Statistical Analysis Plan

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

Protocol:	UX023-CL301
Investigational Product:	KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])
Phase:	3
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Author:	PPD PPD, Biostatistics
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LIST OF ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D
$1,25(OH)_2D$	1,25-dihydroxyvitamin D
6MWT	Six Minute Walk Test
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	Analysis of Covariance
BUN	blood urea nitrogen
CDF	cumulative density function
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	estimated glomerular filtration rate
FGF23	fibroblast growth factor 23
FPS-R	Faces Pain Scale – Revised
GEE	Generalized Estimating Equations
GFR	glomerular filtration rate
HAHA	human anti-human antibody
iPTH	intact parathyroid hormone
kg	Kilogram
LVH	left ventricular hypertrophy
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	pharmacodynamic (s)
PHEX	Phosphate regulating gene with homology to endopeptidases located on the X chromosome
PHS-10	Physical Summary Score
PSS-10	Psychosocial Summary Score
PK	pharmacokinetic(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
PTH	parathyroid hormone
Q2W	biweekly, once every two weeks
QIC	Quasi-Likelihood Information Criterion

RBC	red blood cell
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	serious adverse event
SAP	statistical analysis plan
SF-10	SF-10 for Children Health Survey
TEAE	treatment emergent adverse event
TmP/GFR	ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate
TRP	tubular reabsorption of phosphate
WBC	white blood cell
XLH	X-linked hypophosphatemia

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the UX023-CL301 Protocol original version dated 04APR2016.

2 OBJECTIVES

2.1 Primary Objective:

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

2.2 Secondary Efficacy Objectives:

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

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

2.3 Pharmacokinetic Objective:

Assess the PK of KRN23 throughout the dosing cycle.

2.4 Safety Objective:

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

3 STUDY DESIGN

As background for the statistical methods presented below, this section provides an overview of the study design. This overview is a summary only. The protocol is the definitive reference for all matters discussed in what follows in this section.

3.1 Study Population

UX023-CL301 is a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of KRN23 with the active control (oral phosphate/active vitamin D therapy) in pediatric patients with XLH. The study will be conducted in children with clinical evidence consistent with XLH (aged 1 to ≤ 12 years), including demonstrated hypophosphatemia, radiographic evidence of rickets (≥ 2.0 points RSS total score), and *PHEX* mutation or variants of uncertain significance. Patients will also be required to have received oral phosphate/active vitamin D therapy for ≥ 12 consecutive months (for children ≥3 years of age) or ≥ 6 consecutive months (for children <3 years of age).), 7 days prior to the Randomization Visit.

3.2 Dosage and Administration

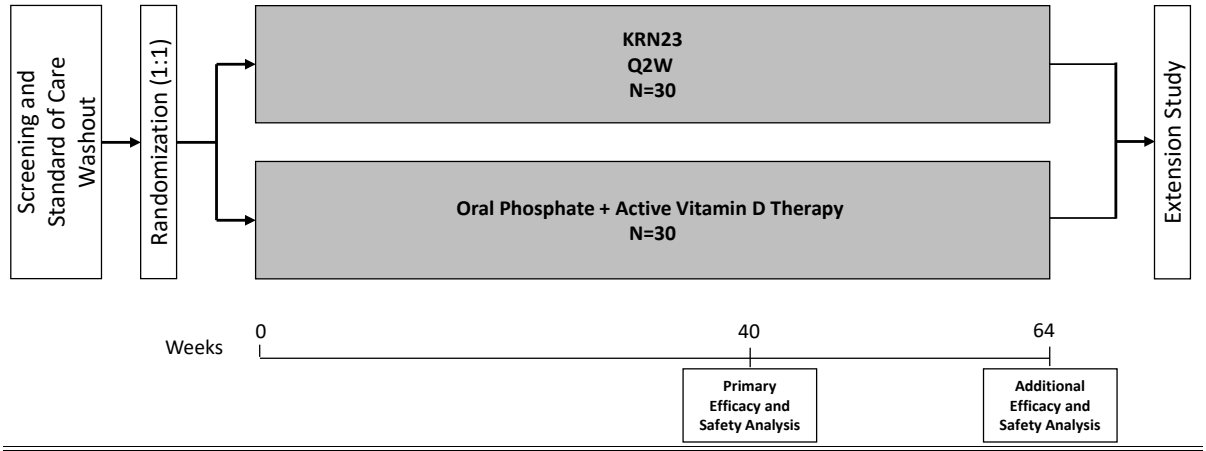
Subjects assigned to the KRN23 treatment group will receive KRN23 at a starting dose of 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of KRN23 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 (i.e., half the dose of either 0.8 mg/kg or 1.2 mg/kg). Serum phosphorus will be followed through unscheduled serum phosphorus assessments approximately 2 weeks post-dose and assessed by central laboratory; the assessments may be repeated as necessary. A subject will resume dosing at the previous full total dose level if they meet the same dose-adjustment criteria listed above (i.e., two consecutive serum phosphorus measurements are below the normal range; serum phosphorus has increased by < 0.7 mg/dL from baseline; and the subject has not missed a dose of KRN23 that would account for the decrease in serum phosphorus). KRN23 will be administered up to a maximum dose of 90 mg in this study with no minimum dose requirement.

Subjects assigned to active control will typically receive multiple daily doses of oral phosphate and active vitamin D. Because of the variability in the doses and dosing frequencies of oral phosphates and active vitamin D therapies in clinical practice, these treatments will be individualized for each subject at the investigator's discretion, but the following general guidance is provided based on expert recommendations in the US and Europe (in Table 7.1.1 and 7.1.2 of the protocol). Detailed information about the brand,

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

The study will be conducted in a pediatric population; as such, additional measures including an external, independent DMC have been incorporated into the study design. Where possible, measures to minimize pain and distress to the subject have been considered for this study protocol including the use of home health visits (KRN23 treatment arm only). At every home health visit for subjects in the KRN23 treatment arm, all subjects randomized to the active control arm will receive a phone call to assess adverse events and concomitant medications. Home Health visits are not applicable to subjects in Japan, Korea or Italy. Where possible, timing of assessments will be coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing. The primary analysis will be at Week 40; analyses at Week 64 will assess the durability of treatment effect, additional efficacy outcomes, and long-term safety. After completing the initial active-controlled Treatment Period of the study (64 weeks), subjects from either treatment groups may be eligible for an extension study and receive KRN23 treatment for up to an additional 96 weeks or until KRN23 is commercially available. Figure 3.2.1 provides a schematic of the overall study design.

Figure 3.2.1: UX023-CL301 Study Schema



The schedule of assessments is shown in Appendix 3.

3.3 Blinding and Randomization Methods

An open-label study design was chosen since blinding such a study would be problematic due to the different methods of administration and the individualized nature and frequent dose adjustments needed with oral phosphate/active vitamin D therapy. Eligible subjects will be enrolled in the study and sequentially assigned an identification number. Subjects will be randomized 1:1 to receive open-label KRN23 by subcutaneous injection or active control via an Interactive Web Response System (IWRS) based on a randomization schedule developed by an independent third-party vendor. Randomization will be stratified by baseline rickets severity, age, and region.

3.4 Stratification Factors

Stratification factors include baseline rickets severity (RSS total score ≤ 2.5 vs > 2.5) and age (< 5 vs ≥ 5). The randomization was also stratified by region (Japan vs. rest of World) for operational and logistic considerations to ensure balance between the two treatment groups in Japan, as small number of subjects are expected to be enrolled.

3.5 Sample Size Considerations

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

The age of eligible subjects will be monitored for enrollment for age distribution. Approximately 20 subjects aged 1 to <5 years will be included (approximately 10 in each treatment group), and no more than 10 subjects between the ages of 1 to < 3 years will be enrolled. No more than 60% female subjects will be enrolled.

3.6 Primary Analysis

The primary analysis is planned at Week 40.

3.7 Additional Analysis

Additional analysis will be performed at Week 64 to assess the durability of treatment effect, additional efficacy outcomes, and long-term safety. In addition, administrative analyses can be performed to support regulatory activities.

3.8 Data Monitoring Committee

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

4 STUDY ENDPOINTS AND COVARIATES

All data are collected according to the schedule of assessments (Appendix 3).

4.1 Primary Efficacy Endpoint

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

4.2 Secondary Efficacy Endpoint(s)

The secondary endpoints listed in Section 4.2.1 and 4.2.2 will be compared between the KRN23 and active control groups:

4.2.1 Key Secondary Endpoint(s)

The key secondary endpoints include:

- Change in lower extremity skeletal abnormalities as assessed by the RGI-C long leg score
- Change from baseline in standing height/recumbent length Z score
- Change from baseline in RSS total score
- Change in serum phosphorus from baseline to mean post-baseline values
- Change from baseline in ALP

For the growth-related endpoints RGI-C long leg score and change from baseline in standing height/recumbent length Z score, the primary assessment time will be Week 64. For other key secondary endpoints, the primary assessment time will be Week 40. Because of the small sample size, no multiplicity will be adjusted for the key secondary endpoints.

4.2.2 Other Secondary Endpoint(s)

- Rickets Endpoint(s)
  - Proportion of subjects with a mean RGI-C global score ≥ +2.0 (substantial healing)
  - Change in rickets as assessed by RGI-C wrist and knee scores
  - Change from baseline in RSS wrist and knee scores
- Growth Endpoint
  - Change in growth velocity Z score from pre-treatment to post-treatment
- PD Endpoint(s)
  - Change from baseline over time in serum phosphorus

- Number of subjects reach the normal range of serum phosphorus (3.2 - 6.1 mg/dL) over time
- Change from baseline over time in serum $1,25(OH)_2D$, urinary phosphorus, TmP/GFR and TRP

- Pain, Fatigue and Physical Function Endpoint(s)
  - Change from baseline in the PROMIS (Patient-Reported Outcomes Measurement Information System) scores in Pediatric Pain Interference, Physical Function Mobility and Fatigue domains
  - Change from baseline in the Faces Pain Scale – Revised (FPS-R)
  - Change from baseline in the Six Minute Walk Test (6MWT) total distance and percent of predicted normal

4.3 Safety Endpoints

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

- Frequency (and %), and severity of adverse events (AEs) and serious adverse events (SAEs)
- Prior and concomitant medications
- Change from baseline to post-baseline visits in vital signs and weight
- Physical examinations
- Change from baseline to post-baseline visits in eGFR (calculated using the Bedside Schwartz equation)
- Shift from baseline to post-baseline visits in renal ultrasound in nephrocalcinosis score
- Change from baseline to post-baseline visits in Echocardiogram (ECHO)
- Change from baseline to post-baseline visits in chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (serum 25(OH)D; lipase; amylase; creatinine; serum calcium and iPTH, and urinary calcium and creatinine)
- Shift from baseline to post-baseline visits in presence of anti-KRN23 antibody
- Change from baseline to post-baseline visits in Electrocardiogram (ECG)

4.4 Pharmacokinetic Endpoint

- Serum KRN23

4.5 Exploratory Endpoints

- Health-related quality of life: Change from baseline to post-baseline visits in the SF-10 for Children Health Survey (SF-10; for subjects ≥ 5 years of age at the Screening Visit) physical summary score (PHS-10) and psychosocial summary score (PSS-10).
- Dental evaluation: number of dental events in dental caries, tooth extraction, root canal, dental abscesses, and gingivitis assessed at baseline and post-baseline visits.

4.6 Potential Covariate(s)

Unless specified otherwise, the randomization stratification factor (RSS total score ≤ 2.5 vs > 2.5) and age (< 5 vs ≥ 5) will be included as independent variables in the model for efficacy analysis. Region (Japan vs. rest of World) is used for randomization for operational and logistic considerations and will not be used as covariates in any analyses. For the GEE and ANCOVA analyses, baseline result of the response variable will be included as the covariate.

Other potential covariates such as gender might be used in growth analyses. If the baseline RSS total score or age is to be used in the statistical model as a continuous covariate, the corresponding randomization stratification factor will not be included in the same model. Refer to Section 8 for the details of statistical models and covariates for each efficacy endpoint.303, 304

4.7 Subgroups

Subgroup analysis by baseline rickets severity (RSS total score ≤2.5 vs >2.5), age (<5 vs ≥5) and region (Japan vs the rest of World) will be conducted for the following endpoints:

- Demographics and baseline characteristics
- Efficacy endpoints including rickets, growth, PD endpoints and ALP

The confidence intervals for difference between treatment groups and treatment effect within individual treatment groups will be provided on efficacy endpoints. Subgroup analysis by region will be presented descriptively only.

In addition, subgroup analysis by region will be performed for PK (serum KRN23) and selected AE summaries. Subgroup analysis by gender will be conducted for rickets and growth endpoints. Additional subgroup analysis by PHEX mutation (positive vs non-positive) may be considered if deemed as appropriate. For PROMIS, FPS-R and 6MWT, subgroup analysis by baseline rickets severity (RSS total score ≤2.5 vs >2.5) may be also considered.

5 DEFINITIONS

5.1 Baseline

Baseline is defined as the last assessments prior to or on the date of initiation of the first dose of investigational product.

5.2 Duration of exposure

Duration of exposure in days is defined as: Last date of investigational product – first date of investigational product + 14 days for KRN23 group and Last date of investigational product – first date of investigational product + 1 day for the active control group.

5.3 Study Day

Study day is calculated as:

- (visit date – date of the first dose of investigational product + 1) if the visit date is on or after the first dose of investigational product;
- (visit date – date of the first dose of investigational product) if the visit data is prior the first dose of investigational product.

5.4 Age

Unless specified, the age at baseline in demographics summary will be derived based on the informed consent date:

Age = (Informed Consent Date – Birth Date +1)/365.25.

Age at study visits for a particular measurement will be derived based on the measurement visit date:

Age = (Visit Date – Birth Date +1)/365.25.

The age will be rounded down to the nearest x.x years and keep one decimal place.

5.5 RGI-C

Changes in the severity of rickets and bowing will be assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative Radiographic Global Impression of Change (RGI-C) scoring system.

The RGI-C is a seven point ordinal scale with possible values:

+3 = very much better (complete or near complete healing of rickets),
+2 = much better (substantial healing of rickets),
+1 = minimally better (i.e., minimal healing of rickets),
0 = unchanged,

-1 = minimally worse (minimal worsening of rickets),
-2 = much worse (moderate worsening of rickets),
-3 = very much worse (severe worsening of rickets),

Raters will be presented with side-by-side images taken from subjects during the UX023-CL301 study with the Baseline image on the left (Image A) and Post-Treatment image (Week 40 and Week 64) on the right (Image B). Raters will be asked to evaluate change in Image B for the abnormalities they consider to be present in the Baseline Image A. This exercise will be performed for the distal radius and ulna from the bilateral wrist X-rays, and the distal femur and proximal tibia and fibula from the bilateral knee X-rays at Week 40 and Week 64. At Week 64, Image A (presented on the left) will remain the Baseline image and Image B (presented on the right) will be the post-treatment image from Week 64. In addition to bilateral wrists and knees, the Week 40 and Week 64 RGI-C analysis will include a rating of the full femur, tibia and fibula from the bilateral standing long leg film with the Baseline standing long leg image on the left (Image A) and the Week 40 (or Week 64) standing long leg image on the right (Image B). See data collection form in Appendix 5.

Prior to rating, the three raters will be trained to gain consensus on the terminology used to describe XLH-related radiographic abnormalities and to establish inter-rater reliability. Following the training, each rater will independently complete a quiz involving the rating of practice images to ensure the success of the training and the reliability of scores among the raters. For the Week 40 and Week 64 analysis, each of the three raters will perform the rating exercise at a work station at the central imaging facility. Only one rater can be present at the facility at any given time to prevent group rating or sharing of scores. Each rater will be presented with side-by-side images of the wrist and knee with Baseline on the left (Image A) and Post-Treatment on the right (Image B). Raters will be asked to evaluate the presence of various abnormalities in the wrist and knee in Image A and change in those abnormalities in Image B. At the Week 40 analysis, each rater will evaluate changes in rickets severity from Baseline to Week 40 in the wrists and knees by assigning a regional score for the wrist, a regional score for the knee, as well as an overall impression score. Raters will be blinded to the treatment group and subject's baseline and demographics information. At Week 64, the same process will be followed as Week 40 except that the raters will also evaluate images from long leg radiographs. RGI-C scores will be entered into an EDC system at the time of the scoring and cannot be retrieved or changed by the rater after submission. RGI-C scores will be transferred electronically from the imaging facility to Ultragenyx after the image rating exercise is complete.

The RGI-C scores for the three raters will be averaged and the mean scores for the wrist, knee, overall impression and RGI-C long leg score will be reported. RGI-C response is defined as an averaged RGI-C global score of at least +2.0 (i.e. substantial healing of rickets).

5.6 RSS

The severity of rickets will be measured using a scale developed by Thomas Thacher, MD for the assessment of nutritional rickets (Thacher et al. 2000). This scale will be referred to as the RSS. The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by Dr. Thacher to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity. Each radiograph is scored individually by Dr. Thacher who will serve as the single central independent rater for all UX023-CL301 X-rays taken at Baseline, Week 40 and Week 64. For the X-rays taken during the UX023-CL301 study, Dr. Thacher will be blinded to the treatment group and subject's baseline and demographics information. Each rating performed by Dr. Thacher is entered into an EDC system at the time of the rating and transferred electronically to a central imaging facility. The scores cannot be retrieved from the system by Dr. Thacher after submission. See RSS data collection form in Appendix 4.

5.7 Growth

5.7.1 Standing height/recumbent length Z-score and Percentile

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.

Growth as measured by standing height or recumbent length will be evaluated on a percentile basis using the Centers for Disease Control/National Center for Health Statistics (CDC/NCHS) Clinical Growth Charts (Kuczmarski et al. 2000). Data used to produce the United States Growth Charts smoothed percentile curves will be downloaded from the official CDC/NCHS web site: http://www.cdc.gov/growthcharts/percentile_data_files.htm

The data files from the CDC/NCHS that are used for this analysis are summarized below. These files represent the different growth curves for children. LMS refers to the parameters in the CDC Growth Charts Percentile Data Files used to construct the growth curves; these are: the power in the Box-Cox transformation (L); the median (M); and the generalized coefficient of variation (S).

The data files used are:

- Length-for-age charts, birth to 36 months, LMS parameters and selected smoothed recumbent length percentiles in centimeters, by sex and age (LENAGEINF).
- Stature-for-age charts, 2 to 20 years, LMS parameters and selected smoothed stature percentiles in centimeters, by gender and age (STATAGE).

Calculation of Z-scores for length/stature values above and below the median will be performed. Using the CDC/NCHS Clinical Growth Charts, the height-for-age Z score will be calculated using the following equation:

$$Z = \{(X/M)^L - 1\} / (L \times S),$$

where X is the physical measurement (stature in cm) and the LMS parameters are obtained from the appropriate CDC/NCHS Clinical Growth Chart corresponding to the age in months of the child. The percentile corresponding to the Z score is then the corresponding percentile from the standard normal distribution.

5.7.2 Weight Z-score and Percentile

Weight will be evaluated by z score and percentile using the same method as Section 5.7.1 based on Centers for Disease Control/National Center for Health Statistics (CDC/NCHS) Clinical Growth Charts (Kuczmarski et al. 2000). The data files used for weight Z-score and percentile are:

- Weight-for-age charts, birth to 36 months, LMS parameters and selected smoothed weight percentiles in kilograms, by sex and age (WTAGEINF).
- Weight-for-age charts, 2 to 20 years, LMS parameters and selected smoothed weight percentiles in kilograms, by sex and age (WTAGE).

5.7.3 Growth Velocity

Growth velocity of recumbent length/standing height in cm/year will be assessed by a model-based approach. A linear regression model for each subject will be built based on all recumbent length/standing height measurements by assuming a linear change in growth:

$$Y_t = \beta_0 + \beta_1 X_t + \varepsilon_i$$

Where Y_t is the recumbent length/standing height (cm) measured at Time t; X_t is the time when recumbent length/standing height is measured; β_0 is the intercept, $\beta_1$is the slope of the regression model; ε_i is random error term.

The growth velocity Z score will be calculated based on Tanner's standard (Tanner et al. 1985) in Appendix 6. Let [T1, T2] denotes the age interval (years) where the growth velocity is estimated from, for example, for post-treatment growth velocity at Week 40, T1 = age (years) at baseline and T2 = age (years) at Week 40. The mid-point of the age interval (T1 + T2)/2 will be used to locate the closest reference age in the reference table.
The corresponding 50th percentile (Mean) and SD values will be used to calculate the growth velocity Z score in the following equation:

$$\text{Growth velocity Z score} = \frac{\text{Growth velocity} - \text{mean}}{\text{SD}}$$

If (T1 + T2)/2 is less than 2.25 years, the growth velocity Z score will not be calculated.

5.8 Percent of Predicted Six-Minute Walk Test

The percent of predicted values will be calculated using published normative data based on age, gender, and height (Geiger et al. 2007). The percent of predicted walking distance 6MWTD is given as:

For males:

$$\text{Percent of predicted six minute walk test} = \frac{\text{Observed 6MWD}}{196.72 + (39.81 * \text{Age}) - (1.36 * \text{Age}^2) + (132.28 * \text{Height})} * 100$$

For females:

$$\text{Percent of predicted six minute walk test} = \frac{\text{Observed 6MWD}}{188.61 + (51.50 * \text{Age}) - (1.86 * \text{Age}^2) + (86.10 * \text{Height})} * 100$$

where Age is the subject's age at the time of the assessment (expressed as one digit decimal) calculated using the following: (date of test – date of birth)/365.25, and height is the subject's standing height at the time of the assessment (in m). If there is no height measured at the time of the 6MWT assessment, the closest prior height will be used.

5.9 Health-related Quality of Life (SF-10 for Children Health Survey)

The SF-10 for Children Health Survey (SF-10) is a caregiver-completed questionnaire designed to assess physical and psychosocial health-related quality of life in healthy and ill children (Saris-Baglama et al. 2006). The 10 items were adapted from the Child Health Questionnaire and utilize a 4-week recall period. Responses are used to generate 2 component summary scores: physical summary score (PHS-10) and psychosocial summary score (PSS-10). The scale scores have been centered so that a score of 50 corresponds to the average score in a comprehensive 2006 sample (a combination of general population and supplemental disability and chronic condition samples). Scale scores are standardized to a mean of 50 and a standard deviation of 10 in the combined U.S. general population. The scoring of the SF-10 will be performed according to the method described in (Saris-Baglama et al. 2007). Higher global scores are associated with better quality of life.

5.10 Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). It uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. High scores mean more of the concept being measured. The domain-specific approach is based on the idea that health attributes, such as pain and

physical function are not unique to a specific disease. The PROMIS contains a bank of questions from which relevant items can be extracted and used to create a custom form. The PROMIS Pain Interference, Physical Function Mobility, and Fatigue domain scores will be administered to subjects ≥ 5 years of age at the Screening Visit. To assess these health domains, items from the Pediatric Pain Interference, Physical Function Mobility, and Fatigue item banks (Version 2.0) were extracted to develop a self-report form that will be completed by children 8 years of age and older at the Screening Visit. For children ages 5 to < 8 years at the Screening Visit, the same items were extracted from the Parent Proxy item banks (Version 2.0) that will be completed by the parent or legal guardian. The Parent/Legal Guardian form will be used for the duration of the study for subjects < 8 years of age at the Screening Visit, even when a subject turns 8 during the study. The answers collected from PROMIS questionnaire will be uploaded to the PROMIS online scoring system http://www.healthmeasures.net/explore-measurement-systems/promis to obtain the final scores for Pain Interference, Physical Function Mobility, and Fatigue domain.

5.11 Faces Pain Scale – Revised (FPS-R)

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

5.12 Blood Pressure and Blood Pressure Percentile

BP will only be collected for subjects who are ≥ 3 years old. At Screening and Baseline the blood pressure will be measured three time at both pre and post study visit assessment. After Baseline the blood pressures will be measured three times at pre-assessment only. At each visit, the average blood pressure will be calculated and used for analysis.

The blood pressure percentile will be derived based on the forth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents (NHLBI 2005). See Appendix 7 for details in deriving blood pressure percentile adjusting for age, gender and height.

5.13 Heart Rate Percentile

The heart rate percentile category will be derived based on the National Health Statistical Reports on resting pulse rate reference data for children, adolescents, and adults: United States, 1999-2008 (Ostchega et al. 2011). See Appendix 8 for details in deriving blood pressure percentile category adjusting for age and gender.

5.14 ECG Normal Ranges

The ECG normal ranges are provided in BMS UX023-CL301 CAMI 7 12-Lead ECG analysis plan (Version 1.0, 15APR2016). See Appendix 9 for details in the normal ranges by age group and gender.

5.15 Adverse Events to Monitor

The definition for each type of adverse events to monitor is as the following:

- Injection Site Reaction is defined by preferred terms under the Medical Dictionary for Regulatory Activities (MedDRA) high-level term (HLT) "Injection site reaction"
- Hypersensitivity AE: Defined using relevant PTs in the narrow SMQs for "Hypersensitivity".
- Hyperphosphataemia AE: Defined by using PTs: "Hyperphosphataemia", "Blood phosphorus increased", "Blood phosphorus abnormal".
- Ectopic calcification related AE: There is no available SMQ. Ectopic calcification related AE is defined using a MedDRA search of 'calcification'.
- Restless leg syndrome AE: Defined by PTs "Restless legs syndrome", "Restlessness", "Akathisia", "Sensory disturbance", "Psychomotor hyperactivity", "Limb discomfort", "Neuromuscular pain", "Formication".

See Appendix 10 for the search criteria.

5.16 Dose-limiting Toxicity (DLT)

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.

If a subject continues to experience increases in serum phosphorus above the ULN (however do not meet the criteria for a DLT) despite dose reduction measures, 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.

5.17 Duration of Conventional therapy before Baseline

The conventional therapy that subjects received before baseline will be identified by reviewing prior medication data.

The definition for duration of conventional therapy a subject received before baseline is as follows:

Duration of conventional therapy = End date of the latest conventional therapy taken - start date of earliest conventional therapy taken prior to randomization

If the date is partially or completely missing, apply the following imputation rule:

Start Dates

- If the FIRST start date of conventional therapy is completely missing, then use the next earliest non-missing date.
- If the year is known and month is missing, then assign 'January 1st';
- If the year and month are both known and day is missing, then assign the first day of the month.

Stop Dates

- If LAST stop date is completely missing, then impute 'one day' prior to the randomization date
- If year is known the month is missing, then assign "December 31th". If this imputed date is after randomization date, use one day prior to randomization date instead.

If year and month are both known and the day is missing, then assign the last day of the month. If this imputed date is after randomization date, use one day prior to randomization date instead.

6 ANALYSIS POPULATIONS

6.1 Screened Population

The Screened Population will consist of all unique subjects who underwent a Screening Visit and received a subject identification number.

6.2 Full Analysis Set (FAS)

The Full Analysis Set will consist of all randomized subjects who received at least one dose of assigned medication and had at least one post-baseline assessment. Subjects will be analyzed according to the assigned treatment at randomization.

6.2.1 Full Analysis Subset – Baseline Age ≥ 5 Years

This is a subset of FAS that consists of all subjects with age ≥ 5 years at baseline. PROMIS, 6MWT and FPS-R will be analyzed using this analysis set.

6.3 Safety Analysis Set

The Safety Analysis Set will consist of all randomized subjects who received at least one dose of assigned medication. Subjects will be analyzed according to the actual treatment received in the study.

6.4 Pharmakinetic (PK) Analysis Set

The PK analysis set consists of all subjects who received at least one dose of KRN23 and had evaluable PK data.

6.5 Pharmacodynamic (PD) Analysis Set

The PD analysis set consists of all subjects who received at least one dose of study therapy and had evaluable serum data.

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

Data will be reviewed periodically. And any questionable data will be reported to the clinical data manager promptly for query and resolution.

7.2 Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

7.2.1 Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
    - If the month and year match the first dose of investigational product start date month and year in this study, then impute the day of the first dose date.
    - Otherwise, assign the first day of the month.
- If the month is unknown, then:
    - If the year matches the year of the first dose of investigational product date in this study, then impute the month and day of the first dose date in this study.
    - Otherwise, assign ‘January’
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

Missing Stop Dates and not ongoing

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign ‘December.’

- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.

If the resulting end date is after the date of study completion/discontinuation/data cutoff, set the imputed end date as close to the date of study completion/discontinuation/data cutoff as possible without overwritten existing information.

If the year is missing for the start date, and stop date (observed or imputed) is on or after the first dose or event is ongoing. The start date will be imputed as the first dose date.

7.2.2 Missing Causal Relationship to Investigational Product for Adverse Events

For the KRN23 group, if the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of investigational product, a causality of "definitely related" will be assigned.

For the active control group, if the causal relationship is missing for both oral phosphate and active vitamin D for an AE that started on or after the date of the first dose of investigational product, a causality of "definitely related" will be assigned to both oral phosphate and active vitamin D. If the causal relationship is missing for one of the oral phosphate or active vitamin D medication and not missing for the other one, the missing causality will not be imputed.

The imputed values for causal relationship to investigational product will be used for the incidence summary; the values will be shown as missing in the data listings.

7.2.3 Visit Time Windows

Unscheduled visit occurred prior to or on the date of initiation of the first dose will be mapped to the baseline visit if it is the last assessment prior to or on the date of initiation of the first dose; otherwise no mapping will be performed.

Unscheduled visits that occurred after the date of initiation of the first dose will be mapped to the post-baseline scheduled visit with the closet target study day (refer to Section 5.3 for study day definition and Appendix 3 for the schedule of events). If the unscheduled visit is in the middle of two scheduled visits, map to the later scheduled visit. For PD, PK and safety assessments (refer to Section 4.2, 4.3 and 4.4), if the time difference between the unscheduled visit and closest scheduled visit is $\geq$ 14 days, the unscheduled visit will not be mapped.

For descriptive summary tables, when more than one measurement is mapped to the same scheduled visit, the measurement taken on the scheduled visit will be used if it is not missing, otherwise the one closest to the target day will be used. If two or more visits have equal distances to the target day, then the later one will be used. If more than one measurement is collected on the same day, use the time or the sequence number to select the latest record.

For listings and shift tables in safety analysis, all data points will be included.

Early termination visit will generally follow the same rule as unscheduled visit except for a special case in X-rays. X-rays will not be performed at the early termination visit if the assessment was conducted within 3 months of termination. Hence if a subject has X-rays at both Week 40 and early termination visits, the X-rays on early termination visit will be mapped to Week 64.

7.3 Testing/Validation Plan

Data will be reviewed by cross functional teams periodically and issues will be addressed by clinical data management.

7.4 Software

SAS® software version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

8 STATISTICAL METHODS AND ANALYSES

8.1 General Principles

The efficacy analyses will be based on the full analysis set. The PD analyses will be based on the PD analysis set. The safety analyses will be based on the safety analysis set. Statistical tests will be two-sided hypothesis tests performed at the 5% level of significance for main effects. Confidence intervals will be 2-sided 95% confidence intervals, which will be provided for both within group estimate and between group difference. P-values will be rounded to and displayed in three decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <.0001. There will be no multiplicity adjustments, or adjustments for multiple comparisons. Continuous variables will be summarized by number of subjects and mean, standard deviation/standard error (SD/SE), median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

If an outlier is identified and/or a pronounced non-normal probability distribution is found for the difference between the two treatment groups, then a non-parametric analysis corresponding to that of the parametric counterpart, e.g. the Wilcoxon rank test for median, will be performed and be considered as the primary analysis to assess the treatment difference between KRN23 and active control groups. Such a model violation may be identified by graphical methods, measures of non-normality (e.g., skewness, kurtosis) or other appropriate methods.

8.2 Subject Accountability

The number and percentage of subjects in each of the analysis populations (Screened, Full, PK and PD) will be summarized by treatment group. Subjects and their data excluded from any analysis set will be listed.

Screen-failure subjects (ie, subjects screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the Screened Population. The number and percentage of subjects who complete the treatment period and of subjects who prematurely discontinue will be presented for each treatment group and pooled across treatment groups for the Full Analysis set. The reasons for premature discontinuation from treatment period as recorded on eCRFs will be summarized.

8.3 Protocol Deviations

Protocol deviations will be summarized by type in each treatment group for the Full Analysis set. All protocol deviations will be listed.

8.4 Investigational Product Administration

8.4.1 Extent of Exposure

Exposure duration to the investigational product for the full analysis set will be summarized for KRN23 therapy and the active control (oral phosphate/active vitamin D) separately.

The total dose and prescribed weight-based dose of KRN23 will be summarized for the KRN23 group. The dosing information for oral phosphate and active vitamin D medications will be provided for the active control group.

8.4.2 Measurement of Treatment Compliance

For KRN23 group, the number of dosing and cumulative dose per subject administered will be summarized. The number of missed dosing will also be summarized.

For active control group, the number of full days with missed oral phosphate or active vitamin D medication will be summarized. The main reason for missed medication will also be summarized.

Descriptive statistics for investigational product compliance will be presented by treatment group for the Full Analysis Set by study visit and overall 40 and 64-week treatment period.

8.4.3 Demographic and Baseline Characteristics

Demographic parameters (age, age subgroup of < 5 years vs ≥ 5 years, sex, race, ethnicity, region, weight, recumbent length/standing height, body mass index [BMI]) and other baseline characteristics (general and disease-specific medical history, conventional therapy duration, age when conventional therapy initiated, XLH treatment history, PHEX mutation, RSS scores, RSS total score subgroup of ≤ 2.5 vs > 2.5, XLH biochemical parameters, renal ultrasound scores) will be summarized descriptively by treatment group on the Full Analysis Set.

8.4.4 Prior and Concomitant Medication

Prior medication is defined as any medication started before the date of the first dose of investigational product (medication start date prior to the first dose date).

Concomitant medication is defined as any medication taken on or after the date of the first dose of investigational product [medication end date on or after first dose date (or ongoing), and medication start date prior or on the last dose date]. Any concomitant medications started after the date of the last dose of investigational product will not be presented in the summary tables but will be included in the subject data listings.

Baseline medication is defined as any medication taken on the first dose date [medication end date on or after first dose date (or ongoing), and medication start date prior or on the first dose date].

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug Dictionary. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

8.5 Efficacy Analysis

The efficacy analyses will be based on the Full Analysis Set.

8.5.1 Generalized Estimating Equations Model (GEE)

For repeated measures such as clinical outcomes, the GEE approach will be used for assessing the change over time. The GEE model will include treatment group, study visit and interaction between treatment group and study visit as categorical variables, stratification factors of baseline RSS total score and age will also be included, unless specified otherwise. To model the covariance structure, the exchangeable covariance matrix will be selected initially. If the exchangeable covariance structure leads to non-convergence, independence covariance structure will be applied. Model based estimates of the changes from baseline, SE and corresponding 95% confidence intervals (CIs) will also be provided along with P- values for assessing statistical significance. Other independent variables will be specified in the analysis section for each individual endpoints.

8.5.2 Sensitivity Analysis for Missing Data

Sensitivity analyses to assess the robustness of the primary analysis result to missing data will be conducted on RSS and RGI-C endpoints. Theses may include, but are not limited to:

- Last Observation Carried Forward (LOCF): the last non-missing post-baseline observation will be carried forward to the corresponding endpoint for evaluation. If no post-baseline observation is available, the baseline observation will be used for evaluation; if no baseline is available, the LOCF approach will not be performed.
- Multiple imputation (MI): the PROC MI procedure in SAS will be utilized to impute missing values using a Markov Chain Monte Carlo (MCMC) approach by 100 times. The imputed dataset will be analyzed by the ANCOVA model at Week 40 analysis or GEE model at Week 64 analysis, the results will be combined using the PROC MIANALYZE procedure in SAS. Baseline RSS total score, treatment group and baseline age stratification factor will be used as predictor variables in the imputation. Other variables such as change from baseline in ALP may also be considered as a predictor variable.

8.5.3 Analysis of Primary Efficacy Endpoint

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

At Week 40 analysis, an Analysis of Covariance (ANCOVA) model will be applied on the RGI-C global score with treatment group and baseline age stratification factor as independent variables, baseline RSS total score as a continuous covariate. The stratification factor of baseline RSS total score will not be included in the model.

For RGI-C knee, wrist and lower limb deformity scores, a similar ANCOVA model with be applied with baseline RSS wrist score used in RGI-C wrist score modeling and baseline RSS knee score used in RGI-C knee score and lower limb deformity score modeling.

At Week 64 analysis, RGI-C (global, knee, wrist and long leg) scores over time including Week 40 will be analyzed using GEE model that includes treatment group, visit, treatment group by visit interaction, baseline age stratification factor as independent variables, baseline RSS total score as a continuous covariate. The stratification factor of baseline RSS total score will not be included in the model.

The estimated difference of RGI-C between KRN23 treatment and active control group will be provided along with 95% CI and p-value. The estimated RGI-C score and its 95% CI within individual treatment groups will also be provided. Descriptive statistics for all RGI-C scores will be provided in both continuous and categorical summary. Summary of abnormality at baseline and change in abnormality at Week 40 and Week 64 will also be provided. A listing of RGI-C scores will be provided for each subject. Graphic displays of RGI-C scores will also be provided over time by treatment group.

If subjects receive orthopedic surgeries before week 40 X-ray visit, a sensitivity analysis will be performed by excluding these subjects from week 40 and week 64 RGI-C analyses.
If subjects receive orthopedic surgery after week 40 but before week 64 X-ray visit, a sensitivity analysis will be performed at week 64 RGI-C analysis, where the week 40 RGI-C data will be used to impute Week 64 data for these subjects.

8.5.4 Analysis of Secondary Efficacy Endpoint(s)

8.5.4.1 RGI-C responder

The proportion of RGI-C responder (subjects with a mean RGI-C global score $\geq +2.0$) will be summarized for each treatment group at Week 40 and Week 64. At Week 40 analysis, a logistic regression model will be applied with treatment group and baseline age stratification factor as independent variables, baseline RSS total score as a continuous covariate.
The stratification factor of baseline RSS total score will not be included in the model.
At Week 64 analysis, a similar repeated measures logistic regression model will be applied including both Week 40 and Week 64 data as dependent variable, treatment group, study visit, interaction between treatment group and study visit, and baseline age stratification

factor as independent variables, baseline RSS total score as a continuous covariate. The stratification factor of baseline RSS total score will not be included in the model. The odds ratio comparing KRN23 treatment to conventional therapy will be provided along with 95% CI and p-value. The estimated responder rate and its 95% CI within individual treatment groups will also be provided.

8.5.4.2 RSS scores

The change from baseline in RSS (total, knee and wrist) scores over time will be analyzed using the same method as that of the RGI-C score. At Week 40 analysis, an ANCOVA model will be applied with treatment group and baseline age stratification factor as independent variables, baseline RSS total score as a continuous covariate. The stratification factor of baseline RSS total score will not be included in the model. At Week 64 analysis, a GEE model will be used with all RSS change from baseline data as dependent variable, treatment group, study visit, interaction between treatment group and study visit, and baseline age stratification factor as independent variables, baseline RSS total score as a continuous covariate. The stratification factor of baseline RSS total score will not be included in the model. The estimated different between KRN23 treatment and active control group will be provided along with 95% CI and p-value. The estimated change from baseline in RSS score and its 95% CI within individual treatment groups will also be provided.

Descriptive statistics for all RSS scores and change from baseline in RSS score will be provided in both continuous and categorical summary. A listing of RSS scores for each subject will be provided. Graphic displays of RSS scores over time will also be provided by treatment group.

8.5.4.3 Growth

Growth in standing height/recumbent length and weight will be summarized over time in observed value, Z-score and percentile. Individual subject growth curves will be plotted with CDC growth charts as reference.

For standing height/recumbent length Z-score, the GEE model will be used to assess the difference between treatment groups. Treatment group and baseline RSS stratification factor will be included as independent variables, baseline age and height/length Z score will be included as continuous covariates. The mid-parental height Z score will be calculated by averaging the height Z scores of parents and may also be considered as a covariate in the model. The stratification factor of baseline age will not be included in the model. The estimated different between KRN23 treatment and active control group will be provided along with 95% CI and p-value. The estimated change from baseline and its 95% CI within individual treatment groups will also be provided.

The growth velocity defined in Section 5.7.3 will be estimated for selected pre-treatment period (e.g. within 1.5 years prior to baseline) and post-treatment period from baseline to Week 40 and from baseline to Week 64 respectively for each subject. If a subject has both

recumbent length and standing height measurements from 1.5 years prior to baseline to post-baseline period, the recumbent length will be subtracted by 0.8 cm before pooling with standing height data (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

An ANCOVA model will be applied on the change in growth velocity Z score from baseline to Week 40 or Week 64 to assess the difference between treatment groups. Treatment group and baseline RSS total score stratification factor will be included as independent variables, baseline Z score and age will be included as continuous covariates. The stratification factor of baseline age will not be included in the model. The estimated different between KRN23 treatment and active control group will be provided along with 95% CI and p-value.
The estimated change from baseline and its 95% CI within individual treatment groups will also be provided.

In addition, descriptive statistics of sitting height during the post-treatment period and its respective change from baseline will be provided by study visits. A listing of standing height/recumbent length and the respective Z score, percentile, growth velocity and sitting height will be provided.

8.5.4.4 Walking Ability (6MWT)

For subjects ≥ 5 years of age at the screening visit, summary statistics of total distance walked and percent of predicted 6MWT will be tabulated for each study visit for the observed measures and their respective change from baseline based on the Full Analysis Subset (Baseline age ≥ 5 years). Change from baseline of total distance walked and percent of predicted 6MWT will be assessed using the GEE approach as outlined in Section 8.5.1 with baseline measures and baseline RSS total score stratification factor included as independent variables.

A listing containing the 6MWT details will be provided. Graphs showing change in total distance walked during 6MWT and percent of predicted 6MWT will be provided by treatment group.

8.5.4.5 Patient Reported Outcomes Measurement Information System (PROMIS)

For subjects aged ≥ 5 years at screening visit, summaries statistics of Pediatric Pain Interference, Physical Function Mobility and Fatigue domain scores will be reported by study visit for both observed measures and their respective change from baseline based on the Full Analysis Subset (Baseline age ≥ 5 years). Change from baseline values over time will be assessed to compare KRN23 therapy with the active control (oral phosphate/active vitamin D) using the GEE approach as outlined in Section 8.5.1 with baseline measures and baseline RSS total score stratification factor included as independent variables.

A listing of Pediatric Pain Interference, Physical Function Mobility and Fatigue domain scores will be provided.

Graphs showing change in Pediatric Pain Interference, Physical Function Mobility and Fatigue domain scores will be provided by treatment group. Cumulative Distribution Function (CDF) of change from baseline in each domain score will also be plotted by treatment group.

8.5.4.6 Faces Pain Scale – Revised (FPS-R)

For subjects aged ≥ 5 years at screening visit, summaries statistics of FPS-R will be reported by study visit for both observed measures and their respective change from baseline based on the Full Analysis Subset (Baseline age ≥ 5 years). Change from baseline of FPS-R over time will be assessed to compare KRN23 therapy with the active control (oral phosphate/active vitamin D) using the GEE approach as outlined in Section 8.5.1 with baseline measures and baseline RSS total score stratification factor included as independent variables.

Descriptive statistics for FPS-R scores as well as it change from baseline will be provided in both continuous and categorical summary. A listing of FPS-R will be provided. Graphs showing change in FPS-R will be provided by treatment group.

8.5.4.7 PD Analysis

The PD parameters will include serum phosphorus, TmP/GFR, serum $1,25(OH)_2D$, TRP, and ALP. All PD analyses will be performed on the PD Analysis Set, unless stated otherwise.

Descriptive statistics of PD parameters and their respective change from baseline and percentage change from baseline will be tabulated by treatment group at each study visit.

The change in serum phosphorus from baseline to mean post-baseline values (average of Week 1, 4, 8, 16, 24, 32 and 40 serum phosphorus for Week 40 analysis and Week 1, 4, 8, 16, 24, 32, 40, 52 and 64 serum phosphorus for Week 64 analysis) will be analyzed using an ANCOVA model. Treatment group, baseline age and RSS total score stratification factors will be included as independent variables, baseline serum phosphorus will be included as a continuous covariate. The estimated difference between KRN23 treatment and active control group will be provided along with 95% CI and p-value. The estimated change from baseline within individual treatment groups will also be provided.

PD endpoints at all scheduled visits will be assessed using the GEE approach as outlined in Section 8.5.1 with change from baseline value as dependent variable, baseline measures and baseline age and RSS total score stratification factors included as independent variables.

The proportion of subjects achieving the normal range (3.2-6.1 mg/dL) will be reported by treatment group at each study visit. Similarly, proportion of subjects achieving TmP/GFR within the normal range (2.6 – 4.4 mg/dL) will be reported by treatment group at each study visit.

A listing containing PD parameters such as serum phosphate level, serum $1,25(OH)_2D$, TmP/GFR, TRP, and ALP will be provided for each subject.

Graphs showing the change over time in PD parameters for both observed measure and the respective change from baseline will be provided by treatment group.

8.6 Analysis of Other Efficacy Endpoint(s)

8.6.1 Health-related Quality of Life (SF-10 for Children Health Survey)

Descriptive summary statistics of the PHS-10 and PSS-10 scores will be reported by study visit for both observed measures and their respective change from baseline based on the Full Analysis Subset (Baseline Age ≥5 years). A listing of PHS-10 and PSS-10 scores will be provided.

8.6.2 Dental Assessment

The number of dental events (dental abscess, dental cavities, tooth extraction, root canal and gingivitis) will be summarized by treatment group at each study visit. A listing of dental events will be provided for each subject.

8.7 Pharmacokinetics

The descriptive statistics for serum KRN23 will be tabulated and the listing of serum KRN23 will be provided based on the PK analysis set.

8.8 Safety Analysis

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

8.8.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose of investigational product and was not present prior to the first dose, or it was present before the first dose but increased in severity during the study.

Subject incidence of TEAEs will be tabulated as the following:

- Summary of TEAEs by treatment group
- TEAEs by SOC and PT (preferred term) by treatment group (sorted by descending frequency by SOC and PT)

- Related TEAEs by SOC and PT by treatment group (sorted by descending frequency by SOC and PT) or TEAE by greatest relationship, SOC and PT by treatment group
- Serious TEAEs by SOC and PT by treatment group (sorted by descending frequency by SOC and PT).
- Serious and Related TEAEs by SOC and PT by treatment group (sorted by descending frequency by SOC and PT).
- Grade 3 or 4 TEAEs by SOC and PT by treatment group (sorted by descending frequency by SOC and PT). or TEAE by greatest severity, treatment group, SOC and PT
- Deaths by SOC and PT by treatment group (sorted by descending frequency by SOC and PT).
- TEAEs leading to discontinuation of study by SOC and PT by treatment group (sorted by descending frequency by SOC and PT).
- TEAEs leading to discontinuation of treatment by SOC and PT by treatment group (sorted by descending frequency by SOC and PT).
- TEAEs by PT by treatment group (sorted by descending frequency of PT)
- Serious TEAEs by PT by treatment group (sorted by descending frequency of PT)
- Related TEAEs by PT by treatment group (sorted by descending frequency of PT)

Subject incidence for each type of events to monitor will be tabulated as the following:

- By PT by treatment group
- By PT and greatest reported severity by treatment group
- By PT and relationship to study drug by treatment group

Detailed listings for all AEs, serious TEAEs, AEs leading to the discontinuation of study, AEs leading to the discontinuation of treatment, and death will also be generated.

The severity will be based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = Death.

8.8.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from the baseline values at each assessment time point will be presented by treatment group for laboratory parameters listed in Appendix 2. Shift table for iPTH at each scheduled visit will be provided to assess to the normality over time. Listings for all clinical laboratory parameters and all abnormal laboratory parameters will be provided for each subject.

8.8.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, systolic and diastolic blood pressure percentiles, pulse rate, and weight) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

The blood pressure will be summarized by study visit in mmHg and percentile to assess the blood pressure change over time.

Heart rate and heart rate percentile category will be tabulated over time by treatment group.

8.8.4 Concomitant Medications

Each medication will be coded to a preferred name and an Anatomic Therapeutic Classification (ATC) code using WHODrug. The number and percentage of subjects taking each concomitant medication will be displayed by medication class (anatomical classification) and preferred name for each treatment group. This display will be created for the safety analysis set. A concomitant medication listing will also be made. Prior medications, e.g. medications that were stopped before the first dose of study therapy, will also be listed.

8.8.5 Physical Examination

Physical exam results will include the assessment of general appearance; head, eyes, ears, nose, and throat (HEENT); the cardiovascular, dermatology, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, neurological systems. The number and percentage of subjects with Normal/Abnormal assessment for each body system will be summarized by visit and treatment group. All physical examination assessments will be listed.

8.8.6 Pregnancy Test

Subject level listing for pregnancy test results will be created for those who had positive pregnancy test.

8.8.7 Renal Ultrasound

Renal ultrasound will be conducted with findings of nephrocalcinosis graded on a 5-point scale by a central reader. These results will be summarized by time point and presented by treatment group. Furthermore, a grade shift table summarizing changes from baseline by time point will also be created.

A listing of renal ultrasound/nephrocalcinosis scores will also be provided.

8.8.8 ECG

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTc) and changes from baseline values at each assessment time point to the end of study will be presented by treatment group. The QTc will be calculated using both the Bazett and Fridericia corrections.

ECG parameters will be summarized by study visit, by the maximum post-baseline value, change from baseline and maximum change from baseline. Shift from baseline to post-baseline visits in overall ECG assessment (normal or abnormal) will also be provided.

A listing of all ECG parameters including the overall assessment will also be created.

8.8.9 ECHO

ECHO data will be read locally to assess for evidence of ectopic mineralization in the heart and aorta and to evaluate for signs of LVH or cardiac dysfunction. Descriptive statistics for the various continuous ECHO measurements will be reported by treatment group at the scheduled time points and will include the change from baseline value. The summary of the descriptive statistics will be displayed by visit. Shift table in presence of ectopic mineralization and aortic valve regurgitation from baseline to post-baseline visits will be provided.

8.8.10 Anti-KRN23 Antibody Testing

Anti-KRN23 antibody will be summarized descriptively by treatment group. Shift table from baseline to post-baseline visit will also be provided.

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10 APPENDICES

APPENDIX 1 SUMMARY OF STATISTICAL ANALYSIS APPROACHES ON EFFICACY ENDPOINTS

Primary Efficacy Endpoint

Endpoint	Scale	Analysis populations	Comparisons	Data Time Points	Week 40 Analysis
RGI-C global score	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40	ANCOVA

Key Secondary Efficacy Endpoint(s)

Endpoints	Scale	Analysis populations	Comparisons	Data Time Points	Week 40 Analysis	Week 64 Analysis
RGI-C long leg score	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40, Week 64	ANCOVA	GEE
Change from baseline in Recumbent length/standing height Z score	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 24, Week 40, Week 64	GEE	GEE
Change from baseline in RSS total score	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40, Week 64	ANCOVA	GEE
Change in serum phosphorus from baseline to mean post-baseline values	Continuous	PD Analysis Set	KRN23 vs SOC	Baseline, Week 1, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 52, and Week 64	ANCOVA	ANCOVA
Change from baseline in ALP	Continuous	PD Analysis Set	KRN23 vs SOC	Baseline, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 52 and Week 64	GEE	GEE

Other Secondary Efficacy Endpoint(s)

Endpoints	Scale	Analysis populations	Comparisons	Data Time Points	Week 40 Analysis	Week 64 Analysis
RGI-C responder	Binary	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40, Week 64	Logistic Regression	Repeated Measures Logistic Regression
RGI-C knee and wrist scores	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40, Week 64	ANCOVA	GEE
Change from baseline in RSS knee and wrist scores	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40, Week 64	ANCOVA	GEE
Change from baseline in Growth velocity Z score	Continuous	Full Analysis Set	KRN23 vs SOC	Baseline, Week 40, Week 64	ANCOVA	ANCOVA
Change from baseline in PROMIS pain, fatigue and physical function scores	Continuous	Full Analysis Subset (Baseline age ≥ 5 years)	KRN23 vs SOC	Baseline, Week 24, Week 40, Week 64	GEE	GEE
Change from baseline in FPS-R score	Continuous	Full Analysis Subset (Baseline age ≥ 5 years)	KRN23 vs SOC	Baseline, Week 24, Week 40, Week 64	GEE	GEE
Change from baseline in 6MWT total distance and percent of predicted normal	Continuous	Full Analysis Subset (Baseline age ≥ 5 years)	KRN23 vs SOC	Baseline, Week 24, Week 40, Week 64	GEE	GEE
Change from baseline in PD parameters	Continuous	PD Analysis Set	KRN23 vs SOC	Baseline, Week 1, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 52, and Week 64 (whichever applies)	GEE	GEE

Note: Week 64 GEE analysis will include the result for Week 40 and other study visits.

APPENDIX 2 CLINICAL LABORATORY ASSESSMENTS FOR SAFETY

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

* Also designated as PD/efficacy parameter

APPENDIX 3 SCHEDULE OF EVENTS

Table 10.1: Schedule of Events – Treatment Period Weeks 1-30

	Screening/ Baseline[1]		Treatment Period															
VISIT ID	**SV**	**BL V1**	**V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**HH V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**HH V13**	**V14**	**HH V15**	**HH V16**	**HH V17**
TIME (WEEK/DAY)	**W-8 to BL**	**W0**	**W 1**	**W2**	**W4**	**W6**	**W 8**	**W1 0**	**W1 2**	**W1 4**	**W16**	**W18**	**W20**	**W22**	**W2 4**	**W2 6**	**W28**	**W30**
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Medical History, Demographics	X																	
Parents' Heights	X																	
Tanner Staging	X																	
PHEX mutation analysis[2]	X																	
Randomization		X																
KRN23 Administration[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Active Control[3,4]		Administered at the discretion of the treating Investigator																
EFFICACY MEASURES																		
Growth (standing height [or length], sitting height)[5]		X													X			
Growth velocity		X																
Bilateral AP knee x-rays[1, 6, 7]	X																	
Bilateral PA hand/wrist x-rays[1,6]	X																	
Standing long leg x-ray[7]		X																
6MWT[8] (aged ≥ 5 years at Screening Visit)	X	X													X			

	Screening/ Baseline[1]		Treatment Period															
VISIT ID	**SV**	**BL V1**	**V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**HH V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**HH V13**	**V14**	**HH V15**	**HH V16**	**HH V17**
TIME (WEEK/DAY)	**W-8 to BL**	**W0**	**W 1**	**W2**	**W4**	**W6**	**W 8**	**W1 0**	**W1 2**	**W1 4**	**W16**	**W18**	**W20**	**W22**	**W2 4**	**W2 6**	**W28**	**W30**
PROMIS Pediatric Pain Interference, Fatigue and Physical Function Mobility (aged ≥ 5 years at Screening Visit)[9]		X													X			
Faces Pain Scale – Revised (aged ≥ 5years at Screening Visit)		X													X			
SF-10 (aged ≥ 5 years at Screening Visit)[10]		X													X			
PD MEASURES																		
Serum Phosphorus[11]		X	X	X	X		X		X		X				X			
Serum $1,25(OH)_2D$[11]		X	X	X	X		X		X		X				X			
ALP[12]		X									X				X			
PHARMACOKINETICS																		
Serum Pre-dose KRN23			X	X	X		X				X				X			
SAFETY MEASURES																		
Vital Signs[13]	X	X			X		X				X				X			
Weight[14]	X	X	X		X		X				X				X			
Physical Examination	X	X					X				X				X			
Concomitant Medication[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound[1]	X														X			
ECG[1]		X													X			

	Screening/ Baseline[1]		Treatment Period															
VISIT ID	**SV**	**BL V1**	**V2**	**HH V3**	**V4**	**HH V5**	**V6**	**HH V7**	**HH V8**	**HH V9**	**V10**	**HH V11**	**HH V12**	**HH V13**	**V14**	**HH V15**	**HH V16**	**HH V17**
TIME (WEEK/DAY)	**W-8 to BL**	**W0**	**W 1**	**W2**	**W4**	**W6**	**W 8**	**W1 0**	**W1 2**	**W1 4**	**W16**	**W18**	**W20**	**W22**	**W2 4**	**W2 6**	**W28**	**W30**
ECHO[1] (ages ≥ 5 years)		X																
Chemistry[16], Hematology, Urinalysis[11]	X	X			X		X				X				X			
Serum 25(OH)D	X	X		X							X							
Serum Calcium[11]	X	X		X	X		X				X				X			
Serum Creatinine[11]	X	X		X	X		X				X				X			
Serum iPTH	X	X			X		X				X				X			
Serum iFGF23		X													X			
2-hr Urine[11,17]		X			X		X				X				X			
24-hr Urine[11,17] (aged ≥ 5 years)		X					X				X				X			
Dental assessment[18]		X			X		X				X				X			
Immunogenicity (HAHA)[19]		X			X		X				X				X			
Urine Pregnancy Test[20]	X	X			X						X				X			

See footnotes after Table 10.2

Table 10.2: Schedule of Events – Treatment Period Weeks 32-64

	Treatment Period																		Safety Visit[21]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**	**V36**
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ ET**	**W76**
Tanner staging						X												X	
KRN23 Administration[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Active Control[3,4]	Administered at the discretion of the treating Investigator																		
EFFICACY MEASURES																			
Growth (standing height [or length], sitting height)[5]						X												X	
Growth velocity						X												X	
Bilateral AP knee x-rays[1, 6, 7]						X												X	
Bilateral PA hand/wrist x-rays[1, 6]						X												X	
Standing long leg x-ray[7]						X												X	
6MWT[8] (aged ≥5 years at Screening Visit)						X												X	

	Treatment Period																		Safety Visit[21]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**	**V36**
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ ET**	**W76**
PROMIS Pediatric Pain Interference, Fatigue and Physical Function Mobility (aged ≥5 years at Screening Visit)[9]						X												X	
Faces Pain Scale – Revised (FPS-R) (aged ≥5 years at Screening Visit)						X												X	
SF-10 (aged ≥5 years at Screening Visit)[10]						X												X	
PD MEASURES																			
Serum Phosphorus[11]	X	X				X						X						X	X
Serum $1,25(OH)_2D$[11]	X	X				X						X						X	X
ALP[12]						X												X	
PHARMACOKINETICS																			
Serum Pre-dose KRN23		X				X												X	

	Treatment Period																		Safety Visit[21]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**	**V36**
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ ET**	**W76**
SAFETY MEASURES																			
Vital Signs[13]	X					X						X						X	X
Weight[14]	X					X						X						X	
Physical Examination	X					X						X						X	X
Concomitant Medication[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound[1]						X												X	
ECG[1]						X												X	
ECHO[1] (ages ≥5 years)						X												X	
Chemistry[16], Hematology, Urinalysis[11]	X					X						X						X	X
Serum 25(OH)D						X												X	
Serum Calcium[11]	X					X						X						X	X
Serum Creatinine[11]	X					X						X						X	
Serum iPTH	X					X						X						X	
Serum iFGF23																		X	
2-hr Urine[11,17]	X					X						X						X	

	Treatment Period																		Safety Visit[21]
VISIT ID	**V18**	**HH V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**HH V27**	**HH V28**	**V29**	**HH V30**	**HH V31**	**HH V32**	**HH V33**	**HH V34**	**V35**	**V36**
TIME (WEEK/DAY)	**W32**	**W33**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64/ ET**	**W76**
24-hr Urine[11,17] (aged ≥5 years)	X					X						X						X	
Dental assessment[18]	X					X						X						X	X
Immunogenicity (HAHA)[19]						X												X	
Urine Pregnancy Test[20]						X												X	

1. Renal ultrasound, ECG, ECHO, and x-rays may be performed within ± 3 days of clinic visit to accommodate scheduling availability. All Screening/Baseline assessments and inclusion/exclusion criteria must be satisfied prior to randomization and dosing. The Screening Visit window may be up to 8 weeks for *PHEX* mutation analysis and washout of oral phosphate and active vitamin D therapy.
2. *PHEX* mutation analysis will be performed in all subjects. Potential subjects with prior confirmation of a *PHEX* mutation or variant of uncertain significance in either self or a family member with appropriate X-linked inheritance who meet other eligibility requirements may enroll before screening *PHEX* mutation results are returned.
3. Patients will be randomized 1:1 to either the KRN23 treatment arm or the active control arm (oral phosphate/active vitamin D therapy).
4. Active control will be administered at the discretion of the treating Investigator. Subjects randomized to the active control arm will visit the clinic at Weeks 1, 4, 8, 16, 24, 32, 40, 52, and 64.
5. In subjects < 2 years old, length will be measured instead of standing height.
6. Screening results will be treated as Baseline data.
7. AP knee and PA hand/wrist x-rays will be acquired for all subjects and standing long leg x-rays will be acquired for all qualifying subjects.
8. 6MWT will be conducted only for subjects ≥5 years of age at the Screening Visit. If a subject is < 5 years of age at the Screening Visit, the 6MWT will not be assessed when the subject is over 5 years of age during the post-baseline visits.
9. For the PROMIS Pediatric Pain Interference, Fatigue, and Physical Function Mobility scales, the parent or legal guardian will complete a Parent/Legal Guardian form for subjects ages 5 to < 8 years of age at the Screening Visit. Subjects ≥ 8 years of age at the Screening Visit will complete a pediatric self-report form. Parent/Legal Guardian forms will be used for the duration of the study for subjects < 8 years of age at the Screening Visit who had a baseline assessment, even when a subject turns 8 during the study.
10. If a subject is < 5 years of age at the Screening Visit and therefore has no baseline data, SF-10 will not be administered even when the subject turns 5 during the study.

11. Blood and urine to be collected after a minimum overnight fasting time of 4 hours and prior to drug administration (if applicable). Record fasting duration on CRF. Serum phosphorus may be collected as an unscheduled lab if necessary.
12. Alkaline phosphatase (ALP)
13. Vital sign measurements consist of seated systolic/diastolic blood pressure (BP) measured in millimeters of mercury (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Vital signs will be obtained at the beginning of each visit before any additional assessments are completed and after the subject has rested for 5 minutes. BP measurements will only be obtained at clinic visits and only for subjects ≥3 years of age. At the Screening Visit and at Baseline, two sets of three BP measurements will be obtained – the first set will be done at the beginning of the visit and the second set at end of the visit after all site procedures are completed. BP measurements should be done after the subject has rested for 5 minutes and a second and third BP measurement should be obtained, each performed 30 seconds apart.
14. Weight from the previous in-clinic visit will be used to calculate KRN23 dose.
15. At every Home Health visit for subjects in the KRN23 treatment arm, all subjects randomized to the active control arm will receive a phone call to assess adverse events and concomitant medications. Home Health visits are not applicable to subjects in Japan or Korea.
16. Serum chemistry panels may include PD parameters (i.e. serum phosphorus and ALP), and safety parameters of interest (i.e. calcium) to avoid duplication of testing.
17. Both 2-hr and 24-hr urine will be used for measurements of urinary phosphorus, creatinine, lipase, amylase, and calcium; 2-hr urine will be used for the derivation of TmP/GFR and TRP. For subjects <5 years of age, spot urine may be collected in place of the 2-hr urine samples for measurements of urinary calcium, phosphorus, and creatine.
18. Separate dental assessments are not required and will be captured under AEs as dental issues arise. At each clinic visit, an oral examination will be conducted and subjects will be proactively asked if they had any dental events from dental caries, delay in eruption of the dentition, enamel hypoplasia, dental abscesses, and gingivitis.
19. HAHA assessment will be performed only for subjects randomized to KRN23. If development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional timepoints on a case by case basis.
20. Pregnancy testing will be performed on any female subject of childbearing potential who has experienced menarche.
21. An additional safety visit will take place 12 weeks ±1 week after the date of the last study drug administration for those subjects who discontinue treatment, or 12 weeks ±1 week after the Week 64 visit for subjects who complete the study and choose not to enroll in an extension study. This visit is not required for subjects who are eligible and choose to take part in an extension study. Every reasonable effort should be made to have required subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic for the final safety visit will be given the option of providing blood and urine samples as part of a Home Health visit.

APPENDIX 4 RSS DATA COLLECTION FORM

WRIST

GRADE DEFINITIONS FOR RADIUS AND ULNA *based on radiographic features below*	
0	Normal growth plate without changes of rickets
0.5	Lucency of metaphyseal margin without fraying or irregularity
1	Widened growth plate, irregularity of metaphyseal margin, but without concave cupping
1.5	Partial metaphyseal concavity or incomplete fraying of metaphyseal margin
2	Metaphyseal concavity with fraying of margins

Grade Radius *circle 1 number*	RADIUS	0	0.5	1	1.5	2
Grade Ulna *circle 1 number*	ULNA	0	0.5	1	1.5	2

Radius Grade ☐ + Ulna Grade ☐ = TOTAL POINTS FOR WRIST *(max of 4 points possible)* ☐ WRIST TOTAL

KNEE

GRADE DEFINITIONS FOR FEMUR AND TIBIA *based on the degree of lucency and widening of zone of provisional calcification*	
0	Normal growth plate without changes of rickets
1	Partial lucency, smooth margin of metaphysis visible
2	Partial lucency, smooth margin of metaphysis NOT visible
3	Complete lucency, epiphysis appears widely separated from distal metaphysis

Grade Femur *circle 1 number*	FEMUR	0	1	2	3
Grade Tibia *circle 1 number*	TIBIA	0	1	2	3

Determine multiplier for FEMUR AND TIBIA	
0.5	≤ one condyle or plateau affected
1	Two condyles or plateaus affected

FEMUR multiplier *circle 1 number*	0.5	1
TIBIA multiplier *circle 1 number*	0.5	1

Femur Grade ☐ x Multiplier ☐ + Tibia Grade ☐ x Multiplier ☐ = Total points for KNEE *(max of 6 points possible)* ☐ KNEE TOTAL

APPENDIX 5 RGI-C DATA COLLECTION FORM

REGIONAL RATING OF RICKETS

How would you rate the change in XLH-related rickets in the HANDS/WRISTS? *Circle one*

−3	−2	−1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

Identify abnormalities in image A on the left and then rate any change seen in image B on the right compared to image A

PA HAND/WRIST SINGLE ABNORMALITY RATING

BILATERAL PA RADIUS	NOT in "A"	DECREASED	UNCHANGED	INCREASED
Metaphyseal lucency	☐	☐	☐	☐
Metaphyseal/epiphyseal separation	☐	☐	☐	☐
Metaphyseal fraying	☐	☐	☐	☐
Metaphyseal concavity	☐	☐	☐	☐

BILATERAL PA ULNA	NOT in "A"	DECREASED	UNCHANGED	INCREASED
Metaphyseal lucency	☐	☐	☐	☐
Metaphyseal/epiphyseal separation	☐	☐	☐	☐
Metaphyseal fraying	☐	☐	☐	☐
Metaphyseal concavity	☐	☐	☐	☐

REGIONAL RATING OF RICKETS

How would you rate the change in XLH-related rickets in the KNEES? *Circle one*

−3	−2	−1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

Identify abnormalities in image A on the left and then rate any change seen in image B on the right compared to image A

AP KNEES SINGLE ABNORMALITY RATING

BILATERAL AP FEMUR	NOT in "A"	DECREASED	UNCHANGED	INCREASED
Metaphyseal lucency	☐	☐	☐	☐
Metaphyseal/epiphyseal separation	☐	☐	☐	☐
Metaphyseal fraying	☐	☐	☐	☐
Metaphyseal concavity	☐	☐	☐	☐

AP KNEES SINGLE ABNORMALITY RATING

BILATERAL AP TIBIA	NOT in "A"	DECREASED	UNCHANGED	INCREASED
Metaphyseal lucency	☐	☐	☐	☐
Metaphyseal/epiphyseal separation	☐	☐	☐	☐
Metaphyseal fraying	☐	☐	☐	☐
Metaphyseal concavity	☐	☐	☐	☐

BILATERAL AP FIBULA	NOT in "A"	DECREASED	UNCHANGED	INCREASED
Metaphyseal lucency	☐	☐	☐	☐
Metaphyseal/epiphyseal separation	☐	☐	☐	☐
Metaphyseal fraying	☐	☐	☐	☐
Metaphyseal concavity	☐	☐	☐	☐

GLOBAL RATING OF RICKETS

How would you rate the change in XLH-related rickets?

The **B** images on the right as compared to **A** images on the left show *circle one*

–3	–2	–1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

RATING OF LOWER LIMB DEFORMITY

How would you rate the change in XLH-related lower limb deformity? *Circle one*

–3	–2	–1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

Identify abnormalities in image **A** on the left and then rate any change seen in image **B** on the right compared to image **A**

SINGLE ABNORMALITY RATING

STANDING LONG LEG	NOT in "A"	VARUS	VALGUS	DECREASED	UNCHANGED	INCREASED
L Tibia	☐	☐	☐	☐	☐	☐
R Tibia	☐	☐	☐	☐	☐	☐
L Fibula	☐	☐	☐	☐	☐	☐
R Fibula	☐	☐	☐	☐	☐	☐
L Femur	☐	☐	☐	☐	☐	☐
R Femur	☐	☐	☐	☐	☐	☐

APPENDIX 6 GROWTH VELOCITY MEAN AND SD VALUES BY AGE AND GENDER

	MALES		FEMALES	
Age (years)	Mean	SD	Mean	SD
2.5	8.3	1.3	8.6	1.3
3	7.8	1.2	8.1	1.2
3.5	7.4	1.1	7.6	1.2
4	7.1	1.1	7.2	1.1
4.5	6.8	1.0	6.8	1.0
5	6.6	1.0	6.6	1.0
5.5	6.4	1.0	6.4	0.9
6	6.2	0.9	6.2	0.9
6.5	6.0	0.9	6.1	0.9
7	5.9	0.9	6.0	0.8
7.5	5.8	0.9	5.9	0.8
8	5.6	0.8	5.8	0.8
8.5	5.4	0.8	5.7	0.8
9	5.3	0.8	5.8	0.8
9.5	5.2	0.7	5.8	0.8
10	5.1	0.7	6.2	0.9
10.5	5.1	0.7	6.8	1.1
11	5.2	0.8	7.7	1.1
11.5	5.3	0.7	8.3	1.1
12	5.7	0.8	7.3	1.0
12.5	6.7	0.9	5.9	1.1
13	8.6	1.2	4.3	1.0
13.5	9.5	1.2	2.9	0.7
14	8.4	1.2	1.8	0.7
14.5	6.5	1.2	1.0	0.5
15	4.7	1.1		
15.5	3.3	1.0		
16	2.2	0.9		
16.5	1.5	0.8		
17	0.9	0.5		
17.5	0.5	0.4		

APPENDIX 7 BLOOD PRESSURE PERCENTILES BY GENDER, AGE AND HEIGHT (NHLBI 2005)

Computation of Blood Pressure Percentiles for Arbitrary Sex, Age, and Height

■ *To compute the systolic blood pressure (SBP) percentile of a boy who is age y years and height h inches with SBP = x mmHg:*

1. Refer to the most recent CDC growth charts, which are available online, and convert the height of h inches to a height Z-score relative to boys of the same age; this is denoted by Zht.

2. Compute the expected SBP (μ) for boys of age y years and height h inches given by

$$\mu = \alpha + \sum_{j=1}^{4} \beta_j (y\text{-}10)^j + \sum_{k=1}^{4} \gamma_k (Zht)^k$$

where α, $\beta_1 \ldots, \beta_4$ and $\gamma_1 \ldots, \gamma_4$ are given in the 3rd column of appendix table B–1.

3. Then convert the boy's observed SBP to a Z-score (Zbp) given by

$$Zbp = (x - \mu)/\sigma$$

where σ is given in the 3rd column of appendix table B–1.

4. To convert the bp Z-score to a percentile (P), compute P = Φ (Zbp) x 100%
where Φ (Z) = area under a standard normal distribution to the left of Z.

Thus, if Zbp = 1.28, then Φ (Zbp) = .90 and the bp percentile = .90 x 100% = 90%.

5. To compute percentiles for SBP for girls, diastolic blood pressure (DBP) (K5) for boys, and DBP (K5) for girls, use the regression coefficients from the 4th, 5th, and 6th columns of appendix table B–1.

TABLE B-1

Regression Coefficients From Blood Pressure Regression Models*

Variable Name	Symbol	Systolic BP		Diastolic BP5	
		Male	Female	Male	Female
Intercept	α	102.19768	102.01027	61.01217	60.50510
Age					
Age–10	β_1	1.82416	1.94397	0.68314	1.01301
$(Age–10)^2$	β_2	0.12776	0.00598	-0.09835	0.01157
$(Age–10)^3$	β_3	0.00249	-0.00789	0.01711	0.00424
$(Age–10)^4$	β_4	-0.00135	-0.00059	0.00045	-0.00137
Normalized height					
Zht	γ^1	2.73157	2.03526	1.46993	1.16641
Zht^2	γ^2	-0.19618	0.02534	-0.07849	0.12795
Zht^3	γ^3	-0.04659	-0.01884	-0.03144	-0.03869
Zht^4	γ^4	0.00947	0.00121	0.00967	-0.00079
Standard deviation	σ	10.7128	10.4855	11.6032	10.9573
ρ†		0.4100	0.3824	0.2436	0.2598
n (persons)		32,161	31,066	24,057	23,443
n (*visits*)		*42,074*	*41,017*	*29,182*	*28,794*

BP, blood pressure; Diastolic BP5, diastolic measurement at Korotkoff 5.

* The coefficients were obtained from mixed-effects linear regression models.

† The value of ρ represents the correlation between BP measurements at different ages for the same child after correcting for age and Zht. This computation was necessary because some studies contributing to the childhood BP database provided BP at more than one age.

APPENDIX 8 HEART RATE PERCENTILES BY GENDER AND AGE

Table 2. Resting pulse rate estimates for U.S. males, by age group: National Health and Nutrition Examination Survey, 1999–2008

Age group	*n*	Mean	SE mean	Percentile										
				1st	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
Under 1 year	972	128	1.1	84	98	102	107	115	125	137	148	155	160	171
1 year	712	116	0.8	†	91	95	100	107	114	122	131	137	146	156
2–3 years	1,148	106	0.4	75	82	85	89	96	104	112	119	124	131	139
4–5 years	864	94	0.6	69	71	74	78	84	92	100	108	112	116	120
6–8 years	1,212	86	0.5	59	63	66	70	76	83	92	100	105	109	114
9–11 years	1,130	80	0.5	56	59	61	66	70	78	86	94	97	102	110
12–15 years	2,190	77	0.4	52	54	57	60	66	74	83	91	97	102	108
16–19 years	2,411	72	0.4	46	50	52	56	61	69	78	87	92	95	104
20–39 years	3,445	71	0.3	47	50	52	55	61	69	76	84	89	95	101
40–59 years	2,559	71	0.3	46	49	52	55	61	68	77	85	90	95	104
60–79 years	1,147	70	0.5	45	48	50	54	60	67	75	84	91	98	102
80 years and over	197	71	1.1	†	48	51	54	61	68	78	86	94	97	†

† Standard error not calculated by SUDAAN.

NOTES: SE is standard error. Data exclude persons with a current medical condition or medication use that would affect the resting pulse rate.

Table 3. Resting pulse rate estimates for U.S. females, by age group: National Health and Nutrition Examination Survey, 1999–2008

Age group	*n*	Mean	SE mean	Percentile										
				1st	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
Under 1 year	931	130	1	96	99	104	108	118	127	137	150	156	163	174
1 year	633	119	0.8	82	92	95	101	110	117	125	135	139	143	158
2–3 years	1,107	108	0.5	78	83	88	91	98	107	114	120	125	130	137
4–5 years	900	97	0.6	70	73	76	81	87	95	104	110	117	122	132
6–8 years	1,264	88	0.5	61	66	69	73	79	87	94	101	106	109	117
9–11 years	1,236	85	0.5	58	63	66	69	76	83	91	98	103	107	113
12–15 years	2,310	80	0.4	54	57	60	63	70	79	87	94	99	103	110
16–19 years	2,082	79	0.4	50	54	58	62	69	77	85	94	99	103	108
20–39 years	3,061	76	0.3	52	55	57	60	66	74	82	89	95	99	104
40–59 years	2,409	73	0.3	51	53	56	59	64	71	79	86	92	97	101
60–79 years	1,163	73	0.4	52	54	56	59	64	70	78	86	92	96	102
80 years and over	219	73	0.9	†	53	56	59	64	71	77	85	93	98	100

† Standard error not calculated by SUDAAN.

NOTES: SE is standard error. Data excludes persons with a current medical condition or medication use that would affect the resting pulse rate.

APPENDIX 9 ECG NORMAL RANGES

Normal Ranges

Age Group 1 to <2 years

Interval	Normal	Abnormal ECG, Clinically Insignificant	Abnormal ECG, Potentially Clinically Significant
HR	Male: 97 – 155 bpm Female: 95 – 178 bpm	Up to the pediatric cardiologist's discretion	Up to the pediatric cardiologist's discretion
PR	Male: 86 – 151 ms Female: 78 – 147 ms	Up to the pediatric cardiologist's discretion	Up to the pediatric cardiologist's discretion
QRS	Male: 54 – 88 ms with no QRS disturbance Female: 54 – 85 ms with no QRS disturbance	Up to the pediatric cardiologist's discretion	Up to the pediatric cardiologist's discretion
QTcF	Male: 383 – 455 ms Female: 381 – 447 ms	Up to the pediatric cardiologist's discretion	Up to the pediatric cardiologist's discretion

Age Group 2 to < 6 years

Interval	Normal	Abnormal ECG, Clinically Insignificant	Abnormal ECG, Potentially Clinically Significant
HR	80-140 bpm	60-79 bpm, or 141-180 bpm	< 60 bpm or >180 bpm
PR	90-150 ms	Short if <90 ms, otherwise first degree AV block if 151-170 ms	> 170 ms
QRS	≤ 90 ms with no QRS disturbance	91-100 ms with no QRS disturbance or IVCD or any QRS disturbance (except Left Posterior Fascicular Block) with a QRS ≤ 100 ms	IVCD or any QRS conduction disturbance with a QRS > 100 ms
QTcF	Males and Females: 320-450 ms	451-480 ms Increase of QTcF (30 - 60 ms)*	QTcF > 480 ms Short QTcF < 320 ms Increase of QTcF (> 60 ms)*

Note: Baseline, Visit 1 (0) will serve as the baseline for assessment of QTcF increase.

Age Group 6 to < 12 years

Interval	Normal	Abnormal ECG, Clinically Insignificant	Abnormal ECG, Potentially Clinically Significant
HR	60-120 bpm	50-59 bpm, or 121-150 bpm	< 50 bpm or >150 bpm
PR	100-170 ms	Short if <100 ms, otherwise first degree AV block if 171-190 ms	> 190 ms
QRS	≤ 100 ms with no QRS disturbance	101-110 ms with no QRS disturbance or IVCD or any QRS disturbance (except Left Posterior Fascicular Block) with QRS ≤ 110 ms	IVCD or any QRS conduction disturbance with a QRS > 110 ms
QTcF	Males and Females: 320-450 ms	451-480 ms Increase of QTcF (30 - 60 ms)*	QTcF > 480 ms Short QTcF < 320 ms Increase of QTcF (> 60 ms)*

Note: Baseline, Visit 1 (0) will serve as the baseline for assessment of QTcF increase.

Age Group 12 years and up

Interval	Normal	Abnormal ECG, Clinically Insignificant	Abnormal ECG, Potentially Clinically Significant
HR	50-100 bpm	40-49 bpm, or 101-150 bpm	< 40 bpm or >150 bpm
PR	110-180 ms	Short if <110 ms, otherwise first degree AV block if 181-220 ms	> 220 ms
QRS	≤ 110 ms with no QRS disturbance	111-120 ms with no QRS disturbance or IVCD or any QRS disturbance (except Left Posterior Fascicular Block) with a QRS ≤ 120 ms	IVCD or any QRS conduction disturbance with a QRS > 120 ms
QTcF	Male: 320-450 ms Female: 320-470 ms	451-500 ms 471-500 ms All ages: Increase of QTcF (30 - 60 ms)*	QTcF > 500 ms QTcF > 500 ms All ages (male/female): Short QTcF < 320 ms All ages: Increase of QTcF (> 60 ms)*

Note: Baseline, Visit 1 (0) will serve as the baseline for assessment of QTcF increase.

APPENDIX 10 EVENTS TO MONITOR

Injection site reactions: based on HLT "Injection site reaction"

Category	PT
Injection site reaction	Embolia cutis medicamentosa
Injection site reaction	Injected limb mobility decreased
Injection site reaction	Injection site abscess
Injection site reaction	Injection site abscess sterile
Injection site reaction	Injection site anaesthesia
Injection site reaction	Injection site atrophy
Injection site reaction	Injection site bruising
Injection site reaction	Injection site calcification
Injection site reaction	Injection site cellulitis
Injection site reaction	Injection site coldness
Injection site reaction	Injection site cyst
Injection site reaction	Injection site dermatitis
Injection site reaction	Injection site discharge
Injection site reaction	Injection site discolouration
Injection site reaction	Injection site discomfort
Injection site reaction	Injection site dryness
Injection site reaction	Injection site dysaesthesia
Injection site reaction	Injection site eczema
Injection site reaction	Injection site erosion
Injection site reaction	Injection site erythema
Injection site reaction	Injection site exfoliation
Injection site reaction	Injection site extravasation
Injection site reaction	Injection site fibrosis
Injection site reaction	Injection site granuloma
Injection site reaction	Injection site haematoma
Injection site reaction	Injection site haemorrhage
Injection site reaction	Injection site hyperaesthesia
Injection site reaction	Injection site hypersensitivity
Injection site reaction	Injection site hypertrichosis
Injection site reaction	Injection site hypertrophy
Injection site reaction	Injection site hypoaesthesia
Injection site reaction	Injection site induration
Injection site reaction	Injection site infection
Injection site reaction	Injection site inflammation
Injection site reaction	Injection site injury
Injection site reaction	Injection site irritation
Injection site reaction	Injection site ischaemia
Injection site reaction	Injection site joint discomfort

Category	PT
Injection site reaction	Injection site joint effusion
Injection site reaction	Injection site joint erythema
Injection site reaction	Injection site joint infection
Injection site reaction	Injection site joint inflammation
Injection site reaction	Injection site joint movement impairment
Injection site reaction	Injection site joint pain
Injection site reaction	Injection site joint swelling
Injection site reaction	Injection site joint warmth
Injection site reaction	Injection site laceration
Injection site reaction	Injection site lymphadenopathy
Injection site reaction	Injection site macule
Injection site reaction	Injection site mass
Injection site reaction	Injection site movement impairment
Injection site reaction	Injection site necrosis
Injection site reaction	Injection site nerve damage
Injection site reaction	Injection site nodule
Injection site reaction	Injection site oedema
Injection site reaction	Injection site pain
Injection site reaction	Injection site pallor
Injection site reaction	Injection site papule
Injection site reaction	Injection site paraesthesia
Injection site reaction	Injection site phlebitis
Injection site reaction	Injection site photosensitivity reaction
Injection site reaction	Injection site plaque
Injection site reaction	Injection site pruritus
Injection site reaction	Injection site pustule
Injection site reaction	Injection site rash
Injection site reaction	Injection site reaction
Injection site reaction	Injection site recall reaction
Injection site reaction	Injection site scab
Injection site reaction	Injection site scar
Injection site reaction	Injection site streaking
Injection site reaction	Injection site swelling
Injection site reaction	Injection site thrombosis
Injection site reaction	Injection site ulcer
Injection site reaction	Injection site urticaria
Injection site reaction	Injection site vasculitis
Injection site reaction	Injection site vesicles
Injection site reaction	Injection site warmth
Injection site reaction	Malabsorption from injection site

Hypersensitivity: based on relevant PTs in the narrow SMQs for "Hypersensitivity",

Category	PT
Hypersensitivity	Acute generalised exanthematous pustulosis
Hypersensitivity	Administration site dermatitis
Hypersensitivity	Administration site eczema
Hypersensitivity	Administration site hypersensitivity
Hypersensitivity	Administration site rash
Hypersensitivity	Administration site recall reaction
Hypersensitivity	Administration site urticaria
Hypersensitivity	Administration site vasculitis
Hypersensitivity	Allergic bronchitis
Hypersensitivity	Allergic colitis
Hypersensitivity	Allergic cough
Hypersensitivity	Allergic cystitis
Hypersensitivity	Allergic eosinophilia
Hypersensitivity	Allergic gastroenteritis
Hypersensitivity	Allergic granulomatous angiitis
Hypersensitivity	Allergic hepatitis
Hypersensitivity	Allergic keratitis
Hypersensitivity	Allergic myocarditis
Hypersensitivity	Allergic oedema
Hypersensitivity	Allergic otitis externa
Hypersensitivity	Allergic otitis media
Hypersensitivity	Allergic pharyngitis
Hypersensitivity	Allergic respiratory disease
Hypersensitivity	Allergic respiratory symptom
Hypersensitivity	Allergic sinusitis
Hypersensitivity	Allergic transfusion reaction
Hypersensitivity	Allergy alert test positive
Hypersensitivity	Allergy test positive
Hypersensitivity	Allergy to immunoglobulin therapy
Hypersensitivity	Allergy to vaccine
Hypersensitivity	Alveolitis allergic
Hypersensitivity	Anaphylactic reaction
Hypersensitivity	Anaphylactic shock
Hypersensitivity	Anaphylactic transfusion reaction
Hypersensitivity	Anaphylactoid reaction
Hypersensitivity	Anaphylactoid shock
Hypersensitivity	Anaphylaxis treatment
Hypersensitivity	Angioedema
Hypersensitivity	Antiallergic therapy
Hypersensitivity	Antiendomysial antibody positive
Hypersensitivity	Anti-neutrophil cytoplasmic antibody positive vasculitis
Hypersensitivity	Application site dermatitis
Hypersensitivity	Application site eczema
Hypersensitivity	Application site hypersensitivity

Category	PT
Hypersensitivity	Application site rash
Hypersensitivity	Application site recall reaction
Hypersensitivity	Application site urticaria
Hypersensitivity	Application site vasculitis
Hypersensitivity	Arthritis allergic
Hypersensitivity	Atopy
Hypersensitivity	Blepharitis allergic
Hypersensitivity	Blood immunoglobulin E abnormal
Hypersensitivity	Blood immunoglobulin E increased
Hypersensitivity	Bromoderma
Hypersensitivity	Bronchospasm
Hypersensitivity	Catheter site dermatitis
Hypersensitivity	Catheter site eczema
Hypersensitivity	Catheter site hypersensitivity
Hypersensitivity	Catheter site rash
Hypersensitivity	Catheter site urticaria
Hypersensitivity	Catheter site vasculitis
Hypersensitivity	Chronic eosinophilic rhinosinusitis
Hypersensitivity	Chronic hyperplastic eosinophilic sinusitis
Hypersensitivity	Circulatory collapse
Hypersensitivity	Circumoral oedema
Hypersensitivity	Conjunctival oedema
Hypersensitivity	Conjunctivitis allergic
Hypersensitivity	Corneal oedema
Hypersensitivity	Cutaneous vasculitis
Hypersensitivity	Dennie-Morgan fold
Hypersensitivity	Dermatitis
Hypersensitivity	Dermatitis acneiform
Hypersensitivity	Dermatitis allergic
Hypersensitivity	Dermatitis atopic
Hypersensitivity	Dermatitis bullous
Hypersensitivity	Dermatitis contact
Hypersensitivity	Dermatitis exfoliative
Hypersensitivity	Dermatitis exfoliative generalised
Hypersensitivity	Dermatitis herpetiformis
Hypersensitivity	Dermatitis infected
Hypersensitivity	Dermatitis psoriasiform
Hypersensitivity	Distributive shock
Hypersensitivity	Documented hypersensitivity to administered product
Hypersensitivity	Drug cross-reactivity
Hypersensitivity	Drug eruption
Hypersensitivity	Drug hypersensitivity
Hypersensitivity	Drug provocation test
Hypersensitivity	Drug reaction with eosinophilia and systemic symptoms
Hypersensitivity	Eczema
Hypersensitivity	Eczema infantile

Category	PT
Hypersensitivity	Eczema nummular
Hypersensitivity	Eczema vaccinatum
Hypersensitivity	Eczema vesicular
Hypersensitivity	Eczema weeping
Hypersensitivity	Encephalitis allergic
Hypersensitivity	Encephalopathy allergic
Hypersensitivity	Epidermal necrosis
Hypersensitivity	Epidermolysis
Hypersensitivity	Epidermolysis bullosa
Hypersensitivity	Epiglottic oedema
Hypersensitivity	Erythema multiforme
Hypersensitivity	Erythema nodosum
Hypersensitivity	Exfoliative rash
Hypersensitivity	Eye allergy
Hypersensitivity	Eye oedema
Hypersensitivity	Eye swelling
Hypersensitivity	Eyelid oedema
Hypersensitivity	Face oedema
Hypersensitivity	Giant papillary conjunctivitis
Hypersensitivity	Gingival oedema
Hypersensitivity	Gingival swelling
Hypersensitivity	Gleich's syndrome
Hypersensitivity	Haemorrhagic urticaria
Hypersensitivity	Hand dermatitis
Hypersensitivity	Henoch-Schonlein purpura
Hypersensitivity	Henoch-Schonlein purpura nephritis
Hypersensitivity	Hereditary angioedema
Hypersensitivity	Hypersensitivity
Hypersensitivity	Hypersensitivity vasculitis
Hypersensitivity	Idiopathic urticaria
Hypersensitivity	Immediate post-injection reaction
Hypersensitivity	Immune thrombocytopenic purpura
Hypersensitivity	Immune tolerance induction
Hypersensitivity	Infusion site dermatitis
Hypersensitivity	Infusion site eczema
Hypersensitivity	Infusion site hypersensitivity
Hypersensitivity	Infusion site rash
Hypersensitivity	Infusion site recall reaction
Hypersensitivity	Infusion site urticaria
Hypersensitivity	Infusion site vasculitis
Hypersensitivity	Injection site dermatitis
Hypersensitivity	Injection site eczema
Hypersensitivity	Injection site hypersensitivity
Hypersensitivity	Injection site rash
Hypersensitivity	Injection site recall reaction
Hypersensitivity	Injection site urticaria

Category	PT
Hypersensitivity	Injection site vasculitis
Hypersensitivity	Instillation site hypersensitivity
Hypersensitivity	Instillation site rash
Hypersensitivity	Instillation site urticaria
Hypersensitivity	Interstitial granulomatous dermatitis
Hypersensitivity	Intestinal angioedema
Hypersensitivity	Iodine allergy
Hypersensitivity	Kaposi's varicelliform eruption
Hypersensitivity	Kounis syndrome
Hypersensitivity	Laryngeal oedema
Hypersensitivity	Laryngitis allergic
Hypersensitivity	Laryngospasm
Hypersensitivity	Laryngotracheal oedema
Hypersensitivity	Limbal swelling
Hypersensitivity	Lip oedema
Hypersensitivity	Lip swelling
Hypersensitivity	Mast cell degranulation present
Hypersensitivity	Mouth swelling
Hypersensitivity	Mucocutaneous rash
Hypersensitivity	Multiple allergies
Hypersensitivity	Nephritis allergic
Hypersensitivity	Nikolsky's sign
Hypersensitivity	Nodular rash
Hypersensitivity	Oculomucocutaneous syndrome
Hypersensitivity	Oculorespiratory syndrome
Hypersensitivity	Oedema mouth
Hypersensitivity	Oral allergy syndrome
Hypersensitivity	Oropharyngeal blistering
Hypersensitivity	Oropharyngeal spasm
Hypersensitivity	Oropharyngeal swelling
Hypersensitivity	Palatal oedema
Hypersensitivity	Palatal swelling
Hypersensitivity	Palisaded neutrophilic granulomatous dermatitis
Hypersensitivity	Palpable purpura
Hypersensitivity	Pathergy reaction
Hypersensitivity	Periorbital oedema
Hypersensitivity	Pharyngeal oedema
Hypersensitivity	Pruritus allergic
Hypersensitivity	Radioallergosorbent test positive
Hypersensitivity	Rash
Hypersensitivity	Rash erythematous
Hypersensitivity	Rash follicular
Hypersensitivity	Rash generalised
Hypersensitivity	Rash macular
Hypersensitivity	Rash maculo-papular
Hypersensitivity	Rash maculovesicular

Category	PT
Hypersensitivity	Rash morbilliform
Hypersensitivity	Rash neonatal
Hypersensitivity	Rash papulosquamous
Hypersensitivity	Rash pruritic
Hypersensitivity	Rash pustular
Hypersensitivity	Rash rubelliform
Hypersensitivity	Rash scarlatiniform
Hypersensitivity	Rash vesicular
Hypersensitivity	Reaction to azo-dyes
Hypersensitivity	Reaction to colouring
Hypersensitivity	Reaction to drug excipients
Hypersensitivity	Reaction to preservatives
Hypersensitivity	Red man syndrome
Hypersensitivity	Rhinitis allergic
Hypersensitivity	Scleral oedema
Hypersensitivity	Scleritis allergic
Hypersensitivity	Scrotal oedema
Hypersensitivity	Serum sickness
Hypersensitivity	Serum sickness-like reaction
Hypersensitivity	Shock
Hypersensitivity	Shock symptom
Hypersensitivity	Skin necrosis
Hypersensitivity	Skin reaction
Hypersensitivity	Skin test positive
Hypersensitivity	Solar urticaria
Hypersensitivity	Solvent sensitivity
Hypersensitivity	Stevens-Johnson syndrome
Hypersensitivity	Stoma site hypersensitivity
Hypersensitivity	Stoma site rash
Hypersensitivity	Swelling face
Hypersensitivity	Swollen tongue
Hypersensitivity	Tongue oedema
Hypersensitivity	Toxic epidermal necrolysis
Hypersensitivity	Toxic skin eruption
Hypersensitivity	Tracheal oedema
Hypersensitivity	Type I hypersensitivity
Hypersensitivity	Type II hypersensitivity
Hypersensitivity	Type III immune complex mediated reaction
Hypersensitivity	Type IV hypersensitivity reaction
Hypersensitivity	Urticaria
Hypersensitivity	Urticaria cholinergic
Hypersensitivity	Urticaria chronic
Hypersensitivity	Urticaria contact
Hypersensitivity	Urticaria papular
Hypersensitivity	Urticaria physical
Hypersensitivity	Urticaria pigmentosa

Category	PT
Hypersensitivity	Urticaria vesiculosa
Hypersensitivity	Vaginal exfoliation
Hypersensitivity	Vaginal ulceration
Hypersensitivity	Vasculitic rash
Hypersensitivity	Vessel puncture site rash
Hypersensitivity	Vulval ulceration
Hypersensitivity	Vulvovaginal rash
Hypersensitivity	Vulvovaginal ulceration

Hyperphosphataemia: based on selected PTs below

Category	PT
Hyperphosphataemia	Hyperphosphataemia
Hyperphosphataemia	Blood phosphorus increased

Ectopic mineralization: based on a MedDRA search of 'calcification'

Category	PT
Ectopic calcification	Adrenal calcification
Ectopic calcification	Aortic calcification
Ectopic calcification	Aortic valve calcification
Ectopic calcification	Aortic valve sclerosis
Ectopic calcification	Articular calcification
Ectopic calcification	Bladder wall calcification
Ectopic calcification	Breast calcifications
Ectopic calcification	Bursa calcification
Ectopic calcification	Calcific deposits removal
Ectopic calcification	Calcification metastatic
Ectopic calcification	Calcification of muscle
Ectopic calcification	Calcinosis
Ectopic calcification	Calculus bladder
Ectopic calcification	Calculus prostatic
Ectopic calcification	Calculus ureteric
Ectopic calcification	Calculus urethral
Ectopic calcification	Calculus urinary
Ectopic calcification	Cardiac valve sclerosis
Ectopic calcification	Cerebral calcification
Ectopic calcification	Chondrocalcinosis
Ectopic calcification	Chondrocalcinosis pyrophosphate
Ectopic calcification	Cutaneous calcification
Ectopic calcification	Dystrophic calcification
Ectopic calcification	Heart valve calcification

Category	PT
Ectopic calcification	Heart valve stenosis
Ectopic calcification	Hepatic calcification
Ectopic calcification	Intervertebral disc calcification
Ectopic calcification	Intestinal calcification
Ectopic calcification	Ligament calcification
Ectopic calcification	Lymph node calcification
Ectopic calcification	Mitral valve calcification
Ectopic calcification	Mitral valve sclerosis
Ectopic calcification	Myocardial calcification
Ectopic calcification	Nephrocalcinosis
Ectopic calcification	Nephrolithiasis
Ectopic calcification	Ovarian calcification
Ectopic calcification	Pancreatic calcification
Ectopic calcification	Pericardial calcification
Ectopic calcification	Pleural calcification
Ectopic calcification	Prostatic calcification
Ectopic calcification	Pulmonary calcification
Ectopic calcification	Pulmonary valve calcification
Ectopic calcification	Pulmonary valve sclerosis
Ectopic calcification	Splenic calcification
Ectopic calcification	Stag horn calculus
Ectopic calcification	Tendon calcification
Ectopic calcification	Tracheal calcification
Ectopic calcification	Tricuspid valve calcification
Ectopic calcification	Tricuspid valve sclerosis
Ectopic calcification	Vascular calcification

Restless legs syndrome

Category	PT
Restless legs syndrome	Restless legs syndrome
Restless legs syndrome	Restlessness
Restless legs syndrome	Akathisia
Restless legs syndrome	Psychomotor hyperactivity
Restless legs syndrome	Sensory disturbance
Restless legs syndrome	Muscle cramp
Restless legs syndrome	Limb discomfort
Restless legs syndrome	Neuromuscular pain
Restless legs syndrome	Formication