Statistical Analysis Plan

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

Protocol Number:	UX023-CL201
Investigational Product:	KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])
Indication:	X-linked Hypophosphatemia (XLH)
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STATISTICAL ANALYSIS PLAN AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

26 April 2016

The major statistical analysis plan changes are summarized below:

1. **General Changes:**

a) Section 3 Study Design has been updated to match the UX023-CL201 Protocol Amendment 5 content.

b) According to Section 8.1.1, Generalized Estimating Equations (GEE) models will be used for primary and secondary clinical efficacy endpoints with two or more post-baseline measurements, including analyses of RSS, RGI-C and growth endpoints. Section 8.7.1.1, 8.7.2.2, 8.7.2.3 and Appendix 2 have been updated accordingly.

Rationale: Clarification on implementation of analyses as outlined in Section 8.1.1 of SAP version 1.0 (10 September, 2015).

c) GEE approach has been removed from all exploratory clinical efficacy endpoints. Section 8.7.3.3 (BOT-2), 8.7.3.4 (Muscle Strength HHD), 8.7.3.5 (SF-10) and Appendix 2 have been updated accordingly.

Rationale: Exploratory endpoints will only be summarized by descriptive statistics.

d) Clarification that subgroup analyses based on baseline RSS total score, percentage of predicted 6MWT and POSNA-PODCI global function score will be performed:

- Baseline RSS total score < 1.5 or ≥ 1.5;
- Baseline percentage of predicted 6MWT $< 80\%$ or $\geq 80\%$, and the subgroups combing with baseline RSS total score < 1.5 or ≥ 1.5;
- Baseline POSNA-PODCI global functioning scale < 40 or ≥ 40, and the subgroups combing with baseline RSS total score < 1.5 or ≥ 1.5.

Section 8.7, 8.8.1.1, 8.8.2 and 8.12.4 have been updated accordingly.

Rationale: The subgroup analyses were not described in SAP version 1.0 but had been pre-specified in mock shells prior to Week 40 analysis snapshot.

e) The analysis of pre-treatment RSS and RGI-C data has been modified to only include pre-treatment data listings. Original Section 8.6.1.1.1 Pre-treatment RSS Total Score, Section 8.6.2.1.1 Pre-treatment RSS Knee and Wrist and Section 8.6.2.2.1 Pre-treatment RGI-C have been removed.

Rationale: The data collected from pre-treatment period are limited, and mostly without matching knee and wrist images taken at the same time point, therefore not sufficient to perform comparison analysis versus post-treatment.

2. RSS score:

a) Exploratory analysis using the sum of RSS scores from bilateral images of wrists and knees will not be performed. The definition in Section 5.2 and analysis in Section 8.6.3.1 from SAP version 1.0 have been removed.

Rationale: Data for this exploratory definition is not collected.

3. Growth:

a) Growth velocity in standing height Z score per year has been removed. The change of standing height Z score from baseline has been added for hypothesis testing and confidence intervals. Section 5.5 and 8.7.2.3 have been updated accordingly.

Rationale: The standing height Z score is adjusted for age and gender, therefore it is unnecessary to adjust for time.

The minor statistical analysis plan changes are listed below:

a) List of Abbreviations: Analysis of Covariance (ANCOVA), estimated glomerular filtration rate (eGFR) and fractional excretion of phosphorus (FEP) have been added to list of abbreviations.

b) Section 4.2.2 Secondary PD measures and Section 5.16 Fractional Excretion of Phosphorus: Fractional excretion of phosphorus has been added in secondary PD measures.

c) Section 4.3.1 General Safety Endpoints, Section 5.14 Events to Monitor, Appendix 10 Events to Monitor: Immunogenicity, hyperphosphatemia, ectopic mineralization, gastrointestinal events and restless legs syndrome have been added to events to monitor; grade 3/4 TEAEs, TEAEs resulting in discontinuation and fatal TEAEs have been added to general safety endpoints. Search criteria for events to monitor have been added to Section 5.14 and Appendix 10.

d) Section 5.7 BOT-2: Strength and agility scaled score has been removed; this variable is not collected.

e) Section 5.8 HHD, Section 9 References and Appendix 9 Normal Muscle Strength Calculation for HHD: The definitions for percent of normal muscle strength have been added. The reference of De Smet and Vercammen 2001 has been added for normal grips strength calculation.

f) Section 5.12 Blood Pressure Percentile, Appendix 7 Blood Pressure by Gender, Age and Height (NHLBI 2005): The derivation of blood pressure percentile adjusted by age, gender and height has been added.

g) Section 5.13 Heart Rate Percentile, Appendix 8 Heart Rate Percentile by Gender and Age: The heart rate percentile and its deviation have been added.

h) Section 5.15 Duration of Standard of Care: The derivation of standard of care (SOC) duration has been added.

i) Section 8.1 General Principles: Standard error (SE) has been added to continuous variable summary statistics.

j) Section 8.2 Demographics and Baseline Characteristics: Sitting height, arm length and leg length have been removed from demographic and baseline characteristics.

k) Section 8.5 Protocol Deviations: This section has been added for analysis of protocol deviations.

l) Section 8.6 Dosing Summary: Dosing summary by cycle has been removed.

m) Section 8.7.1.1 RSS Total, Section 8.7.2.2 RGI-C, Section 8.8.1.1 PD Profiles for Key Pharmacodynamics Parameters: Cumulative distribution function (CDF) graph has been removed; distribution graphs will be explored.

n) Section 8.7.1.1 RSS Total, Section 8.7.2.3 Growth, Section 8.8.1.1 PD Profiles for Key Pharmacodynamics Parameters, Appendix 2 Summary of Statistical Analysis Approaches on Key Endpoints: “One sample paired t test” has been corrected to “one sample t test”

o) Section 8.7.2.5 Functional Disability and Pain: The language of global function scale will be reported as a normative score only has been removed; global function scale will be reported as both normative and standardized scores. The graphs showing change in standardized score has been removed.

p) Section 8.7.3.2 XtremeCT Bone Mineral Density and Bone Geometry: Descriptive statistics have been removed, only data listings will be provided for related parameters.

q) Section 8.11.1 Adverse Events: The summary of TEAEs by preferred term for each event to monitor category has been added.

r) Section 8.11.6 Vital Signs: Summary of blood pressure percentile, summary of heart rate and heart rate percentile category, summary of body weight by study visit have been added; listing of home monitor blood pressure data has been added.

s) Section 9 References: Hager-Ross and Rosblad, 2002 has been removed; De Smet, L and Vercammen A 2001, NHLBI 2005 and Ostchega et al. 2011 references have been added.

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LIST OF ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D
1,25$(OH)_2$D	1,25-dihydroxyvitamin D
6MWT	Six Minute Walk Test
AE	adverse event
ALP	alkaline phosphatase
AP	anteroposterior
ANCOVA	Analysis of Covariance
BALP	bone-specific alkaline phosphatase
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition
BUN	blood urea nitrogen
CT	computed tomography
CTx	carboxy-terminal cross-linked telopeptide of type I collagen
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	estimated glomerular filtration rate
FGF23	fibroblast growth factor 23
FEP	fractional excretion of phosphorus
GEE	Generalized Estimating Equations
GFR	glomerular filtration rate
HAHA	human anti-human antibody
HHD	hand-held dynamometry
iPTH	intact parathyroid hormone
ITT	intent-to-treat
kg	kilogram
KHK	Kyowa Hakko Kirin Pharma, Inc.
LS	least squares
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
P1NP	procollagen type 1 N-propeptide
PD	pharmacodynamic (s)

PHEX	Phosphate regulating gene with homology to endopeptidases located on the X chromosome
PHS-10	Physical Summary Score
PK	pharmacokinetic(s)
PODCI	Pediatric Outcomes Data Collection Instrument
POSNA	Pediatric Orthopedic Society of North America
PSS-10	Psychosocial Summary Score
PT	Preferred Term
PTH	parathyroid hormone
Q2W	biweekly, once every two weeks
Q4W	monthly
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
SOC	standard of care
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

This statistical analysis plan (SAP) describes the planned interim and final analyses for Ultragenyx study UX023-CL201 (protocol version date August 28, 2015) entitled: "A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)." The statistical analysis plans (SAPs) for Week 16 analysis and Week 24 analysis were pre-specified in two separate documents before both analyses took place.

2 OBJECTIVES

The objectives of the study are to:

- Identify a dose and dosing regimen of KRN23, based on safety, tolerability and PD effect, in pediatric XLH patients
- Establish the safety profile of KRN23 for the treatment of children with XLH including assessment for presence of ectopic mineralization risk, for any potential cardiovascular effects, and the immunogenicity profile
- Characterize the PK/PD profile of the KRN23 doses tested in the monthly (Q4W) and biweekly (Q2W) dose regimens in pediatric XLH patients
- Determine the PD effects of KRN23 treatment on markers of bone health (measured by severity of rickets, bowing and growth) in pediatric XLH patients
- Determine the clinical effects of KRN23 on bone health (measured by severity of rickets, bowing and growth) and deformity, muscle strength, and motor function.
- Determine the effects of KRN23 on patient-reported outcomes, including pain, disability, and quality of life in pediatric XLH patients
- Evaluate the long-term safety and efficacy of KRN23

3 STUDY DESIGN

3.1 Overall Study Design and Plan

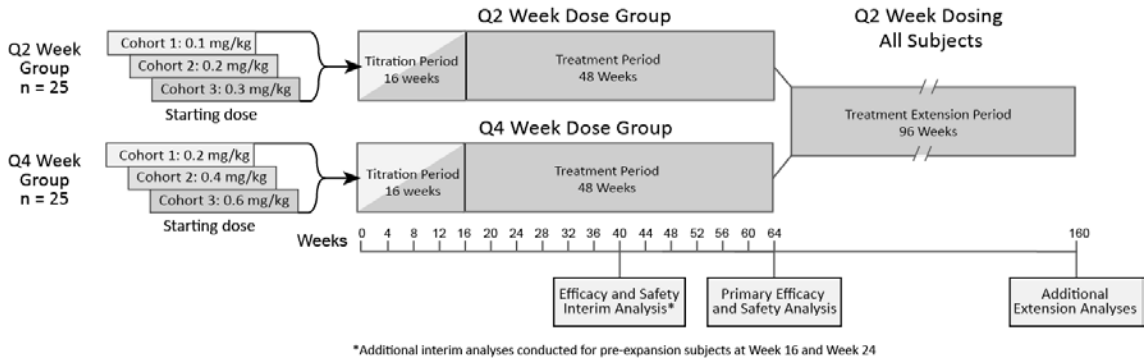
UX023-CL201 is a randomized, multicenter, open-label, dose finding Phase 2 study. The study will be conducted in prepubescent children aged 5-12 years with XLH to assess the PD, efficacy, and safety of KRN23 administered via subcutaneous (SC) injections monthly (Q4W, 28 days) or biweekly (Q2W, 14 days) for a total of 160 weeks. Subjects will need to discontinue oral phosphate and vitamin metabolite therapy prior to randomization and throughout the duration of the study. The study consists of a 16-week individual dose Titration Period, followed by a 48-week Treatment Period, and a 96-week Treatment Extension Period. The study initially enrolled 36 pediatric subjects with XLH and radiographic evidence of bone disease (pre-expansion subjects). The study was expanded to include additional subjects who were required to have a level of rickets severity of at least 1.5 points at the knee as defined by the Rickets Severity Score (RSS) method for a total of approximately 50 subjects overall (protocol amendment 3 dated as of March 2, 2015).

There will be 3 cohorts in this study (n = 10 in cohorts 1 and 2 [pre-expansion subjects] and n = 30 in cohort 3 [comprising both pre-expansion and expansion subjects]); each with a Q4W and Q2W dosing group. Subjects will be randomized 1:1 to the Q4W or Q2W dosing regimens within each cohort; randomization will be stratified on subject gender. In order to maintain a level of gender balance, no more than 20 patients of either sex can be enrolled in the pre-expansion group. No requirement for gender balance will be applied in the expansion group. The cohorts will be enrolled sequentially. The first cohort will examine the lowest doses (0.2 mg/kg Q4 and 0.1 mg/kg Q2) and will be enrolled first. As an added precautionary measure in this pediatric population, the second cohort (0.4 mg/kg Q4 and 0.2 mg/kg Q2) cannot begin dosing until the fourth subject in the first cohort completes the Week 4 visit. The third cohort will be administered the highest starting doses (0.6 mg/kg Q4 and 0.3 mg/kg Q2).

Analyses of safety and available PD and efficacy data are planned at the end of the Titration Period (Week 16) and at Week 24 for pre-expansion subjects. Further analyses in the pre-expansion group alone and for the overall population are planned at Week 40 and at Week 64 at the end of the Treatment Period to compare treatment outcomes to baseline (pre-dose). Analyses of long-term safety and efficacy will be conducted during and at the completion of the Treatment Extension Period (Weeks 64-160).

Figure 3.1.1 provides a schematic of the overall study design.

Figure 3.1.1: UX023-CL201 Study Schema



3.2 Discussion of the Study Design

The goal of the study is to identify a KRN23 dose and dose regimen, while investigating PD, PK, safety and clinical efficacy in pediatric subjects. Evaluations of additional biomarkers will also be performed to provide supportive evidence and confirm surrogate endpoints of efficacy and safety.

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

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

The main efficacy of KRN23 will be assessed by improvement in rickets, bowing and growth. The main pharmacodynamic comparison will focus on dose finding and determining whether Q4W or Q2W dosing provides the optimal profile of phosphate control with acceptable levels of other bone mineral metabolites.

The goal of the 96-week Treatment Extension Period is to evaluate the long-term safety and efficacy of KRN23. During the Treatment Extension Period, all subjects with receive KRN23 with Q2W dosing regimen. It is expected that the maintenance of phosphate control will allow for continued healing of rickets and bowing and maximize growth outcomes. Changes in growth and correction of lower extremity bowing may take longer to observe than the

healing of rickets; thus, these outcomes will continue to be followed in the Treatment Extension Period.

3.3 Determination of Sample Size

A sample size of both 36 subjects (pre-expansion) and 50 subjects (pre- and post-expansion) will provide at least 90% power to detect a mean change from baseline of 0.5 in RSS total with a standard deviation of 0.5 at the two-sided 0.05 level of significance. In addition, a sample size of 18 pre-expansion subjects per regimen (Q2W or Q4W) and 25 pre- and post-expansion subjects per regimen (Q2W or Q4W) will also provide at least 90% power under the same assumptions.

A sample size of at least 10 subjects per cohort will provide at least 90% power to detect a serum phosphorus increase from baseline of at least 0.8 mg/dL, assuming a standard deviation of 0.7 mg/dL or smaller, at the 2-sided level of significance of 0.05. A total sample size of 50 subjects (25 subjects each regimen of Q2W and Q4W) will provide at least 90% power to detect a 0.5 mg/dL difference in serum phosphorus between the two dosing regimens assuming a standard deviation of 0.4 and 2-sided level of significance of 0.05.

3.4 Interim Analysis

During the Titration Period and Treatment Period four analyses were planned at Week 16, Week 24, Week 40 and Week 64 respectively. Week 16 and Week 24 analyses for all 36 subjects (pre-expansion) were completed prior to the finalization of this SAP. Descriptive analyses were pre-specified for both analyses at Week 16 and Week 24 prior to the data snapshot and initiation of analyses, and no formal hypothesis testing was conducted. Week 40 and Week 64 analyses will be conducted as outlined in Section 8 after all 36 subjects (pre-expansion) have completed Week 40 and Week 64 respectively.

During the Extension Period, Week 88 analysis will be performed as outlined in Section 8 after all 36 subjects (pre-expansion) have completed Week 88. At the end of Extension Period, Week 160 analysis will be performed as outlined in Section 8 after all subjects (pre- and post-expansion) have completed Week 160.

Additional interim analyses between Week 40 and Week 160 will be performed based on regulatory needs. Study endpoints that were included for Week 16 and Week 24 analyses and will be included for Week 40, Week 64, Week 88, and Week 160 are summarized in Appendix 1.

3.5 Data Monitoring Committee

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

4 ANALYSIS ENDPOINTS

4.1 Efficacy Endpoints

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

4.1.1 Primary Efficacy Endpoint

- Change from Baseline in severity of rickets as measured by RSS total score

4.1.2 Secondary Efficacy Endpoints

- Change from Baseline in severity of rickets as measured by RSS knee and wrist scores
- Change from Baseline in the radiographic appearance of rickets and bowing as measured by RGI-C global, knee, wrist and long leg scores
- Growth (standing height, sitting height, arm length, and leg length)
- Walking Ability (6MWT)
- Functional disability and pain (POSNA-PODCI)

4.1.3 Exploratory Efficacy Endpoints

- Bone Mineral Density or Content **(**XtremeCT**)**
- Intercondylar and intermalleolar distance
- Gross motor function (BOT-2)
- Muscle strength (HHD)
- Health-related Quality of Life (SF-10 for Children Health Survey)

4.2 Pharmacodynamic Endpoints

To assess the spectrum of KRN23 biological activity on phosphate homeostasis and markers of bone health, and optimize dose level and regimen, a panel of PD markers will be assessed as indicated in the Schedule of Events.

4.2.1 Key PD Measures

- Serum phosphorus

- Serum $1,25(OH)_2D$
- TmP/GFR

4.2.2 Secondary PD measures

- Urinary phosphorus
- TRP
- Bone Biomarkers (P1NP, CTx, ALP, BALP)
- Fractional Excretion of Phosphorus (FEP)

4.2.3 Drug Concentration Measure

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

4.3 Safety Endpoints

4.3.1 General Safety Endpoints

- General safety will include the following parameters: TEAEs
- Treatment Related TEAEs
- TESAEs
- Events to monitor:
  - Injection site reaction (High-Level Term)
  - Immunogenicity
  - Hyperphosphatemia
  - Ectopic mineralization
  - Gastrointestinal events
  - Restless leg syndrome
- Grade 3/4 TEAEs
- TEAEs resulting in discontinuation
- Fatal TEAEs
- Chemistry, hematology, and urinalysis parameters
- Serum 25(OH)D
- eGFR
- FGF23 (total)

- HAHA
- Concomitant medications
- Physical exams
- Pregnancy test
- Vital signs

4.3.2 Ectopic Mineralization Endpoints

Ectopic mineralization safety data will include the following parameters:

- Renal ultrasound
- ECG
- ECHO
- Serum calcium
- Urinary calcium excretion rate
- Serum iPTH
- Serum creatinine

5 DEFINITIONS

5.1 Baseline

Baseline is defined as the most recent assessment prior to or on the date of initiation of treatment with KRN23. If the Week 0 data is missing, the most recent Screening will be used for Baseline.

5.2 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. The RSS is scored using a pre-defined methodology (Biomedical Systems Independent Review Manual September 2014). Each radiograph is scored individually by Dr. Thacher who will serve as the single central independent rater for all UX023-CL201 X-rays taken at Baseline, Week 40 ,Week 64, and additional study visits during the Extension Period, as well as all historical X-rays from UX023-CL201 subjects taken at various time points in the years prior to enrollment in the study. For the X-rays taken during the UX023-CL201 study, Dr. Thacher will be blinded to the study visit at which the X-ray was taken, dose, dose regimen (Q2W vs Q4W), adherence to the study protocol and duration of treatment. For the X-rays taken from UX023-CL201 subjects prior to enrollment in the study, Dr. Thacher will be blinded to treatment status with SOC regimen, SOC treatment duration and adherence to SOC therapy. 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 5.

5.2.1 RSS Responders

Responders are defined as 1) the subjects with a reduction in RSS total score from Baseline of at least 1.0 or 2) subjects who experience complete healing of rickets in the wrists and/or knees defined by a Baseline total score > 0 and a post-Baseline total score of 0.

5.3 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-CL201 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 64 and Week 88 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 64 (or Week 88) standing long leg image on the right (Image B). The RGI-C is scored using a pre-defined methodology (Biomedical Systems Independent Review Manual July 2015). See data collection form in Appendix 6.

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. The RGI-C scores for the three raters will be averaged and the mean scores for the wrist, knee and overall impression will be reported. At Week 64 and Week 88, the same process will be followed as Week 40 except that the raters will also evaluate images from long leg radiographs. The RGI-C scores from the three raters will be averaged to generate a RGI-C long leg score. 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.

5.4 Growth Parameter (Standing Height)

Growth as measured by standing height 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), Advance Data from Vital and Health Statistics). The following variables will be calculated:

- Stature-for-age Z-score: Standardized age- and gender-adjusted stature (i.e. standing height)

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 (weight-for-age and stature-for-age). 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:

- 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 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; to obtain the correct parameters corresponding to the age of the patient, 0.5 months should be added to the integer portion of the patient's age in months when referencing the CDC/NCHS Growth Charts. The percentile corresponding to the Z score is then the corresponding percentile from the standard normal distribution.

5.5 Growth Velocity of Standing Height in cm/year

Growth velocity of 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 standing heights by assuming a linear change in standing height:

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

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

5.6 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).

5.7 BOT-2

The Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition (BOT-2) is a standardized, norm-referenced test of fine and gross motor skills in individuals 4-21 years of age (Bruininks et al. 2005). Only the subtests for running speed/agility and strength will be administered. The running speed and agility subtest is comprised of the following individual tests: 1) shuttle run, 2) stepping sideways over a balance beam, 3) one-legged stationary hop, 4) one-legged side hop, and 5) two-legged side hop. The maximum score for the Running Speed and Agility subtest is 52. The components of the strength subtest are: 1) standing long jump, 2) knee or full push-ups, 3) sit-ups, 4) wall sit, and 5) V-up. The maximum score for this subtest is 42. Raw scores from the individual running speed/agility and strength tests will be reported. In addition, running speed/agility and strength scaled scores and age-equivalent scores will be reported. Results from these subtests will be used to calculate strength and agility standard score and percentile rank.

5.8 HHD

Muscle strength (best effort) will be reported for each individual muscle group in kilograms (kg). HHD scores for the individual muscle groups will be assessed (gross grip, knee flexors, knee extensors, hip flexors, hip extensors and hip abductors).

The percent of predicted normal strength values for HHD grip force will be calculated using published normative data based on age, gender, hand side and dominant side (De Smet et al. 2001):

$$\text{Percent of predicted normal strength} = \frac{\text{Observed Strenth}}{\text{Normal Strength}} * 100\%$$

The normal strength value for each age, gender, hand side and dominant side category is listed in Appendix 9.

The torque values for muscle groups of knee extensors, knee flexors, hip abductors, hip extensors and hip flexors will be calculated using the following formula:

Torque (in Newton-meters) = Muscle force (in Newtons) × tibial or femoral limb length (in meters)

where HHD muscle force in kg will be converted to Newtons and limb length in cm will be converted to meters; tibial length will be used for knee flexion and extension calculation and femoral length will be used for hip flexion, extension and abduction calculation.

The percent of predicted normal strength values will be calculated using published normative data based on age, gender and weight (Eek et al. 2006):

$$\text{Percent of predicted normal strength} = \frac{\text{Observed Strenth}}{\text{Normal Strength}} * 100\%$$

The normal strength value will be calculated based on equations provided in Appendix 9.

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 POSNA PODCI

The Pediatric Outcomes Data Collection Instrument (PODCI) consists of a series of questionnaires developed to measure the functional health of pediatric patients with a variety of musculoskeletal disorders. It was developed by the Pediatric Orthopedic Society of North America (POSNA) in 1994 and is often generically referred to as the POSNA. Each questionnaire yields four functional assessment scores, a global function score and a happiness score. The four functional assessment scores involve upper extremity functioning, transfers and basic mobility, sports and physical function, and comfort/pain. Raw, mean, standardized, and normative scores are calculated for each scale. The global function score is an average of the four functional scores. Standardized scores range from 0 – 100, with 0 representing the poorest outcome or worst health and 100 the best possible outcome or best health. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. For patients 10 years of age and under at Baseline, a parent or legal guardian will complete the Pediatric version of the questionnaire. Patients older than 10 years of age at Baseline will complete the self-report Adolescent version of the questionnaire. Scores are calculated using spreadsheets provided by developers of the instrument at the following: http://www.aaos.org/research/outcomes/outcomes_peds.asp

5.11 Area Under the Curve (AUC) and Time-adjusted Area Under the Curve (AUC)

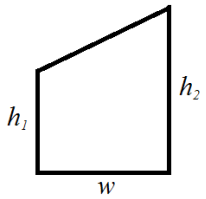
The trapezoidal rule is a numerical method that approximates the value of a definite integral.

$$\int_a^b f(x)dx$$

Response versus time AUCs will be calculated using the trapezoidal rule. The formula for the area of a trapezoid is

$$Area = w\left(\frac{h_1 + h_2}{2}\right)$$

where w is the width of the trapezoid and h1 and h2 are the two heights as shown below



Each pair of consecutive response assessment times t_1 and t_2 form the width of a trapezoid with $w = t_2 - t_1$. The heights h_1 and h_2 are the response values at times t_1 and t_2, respectively. AUC is the sum of trapezoidal areas across specified time point.

$$\int_a^b f(x)dx \approx w\left(\frac{h_1 + h_2}{2}\right) + w\left(\frac{h_2 + h_3}{2}\right) + \cdots + w(\frac{h_{n-1} + h_n}{2})$$

AUC values can be normalized to time-adjusted AUCs by dividing AUC by the duration of time included in AUC calculation.

$$\text{Time-Adjusted AUC} = \frac{\text{AUC}}{\sum t_i}$$

5.12 Blood Pressure Percentile

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 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”
- Immunogenicity AE: Defined using relevant PTs in the narrow SMQs for “Hypersensitivity”.
- Hyperphosphataemia AE: Defined by using PTs: “Hyperphosphataemia”, “Blood phosphorus increased”.
- Ectopic calcification related AE: There is no available SMQ. Ectopic calcification related AE is defined using a MedDRA search of ‘calcification’.
- Gastrointestinal AEs: i.e. nausea, vomiting, abdominal pain, diarrhea. Defined using PTs in the narrow SMQ “Gastrointestinal nonspecific inflammation and dysfunctional conditions”.
- Restless leg syndrome AE:. Defined by PTs “Restless legs syndrome”, “Restlessness”, “Akathisia”, “Sensory disturbance”, “Psychomotor hyperactivity”, “Limb discomfort”, “Neuromuscular pain”, “Formication”.

Please see the search criteria in Appendix 10 for more details.

5.15 Duration of Standard of Care (SOC)

The definition for duration of SOC is as the following:

Duration of SOC = End date of the latest SOC taken - start date of earliest SOC taken

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

Start Dates

- If the FIRST start date of SOC 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.

5.16 Fractional Excretion of Phosphorus (FEP)

Fractional excretion of phosphorus (FEP) is defined as 100% × (urine phosphorus × serum creatinine)/(urine creatinine × serum phosphorus), where the 2-hour urine sample will be used for urine phosphorus and urine creatinine.

6 ANALYSIS POPULATIONS

6.1 Intent to Treat Set (ITT)

The Intent-to-Treat set consists of all subjects who receive at least one dose of study therapy and have at least one post-dose measurement.

6.2 Safety Analysis Set (Safety)

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

6.3 Pharmacokinetic and Pharmacodynamic (PK/PD) Analysis Set

The PK/PD analysis set consists of all subjects who receive at least one dose of therapy and have evaluable serum data.

7 DATA SCREENING AND ACCEPTANCE

7.1 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 a review of tables and listings for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock.

In general, missing data will be treated as missing, unless otherwise specified. When a change from Baseline is assessed, only patients with a Baseline and at least one post-baseline measurement will be included in the analysis.

For the repeated measures analysis such as GEE, the model parameters are simultaneously estimated using all of the observed data. Sensitivity analysis may be performed using weighted GEE by implementing the inverse probability-weighted method to account for dropouts under the missing at random (MAR) assumption (Preisser et al. 2002).

7.2 Missing Date Imputation Rules

For scheduled visits, the visit number will be used for analyses and the missing date will not be imputed. Measurements at unscheduled visits will not be included in the analysis but will be provided in the listing. For measurements that are not limited to occurring at a particular scheduled visit, i.e., adverse events or concomitant medication use, missing dates will be imputed based on the following rule.

Start Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then:
  - If the year matches the first dose date year, then impute the month and day of the first dose date.
  - Otherwise, assign “January.”
- If the day is unknown, then:
  - If the month and year match the first dose date month and year, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.

Stop Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then assign "December"
- If the day is unknown, then assign the last day of the month.

7.3 Software

SAS® software version 9.4 or higher will be used to perform most or all statistical analyses.

8 STATISTICAL METHODS AND ANALYSES

8.1 General Principles

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be 2-sided at the alpha=0.05 significance level and 2-sided 95% confidence interval will be used. All p-values will be presented as nominal p-values. No adjustment on multiplicity will be made. Continuous variables will be summarized with means, standard deviations (SD), standard errors (SE), medians, Q1, Q3, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories. No imputation on missing data will be made, unless stated otherwise. All data obtained from the CRFs as well as any derived data will be included in data listings. In general, descriptive statistics will be summarized by regimen group and overall group.

8.1.1 Statistical Method for Repeated Measurements

For repeated measures such as clinical outcomes, the generalized estimating equations (GEE) approach will be used for assessing the change over time. The GEE model will include regimen group, study visit and interaction between regimen and study visit as categorical variables. To model the covariance structure, the exchangeable covariance matrix will be selected initially. If the exchangeable covariance structure leads to non-convergence, Quasi-Likelihood Information Criterion (QIC) will be used to select the best covariance structure. 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. As exploratory analyses, covariates such as baseline measures, gender and age will be considered for adjustment within GEE models.

For the clinical outcomes such as 6MWT and POSNA-PODCI, the change from Baseline to Week 40 and Week 64 will be tested for statistical significance. For Week 40, Week 64 and Week 88 analysis, only measurements up to Week 40, Week 64 or Week 88 will be included in the model respectively. For Week 160 analysis, all measurements will be included in the model.

8.2 Demographics and Baseline Characteristics

- Age
- Gender
- Ethnicity
- Race
- Standing Height
- Weight

- BMI
- Medical history (general and disease-specific)
- XLH treatment history
- RSS scores
- Renal ultrasound scores

8.3 Disease Characteristics and Medical History

8.3.1 Medical History / XLH Medical History

Medical history will be coded by MedDRA. Counts and percentages of subjects with medical history will be tabulated by system organ class and preferred term by regimen and overall. XLH medical history will be summarized by counts and percentages for each category by dose regimen and overall. Additionally, a subject level listing displaying the pre-existing medical conditions will be created. PHEX mutation analysis will be provided in subject listings.

8.3.2 XLH Treatment History

A summary of subjects' past XLH treatment with oral phosphate (e.g., K-Phos, Phospha, Phosphate-Sandoz) and vitamin D metabolite (e.g. Calcitriol, Rocaltrol, alfacalcidol, Alpha-calcidol/1,alpha, 1,25 Vitamin D3, DHT) therapy will be presented by regimen and overall. Use of calcimimetics (e.g. Cinacalcet, Sensipar, Mimpara) for the treatment of hyperparathyroidism will also be reported. The drug name, duration of treatment, dose and frequency of administration will be reported for each subject for those receiving SOC (phosphate/vitamin D) therapy. A descriptive summary of subjects' past SOC treatment, including duration will be presented by regimen and overall.

8.4 Patient Accountability

Subject statuses will be summarized to display the numbers of subjects by regimen and overall:

- ITT analysis set
- PK/PD analysis set
- Safety analysis set
- Completed 64 weeks Treatment Period
- Discontinued prior to completion of 64 Week Treatment Period and primary reason
- Completed 160 weeks Treatment Extension Period
- Discontinued prior to completion of Treatment Extension Period, and primary reason

In a separate listing, subjects who are screen failures and the primary reason will be listed.

8.5 Protocol Deviations

All protocol deviations will be presented in listings.

8.6 Dosing Summary

The total dose administered and weight-based dose will be summarized by regimen, cohort and study visit. Total dose will be summarized by regimen, and cohort.

8.7 Efficacy Analysis

All efficacy analysis will be performed on ITT set (Q2W, Q4W and overall), unless stated otherwise. Subgroup analysis will also be performed by baseline RSS total score ≥ 1.5 or < 1.5. Other subgroups such as gender and age may be considered. A summary of statistical methods on primary and secondary efficacy endpoints such as RSS, RGI-C and growth is detailed in Appendix 3.

8.7.1 Analysis of Primary Efficacy Endpoint

8.7.1.1 RSS Total

The efficacy analyses evaluating change from Baseline of RSS total score will be performed at time points outlined in Section 3.4. To assess the overall KRN23 effect in improving rickets, the null hypothesis of no change from Baseline of RSS total score will be tested using one sample t test. If the normality assumption is not satisfied, the sign test will be used. A supportive analysis will also be performed using an Analysis of Covariance (ANCOVA) model with change of RSS total score from baseline as dependent variable, baseline RSS total score as covariate and regimen group as categorical independent variable at Week 40.

At Week 64, 88 and 160 analyses, a similar GEE model will be used with all RSS change from baseline data as independent variable, baseline RSS total score as covariate, and regimen group, study visit and interaction between regimen and study visit as categorical independent variables.

The change from Baseline of RSS total score will be summarized by each regimen descriptively. The difference between the two regimens (Q2W and Q4W) will be summarized with 95% C.I.. No formal hypothesis testing will be used.

Responder analyses will be performed for the RSS total score as below:

- Percentage of subjects with a RSS total score reduction from Baseline of at least 1.0 among subjects with Baseline RSS total score at least 1.0
- Percentage of subjects who healed completely among subjects with Baseline RSS total score >0

In addition to responder analysis, the distribution of change from Baseline of RSS total score will be provided.

A listing of RSS total score for each subject will be provided. Pre-treatment RSS scores will also be listed if available.

Graphic displays of RSS total score over time will also be provided by regimen.

8.7.1.1.1 Pre-treatment RSS Total Score

Pre-treatment radiographic images will be collected from subjects enrolled in the UX023-CL201 study as supplemental information to the prospective measures on RSS. RSS for these historical images will be assessed using the same method as outlined in Section 5.2.

Due to the limited information collected, no summary will be performed on the pre-treatment RSS scores. A listing of all pre-treatment and post-treatment RSS total scores will be provided for each subject.

8.7.2 Analysis of Secondary Efficacy Endpoints

8.7.2.1 RSS Knee and Wrist

Similarly, all the analyses planned in Section 8.6.1.1 for primary efficacy endpoint of RSS total score above will be repeated for RSS knee and wrist scores with the exception that no responder analysis will be performed.

8.7.2.2 RGI-C

The efficacy analyses evaluating RGI-C scores will be performed at time points outlined in Section 3.4. The null hypothesis of no change from Baseline in the radiographic appearance of rickets and bowing measured by RGI-C (global, knee, wrist and long leg) scores will be tested using one sample t test. If the normality assumption is not satisfied, the sign test will be used.

A supportive analysis will also be performed using an ANCOVA model with RGI-C score (global, knee, wrist and long leg separately) as dependent variable, baseline RSS total score as covariate and regimen group as categorical independent variable at Week 40.

At Week 64, 88 and 160 analyses, a similar GEE model will be used with all RGI-C data (global, knee, wrist and long leg score separately) as independent variable, baseline RSS total score as covariate, and regimen group, study visit and interaction between regimen and study visit as categorical independent variables.

The RGI-C (global, knee, wrist and long leg) scores will be summarized by each regimen using descriptive statistics. The difference between the two regimens (Q2W and Q4W) will be summarized by descriptive statistics with 95% C.I. No formal hypothesis testing will be

used. As supportive analysis, the distribution of RGI-C (global, knee, wrist and long leg) scores will be provided. Shift tables in radiographic assessment of abnormalities (decreased, unchanged, increased) for knee, wrist and long leg will be provided.

A listing of RGI-C (global, knee, wrist and long leg) scores will be provided for each subject. List of pre-treatment RGI-C scores will be provided if available.

Graphic displays of RGI-C (global, knee, wrist, and long leg) scores will also be provided over time by overall and regimen.

8.7.2.3 Growth

The observed values, Z scores and percentiles of standing height and their respective change from Baseline will be summarized over time.
The standing height Z score will be summarized at baseline and post baseline study visits, change from baseline will be assessed using a GEE model with standing height Z score at selected study visits as independent variable, baseline height, age and gender as candidate covariates, and regimen group, study visit and interaction between regimen and study visit as categorical independent variables.

The growth velocities of standing height in cm/year defined in Section 5.5 will be estimated for selected pre-treatment period (e.g. within 2 years prior to Baseline) and post-treatment period respectively for each subject. The average slopes of growth velocities in cm/year will be summarized for pre-treatment and post-treatment periods descriptively. One sample t will be used to assess the difference of the growth velocities in cm/year between pre-treatment period and post-treatment period. A supportive analysis will be explored using an ANOVA model with baseline height, age and gender as candidate covariates.

The difference between two regimens (Q2W and Q4W) will be summarized by descriptive statistics with 95% C.I.

In addition, descriptive statistics of sitting height, arm length and leg length measured during the post-treatment period and their respective change from Baseline will be provided by study visits.

A listing of standing height and the respective Z scores, percentiles and growth velocities in cm/year, sitting height, arm length and leg length will be provided.

8.7.2.4 Walking Ability (6MWT)

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. Change from Baseline of total distance walked and percent of predicted 6MWT will be assessed using the GEE approach as outlined in Section 8.1.1 with baseline measure included in the model as covariate In addition to the subgroup analysis based on baseline RSS total

score, baseline percentage of predicted 6MWT < 80% or ≥ 80%, and the subgroups combing with baseline RSS total score ≥ 1.5 or < 1.5 will also be considered for subgroup analyses.

A listing containing the 6MWT details will also be provided.

Graphs showing change in total distance walked during 6MWT and percent of predicted 6MWT will be provided by regimen and overall.

8.7.2.5 Functional Disability and Pain (POSNA-PODCI)

Summary statistics of standardized scores and normative scores for the various subscales (upper extremity, transfers/basic mobility, sports/physical function, pain) will be reported by study visit for both observed measures and their respective change from Baseline. Change from Baseline of standardized score and normative score over time will be assessed using the GEE approach as outlined in Section 8.1.1. Global function scale (the mean of the sum of the upper extremity, transfers/basic mobility, sports/physical function and pain subscale scores) will be reported and the respective change will be assessed using the GEE approach outlined in Section 8.1.1 with baseline score included in the model as covariate. In addition to the subgroup analysis based on baseline RSS total score, baseline global functioning scale < 40 or ≥ 40, and the subgroups combing with baseline RSS total score ≥ 1.5 or < 1.5 will also be considered for subgroup analyses.

A listing containing the POSNA-PODCI results will also be created.

Graphs showing change in normative score for each subscale as well as the global function scale will be provided by regimen and overall.

8.7.3 Analysis of Exploratory Efficacy Endpoints

8.7.3.1 Lower Extremity Deformity

To assess the severity of genu varum (bowing of the legs) and genu valgum (knock knees), the intercondylar distance (distance between the knees) and intermalleolar distance (distance between the ankles) will be obtained at Screening, and Week 40 and Week 64/Early Termination study visits. Summaries of the intercondylar distance, intermalleolar distance, and their respective change from Baseline values will be presented using descriptive statistics by disease category (genu varum and genu valgum). A listing of intercondylar distances and intermalleolar distances will also be provided.

8.7.3.2 XtremeCT Bone Mineral Density and Bone Geometry

XtremeCT of the forearm and tibia will be performed to assess bone mineral density or content at the cortical and trabecular compartment. XtremeCT will be performed at Baseline (Week 0) and Week 64/Early Termination. The following bone mineral density and bone geometry parameters will be measured:

- Total bone area
- Cortical area (Ct.area)
- Trabecular area (Tb.area)
- Periosteal perimeter
- Endosteal perimeter
- Total volumetric bone mineral density (Total vBMD)
- Cortical volumetric bone mineral density (Ct.vBMD)
- Trabecular volumetric bone mineral density (Tb.vBMD)
- Trabecular bone volume density (Tb.BV/TV)
- Trabecular number (Tb.N)
- Trabecular separation (Tb.Sp)
- Tb.1/NSD = network inhomogeneity
- Cortical thickness (Ct.Th)
- Cortical porosity (Ct.Po)
- Total bone stiffness
- Estimated failure load

A listing of all bone mineral density and bone geometry parameters will be provided.

8.7.3.3 Gross Motor Function (BOT-2)

Summary statistics of running speed/agility and strength subtest scaled and age-equivalent scores, in addition to the Strength and Agility standard and percentile rank scores will be tabulated by study visit for both observed measures and their respective change from Baseline.

A listing containing the BOT-2 outcome details will also be provided.

Graphs showing change in running speed/agility and strength scaled scores as well as Strength and Agility standard scores and percentiles will be provided by regimen and overall.

8.7.3.4 Muscle Strength (HHD)

Summary statistics of bilateral average raw and percent of predicted normal strength for the individual muscle groups assessed (knee flexors, knee extensors, hip flexors, hip extensors, hip abductors and gross grip) will be reported by visit in both an observed and change from Baseline fashion.

Graphs showing change in the bilateral average of individual muscle raw and percent of predicted normal scores will be provided by regimen and overall.

A listing containing the HHD assessment scores will also be provided.

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

Summaries 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.

A listing of PHS-10 and PSS-10 scores will also be created.

Graphs showing change in PHS-10 and PSS-10 will be provided by regimen and overall.

8.8 PD Analysis

The PD parameters will include serum phosphorus, TmP/GFR, serum $1,25(OH)_2D$, urinary phosphorus, TRP, Bone Biomarkers (P1NP, CTx, ALP, BALP). All PD analyses will be performed on the PD/PK Analysis Set (Q2W, Q4W and overall), unless stated otherwise.

8.8.1 Key Pharmacodynamics Parameters

8.8.1.1 PD Profiles for Key Pharmacodynamics Parameters

Key PD parameters include serum phosphorus, serum $1,25(OH)_2D$ and TmP/GFR.

Key PD endpoints at selected study visits such as Week 14 and Week 16, Week 22 and Week 24, Week 38 and Week 40 and Week 62 and Week 64 (whichever applies) will be analyzed using a one sample t test to assess the change from Baseline. If normality assumption is not satisfied, the sign test will be used.

As supportive analysis, descriptive statistics of time-adjusted Area Under the Curve (AUC) of key PD endpoints using trapezoidal rule will be reported at selected study visits such as Week 16, Week 24, Week 40 and Week 64 (whichever applies) by regimen and overall. Graph of each of key PD parameters at selected study visits such as Week 16, Week 24, Week 40 and Week 64 (whichever applies) will be provided by regimen and overall

Descriptive statistics of key PD parameters and their respective change from Baseline and percentage change from Baseline will be tabulated by regimen and overall at each study visit.

Subgroup analysis will also be performed by baseline RSS total score ≥ 1.5 or < 1.5. Other subgroups such as gender and age may be considered.

As supportive analysis, the proportion of subjects achieving the normal range (3.2-6.1 mg/dL), no less than 0.5 mg/dL change from Baseline or no less than 1.0 mg/dL change from Baseline on serum phosphorus level will be reported respectively by regimen and overall 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 regimen and overall at each study visit.

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

Graphs showing the change over time in key PD parameters for both observed measure and the respective change from Baseline will be provided by regimen.

To assess the PD profiles under three different starting doses (cohorts), descriptive statistics of key PD parameters will be provided by cohort and regimen during the first dose cycle (Baseline to Week 4). Graphs showing the change over time in key PD parameters during the first dosing cycle will be provided by cohort and regimen.

8.8.2 Other Pharmacodynamics Parameters

Secondary PD parameters such as urine phosphorus, TRP and bone biomarkers (P1NP, CTx, ALP, BALP) will be summarized descriptively by regimen and overall for both observed measure and the respective change from Baseline.

A listing containing all the details on urine phosphorus, TRP and bone biomarkers will be provided. Subgroup analysis by baseline RSS total score ≥ 1.5 or < 1.5 and graphs showing the change over time in selected secondary PD parameters for both observed measure and change from Baseline will be provided by regimen. Other subgroups such as gender and age may be considered.

8.9 Correlation Analyses

Correlation analyses of Baseline measurements and change from Baseline will be explored between key PD parameters and key efficacy endpoints such as RSS scores, RGI-C scores, growth and clinical outcome variables.

8.10 Pharmacokinetics

The PK analysis will be performed on the PK/PD analysis set, unless stated otherwise. The descriptive statistics for serum KRN23 will be tabulated by regimen and overall. The listing of serum KRN23 will also be provided.

The PK modeling will be detailed in a separate PK analysis plan.

8.11 General Safety

All safety analyses will be performed on the safety analysis set, unless stated otherwise. General safety will include AEs, treatment related AEs, SAEs, injection site reaction (grouped by High-Level Term), chemistry, hematology, and urinalysis parameters, serum 25(OH) D, eGFR, FGF23 (total), HAHA, concomitant medications, physical exams, pregnancy test and vital signs. In general, all descriptive statistics for safety endpoints will be summarized by regimen and overall. No hypothesis testing is planned for safety data.

8.11.1 Adverse Events

Adverse event and injection site reaction rate tables based on the MedDRA dictionary will be created and presented overall and for each dosing regimen. Adverse events that occur prior to receiving treatment will be presented separately from treatment emergent adverse events (TEAEs). TEAEs are defined as AEs with onset on or after the time of initiation of study drug administration. If the start date of an AE is partially or completely missing and the resolution date of the AE does not suggest that the AE occurred prior to first study drug administration, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug administration, then the AE will be considered treatment-emergent. Else,
- If the start year is the same as the year of the first study drug administration and the start month is the same or after the month of the first study drug administration, then the AE will be considered treatment-emergent. Else,
- If the start date is completely missing, then the AE is treatment-emergent.

An overall summary table of AEs will be presented that will summarize the frequency and percentage of subjects who experienced any AE, events to monitor, experienced any TEAE, experienced a treatment-related TEAE, a treatment-emergent SAE, discontinued due to a TEAE, and experienced an AE leading to death. For this purpose, a treatment-related AE is defined as an AE that is either definitely, possibly or probably related to study medication.

Subjects for TEAEs will be tabulated in the following manner: by system organ class/preferred term, by system organ class/preferred term/relationship to study drug, by system organ class/preferred term/severity, and by preferred term for each event to monitor category. Additionally, treatment-emergent SAEs, TEAEs leading to study discontinuations and TEAEs leading to death will be tabulated by system organ class/preferred term.

The incidence of injection site reactions will be summarized by study period and regimen to assess the trend over time. The summary of incidence over time will also be explored for other events to monitor categories.

Listings will be created for AEs which lead to death, discontinuation of treatment, and SAEs.

8.11.2 Safety Lab Parameters

The descriptive statistics will be provided by regimen and overall for other lab safety parameters (chemistry, hematology, and urinalysis parameters, GFR, FGF23, HAHA and Serum 25(OH) D). In addition, a shift table by regimen and overall will be provided for HAHA.

8.11.3 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 dosing regimen and overall. 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.

8.11.4 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 regimen. All physical examination assessments will be listed.

8.11.5 Pregnancy Test

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

8.11.6 Vital Signs

The subject body weight collected at study visits will be summarized by descriptive statistics.

The blood pressure will be summarized by study visit in mmHg and percentile to assess the blood pressure change over time by regimen and overall. When blood pressure is measured at both beginning and end of study visit, the average value will be calculated and used in summary. The heart rate and heart rate percentile category (please see Appendix 8) adjusted by gender and age will also be summarized over study visit.

Listing of home monitoring blood pressure data will be provided for each subject. A subject level listing for vital signs collected at study visits will also be provided.

8.12 Ectopic Mineralization Safety

Ectopic mineralization safety data includes renal ultrasound, ECG, ECHO, serum calcium, urinary calcium excretion rate, serum iPTH, serum creatinine.

8.12.1 Renal Ultrasound and eGFR Testing

Renal ultrasound will be conducted with findings of nephrocalcinosis graded on a 5-point scale by a central reader. The renal ultrasound is read using a pre-defined methodology (Biomedical Systems Independent Review Manual November 2014).These results will be summarized by time point and presented by dosing regimen and overall. Furthermore, a grade shift table summarizing changes from Baseline by time point will also be created.

Descriptive statistics for the eGFR will be calculated overall and for each dosing regimen at each scheduled time point and will include the change from Baseline (e.g., value at current time point minus value at Baseline). The summary of the descriptive statistics will be displayed by visit. A listing of renal ultrasound/nephrocalcinosis scores and eGFR calculations will also be provided.

8.12.2 ECG

Descriptive statistics for the absolute measurements and changes from Baseline for selected ECG parameters will be reported by regimen and overall. These include the ECG heart rate, and the following intervals: QT, QT corrected for heart rate using Fridericia's formula (QTcF), QT corrected for heart rate using Bazette's formula (QTcB), the time elapsed between 2 consecutive R waves (RR), the time elapsed from the onset of atrial depolarization to the onset of ventricular depolarization (PR), and time elapsed for depolarization of the ventricles (QRS).

The frequency of subjects with a maximum increase from Baseline in QTcB and QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcB and QTcF post dose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by regimen and overall.

The normality or abnormality of the ECG tracing, as determined by the investigator, will be summarized using shift tables of numbers of subjects who have a normal/abnormal ECG tracing at each scheduled time of assessment.

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

8.12.3 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 (e.g., left ventricular mass, mass index,

end-diastolic diameter, LVEF, etc.) will be reported by regimen and overall at the scheduled time points and will include the change from Baseline value. The summary of the descriptive statistics will be displayed by visit. Categorical ECHO measurements (e.g., calcification detection, valvular assessment for regurgitation, etc.) will be summarized via frequency counts and percentage displays.

8.12.4 Other Ectopic Mineralization Safety Labs

Other ectopic mineralization safety parameters (urinary calcium excretion rate, serum iPTH, serum creatinine) will be tabulated by descriptive statistics by regimen and overall for both observed measure and the respective change from Baseline. Subgroup analysis by baseline RSS total score ≥ 1.5 or < 1.5 will be performed for selected parameters. Other subgroups such as gender and age may be considered. A shift table for iPTH at each scheduled visit will also be provided to assess to the normality over time. Listings of ectopic mineralization safety labs containing all details will also be provided.

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10 APPENDICES

Appendix 1: Summary of Endpoints for Interim Analysis

Titration Period	Treatment Period			Treatment Extension Period
Week 16 (N=36)	**Week 24 (N=36)**	**Week 40 (N=36)**	**Week 64 (N=36)**	**Week 88 - Week160 (N=52)**
Subject accountability	Subject accountability	Subject accountability	Subject accountability	Subject accountability
Dosing summary	Dosing summary	Dosing summary	Dosing summary	Dosing summary
Baseline data	Baseline data	Baseline data	Baseline data	Baseline data
Medical history/ XLH medical history, XLH treatment history	Medical history/ XLH medical history, XLH treatment history	Medical history/ XLH medical history, XLH treatment history	Medical history/ XLH medical history, XLH treatment history	Medical history/ XLH medical history, XLH treatment history
Efficacy Measures: None	Efficacy Measures: RSS scores POSNA/PODCI SF-10	Efficacy Measures: RSS scores RGI-C scores Growth (standing height, sitting height, arm length, leg length) POSNA/PODCI SF-10 6MWT BOT-2 HDD Intercondylar and intermalleolar distance XtremeCT	Efficacy Measures: RSS scores RGI-C scores Growth (standing height, sitting height, arm length, leg length) POSNA/PODCI SF-10 6MWT BOT-2 HDD Intercondylar and intermalleolar distance XtremeCT	Efficacy Measures: RSS scores RGI-C scores Growth (standing height, leg length) POSNA/PODCI SF-10
PD Measures: Serum phosphorus Serum 1,25$(OH)_2$D TmP/GFR Urine phosphorus TRP Bone biomarkers(P1NP, CTx, ALP, BALP)	PD Measures: Serum phosphorus Serum 1,25$(OH)_2$D TmP/GFR Urine phosphorus TRP Bone biomarkers(P1NP, CTx, ALP, BALP)	PD Measures: Serum phosphorus Serum 1,25$(OH)_2$D TmP/GFR Urine phosphorus TRP Bone biomarkers(P1NP, CTx, ALP, BALP)	PD Measures: Serum phosphorus Serum 1,25$(OH)_2$D TmP/GFR Urine phosphorus TRP Bone biomarkers(P1NP, CTx, ALP, BALP)	PD Measures: Serum phosphorus Serum 1,25$(OH)_2$D TmP/GFR Urine phosphorus TRP Bone biomarkers(ALP)
PK Measures: Serum pre-dose KRN23	PK Measures: Serum pre-dose KRN23	PK Measures: Serum pre-dose KRN23	PK Measures: Serum pre-dose KRN23	PK Measures: Serum pre-dose KRN23

Titration Period	Treatment Period			Treatment Extension Period
Week 16 (N=36)	**Week 24 (N=36)**	**Week 40 (N=36)**	**Week 64 (N=36)**	**Week 88 - Week160 (N=52)**
Safety Measures: AEs Treatnent Related AEs SAEs Injection site reaction Concomitant medications Pregnancy test Vital signs	Safety Measures: AEs TEAEs SAEs Injection site reaction Concomitant medications Pregnancy test Vital signs	Safety Measures: AEs TEAEs SAEs Injection site reaction Concomitant medications Pregnancy test Vital signs	Safety Measures: AEs TEAEs SAEs Injection site reaction Concomitant medications Pregnancy test Vital signs	Safety Measures: AEs TEAEs SAEs Injection site reaction Concomitant medications Pregnancy test Vital signs
Safety Lab Measures: Chemistry, hematology and urinalysis GFR FGF23(total) HAHA Physical exam	Safety Lab Measures: Chemistry, hematology and urinalysis GFR FGF23(total) HAHA Serum 25(OH)D Physical exam	Safety Lab Measures: Chemistry, hematology and urinalysis GFR FGF23(total) HAHA Serum 25(OH)D Physical exam	Safety Lab Measures: Chemistry, hematology and urinalysis GFR FGF23(total) HAHA Serum 25(OH)D Physical exam	Safety Lab Measures: Chemistry, hematology and urinalysis GFR FGF23(total) HAHA Serum 25(OH)D Physical exam
Ectopic Mineralization: Renal ultrasound Serum calcium Urinary calcium Serum iPTH Serum creatinine	Ectopic Mineralization: Renal ultrasound Serum calcium Urinary calcium Serum iPTH Serum creatinine	Ectopic Mineralization: Renal ultrasound ECHO ECG Serum calcium Urinary calcium Serum iPTH Serum creatinine	Ectopic Mineralization: Renal ultrasound ECHO ECG Serum calcium Urinary calcium Serum iPTH Serum creatinine	Ectopic Mineralization: Renal ultrasound ECHO ECG Serum calcium Urinary calcium Serum iPTH Serum creatinine

Note: Additional interim analysis between Week 40 and Week 160 may occur based on regulatory needs.

Appendix 2: Summary of Statistical Analysis Approaches on Key Endpoints

Endpoints	Scale	Analysis populations	Comparisons	Analysis Type	Data Time Points	Week 40 Analysis	Week 64 Analysis	Week 88/160 Analysis
RSS total score	Continuous	Q2W, Q4W, Overall	Baseline vs Post-baseline	Primary efficacy analysis	Baseline, Week 40, 64, 88, 160	One sample t test (or sign test)	GEE	GEE
			Baseline vs Post-baseline	Supportive Analysis	Baseline, Week 40, 64, 88, 160	ANCOVA	One sample t test (or sign test)	One sample t test (or sign test)
RSS knee and wrist scores	Continuous	Q2W, Q4W, Overall	Baseline vs Post-baseline	Secondary efficacy analysis	Baseline, Week 40, 64, 88, 160	One sample t test (or sign test)	GEE	GEE
			Baseline vs Post-baseline	Supportive Analysis	Baseline, Week 40, 64, 88, 160	ANCOVA	One sample t test (or sign test)	One sample t test (or sign test)
RGI-C global*, knee, wrist, long leg* scores	Continuous	Q2W, Q4W, Overall	Post-baseline	Secondary efficacy analysis	Week 40, 64, 88, 160	One sample t test (or sign test)	GEE	GEE
			Post-baseline	Supportive analysis	Week 40, 64, 88, 160	ANCOVA	One sample t test (or sign test)	One sample t test (or sign test)
Growth velocity (cm/year)	Continuous	Q2W, Q4W, Overall	Pre-treatment vs Post-treatment	Secondary efficacy analysis	Pre-treatment, Baseline, Week16, 24, 40, 56, 64, 88, 112, 136, 160	One sample t test (or sign test)	One sample t test (or sign test)	One sample t test (or sign test)
			Pre-treatment vs Post-treatment	Supportive analysis	Pre-treatment, Baseline, Week16, 24, 40, 56, 64, 88, 112, 136, 160	ANCOVA	ANCOVA	ANCOVA

Endpoints	Scale	Analysis populations	Comparisons	Analysis Type	Data Time Points	Week 40 Analysis	Week 64 Analysis	Week 88/160 Analysis
Growth (standing height Z score)	Continuous	Q2W, Q4W, Overall	Baseline vs Post-baseline	Secondary efficacy analysis	Baseline, Week 40, 64, 88, 160	GEE	GEE	GEE
			Baseline vs Post-baseline	Supportive Analysis	Baseline, Week16, 24, 40, 56, 64, 88, 112, 136, 160	One sample t test (or sign test)	One sample t test (or sign test)	One sample t test (or sign test)
Growth (standing height, sitting height, arm length, leg length)	Continuous	Q2W, Q4W, Overall	Baseline vs post-Baseline	Secondary efficacy analysis	Baseline,Week16, 24, 40,56, 64, 88, 112, 136, 160	Descriptive	Descriptive	Descriptive
Other Clinical outcomes*	Continuous	Q2W, Q4W, Overall	Baseline vs post-baseline	Secondary/ Exploratory efficacy analysis	Baseline, Week16, 24, 40, 56, 64, 88, 112, 136, 160	Descriptive	Descriptive	Descriptive
Key PD	Continuous	Q2W, Q4W, Overall	Baseline vs Post-baseline	Key PD analysis	Every 2 weeks (Q2W) Every 4 weeks (Q4W)	One sample t test (or sign test) on selected visits	One sample t test (or sign test) on selected visits	Descriptive

Note: 1) See Appendix 4 (Schedule of Events) for detailed scheduled visit for X-rays taken for long leg and clinical outcomes. 2) The difference of key endpoints between two regimens (Q2W and Q4W) will be provided by descriptive statistics with 95% C.I.

Appendix 3: Clinical Laboratory Assessments for Safety

Chemistry	**Hematology**	**Urinalysis**
25(OH) D	Hematocrit	Appearance
Alanine aminotransferase (ALT)	Hemoglobin	Color
Alkaline phosphatase (ALP)*	Platelet count	pH
Amylase	Red blood cell (RBC) count	Specific gravity
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		
		24-hour Urine
Carbon dioxide (CO_2)		Calcium
Cholesterol (total)		Calcium/creatinine ratio
Creatinine		Creatinine
Gamma-glutamyl transpeptidase (GGT)		Phosphorus/creatinine ratio
Glucose		
FGF23 (total and unbound)		**2-hour Urine**
Intact parathyroid hormone (iPTH)		Calcium
Lactate deyhydrogenase (LDH)		Phosphorus
Phosphorus*		Creatinine
Potassium		Pregnancy Test (if applicable)
Protein (albumin and total)		
Sodium		
Uric acid		

* Also designated as PD/efficacy parameter

Appendix 4: Schedule of Events

Titration Period Visits

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

	Screening		Baseline[1]	Titration Period [2]								
VISIT TYPE/NUMBER	**SV1**	**SV2[1]**	**V1**	**HH[3] V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
WEEK	**W-4 to -2**	**Day -1**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**
POSNA-PODCI, SF-10			X[1]									
PHARMACOKINETICS												
Serum Pre-Dose KRN23[13]			X	X[14]	X	X				X	X	X
SAFETY												
Vital Signs [15]	X		X	X	X	X	X	X	X	X	X	X
Weight	X		X		X	X	X	X	X	X	X	X
Physical Examination	X	X				X		X			X	
Interval History		X			X	X		X		X		X
Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound [1]	X [10]											X
ECHO [1]			X									X
ECG [1]			X									X
Chemistry, Hematology, Urinalysis [16]	X[6]		X			X		X				X
Serum 25(OH) D	X											X
Serum Calcium [6]	X	X[6]	X	X	X	X	X	X	X	X	X	X
Serum Creatinine [6]		X[6]	X		X		X	X			X	X
Serum iPTH	X	X						X				
Serum FGF23 [13]	X[17]	X[17]						X				X
Anti-KRN23 antibody (HAHA) [13, 18]			X									X
Pregnancy Test[19]	X		X			X		X		X		X

	Screening		Baseline[1]	Titration Period [2]								
VISIT TYPE/NUMBER	SV1	SV2[1]	V1	HH[3] V2	V3	V4	V5	V6	V7	V8	V9	V10
WEEK	W-4 to -2	Day -1	W0	W1	W2	W4	W6	W8	W10	W12	W14	W16
DOSE ADJUSTMENT (AS NEEDED)						X		X		X		X
DRUG ADMINISTRATION[20]			Q2, Q4		Q2	Q2, Q4	Q2	Q2, Q4	Q2	Q2, Q4	Q2	Q2, Q4

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

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

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

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

5 PHEX mutation analysis will be performed for all subjects.

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

7 2-hour urine collections for TmP/GFR, TRP, and urinary calcium

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

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

10 Screening results will be treated as baseline data

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

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

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

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

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

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

[16] Serum chemistry panels may include PD parameters (i.e. serum phosphorus and ALP), and safety parameters of interest (i.e. calcium) to avoid duplication of testing

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

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

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

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

Treatment Period Visits (Weeks 18 – 40)

	Treatment Period [21]											
VISIT TYPE/NUMBER	HH [22] V11	V12	HH V13	V14	HH V15	V16	HH V17	V18	HH V19	V20	V21	V22 [34]
WEEK	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36	W38	W40
PD MEASURES												
Serum Phosphorus [23]		X	X	X		X	X	X		X	X	X
$1,25(OH)_2$ D [23]						X					X	X
2-hour urine [23,24]				X							X	X
24-hour urine [25]												X
Bone biomarkers: P1NP, CTx, ALP, BALP [23]												X
EFFICACY MEASURES												
Growth (standing height, sitting height, arm length and leg length)				X								X
Bilateral PA hand/wrist and AP knee X-ray												X
Intercondylar and Intermalleolar distance												X
XtremeCT of forearm, tibia [26]												
6MWT, BOT-2, HHD				X								X
POSNA-PODCI, SF-10				X								X
PHARMACOKINETICS												
Serum Pre-Dose KRN23[27]										X	X	X
SAFETY												
Vital Signs [28]	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X		X		X		X		X	X	X
Physical Examination		X						X				X

	Treatment Period [21]											
VISIT TYPE/NUMBER	**HH [22] V11**	**V12**	**HH V13**	**V14**	**HH V15**	**V16**	**HH V17**	**V18**	**HH V19**	**V20**	**V21**	**V22 [34]**
WEEK	**W18**	**W20**	**W22**	**W24**	**W26**	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**
Interval History		X		X		X		X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound												X
ECHO												X
ECG												X
Chemistry, Hematology, Urinalysis [29]				X								X
Serum 25(OH) D								X				
Serum Calcium [23]		X	X	X		X	X	X		X	X	X
Serum Creatinine [23]				X							X	X
Serum iPTH		X				X				X		
Serum FGF23 [27]						X					X	
Anti-KRN23 antibody (HAHA) [27, 30]				X						X		
Pregnancy Test [31]		X		X		X		X		X		X
DOSE ADJUSTMENT (AS NEEDED)[32]				X				X				X
DRUG ADMINISTRATION [33]	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2, Q4

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

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

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

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

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

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

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

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

[29] 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

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

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

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

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

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

Treatment Period Visits (Weeks 42 – 64)

	Treatment Period [35]											
VISIT TYPE/NUMBER	HH [36] V23	HH V24	V25	HH V26	HH V27	HH V28	HH V29	V30	HH V31	HH V32	HH V33	V34
WEEK	W42	W44	W46	W48	W50	W52	W54	W56	W58	W60	W62	W64[47]
PD MEASURES												
Serum Phosphorus [37]			X	X			X	X			X	X
$1,25(OH)_2$ D [37]							X	X			X	X
2-hour urine [37, 38]												X
24-hour urine [39]												X
Bone biomarkers: P1NP, CTx, ALP, BALP [37]												X
EFFICACY MEASURES												
Growth (standing height, sitting height, arm length and leg length)								X				X
Bilateral PA hand/wrist and AP knee X-ray												X
Standing long leg X-ray												X
Intercondylar and Intermalleolar distance												X
XtremeCT of forearm, tibia [40]												X
6MWT, BOT-2, HHD												X
POSNA-PODCI, SF-10												X
Serum Pre-DoseKRN23 [43]								X				X
SAFETY												
Vital Signs [41]	X	X	X	X	X	X	X	X	X	X	X	X
Weight			X					X				X
Physical Examination			X					X				X

	Treatment Period [35]											
VISIT TYPE/NUMBER	**HH [36] V23**	**HH V24**	**V25**	**HH V26**	**HH V27**	**HH V28**	**HH V29**	**V30**	**HH V31**	**HH V32**	**HH V33**	**V34**
WEEK	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**	**W54**	**W56**	**W58**	**W60**	**W62**	**W64[47]**
Interval History			X					X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Renal Ultrasound												X
ECHO												X
ECG												X
Chemistry, Hematology, Urinalysis [42]			X					X				X
Serum 25(OH) D			X									X
Serum Calcium [37]			X	X			X	X			X	X
Serum Creatinine [37]												X
Serum iPTH			X					X				X
Serum FGF23 [43]												X
Anti-KRN23 antibody (HAHA) [43,44]								X				X
Pregnancy Test [45]			X			X		X		X		X
DRUG ADMINISTRATION [46]	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2 Q4	Q2	Q2

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

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

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

[38] 2-hour urine collections for TmP/GFR, TRP, and urinary calcium

[39] 24-hour urine collections for urinary phosphorus, calcium, creatinine, and GFR

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

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

[42] 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

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

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

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

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

[47] The Week 64 visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days. Radiography (x-rays), XtremeCT, 6MWT, BOT-2, HHD and ECHO will not be performed at the ET Visit if the assessment was conducted within 3 months of termination. XtremeCT will be performed for ET visits occurring between Week 40 and Week 64.

Treatment Extension Period Visits (Weeks 66 – 160)

	Treatment Extension Period[48]										Safety Visit[63]
VISIT TYPE/NUMBER	**HH[49]**	**HH V36**	**HH V37**	**HH V39**	**HH V40**	**HH V41**	**V46**	**HH V52**	**V58**	**V70**	**V82**	**V83**
	Q2	**W68**	**W70**	**W74**	**W76**	**W78**	**W88**	**W100**	**W112**	**W136**	**W160/ET[62]**	**W172**
PD MEASURES												
Serum Phosphorus[50,51]		X[51]		X[51]		X	X	X	X	X	X	X
$1,25(OH)_2$ D[50,51]		X[51]		X[51]		X	X	X	X	X	X	X
2-hour urine[50,52]							X		X	X	X	
24-hour urine[53]							X		X	X	X	
Bone biomarkers: ALP[50]							X		X	X	X	
EFFICACY MEASURES												
Growth (standing height, sitting height, arm length and leg length)							X		X	X	X	
Bilateral PA hand/wrist X-ray							X				X	
Bilateral AP knee X-ray							X					
Standing long leg X-ray							X				X	
6MWT							X					
POSNA-PODCI, SF-10							X		X	X	X	
PHARMACOKINETICS												
Serum Pre-DoseKRN23 [54]							X		X	X	X	
SAFETY												
Vital Signs[55]	X[56]	X			X		X	X	X	X	X	X
Weight							X		X	X	X	
Physical Examination							X		X	X	X	X

	Treatment Extension Period[48]											Safety Visit[63]
VISIT TYPE/NUMBER	**HH[49]**	**HH V36**	**HH V37**	**HH V39**	**HH V40**	**HH V41**	**V46**	**HH V52**	**V58**	**V70**	**V82**	**V83**
	Q2	**W68**	**W70**	**W74**	**W76**	**W78**	**W88**	**W100**	**W112**	**W136**	**W160/ET[62]**	**W172**
Interval History							X		X	X	X	
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X
Renal Ultrasound							X		X	X	X	
ECHO							X		X	X	X	
ECG							X		X	X	X	
Chemistry, Hematology, Urinalysis[57]							X		X	X	X	X
Serum 25(OH) D							X		X	X	X	
Serum Calcium[50]		X		X		X	X		X	X	X	X
Serum Creatinine[50]							X		X	X	X	
Serum iPTH							X		X	X	X	
Serum FGF23[54]							X		X	X	X	X
Anti-KRN23 antibody (HAHA)[53,58]							X		X	X	X	
Pregnancy Test[59]	X[57]	X		X		X	X	X	X	X	X	
DOSE TITRATION[60]			X		X							
DRUG ADMINISTRATION[61]	Q2	X	X	X	X	X	X	X	X	X		

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

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

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

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

[52] 2-hour urine collections for TmP/GFR, TRP, and urinary calcium

[53] 24-hour urine collections for urinary phosphorus, calcium, creatinine, and GFR

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

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

[56] At home health visits during Weeks 66-160, vital signs will be measured every 4 weeks and will consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg) and HR (beats per minute). Obtain at the beginning of each visit before any additional assessments are completed and after the subject has rested for 5 minutes. A second BP measurement should be obtained at the end of the study visit after all procedures have been performed.

[57] 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

[58] Blood draws for Anti-KRN23 antibody will take place at Week 136 or Early Termination; no additional sample is needed at Week 160. If the development of anti-KRN23 antibodies is suspected in a given subject, samples may be obtained at additional time points, and may include additional blood volume required to perform a neutralization assay on a case-by-case basis, if warranted.

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

[60] Dose titration during the Treatment Extension Period will apply only to subjects transitioning from Q4 to Q2 dosing.

[61] Subjects will be dosed at Q2 week intervals (± 5 days and no fewer than 8 days apart). Subjects should be observed for 3-4 hours following the first dose of study drug. Subjects should be observed for 30 minutes following subsequent doses of study drug.

[62] For early termination visit(s) (if applicable) the assessments performed should be those scheduled for the closest major visit (ie, Week 16, 40, 64, 88, 112, 136, or 160). These visits or the ET visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days. Radiography (x-rays), XtremeCT, 6MWT, BOT-2, HHD and ECHO will not be performed at the ET Visit if the assessment was conducted within 3 months of termination. XtremeCT will be performed for ET visits occurring between Week 40 and Week 64.

[63] 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 160 visit. Every reasonable effort should be made to have subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic for the final safety visit will be given the option of providing blood and urine samples as part of a HH visit.

Appendix 5: RSS Data Collection Form

WRIST

GRADE DEFINITIONS FOR RADIUS AND ULNA *based on radiographic features below*	
1	Widened growth plate, irregularity of metaphyseal margin, but without concave cupping
2	Metaphyseal concavity with fraying of margins

Grade radius *circle 1 or 2*	RADIUS	1
		2
Grade ulna *circle 1 or 2*	ULNA	1
		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*
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, 2, or 3*

FEMUR
1
2
3

Determine multiplier for femur *circle 0.5 or 1*

Based on portion of growth plate affected

≤ one condyle or plateau affected	0.5
Two condyles or plateaus affected	1

Grade tibia *circle 1, 2, or 3*

TIBIA
1
2
3

Determine multiplier for tibia *circle 0.5 or 1*

Based on portion of growth plate affected

≤ one condyle or plateau affected	0.5
Two condyles or plateaus affected	1

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

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Appendix 6: 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 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: Normal Muscle Strength Calculation for HHD

Normal grip force table (De Smet and Vercammen 2001)

TABLE 2. *Grip force in right-handed and left-handed boys and girls, aged 5 years to 15 years, dominant and non-dominant hands*

Age (years)	Hand	Boys				Girls			
		Right handed		Left handed		Right handed		Left handed	
		Grip force	SD	Grip force	SD	Grip force	SD	Grip force	SD
5	Dominant	7.6	1.89	10.3	2.27	6.9	1.54	6.7	1.25
	Nondominant	7.3	1.61	9.7	3.16	6.2	1.79	6.7	1.25
6	Dominant	9.8	1.41	6.0	0.00	10.0	1.41	9.5	0.50
	Nondominant	8.2	1.67	9.0	0.00	8.7	0.88	10.0	0.00
7	Dominant	11.4	1.57	10.0	0.00	9.6	2.79	10.0	0.00
	Nondominant	10.6	1.80	10.0	0.00	8.7	2.94	10.0	0.00
8	Dominant	13.5	3.59	10.3	1.07	11.2	1.48	13.0	0.70
	Nondominant	13.7	2.81	12.0	1.41	11.2	1.77	11.8	2.28
9	Dominant	15.0	4.07	19.0	0.00	14.4	2.01	–	–
	Nondominant	14.1	4.36	18.0	0.00	14.5	2.21	–	–
10	Dominant	18.8	4.12	18.5	2.50	15.3	4.24	–	–
	Nondominant	18.0	3.76	17.5	0.50	14.9	3.75	–	–
11	Dominant	21.8	4.73	18.5	0.50	18.5	2.59	11.0	0.00
	Nondominant	20.6	3.59	18.5	0.50	17.5	3.48	12.0	0.00
12	Dominant	24.1	3.45	22.3	3.16	24.6	4.78	20.0	3.27
	Nondominant	22.6	3.05	22.2	3.15	22.8	4.88	18.7	1.70
13	Dominant	29.9	6.71	23.6	7.96	22.5	5.36	20.2	2.50
	Nondominant	27.6	6.25	21.8	8.59	25.2	4.59	19.4	4.22
14	Dominant	34.3	6.64	38.8	7.02	27.6	4.62	33.0	7.81
	Nondominant	32.5	6.56	35.5	6.69	25.8	3.84	32.3	6.52
15	Dominant	38.4	8.46	41.0	6.32	29.1	4.53	31.0	3.67
	Nondominant	34.6	7.98	40.8	3.37	28.2	3.38	30.5	3.20

SD, Standard deviation.

Equations for normal strength calculation for knee and hip muscle groups (Eek et al. 2006)

Table 8: Equation for 3 Independent Variables and Muscle Strength (Nm) and With Coefficient of Correlation

Muscle Group	Regression Equation	R^2
ln(shoulder abductors)	$=-1.00+0.90\times\ln(age)+0.55\times\ln(weight)-0.09\times(age\times sex)$	.797
ln(elbow extensors 1)	$=-0.92+0.45\times\ln(age)+0.78\times\ln(weight)+0.12\times(age\times sex)$	.774
ln(elbow extensors 2)	$=-0.95+0.51\times\ln(age)+0.70\times\ln(weight)+0.11\times(age\times sex)$	.823
ln(elbow flexors)	$=-1.03+0.76\times\ln(age)+0.64\times\ln(weight)+0.05\times(age\times sex)$	.865
ln(wrist dorsiflexors)	$=-3.68+0.64\times\ln(age)+1.02\times\ln(weight)+0.39\times(age\times sex)$	.709
ln(hip extensors 1)	$=-0.83+1.05\times\ln(age)+0.69\times\ln(weight)+0.04\times(age\times sex)$	.812
ln(hip extensors 2)	$=-1.72+1.39\times\ln(age)+0.71\times\ln(weight)+0.02\times(age\times sex)$	.914
ln(hip flexors 1)	$=-1.41+1.08\times\ln(age)+0.79\times\ln(weight)+0.04\times(age\times sex)$	.898
ln(hip flexors 2)	$=-0.74+0.80\times\ln(age)+0.73\times\ln(weight)+0.04\times(age\times sex)$	.866
ln(hip abductors)	$=-1.68+0.86\times\ln(age)+1.01\times\ln(weight)+0.03\times(age\times sex)$	.920
ln(hip adductors)	$=-1.56+1.09\times\ln(age)+0.80\times\ln(weight)+0.07\times(age\times sex)$	.904
ln(knee extensors)	$=-0.93+0.55\times\ln(age)+1.01\times\ln(weight)+0.03\times(age\times sex)$	.931
ln(knee flexors 1)	$=-1.34+0.72\times\ln(age)+0.95\times\ln(weight)+0.03\times(age\times sex)$	.922
ln(knee flexors 2)	$=-1.25+0.77\times\ln(age)+0.82\times\ln(weight)+0.05\times(age\times sex)$	.888
ln(ankle dorsiflexors)	$=-1.15+0.82\times\ln(age)+0.62\times\ln(weight)+0.01\times(age\times sex)$	.823

NOTE. Sex is included when age is ≥13 (boy = 1, girl = 0).

Note: for knee flexors muscle group, use equation knee flexors 1; for hip flexors muscle group, use equation hip flexors 1; for hip extensors muscle group, use equation hip extensors 1.

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

Immunogenicity: 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
Hypersensitivity	Application site rash
Hypersensitivity	Application site recall reaction

Category	PT
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
Hypersensitivity	Eczema nummular
Hypersensitivity	Eczema vaccinatum

Category	PT
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
Hypersensitivity	Injection site vasculitis
Hypersensitivity	Instillation site hypersensitivity

Category	PT
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
Hypersensitivity	Rash morbilliform
Hypersensitivity	Rash neonatal

Category	PT
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
Hypersensitivity	Urticaria vesiculosa
Hypersensitivity	Vaginal exfoliation

Category	PT
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
Ectopic calcification	Heart valve stenosis

Category	PT
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

Gastrointestinal events: based on narrow SMQ “Gastrointestinal nonspecific inflammation and dysfunctional conditions”

Category	PT
Gastrointestinal	Acid peptic disease
Gastrointestinal	Duodenogastric reflux
Gastrointestinal	Dyspepsia
Gastrointestinal	Gastrooesophageal reflux disease
Gastrointestinal	Gastrooesophageal sphincter insufficiency
Gastrointestinal	Chronic gastritis
Gastrointestinal	Colitis
Gastrointestinal	Duodenitis
Gastrointestinal	Enteritis
Gastrointestinal	Erosive duodenitis
Gastrointestinal	Erosive oesophagitis

Category	PT
Gastrointestinal	Feline oesophagus
Gastrointestinal	Functional gastrointestinal disorder
Gastrointestinal	Gastric mucosa erythema
Gastrointestinal	Gastritis
Gastrointestinal	Gastritis erosive
Gastrointestinal	Gastroduodenitis
Gastrointestinal	Gastrointestinal erosion
Gastrointestinal	Gastrointestinal mucosa hyperaemia
Gastrointestinal	Gastrointestinal mucosal exfoliation
Gastrointestinal	Haemorrhagic erosive gastritis
Gastrointestinal	Intestinal angioedema
Gastrointestinal	Oesophageal mucosa erythema
Gastrointestinal	Oesophagitis
Gastrointestinal	Reactive gastropathy
Gastrointestinal	Reflux gastritis
Gastrointestinal	Remnant gastritis
Gastrointestinal	Ulcerative gastritis
Gastrointestinal	Abdominal discomfort
Gastrointestinal	Abdominal distension
Gastrointestinal	Abdominal pain
Gastrointestinal	Abdominal pain lower
Gastrointestinal	Abdominal pain upper
Gastrointestinal	Abdominal symptom
Gastrointestinal	Abdominal tenderness
Gastrointestinal	Abnormal faeces
Gastrointestinal	Aerophagia
Gastrointestinal	Anorectal discomfort
Gastrointestinal	Bowel movement irregularity
Gastrointestinal	Change of bowel habit
Gastrointestinal	Constipation
Gastrointestinal	Defaecation urgency
Gastrointestinal	Diarrhoea
Gastrointestinal	Epigastric discomfort
Gastrointestinal	Eructation
Gastrointestinal	Faecal volume decreased
Gastrointestinal	Faecal volume increased
Gastrointestinal	Faeces hard
Gastrointestinal	Faeces soft
Gastrointestinal	Flatulence
Gastrointestinal	Frequent bowel movements
Gastrointestinal	Gastrointestinal pain
Gastrointestinal	Gastrointestinal sounds abnormal

Category	PT
Gastrointestinal	Gastrointestinal toxicity
Gastrointestinal	Infrequent bowel movements
Gastrointestinal	Nausea
Gastrointestinal	Non-cardiac chest pain
Gastrointestinal	Oesophageal discomfort
Gastrointestinal	Oesophageal pain
Gastrointestinal	Vomiting

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