug concentration levels are being assessed at time points corresponding to 1 week post dose in addition to time points prior to the first dose or at trough.

2. **Overall Study Design and Plan:** The provision to maintain gender balance has been modified:

   *To maintain a level of gender balance, no more than ~~7~~ **70% of** subjects of either gender will be enrolled.*

   Rationale: The original protocol planned sample size was 10 subjects, therefore 7 subjects (ie, 70% of the study population) were selected. The change more accurately reflects the total enrollment of 13 subjects (9 male; 69%).

3. **Study Duration:** An Extension Period of 96 weeks has been added.

   Rationale: The Extension Period has been added to the study for continued assessment of long-term safety and efficacy of KRN23 in younger children.

4. **Removal of Subjects:** In Section 7.3.3, language has been added to allow orthopedic surgery during the Extension Period if recommended by the investigator or consulting physician. In addition, subjects who develop hyperparathyroidism may remain on study, but use of medication to suppress PTH (eg, Sensipar®, cinacalcet, calcimimetics) is not permitted at any time. Subjects should be removed from study if treatment for hyperparathyroidism becomes medically necessary.

   Rationale: Given that the study duration was increased, certain conditions or the need for medical procedures may develop during the study. The additional provisions

allow subjects to remain on study should orthopedic surgery be recommended or mild hyperparathyroidism develop.

5. **Treatment:** Section 7.4.1 has been updated to allow for a parent or caregiver to administer KRN23 to the subject after proper training by study personnel in subcutaneous injection technique and documentation of proficiency. Section 7.4.4 has been updated to describe timing of dose adjustments during the Extension Period. Sections 7.4.6 and 8.3 have been updated to describe methods for monitoring treatment compliance in the home setting via telephone contact and physical inventory of empty vials at site visits for study drug accountability.

   Rationale: Allowing subjects' parents or caregivers to administer KRN23 in the home setting will reduce burden on the subjects. Instructions for Use (IFU) have been thoughtfully developed with input from XLH patients and will be used to guide parents and caregivers through the injection process. The IFU will be provided to sites and IRBs for approval prior to the initiation of parent/caregiver administration. To avoid potential errors with any dose adjustments, dose changes during the Extension Period will be initially implemented at the clinic visits. Site personnel will collect information on treatment compliance in the home setting and monitor the home administration via telephone contact.

6. **Study Procedures and Assessments:** Several changes have been made in Section 7.5; a new Schedule of Events table (Table 2.3) was included to describe visits and assessments during the Extension Period.

   a) During the Extension Period, clinic visits will occur at approximately 12-week intervals (±5 days). Home health or telephone visits will occur every 2 weeks. For telephone visits, study sites will schedule biweekly telephone calls with the subjects' parent/caregiver to confirm administration of study drug, and for collection of adverse events and concomitant medication information. Site personnel will initiate a safety follow-up telephone call 5 weeks (+5 days) after the Week 160 visit to determine if the subject is receiving KRN23 therapy under commercial use or another mechanism and to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications for subjects not receiving KRN23. The additional safety visit (10 weeks ± 5 days after Week 160) will apply to subjects who discontinue treatment early or choose not to continue KRN23 therapy as commercial product or through another mechanism once the study ends.

   Rationale: Additional clinic visits and telephone calls have been included in the Extension Period to monitor long-term safety, compliance, and efficacy at an interval deemed appropriate for the age of the population and duration of treatment.

   b) As previously communicated by memorandum (20 Oct 2016), Section 7.5.2 has been updated to remove TmP/GFR and TRP as estimates of renal phosphate

reabsorption due to the breadth of available data and burden of obtaining urine samples in this study population (under 5 years of age).

c) As previously communicated by memorandum (20 Oct 2016), the Week 22 serum calcium assessment has been removed from the Schedule of Events Table 2.1.

d) As previously communicated by memorandum (05 Apr 2016), Section 7.5.5.2 has been updated such that blood pressure will be obtained for subjects aged 3 years or above (at study entry or beginning when the subject turns 3 years of age). The provision for training on blood pressure measurements at the site initiation visit was removed.

e) As previously communicated by memorandum (13 Dec 2016), Section 7.5.5.4 has been updated to indicate that the scope of the genitourinary exam should be non-invasive and as per age-appropriate standard of care, at the investigator's discretion based on clinical judgement.

Rationale: The changes to pharmacodynamic assessments, blood pressure and genitourinary examinations provide clarification of study procedures for the investigator.

f) In Section 7.5.5, Electrocardiogram (ECG) has been changed from an ectopic mineralization assessment to a general safety assessment.

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.

g) As described in Section 7.5.5.8, concomitant medications and therapies will be reviewed between site visits by telephone call from the study site every 2 weeks and recorded in the subject's CRF.

Rationale: Inclusion of telephone calls provides a mechanism to track use of concomitant medications and therapies at a consistent frequency during the Extension Period.

7. **Statistical Analysis and Data Monitoring Committee:** The statistical models for efficacy analysis have been updated in Section 7.6.3. A new Section 7.6.4 has been inserted to describe the timing of planned analysis for the study. During the Extension Period, safety data will be reviewed by the Ultragenyx Study Safety Review Team (SSRT) on an ongoing basis (Sections 7.6.5 and 8.5.6).

Rationale: The analysis is updated to incorporate baseline adjustment and repeated measures at multiple time points. Section 7.6.4 clarifies the times during the study when safety and efficacy data may be analyzed and more precisely defines the end of the study. Sections 7.6.5 and 8.5.6 stipulate the Data Monitoring Committee will

review safety data through the Treatment Period (Week 64); long-term safety during the Extension Period will be reviewed by the Sponsor.

8. **Investigators and Study Administrative Structure:** As previously communicated by memorandum (30 Sept 2016), Section 8.2 has been updated to include language describing the Coordinating Investigator for the study. The Coordinating Investigator is Erik Imel, MD (Indiana University School of Medicine).

   Rationale: Regulatory guidance requires selection of a Coordinating Investigator for a multicenter clinical trial.

9. **Reporting and Follow-up of Adverse Events:** Section 8.5 has been updated to define the reporting periods for adverse events as:

   ….the time that the subject signs informed consent through ***the final protocol-defined safety follow-up telephone call or safety visit*** ~~12 weeks (approximately 5 times the elimination half-life) following the last dose of study drug~~.

   Rationale: The revised language reflects the revised study design and safety follow-up procedures.

10. In Section 7.5.5.7.2 and the Schedules of Events, the parenthetical explanation of anti-KRN23 antibodies has been changed from human anti-human antibodies (HAHA) to anti-drug antibodies (ADA).

    Rationale: The 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.

2 SYNOPSIS

TITLE OF STUDY:

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

PROTOCOL NUMBER:

UX023-CL205

STUDY SITES:

Approximately 3 sites in the United States

PHASE OF DEVELOPMENT:

Phase 2

RATIONALE FOR THIS STUDY:

X-linked hypophosphatemia (XLH) is a disorder of hypophosphatemia, renal phosphate wasting, defective bone mineralization, and impaired growth plate or endochondral ossification caused by inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), and is the most common form of heritable rickets. In the absence of functional *PHEX*, FGF23 production by osteocytes is greatly increased, leading to impaired conservation of phosphate by the kidney and consequent hypophosphatemia. FGF23 also suppresses 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production resulting in decreased intestinal absorption of calcium and phosphate. The chronic presence of low serum phosphorus levels leads to defective bone mineralization and the two major pathologic consequences of the hypophosphatemia, rickets and osteomalacia. Rickets and osteomalacia are both disorders of bone mineralization; however, rickets is a disease of the growth plates specifically, characterized by deficient mineralization as well as by delayed endochondral ossification, leading to reduced growth and skeletal deformities. The goal of therapy in children with XLH is to correct or minimize rickets, radiographic abnormalities, and skeletal deformities, and to promote maximal growth potential while preventing the lifelong bone- and joint-related complications of rickets. Published retrospective data suggest that earlier treatment leads to better outcomes for children with XLH (Makitie et al. 2003), (Quinlan et al. 2012).

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

KRN23 is a recombinant human IgG_1 monoclonal antibody that binds to and inhibits the activity of FGF23. Phase 1 and Phase 2 studies in adults and children (aged 5-12 years) with XLH have shown that KRN23 treatment increases serum phosphorus and $1,25(OH)_2D$ levels and the ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR). Initial Phase 2 data in children with XLH suggest KRN23 treatment also improves rickets severity with a

favorable safety profile.

Early treatment of children with XLH is associated with better growth and skeletal outcomes. In retrospective studies, children beginning treatment before age 1 had consistently higher z scores and lower alkaline phosphatase (ALP) levels than children starting treatment later (Makitie et al. 2003), (Quinlan et al. 2012), suggesting that growth deficits accumulated before treatment may lead to permanent height loss. The current study will provide information about the safety profile, dosing, and effect of KRN23 on phosphate metabolism in children with XLH (1 to 4 years of age, inclusive) and confirmed evidence of rickets. In addition, this study will evaluate whether biweekly dosing of KRN23 improves rickets, growth, and lower extremity deformity in young children with XLH.

OBJECTIVES:

The primary objectives of the study are to:

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

Additional study objectives are to assess the following in children between 1 and 4 years old with XLH

- Effects of KRN23 on rickets
- Effects of KRN23 on growth and lower extremity deformity
- KRN23 drug concentration levels (PK)

STUDY DESIGN AND METHODOLOGY:

UX023-CL205 is a multicenter, open-label, Phase 2 study in children from 1 to 4 years old with XLH who are naïve to therapy or have previously received standard therapy with oral phosphate and active vitamin D to assess the safety, PD, and efficacy of KRN23 administered via subcutaneous (SC) injections every 2 weeks (Q2W) for a 64-week Treatment Period. Subjects may continue to receive KRN23 for up to an additional 96 weeks during the Extension Period.

The study will enroll approximately 10 pediatric subjects between 1 and 4 years old, inclusive, with clinical findings consistent with XLH including hypophosphatemia and radiographic evidence of rickets (at least 5 subjects will have a rickets severity score (RSS) at the knee of ≥1.5 points at Screening), and a confirmed *PHEX* mutation or variant of uncertain significance. To maintain a level of gender balance, no more than 70% of subjects of either gender will be enrolled. Subjects will discontinue oral phosphate and active vitamin D therapy during Screening and for the duration of the study.

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

At any time during the study, if serum phosphorus increases above the upper limit of normal (ULN) for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received. Serum phosphorus will be followed through unscheduled serum phosphorus assessments. A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

NUMBER OF SUBJECTS PLANNED:

Approximately 10 subjects

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

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

1) Male or female, aged ≥1 year and < 5 years
2) *PHEX* mutation or variant of uncertain significance in either the patient or in a directly related family member with appropriate X-linked inheritance
3) Biochemical findings associated with XLH including:
   a. Serum phosphorus < 3.0 mg/dL (0.97 mmol/L)*
   b. Serum creatinine within age-adjusted normal range*
4) Radiographic evidence of rickets; at least 5 subjects will be required to have a rickets severity score (RSS) at the knee of at least 1.5 points as determined by central read
5) Willing to provide access to prior medical records for the collection of historical growth, biochemical, and radiographic data and disease history
6) Provide written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
7) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule, and comply with the assessments

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

1) Unwilling to stop treatment with oral phosphate and/or pharmacologic vitamin D metabolite or analog (e.g. calcitriol, alfacalcidol) during the screening period and for the duration of the study
2) Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale:
   0 = Normal
   1 = Faint hyperechogenic rim around the medullary pyramids
   2 = More intense echogenic rim with echoes faintly filling the entire pyramid
   3 = Uniformly intense echoes throughout the pyramid
   4 = Stone formation: solitary focus of echoes at the tip of the pyramid
3) Planned or recommended orthopedic surgery including staples, 8-plates or osteotomy, within the clinical trial period
4) Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits*

5) Presence or history of any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study
6) Presence of a concurrent disease or condition that would interfere with study participation or affect safety
7) History of recurrent infection or predisposition to infection, or of known immunodeficiency
8) Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments

* Criteria to be determined based on fasting (min. 4 hours) values collected at Baseline

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. Subjects will receive KRN23 at a starting total dose of 0.8 mg/kg. The dose may be increased to 1.2 mg/kg at any time if a subject meets the following dose adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. At any time during the study, if serum phosphorus increases above the ULN for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received. Serum phosphorus will be followed through unscheduled serum phosphorus assessments. A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

KRN23 will be administered via SC injection to the abdomen, upper arms or thighs; the injection site will be rotated with each injection. After proper training, a parent or caregiver may administer KRN23 to the subject.

REFERENCE THERAPY(IES), DOSEAND MODE OF ADMINISTRATION:

This is single-arm, open-label study. All subjects will receive KRN23. No placebo or reference therapy will be administered.

DURATION OF TREATMENT:

The Treatment Period in this study is 64 weeks. Subjects who complete the Treatment Period may continue to receive KRN23 for an additional 96 weeks during the Extension Period.

CRITERIA FOR EVALUATION:

Primary Assessments:

Safety:

Safety will be evaluated by the incidence, frequency and severity of adverse events (AEs) and serious adverse events (SAEs), including clinically significant changes in laboratory test results from baseline to scheduled time points (refer to Table 2.1, Table 2.2, and Table 2.3)

General Safety Variables will include the following:

- Vital signs and weight
- Physical examinations
- Glomerular filtration rate (GFR)
- Chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (serum calcium, intact parathyroid hormone [iPTH], 25-hydroxyvitamin D [25(OH)D], amylase, lipase, and creatinine; and urinary calcium and creatinine)
- Anti-KRN23 antibody testing and dose-limiting toxicities
- Concomitant medications
- Electrocardiogram (ECG)

Ectopic Mineralization Safety Assessments include:

- Renal ultrasound

Pharmacodynamics:

The primary efficacy endpoint is the change from baseline over time in serum phosphorus.

Additional pharmacodynamics assessments include:

- Change from baseline over time in serum $1,25(OH)_2D$ and urinary phosphorus

Secondary Assessments:

- Change in rickets at Week 40 as assessed by the Radiograph Global Impression of Change (RGI C) global score
- Change in rickets at Week 64 as assessed by RGI-C global score
- Change from baseline in RSS total score at Weeks 40 and 64
- Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at Weeks 40 and 64
- Change in recumbent length/standing height from baseline to post-treatment study time points in cm, height-for-age z-scores, and percentiles. Historical growth records may be used to evaluate change in growth velocity
- Change and percent change from baseline over time in serum alkaline phosphatase (ALP)
- Serum KRN23 concentrations at indicated study time points

STATISTICAL METHODS:

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

Safety Analysis:

All subjects who receive at least one dose of study drug will be included in the safety analysis.
An independent DMC that includes members with expertise in metabolic bone disease, cardiology, and nephrology and the conduct of clinical trials in children will act in an advisory capacity to

monitor subject safety on a routine basis through the Treatment Period (Week 64). The DMC will meet approximately twice a year. During the Extension Period, safety data will be reviewed by the Ultragenyx Study Safety Review Team (SSRT) on an ongoing basis.

Pharmacodynamics and Efficacy Analysis:

Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, interquartile range (Q1, Q3), minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Changes over time and the association of the efficacy with the PD variables will be summarized and evaluated.

Pharmacokinetic Analyses:

PK parameters will be summarized at each time point.

Table 2.1: Schedule of Events – Screening, Baseline, and Treatment Period Weeks 1-30

	Screening/ Baseline[1]		Treatment Period[3]																
VISIT TYPE/NUMBER	**SV**	**BL V1[2]**	**HH[4] V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**V13**	**HH V14**	**V15**	**HH V16**	**HH V17**	**HH V18**
WEEK	**W -6 to BL**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W 10**	**W 12**	**W 14**	**W 15**	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 26**	**W 28**	**W 30**
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical History & Demographics	X																		
PHEX mutation analysis [5]	X																		
PD MEASURES																			
Serum Phosphorus [6]		X	X		X		X		X		X			X					
$1,25(OH)_2$ D [6]		X	X						X					X					
Spot urine [6,7]		X			X				X		X			X					
ALP only [6]		X												X					
EFFICACY MEASURES																			
Growth (recumbent length/standing height)		X							X							X			
Bilateral AP knee X-rays [2]	X																		
Bilateral PA hand/wrist[2]		X																	
Standing long leg X-Ray[2]		X																	
PHARMACOKINETICS																			
Serum KRN23[6]			X		X				X										

	Screening/ Baseline[1]		Treatment Period[3]																
VISIT TYPE/NUMBER	**SV**	**BL V1[2]**	**HH[4] V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**V13**	**HH V14**	**V15**	**HH V16**	**HH V17**	**HH V18**
WEEK	**W -6 to BL**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W 10**	**W 12**	**W 14**	**W 15**	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 26**	**W 28**	**W 30**
SAFETY																			
Vital Signs [8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X			X				X							X			
Physical Examination	X	X														X			
Concomitant Medications	X	X	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	X	X
Renal Ultrasound [2]	X																		
ECG [2]		X							X										
Chemistry, Hematology, Urinalysis [6,7,10]	X	X			X				X					X					
Serum 25(OH)D[6]	X								X										
Serum Calcium [6]	X	X	X		X		X		X		X			X					
Serum Creatinine [6]	X	X			X				X		X			X					
Serum iPTH [6]	X	X							X					X					
Serum FGF23 [6]		X														X			
Anti-KRN23 antibody (ADA) [6,11]		X			X				X										
DRUG ADMINISTRATION		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

See footnotes after Table 2.3

Table 2.2: Schedule of Events – Treatment Period Weeks 32 – 64

	Treatment Period[3]																
Visit Type/Number	**V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**V27**	**HH V28**	**HH V29**	**HH V30**	**V31**	**HH V32**	**HH V33**	**HH V34**	**V35**
Week	**W 32**	**W 34**	**W 36**	**W 38**	**W 40**	**W 42**	**W 44**	**W 46**	**W 48**	**W 50**	**W 52**	**W 54**	**W 56**	**W 58**	**W 60**	**W 62**	**W64**
PD MEASURES																	
Serum Phosphorus [6]	X				X				X				X				X
$1,25(OH)_2$ D [6]	X				X				X				X				X
Spot urine [6,7]	X				X				X				X				X
ALP only [6]					X												X
EFFICACY MEASURES																	
Growth (length/standing height)					X												X
Bilateral AP knee X-rays [2]					X												X
Bilateral PA hand/wrist X-rays [2]					X												X
Standing long leg X-ray [2]					X												X
PHARMACOKINETICS																	
Serum KRN23[6]					X												X
SAFETY																	
Vital Signs [8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X				X				X				X				X
Physical Examination					X												X
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
Renal Ultrasound [2]					X												X
ECG [2]					X												X

	Treatment Period[3]																
Visit Type/Number	**V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**V27**	**HH V28**	**HH V29**	**HH V30**	**V31**	**HH V32**	**HH V33**	**HH V34**	**V35**
Week	**W 32**	**W 34**	**W 36**	**W 38**	**W 40**	**W 42**	**W 44**	**W 46**	**W 48**	**W 50**	**W 52**	**W 54**	**W 56**	**W 58**	**W 60**	**W 62**	**W64**
Chemistry, Hematology, Urinalysis [6,7,10]					X				X				X				X
Serum 25(OH)D[6]					X												X
Serum Calcium [6]	X				X				X				X				X
Serum Creatinine [6]	X				X				X				X				X
Serum iPTH [6]					X												X
Serum FGF23[6]																	X
Anti-KRN23 antibody (ADA) [6, 11]					X												X
DRUG ADMINISTRATION	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2.3: Schedule of Events – Extension Period (Week 66 – End of Study)

	Extension Period[3]										
Visit Type/Number	**HH/ TV[13]**	**V41**	**V47**	**V53**	**V59**	**V65**	**V71**	**V77**	**V83**	**Safety Call [15]**	**Safety Visit [16]**
Week/Frequency	**Q2W**	**W 76**	**W 88**	**W 100**	**W 112**	**W 124**	**W 136**	**W 148**	**W 160/ET[14]**	**W 165**	**W 170**
PD MEASURES											
Serum Phosphorus [6]		X	X	X	X	X	X	X	X		X
$1,25(OH)_2$ D [6]		X	X	X	X	X	X	X	X		X
Spot urine [6,7]					X				X		X
ALP only [6]					X				X		
EFFICACY MEASURES											
Growth (length/standing height)			X		X		X		X		
Bilateral AP knee X-rays [2]					X				X		
Bilateral PA hand/wrist X-rays [2]					X				X		
Standing long leg X-ray [2]					X				X		
PHARMACOKINETICS											
Serum KRN23[6]									X		
SAFETY											
Vital Signs [8,9]		X	X	X	X	X	X	X	X		X
Weight		X	X	X	X	X	X	X			
Physical Examination		X	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound [2]									X		

	Extension Period[3]										
Visit Type/Number	**HH/ TV[13]**	**V41**	**V47**	**V53**	**V59**	**V65**	**V71**	**V77**	**V83**	**Safety Call [15]**	**Safety Visit [16]**
Week/Frequency	**Q2W**	**W 76**	**W 88**	**W 100**	**W 112**	**W 124**	**W 136**	**W 148**	**W 160/ET[14]**	**W 165**	**W 170**
ECG [2]									X		
Chemistry, Hematology, Urinalysis [6,7,10]		X	X	X	X	X	X	X	X		X
Serum 25(OH)D[6]			X		X		X		X		
Serum Calcium [6]			X		X		X		X		X
Serum Creatinine [6]			X		X		X		X		
Serum iPTH [6]			X		X		X		X		
Serum FGF23[6]									X		
Anti-KRN23 antibody (ADA) [6, 11]									X		
DRUG ADMINISTRATION [12]	Q2	X	X	X	X	X	X	X			

FOOTNOTES FOR Table 2.1, Table 2.2, AND Table 2.3:

1 The baseline visit may occur up to approximately 6 weeks after Screening in those subjects without a previously documented *PHEX* mutation to allow for *PHEX* mutation results to be determined

2 All Screening/Baseline assessments and inclusion/exclusion criteria based on local lab results must be satisfied prior to randomization and dosing. Renal ultrasound, ECG, and x-rays may be performed within ± 3 days of clinic visit to accommodate scheduling availability.

3 Subjects will return to the clinic for site visits at approximately 4-week intervals from Baseline to Week 24 and at 8-week intervals from Week 24 to Week 64. The visit window is ± 3 days. During the Extension Period, clinic visits will occur at 12-week intervals (± 5 days).

4 Home health (HH) visits may also be conducted at the clinic depending on proximity of the subject to the investigational site and local availability of home health care resources. The visit window is ± 3 days.

5 *PHEX* mutation analysis will be performed for all subjects. Potential subjects with prior confirmation of a *PHEX* mutation or variant of uncertain significance in either self or a family member with appropriate X-linked inheritance who meet other eligibility requirements may enroll before screening *PHEX* mutation results are returned.

[6] Blood and urine to be collected after a minimum fasting time of 4 hours and prior to drug administration (if applicable). Record fasting duration on CRF. Subjects who live more than 45 minutes from the site may stay overnight on the night before the site visit to facilitate fasting sample collection. At Baseline, local lab values will be used to confirm eligibility. Baseline samples will also be sent to the central lab for data analysis. Serum phosphorus may be collected as an unscheduled lab if necessary

[7] Spot urine collections for urinary calcium, phosphorus, and creatinine

[8] At site visits, vital sign measurements consist of seated systolic/diastolic blood pressure (BP) measured in millimeters of mercury (mm Hg), heart rate (HR; beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Blood pressure will only be obtained for subjects age 3 years or above (at study entry or beginning when a subject turns 3 years of age). Obtain HR, respiration rate, and temperature at the beginning of each visit before any additional assessments are completed. At the Screening Visit BP should be measured 3 times, 30 seconds apart at the beginning of each visit; 3 additional BP measurements, 30 seconds apart, should be obtained at the end of the study visit after all procedures have been performed. At baseline and post-baseline visits, 3 BP measurements 30 seconds apart, should be obtained at the beginning of the study visit.

[9] At HH visits, vital sign measurements consist of HR (beats per minute) and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed.

[10] Serum chemistry panels may include PD parameters (i.e., serum phosphorus and ALP), and safety parameters of interest (i.e., calcium) to avoid duplication of testing. Urinalysis will be conducted if possible based on urine volume collected.

[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] During the Extension Period, study drug may be administered by a subject's parent or caregiver without healthcare provider supervision after proper training and documentation of competency in subcutaneous injection technique. In these cases study drug administration will be confirmed by telephone visit (TV).

[13] In addition to the specific visits noted, during the Extension Period additional HH or telephone visits (TV) will occur at Q2 week intervals (± 5 days and no fewer than 8 days apart) (ie, beginning at Week 66). In the case of TV, study drug administration will be confirmed; concomitant medications and AEs and SAEs will also be recorded.

[14] Radiography (x-rays) of the wrists and knees will not be performed at the early termination (ET) visit if conducted within 3 months of termination. Standing long leg radiographs will not be performed at the ET visit if conducted within 6 months of termination.

[15] To be completed for those subjects who complete Week 160 and do not continue on KRN23 treatment immediately through commercial use or through another mechanism. Site personnel will initiate a safety follow-up telephone call 5 weeks (+ 5 days) after the Week 160 visit to collect information on whether KRN23 has been started through another mechanism and, if not, any ongoing or new AEs, SAEs, or concomitant medications.

[16] An additional safety visit will take place 10 weeks ± 5 days after the Week 160/ET visit for those subjects who discontinue treatment, or do not continue on KRN23 through commercial use or another mechanism. This safety visit will not occur for subjects who complete the Week 160 visit and are documented to be continuing on KRN23 through commercial use or another mechanism. Every reasonable effort should be made to have required subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic, the final safety visit will be conducted via telephone call.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
ADA	Anti-drug antibody
AE	Adverse Event
ALP	Alkaline phosphatase
ANCOVA	Analysis of Covariance
AP	Anteroposterior
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECLA	Electrochemiluminescent assay
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FGF23	Fibroblast growth factor 23
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GFR	Glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
Hyp	Hypophosphatemic
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IND	Investigational New Drug (application)
IP	Investigational Product

IRB	Institutional Review Board
iPTH	Intact parathyroid hormone
IV	Intravenous
KHK	Kyowa Hakko Kirin Pharma, Inc.
LVH	Left ventricular hypertrophy
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No adverse effect level
PA	Posteroanterior
PD	Pharmacodynamic(s)
PHEX	Phosphate regulating gene with homology to endopeptidases located on the X chromosome
PK	Pharmacokinetic(s)
PT	Preferred term
Q2W	Biweekly, once every two weeks
Q4W	Monthly, once every four weeks
REB	Research Ethics Board
RGI-C	Radiographic Global Impression of Change
RSS	Rickets severity score
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDV	Source data verification
SSRT	Ultragenyx Study Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
TmP/GFR	Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
ULN	Upper limit of normal
US	United States
XLH	X-linked hypophosphatemia

Definition of Terms

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

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

5 INTRODUCTION

X-linked hypophosphatemia (XLH) is a disorder of hypophosphatemia, renal phosphate wasting, defective bone mineralization, and impaired growth plate or endochondral ossification caused by inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), and is the most common form of heritable rickets. In the absence of functional *PHEX*, release of fibroblast growth factor 23 (FGF23) by osteocytes is greatly increased, leading to impaired conservation of phosphate by the kidney and consequent hypophosphatemia. FGF23 also suppresses 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production resulting in decreased intestinal absorption of calcium and phosphate.

Chronic hypophosphatemia leads to rickets in children and osteomalacia in adults, the two major pathologic features of XLH. Rickets and osteomalacia are both disorders of bone mineralization; however, rickets is a disease of the growth plates specifically, characterized by deficient mineralization as well as by delayed endochondral ossification, leading to reduced growth and skeletal deformities (Shore et al. 2013). Osteomalacia occurs in both children and adults wherein low levels of phosphorus prevent normal mineralization of osteoid, resulting in low bone turnover and poor quality bone (Shore et al. 2013). The goal of therapy in children with XLH is to correct or minimize rickets, radiographic abnormalities, and skeletal deformities, and to promote maximal growth potential while preventing the lifelong bone- and joint-related complications of rickets. Published data suggest that earlier treatment may lead to better long-term outcomes. In retrospective studies, children beginning treatment before age 1 had consistently higher z scores and lower alkaline phosphatase (ALP) levels than children starting treatment later (Makitie et al. 2003), (Quinlan et al. 2012).

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

Proof-of-concept studies in a relevant murine model support the use of an anti-FGF23 monoclonal antibody (mAb) as a treatment for XLH. Experiments in both juvenile and adult hypophosphatemic mice provided evidence that treatment with an anti-FGF23 mAb normalized or ameliorated many of the characteristic abnormalities associated with XLH

(Aono et al. 2009), (Aono et al. 2011). KRN23 is a fully human IgG_1 mAb that binds to and inhibits FGF23. The Sponsor and development partner, Kyowa Hakko Kirin Co. Ltd. (KHK) are investigating KRN23 as a potential therapeutic candidate for the treatment of XLH, a disease distinguished by high levels of serum FGF23.

KHK has conducted a series of nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies supporting the investigation of KRN23 in adults and children.
Three clinical studies have been completed in adult patients with XLH: a single dose Phase 1 safety and tolerability study of KRN23, a repeat dose Phase 1/2 dose escalation study, and an associated treatment extension study. An additional open-label, long-term extension study in adults is ongoing. A Phase 2 study (UX023-CL201) in pediatric XLH patients aged 5 to 12 years receiving KRN23 at multiple doses up to 2.0 mg/kg every 2 weeks (Q2W) or every 4 weeks (Q4W) is ongoing and no new safety concerns have been identified.

This Phase 2 study will be conducted in children with XLH, aged 1 to 4 years, inclusive, to provide information about the safety profile, dosing, and effect of KRN23 on phosphate metabolism in children under 5 years old. In addition, this study will evaluate whether Q2W dosing of KRN23 improves rickets, growth, and lower extremity deformity in young children with XLH.

5.1 Overview of XLH

XLH is a rare, genetic disorder that is serious, chronically debilitating, and represents an unmet medical need. This genetic deficiency is estimated to occur in about 1:20,000 live births (Burnett et al. 1964), (Imel et al. 2005), (Beck-Nielsen et al. 2009). XLH is the most common inherited form of rickets and the most common inherited defect in renal tubular phosphate transport. XLH is transmitted as an X-linked dominant disorder (Dixon et al. 1998). Mutations resulting in the loss of function of *PHEX* form the genetic basis for XLH (Carpenter et al. 2011). More than 300 different *PHEX* gene mutations have been identified in patients with XLH (PHEXdb); however, few definitive correlations have been observed between specific mutations and phenotypic severity.

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

Patients with XLH often present during childhood with rickets due to hypophosphatemia and frequently develop skeletal abnormalities (e.g., bowed legs), impaired growth, and short adult stature (Tenenhouse et al. 2001). As young patients age and progress into adulthood, the

symptom pattern evolves due to decreased phosphate requirements for bone growth. Adult XLH patients suffer from bone pain and osteomalacia, increased risk of bone fractures, joint abnormalities and joint pain, enthesopathy, and osteoarthritis (Carpenter et al. 2011). There is a great deal of variability in the manifestations of XLH. In more severe disease, hypophosphatemia leads to decreased mineralization of newly formed bone and rickets. Surgical correction of limb deformities is often required (Santos et al. 2013), (Zivicnjak et al. 2011).

The current therapy for pediatric XLH patients consists of multiple daily doses of oral phosphate often combined with doses of active vitamin D metabolites (e.g., calcitriol and alfacalcidol). No consensus exists regarding treatment of adult patients with XLH (Linglart et al. 2014). The use of oral phosphate and vitamin D may be initiated for the treatment of osteomalacia, bone/joint pain, and pseudofractures in symptomatic patients, although evidence of efficacy in adults is limited (Sullivan et al. 1992). Treatment with oral phosphate and active vitamin D requires frequent and continued monitoring of patients. Serum and urine mineral metabolite levels and imaging studies are required to assess toxicity and secondary complications, including nephrocalcinosis, hypercalciuria, and hyperparathyroidism (Carpenter et al. 2011).

5.2 Brief Overview of KRN23 Development

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

5.2.1 Brief Description of KRN23

KRN23 is a recombinant human IgG_1 mAb that binds to an0064 inhibits the activity of FGF23. KRN23 is expressed in Chinese hamster ovary dihydrofolate reductase-deficient cells. The secreted KRN23 antibody is recovered from the culture medium and purified using a series of chromatographic and filtration steps. Based on the amino acid sequence, the predicted molecular mass of KRN23 is approximately 140 kilodaltons (kDa). Nonclinical studies demonstrated KRN23 possesses high binding affinity to the N-terminal domain of FGF23. KRN23 binds to FGF23 from humans, cynomolgus monkeys and rabbits, but not to other species tested.

5.2.1.1 Mechanism of Action in XLH

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

KRN23 has the potential to block or reduce FGF23 action and improve phosphate homeostasis in XLH patients. KRN23 binds the amino-terminal domain of FGF23 that interacts with the FGF-binding portion of the combination FGFR1/Klotho receptor, preventing FGF23 from binding to and signaling from its receptor. Both intact and fragmented FGF23 polypeptides are immunoprecipitated with KRN23 (Yamazaki et al. 2008). By inhibiting FGF23, KRN23 restores tubular reabsorption of phosphate (TmP/GFR) from the kidney and increases the production of $1,25(OH)_2D$ that also enhances intestinal absorption of phosphate. It is expected that by directly inhibiting excess FGF23, the underlying cause of XLH, and thereby improving phosphate homeostasis and healing rickets, KRN23 has the potential to significantly alter the natural history of the disease.

5.2.2 Nonclinical Studies

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

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

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

- The no adverse effect level (NOAEL) in a 40-week toxicity study in adult cynomolgus monkeys was 0.03 mg/kg KRN23 for males and 0.3 mg/kg KRN23 for females. The NOAEL in a 40-week toxicity study in juvenile cynomolgus monkeys and a single-dose study in rabbits was 0.3 mg/kg KRN23.
- Soft tissue and organ mineralization was a consistent finding associated with prolonged and excessive serum phosphate levels including the kidney where nephrocalcinosis was

observed at the highest dose tested and reversibility of mineralization could not be established.

- The most prominent pharmacologic actions of KRN23 were dose-dependent changes in serum inorganic phosphorus and 1,25$(OH)_2$D in rabbits and juvenile, adult and pregnant cynomolgus monkeys.
- No gross or histopathological abnormalities were observed at the intravenous (IV) infusion sites or subcutaneous (SC) injection sites in the 40-week repeat dose toxicity studies in adult and juvenile cynomolgus monkeys.
- KRN23 demonstrated consistent and predictable PK behavior in both rabbits and cynomolgus monkeys based on the results of single and repeat dose studies where exposure was by either the IV or SC route.

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

5.2.3 Clinical Studies

Multiple clinical studies of FGF23 in adults or children with XLH are completed or ongoing. Four clinical studies have been conducted in adult patients with XLH: a single dose Phase 1 safety and tolerability study of KRN23 (KRN23-US-02), a single dose Phase 1 safety and tolerability study in Japan and Korea (KRN23-001), a repeat dose Phase 1/2 dose escalation study (KRN23-INT-001), and an associated treatment extension study (KRN23 INT-002). An additional open-label long-term extension study (UX023-CL203) in adults, a double-blind, placebo-controlled, Phase 3 study (UX023-CL303), and an open-label, paired bone biopsy Phase 3 study to evaluate changes in osteomalacia at the tissue level with KRN23 treatment are ongoing. Details of study parameters and PK, PD, clinical efficacy, and safety results are provided in the IB. A Phase 2 study evaluating dose, PD, efficacy, and safety is also ongoing in pediatric XLH patients (UX023-CL201) aged 5 to 12 years.

Data from clinical studies to date are consistent with the proposed mechanism of action: that KRN23 blocks FGF23 action, leading to a sustained increase in serum phosphorus levels due to increased TmP/GFR and increased intestinal absorption caused by increased 1,25$(OH)_2$D. Single and repeat-dose clinical studies indicate SC administration of KRN23 consistently increased and sustained serum phosphorus levels and TmP/GFR, without a major impact on urine calcium levels or vitamin D metabolism (Carpenter et al. 2014), (Imel et al. 2015). Data from the extension study in adults suggest KRN23 could provide sustained increases in serum phosphorus levels sufficiently such that improvements in bone physiology, structure, and function would be expected (Imel et al. 2015).

Repeated doses of KRN23 up to 1.0 mg/kg were well tolerated by adult XLH subjects throughout the Phase 1/2 dose escalation study and associated treatment extension study

(Imel et al. 2015). No deaths or life threatening treatment emergent adverse events (AEs) have been reported. In the extension study, serious adverse events (SAEs) reported for 3 subjects were unlikely to be or were not study drug related: breast cancer, hypertensive crisis, and cervical spinal stenosis. Throughout the long-term extension study, treatment-related AEs were reported for 14 subjects (63.6%) treated with KRN23 and included injection site reaction (5 subjects, 22.7%), arthralgia (3 subjects, 13.6%), restless legs syndrome (2 subjects, 9.1%), and injection site pain (2 subjects, 9.1%). No discernible clinically significant trends of lab abnormalities suggestive of a treatment-related adverse effect were noted. Overall, no immunogenicity or patterns of dose-limiting toxicity have been associated with KRN23 treatment.

Similar to the adult studies, interim analyses from the Phase 2 pediatric study (UX023-CL201) showed KRN23 treatment up to 2 mg/kg Q2W or Q4W increased serum phosphorus levels, TmP/GFR, and $1,25(OH)_2D$ levels. Interim results also show KRN23 improved rickets, with a mean reduction in rickets severity score (RSS) from Baseline to Week 40. Consistency in the rickets results was observed using the Radiographic Global Impression of Change (RGI-C) scoring method. Overall, the dose-response and pharmacodynamic (PD) results observed in the pediatric study were consistent with the adult XLH data generated to date. None of the subjects had serum phosphorus levels above the normal range in either dosing group. Most treatment-related AEs were mild, most commonly a transient injection site reaction (39%). One child experienced a serious AE and was hospitalized for fever/muscle pain that improved and continues in the trial. No clinically meaningful changes occurred in serum or urine calcium, serum iPTH, or renal ultrasound.

5.3 Summary of Overall Risks and Potential Benefits

KRN23, a fully human mAb that binds and inhibits FGF23, is being developed as a potential therapeutic candidate for XLH, a rare genetic disorder characterized by chronic hypophosphatemia resulting from excess FGF23. By blocking the activity of FGF23, KRN23 can restore phosphate, vitamin D, and bone metabolism homeostasis, and has the potential to improve the lives of children with this disorder by correcting or minimizing rickets, radiographic abnormalities, and skeletal deformities, and by promoting maximal growth potential while preventing the lifelong bone- and joint-related complications of rickets. This therapeutic approach directly targets the inherent dysregulation in XLH (i.e., excess FGF23). In contrast, supplementation therapy with phosphate and/or $1,25(OH)_2D$, is only partially effective and carries a significant burden and risk of ectopic mineralization, particularly nephrocalcinosis.

Clinical studies to date have demonstrated that KRN23 treatment blocks FGF23 action and leads to a sustained increase in serum phosphorus levels due to increased TmP/GFR. Increased $1,25(OH)_2D$ was also observed, as expected, based on the inhibition of the excess of FGF23. Bone formation and resorption markers also increased. Preliminary data in children with XLH suggest that KRN23 treatment may also improve rickets. No major safety concerns were observed with KRN23 in the population studied; there was no evidence of immunogenicity, and no evidence of left ventricular hypertrophy (LVH) based on

electrocardiogram (ECG) even though FGF23 levels were increased following KRN23 treatment. Although ectopic mineralization is a known risk related to XLH disease and is exacerbated by oral phosphate and/or active vitamin D supplementation, KRN23 does not appear to be associated with progression of cardiac or renal ectopic mineralization beyond the natural course of pre-existing disease.

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

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

5.4 Study Rationale

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

There is no available medicine that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphatemia in XLH. The current therapy for pediatric XLH patients consists of multiple daily doses of oral phosphate often combined with doses of active vitamin D analogs. Dosing is individualized and depends on tolerability of the phosphate dose and the age, size, and growth of the child. The goal of therapy with phosphate and vitamin D is to sufficiently supplement the body's pool of phosphate to allow mineralization of bone and improve skeletal outcomes; however, because supplementation therapy does not address the mechanism of urinary phosphate wasting, increasing phosphate through supplementation also increases renal phosphate throughput and urinary phosphate

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

KRN23 is a recombinant human IgG_1 mAb that binds to and inhibits the activity of FGF23. Phase 1 and Phase 2 studies in adults and children (aged 5-12 years) with XLH have shown that KRN23 treatment increases serum phosphorus and $1,25(OH)_2D$ levels and TmP/GFR. Interim Phase 2 data in children with XLH suggest KRN23 treatment also improves rickets severity with a favorable safety profile.

Early treatment of children with XLH is associated with better growth and skeletal and outcomes. In retrospective studies, children beginning treatment before age 1 had consistently higher z scores and lower ALP levels than children starting treatment later (Makitie et al. 2003), (Quinlan et al. 2012) suggesting that growth deficits accumulated before treatment may lead to permanent height loss. The current study will provide information about the safety profile, dosing, and effect of KRN23 on phosphate metabolism in children 1 to 4 years of age, inclusive. In addition, this study will evaluate whether biweekly dosing of KRN23 improves rickets, growth, and lower extremity deformity in young children with XLH.

6 STUDY OBJECTIVES

The primary objectives of the study are to:

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

Additional study objectives are to assess the following in children between 1 and 4 years old with XLH:

- Effects of KRN23 on rickets
- Effects of KRN23 on growth and lower extremity deformity
- KRN23 drug concentration levels (PK)

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

UX023-CL205 is a multicenter, open-label, Phase 2 study in children from 1 to 4 years old with XLH who are naïve to therapy or have previously received standard therapy with oral phosphate and active vitamin D to assess the safety, PD, and efficacy of KRN23 administered via SC injections Q2W for a 64-week Treatment Period. Subjects may continue to receive KRN23 for an additional 96 weeks during the Extension Period.

The study will enroll approximately 10 pediatric subjects between 1 and 4 years old, inclusive, with clinical findings consistent with XLH including hypophosphatemia and radiographic evidence of rickets (at least 5 subjects will have a rickets severity score (RSS) at the knee of ≥1.5 points at Screening), and a confirmed *PHEX* mutation or variant of uncertain significance. To maintain a level of gender balance, no more than 70% of subjects of either gender will be enrolled. Those subjects who are receiving oral phosphate and active vitamin D therapy will discontinue treatment during Screening (after confirmation of *PHEX* mutation and rickets eligibility criteria) and for the duration of the study. Safety, PD, PK, and efficacy measures (rickets, growth, lower extremity deformity) will be evaluated throughout the study.

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

At any time during the study, if serum phosphorus increases above the ULN for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received. Serum phosphorus will be followed through unscheduled serum phosphorus assessments. A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

The study will be conducted in a pediatric population; as such, additional measures including a DMC have been incorporated into the study design. Where possible, measures to minimize pain and distress to the subject have been considered for this study protocol including the use of home health visits. Where possible, timing of blood draws for efficacy assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing. The primary analysis is planned at Week 40. Additional efficacy and safety analyses will be conducted at Week 64. A final analysis will be conducted at the end of the study ("study completion"), which is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in

the study. As this is an open-label study, analyses may also be performed at additional time points.

7.2 Discussion of Study Design, Including Choice of Control Group

This Phase 2 study is designed as an open-label clinical trial intended to provide information about the safety profile, dose-response, and effect of KRN23 on phosphate metabolism in children 1 to 4 years of age, inclusive, with XLH. In addition, this study will evaluate whether Q2W dosing of KRN23 improves rickets, growth, and lower extremity deformity in young children with XLH. No control group will be included. To demonstrate safety and efficacy in a controlled study, a larger randomized, Phase 3 study in children with a broader age range is being planned that will include two treatment arms: one group will receive KRN23 and one group will receive oral phosphate/active vitamin D therapy.

7.3 Selection of Study Population

The study will enroll approximately 10 pediatric subjects between 1 and 4 years old with XLH who are naïve to therapy or have previously received standard therapy with oral phosphate and active vitamin D. To maintain a level of gender balance, no more than 70% of subjects of either gender will be enrolled.

To ensure that appropriate subjects are selected, eligibility requirements include demonstrated hypophosphatemia, radiographic evidence of rickets (at least 5 subjects will have a minimum RSS score of 1.5 points at the knee), and genetic evidence consistent with a diagnosis of XLH. *PHEX* sequence variants will be classified according to the joint consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al. 2015). Patients with *PHEX* mutations classified as pathogenic, likely pathogenic, and possibly pathogenic will be included. Patients with *PHEX* variants of uncertain significance will also be included, as was recommended by experts in pediatric XLH. There are hundreds of variants of the *PHEX* gene and many of these have not yet been fully characterized.

Children with XLH undergo a normal pubertal growth spurt. Post-pubertal height is predicted by pre-pubertal height, indicating that loss of height potential generally occurs prior to puberty. Several studies suggest that early height loss cannot be recovered and that earlier treatment leads to better growth outcomes (Makitie et al. 2003), (Quinlan et al. 2012). Thus, initiation of therapy at early ages is recommended to achieve improved height outcomes (Carpenter et al. 2011). Interim data from an ongoing study in children aged 5-12 years has shown KRN23 treatment at doses up to 2 mg/kg Q2W increases serum phosphorus and improves rickets severity. The present study will enroll children 1 to 4 years old to determine if the PK and PD profile of KRN23 is similar in younger children who may obtain maximum benefit from treatment. The study will also provide preliminary evidence of efficacy in healing rickets in younger children.

The Sponsor has taken reasonable measures to ensure the protection and safety of this population. The blood volumes drawn and radiation exposure are within the required limits

for subjects under 5 years of age. Appropriate pediatric expertise will be available at all trial sites, and site personnel will be focused on minimizing risk, fear, pain, and distress during conduct of the study.

7.3.1 Inclusion Criteria

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

1) Male or female, aged ≥1 year and < 5 years:
2) *PHEX* mutation or variant of uncertain significance in either the patient or a directly related family member with appropriate X-linked inheritance
3) Biochemical findings associated with XLH including:
   - Serum phosphorus < 3.0 mg/dL (0.97 mmol/L)*
   - Serum creatinine within age-adjusted normal range*
4) Radiographic evidence of rickets; at least 5 subjects will be required to have a RSS at the knee of at least 1.5 points as determined by central read
5) Willing to provide access to prior medical records for the collection of historical growth, biochemical, and radiographic data and disease history
6) Provide written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
7) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule and comply with the assessments

* Criteria to be determined based on fasting (min. 4 hours) values collected Baseline

7.3.2 Exclusion Criteria

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

1) Unwilling to stop treatment with oral phosphate and/or pharmacologic vitamin D metabolite or analog (e.g., calcitriol, alfacalcidol) during the screening period and for the duration of the study
2) Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale:

   0 = Normal
   1 = Faint hyperechogenic rim around the medullary pyramids
   2 = More intense echogenic rim with echoes faintly filling the entire pyramid
   3 = Uniformly intense echoes throughout the pyramid
   4 = Stone formation: solitary focus of echoes at the tip of the pyramid

3) Planned or recommended orthopedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period
4) Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits*
5) Presence or history of any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study.
6) Presence of a concurrent disease or condition that would interfere with study participation or affect safety
7) History of recurrent infection or predisposition to infection, or of known immunodeficiency
8) Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments

* Criteria to be determined based on fasting (min. 4 hours) values collected at Baseline

7.3.3 Removal of Subjects from Therapy or Assessment

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

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

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

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

If the reason for removal of a subject from the study is an AE, the AE and any related test or procedure results will be recorded in the source documents and transcribed onto the Case

Report Form (CRF). Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within 12 weeks after the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation, and to complete the protocol-specified Safety Follow-up, as applicable.

7.3.3.1 Stopping Rules

A Data Monitoring Committee (DMC) will be established for Study UX023-CL205 and will act in an advisory capacity to monitor the safety of KRN23 on a routine basis through Week 64 (Section 7.6.4). The DMC may provide advice to Ultragenyx to aid in the determination of whether study enrollment should be paused or if the study should be stopped. If the Sponsor deems it appropriate to restart the trial following an internal safety review, this will be done only following approval by Regulatory Authorities. During the Extension Period, safety data will be reviewed by the Ultragenyx Study Safety Review Team (SSRT) on an ongoing basis.

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

Individual subjects will be monitored for ectopic mineralization by renal ultrasound (Section 7.5.5.5). If new or clinically significant worsening in mineralization is considered clinically meaningful by the investigator and/or sponsor and related to study drug, the subject will be discontinued from the study.

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

7.4 Treatment

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

The amount of drug administered will be calculated based on a subject's weight (Section 7.4.4). All subjects will receive KRN23 at a Q2W dosing regimen. Selection of doses and dose adjustments are described in Section 7.4.4.

7.4.1 Investigational Product

KRN23 is a sterile, clear, colorless, and preservative-free solution supplied 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 without dilution based on body weight (Section 7.4.4).

Subjects will receive study drug via SC injection to the abdomen, upper arms, or thighs; the injection site will be rotated with each injection. After proper training by study personnel in SC injection technique, a parent or caregiver may administer KRN23 to the subject between site visits. Parents or caregivers will be instructed to follow the directions provided in the Instructions for Use. The parent or caregiver must have demonstrated competency in administration of SC injections, including study drug preparation, administration, and disposal, and this competency be documented, before unsupervised home administration will be permitted. Thereafter, study drug may be administered by a parent or caregiver at home, except for study weeks that correspond to a site visit when parent/caregiver administration is optional. Study personnel should periodically observe parent/caregiver administration of study drug to ensure they are using proper technique. For subjects whose parent/caregiver is unable to administer study drug, study drug will be administered at the study site or at home health visits for the remainder of the study.

7.4.2 Reference Therapy

This is a single-arm, open label study. All subjects will receive KRN23. No placebo or reference therapy will be administered.

7.4.3 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 active treatment with KRN23.

7.4.4 Selection of Doses

The KRN23 dose planned for this study: 0.8 or 1.2 mg/kg Q2W is based on Week 40 data from an ongoing Phase 2 clinical study (UX023-CL201) that included 18 subjects (ages 5-12) receiving KRN23 at Q2W dosing and by PK/PD modeling extrapolated to patients aged 1-5 years.

KRN23, administered Q2W at approximately 0.8 mg/kg for 40 weeks, increased serum phosphorus by an average of 0.7 mg/dL; increases of > 0.5 mg/dL were seen in 83.3% of subjects. No subjects experienced hyperphosphatemia even at upper doses of 1.3 mg/kg Q2W, providing a wide margin for safety. Serum $1,25(OH)_2D$ concentrations and TmP/GFR levels also increased, demonstrating overall improved phosphorus homeostasis. The

increases in serum phosphorus and 1,25$(OH)_2$D were sufficient to provide substantial healing of rickets (as assessed by RGI-C) in 8 of 9 subjects (88.9%) with more severe rickets (total RSS ≥ 1.5).

Similar increases in serum phosphorus were extrapolated for younger patients (ages 1 to 5 years) as estimated by PK/PD modeling. In simulations of a KRN23 starting dose of 0.8 mg/kg, median minimum serum phosphorus changes from baseline are predicted to be 0.830 mg/dL in patients aged 1 to 5 years. In simulations of a KRN23 escalated dose of 1.2 mg/kg, median minimum serum phosphorus changes from baseline are predicted 0.873 mg/dL in patients aged 1 to 5 years. Up to 95% of patients aged 1 to 5 years are expected to achieve an improvement of at least 0.5 mg/dL in serum phosphorus at the proposed dose. As was seen in Study UX023-CL201, these serum phosphorus increases are expected to be sufficient to improve bone disease in most pediatric patients administered KRN23 at the proposed dose and regimen.

Thus, all subjects will receive KRN23 at a starting dose of 0.8 mg/kg. The dose may be increased to 1.2 mg/kg at any time if a subject meets the following dose adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus.

At any time during the study, if serum phosphorus increases above the ULN for age, the subsequent dose(s) will be withheld and the site will contact the medical monitor before dosing resumes. Once other causes of increased serum phosphorus are excluded, KRN23 treatment will resume at half the total dose of the last dose received. Serum phosphorus will be followed through unscheduled serum phosphorus assessments. A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above.

Dose adjustments may also be made based on the weight of the subject (Section 7.5.5.3). Any dose changes needed during the Extension Period will be implemented at clinic visits.

7.4.5 Prior and Concomitant Therapy

Throughout the study, there should be no significant changes to a subject's diet or medication schedule unless medically indicated. Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except those listed in Section 7.4.5.1. All concomitant medications taken during the study will be recorded in the CRF with indication, dose information, and dates of administration. Any changes to concomitant medication will also be documented.

7.4.5.1 Prohibited Medications

Medications that are known to affect bone or calcium and phosphorus metabolism will be prohibited during the study. Thus, to be eligible for the study, subjects must agree to

discontinue and/or not to use certain medications prior to randomization and for the duration of the study.

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

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

7.4.5.2 Permitted Medications

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

7.4.6 Treatment Compliance

Each administration of study drug will be recorded on the CRF. Parents or caregivers administering study drug will be instructed to follow the directions provided in the Instructions for Use. If a parent/caregiver is administering study drug, confirmation of dosing will be communicated to the study site during scheduled biweekly telephone visits; site personnel will record the related information about each administration of study drug on the CRF. If the parent or 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 visits for home administration. Empty vials will be returned to the study site for drug accountability records.

If a subject does not receive a dose within 10 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

7.5.1 Schedule of Events

The schedules of visits and assessments are provided in Table 2.1, Table 2.2, and Table 2.3. Home health visits may also be conducted at the investigational site depending on the preference of the subject and proximity of the subject to the clinic. Telephone visits may replace home health visits during the Extension Period for subjects whose parent or caregiver has been trained to administer study drug. Refer to the Study Reference Manual for additional details and a recommended schedule of specific assessments.

Potential subjects will come in to the site for an initial screening visit and provide informed consent. All subjects will have bilateral knee x-rays obtained locally at the Screening Visit. Screening knee x-rays will be evaluated by central read to determine if the subject meets the eligibility criteria. Blood for *PHEX* mutation analysis will be collected for all subjects at the Screening Visit.

Potential subjects with a previously identified *PHEX* mutation or variant of uncertain significance in either self or a family member with appropriate X-linked inheritance and confirmed rickets severity eligibility by central read (required for at least 5 subjects) may proceed to Baseline without waiting for the *PHEX* mutation analysis result. Potential subjects without a previously identified *PHEX* mutation will be notified of *PHEX* mutation results, and if presence of a mutation is confirmed, will have the baseline visit scheduled.

Subjects who successfully pass the requirements at the Screening Visit will discontinue oral phosphate for a minimum of 7 days and active vitamin D therapy for a minimum of 7 days prior to the Baseline visit. The remaining screening assessments to confirm eligibility will be performed. At Screening/Baseline, renal ultrasound, ECG, and x-rays may be performed ± 3 days of the clinic visit to accommodate scheduling availability. All Screening/Baseline assessments and inclusion/exclusion criteria must be satisfied prior to dosing.

Clinic visits will occur at approximately 4-week intervals (± 3 days) for the first 24 weeks of the study. Thereafter, clinic visits will occur every 8 weeks (± 3 days) for the remainder of the Treatment Period. During the Treatment Period, subjects may be monitored and dosed between site visits through a series of home health visits depending on the preference of the subject and the proximity of the subject to the site. The visit window for home health visits is ± 3 days.

During the Extension Period, clinic visits will occur at approximately 12-week intervals (±5 days). Biweekly home health visits or telephone visits will be conducted (±5 days) for administration of or to confirm administration of study drug, and for collection of AEs and concomitant medication information.

For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination visit procedures within 4 weeks of discontinuation. X-rays of the wrists and knees will not be performed at the Early Termination visit if

post-treatment x-rays have been performed within 3 months (hands/wrists and knees) or 6 months (standing long legs) of Early Termination.

A follow-up safety telephone call will take place 5 weeks (+ 5 days) after the Week 160 visit to determine if the subject is receiving KRN23 therapy under commercial use or another mechanism and to collect information on any ongoing or new AEs, SAEs, and concomitant medications. An additional safety visit will take place 10 weeks ± 5 days (approximately 5 times the elimination half-life) after the ET visit for those subjects who discontinue treatment before the Week 160 visit, or for those subjects who complete the Week 160 visit and do not continue on KRN23 through commercial use or another mechanism. This safety visit will not occur for subjects who complete the Week 160 visit and are documented to be continuing on KRN23 on commercial use or through another mechanism.

7.5.2 Pharmacodynamic Assessments

KRN23 binds to and inhibits FGF23, which is an important regulator of serum phosphorus levels. Serum phosphorus levels will be measured as a key PD assessment in this study. Serum $1,25(OH)_2D$, urinary phosphorus, and serum levels of ALP will also be assessed to determine the PD profile of KRN23 in children 1-4 years old.

7.5.2.1 Serum Phosphorus

Serum samples will be obtained following a minimum fasting time of 4 hours and prior to study drug administration (if applicable). Samples should be obtained in the morning at approximately the same time for each visit due to known fluctuations in serum phosphorous levels associated with circadian rhythm. The time of sample collection and the duration of fasting will be noted on the CRF. Subjects who live more than 45 minutes from the site may stay overnight on the night before the site visit to facilitate fasting sample collection.

Serum phosphorus levels will be assessed by the local lab at Baseline for eligibility; a second sample will be sent to the central laboratory for the Baseline measure. Serum phosphorus levels will also be determined by central laboratory at Weeks 1, 4, 8, 12, 15, 20, 32, 40, 48, 56, 64, and every 12 weeks thereafter through Week 160 (or Early Termination) and at the Safety Visit (if applicable). Where possible, the blood sample obtained for serum phosphorus will be assessed as part of the standard clinical laboratory safety tests (Section 7.5.5.7) to reduce the number and volume of blood draws. Refer to the Study Reference Manual for additional details on serum phosphorus measurements.

7.5.2.2 Additional Pharmacodynamic Markers

To demonstrate the positive impact of KRN23 on bone metabolism and phosphate homeostasis, additional PD markers will be assessed, including serum $1,25(OH)_2D$ and urinary phosphorus. These measures will directly reflect the mechanism by which KRN23 restores phosphorus homeostasis by inhibiting excess FGF23.

Fasting spot urine will be used for measurements of urinary phosphorus, creatinine, and calcium. Spot urine collection will be performed pre-treatment at Baseline and at Weeks 4, 12, 15, 20, 32, 40, 48, 56, and 64, 112, 160/ Early Termination and at the Safety Visit (if applicable) as indicated in the Schedules of Events (Table 2.1, Table 2.2 and Table 2.3). Urine samples will be sent to the central lab for analysis. The duration of fasting time for all PD parameters will be recorded on the CRF.

7.5.2.3 Serum Alkaline Phosphatase

Children with XLH have low bone turnover as a result of chronic hypophosphatemia. Serum levels of alkaline phosphatase will be measured at Baseline and at Weeks 20, 40, 64, 112, and 160/ Early Termination visits as indicated in the Schedules of Events (Table 2.1, Table 2.2, and Table 2.3).

7.5.3 Clinical Efficacy Measures

The goal of therapy in children with XLH is to correct or minimize rickets, radiographic abnormalities, and skeletal deformities, and to promote maximal growth potential.
The clinical efficacy measures to be evaluated in this study will seek to determine the ability of KRN23 treatment to achieve these goals.

7.5.3.1 Radiographs

Bilateral anteroposterior (AP) knee radiographs will be taken at the Screening Visit to confirm eligibility and at the Week 40, Week 64, Week 112, and Week 160 (or Early Termination) visits. Screening knee radiographs will be read centrally; an RSS score of at least 1.5 points at the knee is required for eligibility in at least 5 subjects. Bilateral posteroanterior (PA) hand/wrist radiographs will be taken at Baseline and at the Week 40, 64, 112, and 160 (or Early Termination, if applicable) study visits. Standing long-leg radiographs will be taken at Baseline, Week 40, 64, 112, and 160 (or Early Termination, if applicable). Knee and hand/wrist radiographs will be taken at Early Termination if post-baseline radiographs have not been obtained within 3 months of termination. Standing long leg radiographs will be taken at Early Termination if post-baseline radiographs have not been obtained within 6 months of termination. Radiographs will be read centrally and will be interpreted. Changes in the severity of rickets and epiphyseal (growth plate) abnormalities will be assessed by central readings using two methods, a disease-specific qualitative Radiograph Global Impression of Change (RGI-C) scoring system and the RSS method.

A disease-specific qualitative RGI-C scoring system will be used. Pairs of wrist, knee and standing long leg images from treated subjects will be presented to a rater with the Screening/Baseline image on the left and the later image (Week 40 or 64, or Early Termination) on the right. Raters will be asked to assess change in rickets severity in the wrists and knees and extent of bowing in the legs using a 7-point ordinal RGI-C scale score ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets). Ratings will be performed by 3 independent pediatric radiologists. X-ray pairs will be presented for review in random order and the

radiologists will not be provided access to the protocol, subject identifiers, or information related to KRN23 treatment.

The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying and cupping and the proportion of the growth plate affected (Thacher et al. 2000). With the RSS method, each radiograph is scored individually by a central rater who is blinded to subject number and radiograph sequence.

7.5.3.2 Growth

Short stature is one of the predominant features in growing children with XLH. Growth of the legs and trunk has been shown to be uncoupled in XLH and related to serum phosphate levels (Zivicnjak et al. 2011). Growth will be measured by changes in standing height or recumbent length (and percentiles) prior to and following treatment. Recumbent length will be measured in subjects <2 years old or those unable or unwilling to stand for the measurement. Standing height/recumbent length measurements prior to treatment will be abstracted from medical records where available. To assess growth during KRN23 treatment, recumbent length/standing height will be measured by a clinical evaluator at Baseline and Weeks 12, 24, 40 and 64, at 24-week intervals during the Extension Period, and at the Week 160 (or Early Termination) visits. Historical growth records may be used to evaluate change in growth velocity.

7.5.4 Pharmacokinetic Assessment

To assess KRN23 concentration and allow evaluation of the PK/PD relationship in children aged 1-4 years, serum KRN23 levels will be evaluated as a PK parameter in this study. A blood sample will be obtained prior to dosing (if applicable) at Weeks 1, 4, 12 and 40, 64, and at the Week 160 (or Early Termination) visit. For each sample collection, the time elapsed since last study drug administration will be determined.

7.5.5 Safety Measurements

Safety will be evaluated by the incidence, frequency, and severity of AEs and SAEs, including clinically significant changes from baseline to scheduled time points in vital signs, weight, and physical examination, GFR, clinical laboratory evaluations (including additional KRN23/XLH biochemical parameters of interest such as serum calcium, intact parathyroid hormone (iPTH), 25-hydroxyvitamin D ($25(OH)_2D$), amylase, lipase, and creatinine; and urinary calcium and creatinine), concomitant medications, and ECG. Ectopic mineralization safety assessments include renal ultrasound. The development of anti-KRN23 antibodies and dose limiting toxicities (DLTs) will also be assessed.

7.5.5.1 Medical History

General medical information includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, and surgeries. The height of both parents

will also be recorded. The review will also include an assessment of symptoms and conditions associated with XLH and SOC (e.g., oral phosphate/active vitamin D) treatment.

Subjects must be willing to provide access to prior medical records for the collection of biochemical and radiographic data, as well as disease history. The specific diagnosis of XLH will be recorded, along with date of onset, clinical presentation, and date and method of diagnosis. Any available family history of XLH will be noted, including any available previous *PHEX* mutation analysis results for the subject or relevant family members with appropriate X-linked inheritance pattern.

XLH treatment history and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Previous treatments may include calcitriol and oral phosphate and/or other adjunctive therapy. Medications include investigational, prescription, over-the-counter, herbal and nutritional supplements. Any relevant concomitant therapy, including physical/occupational therapy will be recorded. Use of pain medications will also be recorded. Refer to Section 7.4.5.1 for prohibited medications during the study.

7.5.5.2 Vital Signs

Vital sign measurements will be obtained as indicated in the Schedules of Events (Table 2.1, Table 2.2, and Table 2.3). Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Blood pressure measurements will be obtained only in children aged 3 years or above at study entry or beginning when a subject turns 3 years of age and will only be obtained at clinic visits. Vital signs measured at home health visits will include heart rate in beats per minute and temperature (°C).

US Department of Health and Human Services guidelines for Blood Pressure Measurement in Children will be used as a reference for BP measurement (NHLBI 2005).

Subjects will be instructed to refrain from exercise for at least 30 minutes before and until completion of BP measurements. They will also be instructed to refrain from playing video games, or other activities that may affect BP until all measurements are obtained. At each study visit, before BP determination, arm circumference is measured (in centimeters) with a plastic measuring tape at the midpoint of the upper arm between the acromium (tip of shoulder) and olecranon (tip of elbow) and a cuff is then selected so that the length of the cuff bladder is equal to 80% to 100% of the arm circumference. Effort should be made to use the same BP measuring device for subsequent BP measurements during site visits. After 5 minutes of rest, pulse and BP measurements begin. The BP measurements are obtained by auscultation of the brachial artery using the first Korotkoff sound for systolic BP (SBP) and the fifth Korotkoff sound for diastolic BP (DBP).

At the Screening Visit, BP should be measured 3 times, 30 seconds apart at the beginning of each visit; 3 additional BP measurements, 30 seconds apart, should be obtained at the end of the study visit after all procedures have been performed. Thus, there will be 2 average BP

recordings for the Screening Visit (one being the average of the first 3 BP recordings at the beginning of the visit and the second, the average of the additional 3 BP recordings at the end of the study visit). At the baseline and post-baseline visits, 3 BP measurements 30 seconds apart, should be obtained at the beginning of the study visit. The average of the three BP measurements is recorded as the participant's BP for the study visit.

In addition, after subjects are deemed eligible to participate in the study, if available, historical BP measurements will be obtained from the subjects' medical records and documented in the past medical history BP recordings section of case report form.

7.5.5.3 Weight

Weight will be obtained using a scale and recorded in kilograms at specified site visits (Table 2.1, Table 2.2, and Table 2.3). Weight measurements will be used to calculate the appropriate KRN23 dose to be administered. Weight from the previous site visit will be used to calculate KRN23 dose.

7.5.5.4 Physical Examination

Complete physical examinations will be performed at Screening, Baseline, and at the Week 24, 40, and 64 study visits, at 12-week intervals during the Extension Period (or at Early Termination), and at the Safety Visit (if applicable). Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. The genitourinary exam scope should be non-invasive, as per age-appropriate standard of care, and at the investigator's discretion based on clinical judgement.

7.5.5.5 Renal Ultrasound and Glomerular Filtration Rate

Renal ultrasounds will be conducted at Screening and the Week 40, 64, and 160 (or Early Termination) visit.

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

The eGFR will be calculated by using the Bedside Schwartz equation (Schwartz et al. 2009).

7.5.5.6 Electrocardiogram

A standardized 12-lead ECG will measure PR, QRS, QT, and QTc at Baseline and Weeks 12, 40, and 64, and at the Week 160 (or Early Termination) visit. The goal is to evaluate both 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 centrally by qualified

personnel blinded to subject data. The ECG results will be assessed for any clinically significant abnormality or relevant changes from baseline.

7.5.5.7 Clinical Laboratory Tests for Safety

A comprehensive serum metabolic panel (Chem-20), complete blood count, and urinalysis (when possible) will be used as routine screens to assess KRN23 safety. Certain analytes (i.e., serum phosphorus) in the routine Chem-20 panel are also designated as PD/efficacy parameters in this study. Additional KRN23/XLH biochemical parameters of interest include serum $1,25(OH)_2D$, calcium, creatinine, and iPTH; and urinary phosphorus, calcium, and creatinine.

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

Fasting for a minimum of 4 hours is required prior to each blood draw or urine collection; the duration of fasting will be recorded on the CRF. Subjects who live more than 45 minutes from the site may stay overnight on the night before the site visit to facilitate fasting sample collection. Clinical laboratory parameters to be assessed for safety are provided in Table 7.5.5.7.1. See the Study Reference Manual for details on sample collection and processing.

Table 7.5.5.7.1: Clinical Laboratory Assessments

Chemistry	**Hematology**	**Urinalysis**[1]
$1,25(OH)_2D$[2]	Hematocrit	Appearance
$25(OH)_2D$	Hemoglobin	Color
Alanine aminotransferase (ALT)	Platelet count	pH
Alkaline phosphatase (ALP)[2]	Red blood cell (RBC) count	Specific gravity
Amylase	White blood cell (WBC) count	Ketones
Aspartate aminotransferase (AST)	Mean corpuscular volume (MCV)	Protein
Bilirubin (direct and total)	Mean corpuscular hemoglobin (MCH)	Glucose
Blood urea nitrogen (BUN)	MCH concentration	
Calcium (total)		
Chloride		
Carbon dioxide (CO_2)		
Cholesterol (total)		
Creatinine		
Gamma-glutamyl transpeptidase (GGT)		
Glucose		
FGF23		
Intact parathyroid hormone (iPTH)		
Lactate dehydrogenase (LDH)		**Spot Urine**
Lipase		Calcium
Phosphorus[2]		Creatinine
Potassium		Phosphorus
Protein (albumin and total)		
Sodium		
Uric acid		

[1]Urinalysis to be conducted if possible based on urine volume collected.

[2]Also designated as a PD/efficacy parameter

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

7.5.5.7.1 Fibroblast Growth Factor 23

Serum FGF23 concentrations will be measured at the Baseline, Week 24, Week 64, and Week 160/Early Termination visits in all subjects using a validated assay run by a central lab. Blood samples will be collected after a minimum fasting time of 4 hours and prior to drug administration.

7.5.5.7.2 Anti-KRN23 Antibody Testing

To determine the immunogenicity profile of KRN23 in children aged 1-4 years with XLH, blood samples will be obtained for anti-KRN23 antibody (ADA) testing at Baseline and Weeks 4, 12, 40, 64, and Week 160/Early Termination visits. PK samples will be obtained on post-baseline days of ADA testing to assess potential neutralizing effects if ADA are detected. The formation of anti-KRN23 antibodies in human serum will be determined using a validated ECLA and a 2-tiered strategy: screening assay and specificity confirmation assay. If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points on a case-by-case basis, if warranted.

7.5.5.8 Concomitant Medications/Therapies

Concomitant medications and therapies will be reviewed and recorded in the subject's CRF at each study visit to the investigational site and during home health visits. Between site visits during the Extension Period, concomitant medications and therapies will be reviewed by telephone call from the study site to the subject's parent/caregiver every 2 weeks and recorded in the subject's CRF if home health visits have been replaced by parent/caregiver study drug administration.

Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded. Therapies (physical therapy, occupational therapy as well as mobility and walking devices, including ankle-foot orthosis, braces, cane, crutches, walker, wheelchair etc.) utilized during the 30 days prior to Screening will also be reviewed and recorded. At each subsequent visit (or telephone call), change in medications and therapies since the previous visit will be recorded. A discussion of concomitant medications and therapies is provided in Section 7.4.5.

7.5.5.9 Dose Limiting Toxicity

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

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

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

7.5.5.10 Adverse Events

All AEs will be recorded from the time the subject's parent/guardian signs the informed consent through the final safety protocol-defined follow-up (telephone or visit).
The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit, subjects will be asked about any new or ongoing AEs since the previous visit. Assessments of AEs will occur at each visit to the investigational site, at home health visits, and at telephone visits.

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

7.5.6 Appropriateness of Measurements

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

Additional assessments are included both as PD measures and safety indicators of potential secondary complications associated with treatment, including serum calcium, $1,25(OH)_2D$ and urinary calcium, creatinine, and phosphorus, as hypercalciuria may occur in the absence of hypercalcemia. Intact PTH (iPTH) levels are routinely measured as a part of standard oral phosphate and active vitamin D therapy in XLH, as secondary hyperparathyroidism is common. ALP will be measured as a biochemical marker of bone turnover, which may provide an indication of treatment effect. Where possible, timing of assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing.

Radiographs are routinely recommended during the initial evaluation of XLH, and to evaluate healing of rickets and skeletal deformities. Growth will be measured and may be compared with historical growth measurements to determine a change in growth velocity before and after KRN23 treatment.

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, serum chemistry, concomitant medications, and other routine clinical and laboratory procedures.

Routine, non-invasive procedures will provide relevant indicators of possible renal and cardiac risk; renal ultrasounds will be used to detect any calcinosis in susceptible organs. Since elevated free FGF23 has been associated with LVH in patients with chronic kidney disease, ECGs will examine the potential risk in XLH subjects.

The study will be conducted in a pediatric population; as such, additional safety measures including home health care visits and a DMC have been incorporated into the study design. Where possible, measures to minimize pain and distress to the subject have been considered for this study protocol. The maximum blood volume obtained throughout the Treatment Period is estimated to be approximately 169 mL. Any unscheduled blood draws would be in addition to this volume.

7.6 Statistical Methods and Determination of Sample Size

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

7.6.1 Determination of Sample Size

Approximately 10 children aged 1-4 years with XLH will be enrolled in the study.
This sample size is considered appropriate to evaluate the KRN23 dose and PD relationship to confirm if the profile is similar in these younger children to that observed in older children (age 5-12) in the Phase 2 study UX023-CL201. Preliminary clinical efficacy assessments will also be evaluated in this study. To demonstrate safety and efficacy in a controlled study, a larger randomized, Phase 3 study in children with a broader age range is being planned that will include two treatment arms: one group will receive KRN23 and one group will receive oral phosphate/active vitamin D therapy.

7.6.2 Analysis Populations

7.6.2.1 Efficacy Analysis Set

The Efficacy Analysis population will consist of all subjects who receive at least one dose of study drug and have at least one post-study drug measurement.

7.6.2.2 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who receive at least one dose of study drug.

7.6.2.3 Pharmacokinetic and Pharmacodynamic Analysis Set

The PK/PD analyses sets will consist of all subjects who receive at least one dose of study drug and have evaluable blood samples.

7.6.3 General Principles

Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, interquartile range (Q1, Q3), minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Statistical tests will be two-sided at the alpha = 0.05 significance level. Two-sided 95% confidence intervals will also be presented.

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analyses will be presented in the SAP. In general, missing data will be treated as missing and no statistical imputation method will be used unless stated otherwise.

No adjustment on multiplicity will be made for statistical comparisons unless stated otherwise.

7.6.3.1 Subject Accountability

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

7.6.3.2 Demographics and Baseline Characteristics

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

7.6.3.3 Pharmacodynamic Analyses

The primary efficacy endpoint is the change from baseline over time in serum phosphorus. PD parameters and their respective change from baseline will be summarized at each time point. A repeated measure model will be used for assessing the change from baseline at each time point. In the case when model assumption is not met, analyses using alternative methods such as non-parametric tests will be performed.

7.6.3.4 Clinical Efficacy Analysis

The radiographic measures including RGI-C global score, RGI-C long leg score and RSS scores and the change from baseline of RSS scores will be summarized at Weeks 40, 64, 112, and 160. RGI-C global score at Week 40 will be the key rickets assessment.
An Analysis of Covariance (ANCOVA) model will be used for assessing the RGI-C score and the change from Baseline of RSS score at Week 40. At Weeks 64, 112, and 160, RGI-C global score over time will be analyzed using the repeat measurement model that includes visit as a categorical variable, and adjusted for baseline age and rickets severity. The RGI-C

long leg score and change from baseline in RSS total score over time will be analyzed using the same method.

Growth parameters such as recumbent length/standing height will be summarized at each time point. The z scores and percentiles and their respective change from baseline of standing height will be summarized. In addition, the growth velocity will be evaluated for recumbent length/standing height. The SAP will provide additional details on the planned efficacy analyses.

7.6.3.5 Pharmacokinetics Analyses

PK parameters will be summarized at each time point.

7.6.3.6 Safety Analyses

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

Clinical laboratory data will be summarized by the type of laboratory test. Reference ranges and markedly abnormal results 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. A shift table for iPTH at each scheduled visit will be provided to assess the normality over time. A listing of subjects with any markedly abnormal laboratory results will be provided. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

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

7.6.4 Timing of Analysis

Analysis of select safety and efficacy variables will be conducted at Week 40; a full analysis of safety and efficacy variables will be conducted at the end of the Treatment Period (Week 64). The final analysis of long-term safety and efficacy variables will be completed at the end of the study (“study completion”), which is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

7.6.5 Data Monitoring Committee

An independent DMC that includes members with expertise in metabolic bone disease, cardiology and nephrology and the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis through the Treatment Period (Week 64). The DMC will meet approximately twice a year. The roles and responsibilities of the DMC will be defined in the DMC Charter. During the Extension Period, safety data will be reviewed by the SSRT on an ongoing basis.

8 STUDY CONDUCT

8.1 Ethics

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

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

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

8.1.2 Ethical Conduct of Study

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

8.1.3 Subject Information and Consent

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

It is the Investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The Investigator must explain to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time. Subjects under the age of 18 years (or 16 years, depending on the region) will provide written assent (if possible), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects.

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

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

8.2 Investigators and Study Administrative Structure

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

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

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

8.3 Investigational Product Accountability

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

A drug accountability record must be maintained for all 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. During the Extension Period, subject caregivers will retain empty vials and return them to the study site as directed by study personnel for drug accountability. Following the close-out of the study, all unused Investigational Product 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 electronic CRFs. Data must be recorded on CRFs approved by Ultragenyx or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

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

8.4.2 Data Quality Assurance

Monitoring and auditing procedures developed by Ultragenyx and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's designated representative (the monitor) will contact the investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof

of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterruptable data will be resolved in coordination with the investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

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

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

An 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.

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 adverse event caused by a drug.

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

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 disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect

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

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

8.5.2 Severity of Adverse Events

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

8.5.3 Relationship of Adverse Events to Study Drug

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

Categories of attributions for "Unrelated" events:

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

Categories of attributions for "Related" events:

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

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

8.5.4 Adverse Event Reporting

8.5.4.1 General

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

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

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

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

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

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

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

8.5.5 Communication Plan

8.5.5.1 Serious Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), ECs, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

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

8.5.5.2 Urgent Safety Matters and Non-SUSAR Reporting

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

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

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

8.5.6 Review of Safety Data

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

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

8.5.7 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: PPD e-mail: PPD	Javier San Martin, MD Telephone: PPD Mobile: PPD e-mail: PPD

8.6 Financing and Insurance

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

8.7 Publication Policy

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

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10 SIGNATURE PAGE

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

Protocol Number: UX023-CL205 Amendment 2

I have read Protocol UX023-CL205 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

PPD

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

Date