STATISTICAL ANALYSIS PLAN

Title	An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH)
Protocol:	UX023-CL205
Investigational Product:	KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])
Phase:	2
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
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ABBREVIATIONS

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
AE	Adverse Event
ALP	Alkaline Phosphatase
BP	Blood Pressure
CRF	Case Report Form
CDC/NCHS	Centers for Disease Control/National Center for Health Statistics
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
iPTH	Intact Parathyroid Hormone
IP	Investigational Product
ISR	Injection Site Reaction
HAHA	Human Anti-Human Antibody
HR	Heart Rate
HLT	High-Level Term
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
RR	Respiratory Rate
RSS	Rickets Severity Score
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
XLH	X-linked Hypophosphatemia

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the UX023-CL205 Protocol Amendment 1 dated 28 March 2016. The SAP for Week 4 analysis was pre-specified in a separate document (UX023-CL205 Statistical Analysis Plan Week 4 Analysis) before the analysis took place.

2 STUDY OBJECTIVE(S)

2.1 Primary Objective

The primary objectives of the study are to:

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

2.2 Other Objective

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

- Effects of KRN23 on rickets
- Effects of KRN23 on growth and lower extremity deformity
- Pre-dose KRN23 drug concentration levels

3 STUDY DESIGN

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

3.1 Study Population

UX023-CL205 is a multicenter, open-label, Phase 2 study in children from 1 to 4 years old with XLH who are naïve to therapy or have previously received standard therapy with oral phosphate and active vitamin D to assess the safety, PD, and efficacy of KRN23 administered via subcutaneous injections Q2W for a total of 64 weeks.

3.2 Dosage and Administration

The length of this study will be 64 weeks. All subjects will receive KRN23 at a starting dose of 0.8 mg/kg every two weeks (Q2W). The dose may be increased to 1.2 mg/kg at any time if a subject meets the following dose adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus.

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

Serum phosphorus assessments will be conducted at the clinic at the ends of Weeks 1, 4, 8, 12, 15, 20, 32, 40, 48, 56 and 64. Growth (recumbent length/standing height) assessment will be conducted at the ends of Week 12, 24, 40 and 64. Bilateral AP knee X-rays, bilateral PA hand/wrist X-rays and standing long leg X-rays will be conducted at Week 40 and 64. The schedule of assessments is shown in Appendix 3.

3.3 Blinding and Randomization Methods

The UX023-CL205 is an open-label Phase 2 study; all subjects will receive same starting dose Q2W. Blinding or randomization methods are not applicable for this study.

3.4 Stratification Factors

Stratification factors are not applicable for this study.

3.5 Sample Size Considerations

The study will enroll approximately 10 pediatric subjects between 1 and 4 years old, inclusive, with clinical findings consistent with XLH including hypophosphatemia and radiographic evidence of rickets (at least 5 subjects will have a rickets severity score (RSS) at the knee of ≥1.5 points at Screening), and a confirmed *PHEX* mutation or variant of uncertain significance. To maintain a level of gender balance, no more than 7 subjects of either gender will be enrolled.

3.6 Planned Analyses

The primary analysis is planned at Week 40. Additional efficacy and safety analyses will be conducted at Week 64. A Week 24 analysis has been planned as an administrative analysis to support regulatory interaction. The analysis will include safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and growth assessments; rickets assessment from radiographs will not be included as the radiographs are not scheduled until Week 40. Additional administrative analyses may be done at the sponsor's discretion to support regulatory submission or product planning.

3.7 Data Monitoring Committee

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

4 STUDY ENDPOINTS, COVARIATES

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

4.1 Primary Efficacy Endpoints

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

4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include

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

4.3 Other Efficacy Endpoints

Other efficacy endpoints include

- Change from baseline over time in serum $1,25(OH)_2D$ and urinary phosphorus
- Change in rickets at Week 40 and 64 as assessed by RGI-C wrist score and knee score
- Change from baseline in RSS wrist score and knee scores at Week 40 and 64

4.4 Safety Endpoints

General Safety Variables will include the following:

- Treatment Emergent Adverse Events (TEAEs)
- Treatment Related TEAEs
- Treatment Emergent Serious Adverse Events (TESAEs)
- Events to monitor:
  - Injection site reaction (High-Level Term)
  - Immunogenicity

  - Hyperphosphatemia
  - Ectopic mineralization
  - Restless leg syndrome
- Grade 3/4 TEAEs
- TEAEs leading to discontinuation from the study
- TEAEs leading to discontinuation from the study drug treatment
- TEAEs leading to death
- Vital signs and weight
- Physical examinations
- Estimated Glomerular Filtration Rate (eGFR)
- Chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (serum calcium, intact parathyroid hormone[iPTH], 25-hydroxyvitamin D [25(OH)D], amylase, lipase, and creatinine; and urinary calcium and creatinine)
- FGF23
- Anti-KRN23 antibody (HAHA) testing and Dose-Limiting Toxicities (DLT)
- Concomitant medications

Ectopic Mineralization Safety Assessments include:

- Renal ultrasound
- Electrocardiogram (ECG)

4.5 Drug Concentration Measure

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

4.6 Covariate(s)

Baseline measures will be used as covariates. For example, baseline RSS score will be used in the modeling for change in baseline in RSS score and for RGI-C score. Age and gender may also be used as covariates in growth endpoint models.

5 DEFINITIONS

5.1 Baseline

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

5.2 Study Day

Study day is calculated as:

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

5.3 Age

Unless specified, the age will be derived based on the informed consent date: Age = (Informed Consent Date – Birth Date +1)/365.25. The age will be rounded down to the nearest x.x years and keep one decimal place.

5.4 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-CL205 study with the Baseline image on the left (Image A) and Post-Treatment image (Week 40 and Week 64) on the right (Image B). Raters will be asked to evaluate change in Image B for the abnormalities they consider to be present in the Baseline Image A. This exercise will be performed for the distal radius and ulna from the bilateral wrist X-rays, and the distal femur and proximal tibia and fibula from the bilateral knee X-rays at Week 40 and Week 64. At Week 64, Image A (presented on the left) will remain the Baseline image and Image B (presented on the right) will be the post-treatment image from Week 64.

In addition to bilateral wrists and knees, the Week 40 and Week 64 RGI-C analysis will include a rating of the full femur, tibia and fibula from the bilateral standing long leg film with the Baseline standing long leg image on the left (Image A) and the Week 40 (or Week 64) standing long leg image on the right (Image B). The RGI-C is scored using a pre-defined methodology (Biomedical Systems Independent Review Manual July 2015). See data collection form in Appendix 5.

Prior to rating, the three raters will be trained to gain consensus on the terminology used to describe XLH-related radiographic abnormalities and to establish inter-rater reliability. Following the training, each rater will independently complete a quiz involving the rating of practice images to ensure the success of the training and the reliability of scores among the raters. For the Week 40 and Week 64 analysis, each of the three raters will perform the rating exercise at a work station at the central imaging facility. Only one rater can be present at the facility at any given time to prevent group rating or sharing of scores. Each rater will be presented with side-by-side images of the wrist and knee with Baseline on the left (Image A) and Post-Treatment on the right (Image B). Raters will be asked to evaluate the presence of various abnormalities in the wrist and knee in Image A and change in those abnormalities in Image B. At the Week 40 and Week 64 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 (RGI-C global 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. 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 lower limb deformity 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.

RGI-C response is defined as an averaged RGI-C global score of at least +2.0 (i.e. substantial healing of rickets).

5.5 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 the rater 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-CL205 X-rays taken at Baseline, Week 40 and Week 64. For the X-rays taken during the

UX023-CL205 study, Dr. Thacher will be blinded to the study visit at which the X-ray was taken, adherence to the study protocol and duration of treatment. Each rating performed by Dr. Thacher is entered into an EDC system at the time of the rating and transferred electronically to a central imaging facility. The scores cannot be retrieved from the system by Dr. Thacher after submission. See RSS data collection form in Appendix 4.

5.6 Growth

5.6.1 Standing height/recumbent length Z-score and Percentile

Recumbent length will be measured in subjects < 2 years old or those unable or unwilling to stand for the measurement. Standing height/recumbent length measurements prior to treatment will be abstracted from medical records where available.

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

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

The data files used are:

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

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

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

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

5.6.2 Weight Z-score and Percentile

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

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

5.7 Blood Pressure Percentile

The blood pressure percentile will be derived based on the Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents (NHLBI 2005). See Appendix 6 for details in deriving blood pressure percentile adjusting for age, gender and height.

5.8 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 7 for details in deriving heart rate percentile category adjusting for age and gender.

5.9 Events to Monitor

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

- 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”.
- Hyperphosphatemia AE: Defined by using PTs: “Hyperphosphataemia”, “Blood phosphorus increased”, “Blood phosphorus abnormal”.
- Ectopic calcification related AE: There is no available SMQ. Ectopic calcification related AE is defined using a MedDRA search of ‘calcification’.
- Restless leg syndrome AE: Defined by PTs “Restless legs syndrome”, “Restlessness”, “Akathisia”, “Sensory disturbance”, “Psychomotor hyperactivity”, “Limb discomfort”, “Neuromuscular pain”, “Formication”.

Please see the search criteria in Appendix 8 for more details.

5.10 Dose Limiting Toxicity

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

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

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

5.11 Duration of SOC

The definition for duration of SOC is as the following:

Duration of SOC = End date of the last SOC taken - start date of first SOC taken + 1 day

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 inform consent date
- If year is known the month is missing, then assign "December 31st". If this imputed date is after the informed consent date, use one day prior to the informed consent 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 the informed consent date, use one day prior to the informed consent date instead

6 ANALYSIS POPULATIONS

6.1 Efficacy Analysis Set

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

6.2 Safety Analysis Set

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

6.3 Pharmacokinetic (PK) and Pharmacodynamic (PD) Analysis Set

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

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

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

7.2 Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through 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 or database snapshot.

If not specified, only the actual data (not imputed data) will be presented in listings.

7.2.1 Missing Date Information for Adverse Events and Concomitant Medications

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

Missing Start Dates

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

Missing Stop Dates for events not ongoing

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded

as resolved/recovered, all efforts should be made to obtain the date from the Investigator.

- If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date as the date of study completion / discontinuation/ data cutoff.

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

7.2.2 Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of investigational product, a causality of "definitely related" will be assigned. The imputed values for causal relationship to investigational product will be used for the incidence summary; the values will be shown as missing in the data listings.

7.3 Unscheduled and Early Termination Visits

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

Unscheduled visits that occurred after the date of initiation of the first dose will be mapped to the post-baseline scheduled visit with the closet target study day (refer to Section 5.2 for study day definition and Appendix 3 for the schedule of events). If the unscheduled visit is in the middle of two scheduled visits, map to the later scheduled visit.

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

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

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

7.4 Software

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

8 STATISTICAL METHODS OF ANALYSES

8.1 General Principles

The efficacy analyses for PK/PD parameters will be based on PK/PD Analysis Set, other efficacy analyses (RGI-C, RSS and growth) will be based on the Efficacy Analysis Set, and safety analyses will be based on Safety Analysis Set. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, standard error, median, interquartile range (Q1, Q3), minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Statistical tests will be two-sided at the alpha = 0.05 significance level. Two-sided 95% confidence intervals will also be presented. In general, missing data will be treated as missing and no statistical imputation method will be used unless stated otherwise. No adjustment on multiplicity will be made for statistical comparisons unless stated otherwise. All data obtained from the CRFs as well as any derived data will be included in data listings.

8.2 Subject Accountability

The number and percentage of subjects in each study population will be summarized. Screen-failure subjects and the associated reasons for failure to randomize will be tabulated. The number and percentage of subjects who complete the treatment period and of subjects who prematurely discontinue will be presented. The reasons for premature discontinuation from treatment period will be presented.

8.3 Protocol Deviations

All protocol deviations will be presented in listings.

8.4 Investigational Product Administration

The total dose administered and weight-based dose will be summarized by study visit.

8.5 Demographic and Baseline Characteristics

The following demographic parameters and baseline characteristics will be summarized descriptively for the Efficacy Analysis Set:

- Age
- Gender
- Ethnicity
- Race
- Recumbent length/standing height
- Weight
- BMI

- SOC duration, age when SOC initiated
- RSS scores
- XLH biochemical parameters
- PHEX mutation
- Renal ultrasound scores

8.6 Prior and Concomitant Medication

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

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHODRUG version 2015Q3 or the latest version at the time of snapshot/database lock. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject would be counted only once for the coded drug name or therapeutic class.

8.7 Medical History / XLH Medical and Family History

Medical history will be coded by MedDRA version 18.1 or the latest version at the time of snapshot/database lock. Counts and percentages of subjects with medical history will be tabulated by system organ class and preferred term. Subject level listings for the pre-existing medical conditions, XLH medical history and family history will be provided.

8.8 Efficacy Analysis

The efficacy analyses for PD parameters will be performed on PK/PD Analysis Set.
The efficacy analyses for clinical endpoints (RSS, RGI-C and growth) will be performed on Efficacy Analysis Set.

8.8.1 Generalized Estimating Equations Model

By-visit analyses using the Generalized Estimating Equations (GEE) model will be presented for all efficacy parameters. The GEE model will include 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, independence covariance structure will be applied. 95% confidence intervals (CIs) and p-values will be provided for statistical significance assessment. Baseline measures will be used as covariates.

For example, baseline RSS score will be used in the modeling for change in baseline in RSS score and for RGI-C score. Age and gender may also be used as covariates in growth endpoint models.

8.8.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline over time in serum phosphorus. Descriptive statistics will be provided for observed value in serum phosphorus, change from baseline and percentage of change from baseline at each visit. The GEE model will be applied to obtain the 95% CIs and p-values. Baseline serum phosphorus measures may be included as covariate in the model.

The proportion of subjects achieving the normal range (3.2-6.1 mg/dL) will be reported. The percentage of time a subject reaches the normal range of serum phosphorus will also be summarized.

In addition, graphs showing the change of serum phosphorus over time will be provided.

8.8.3 Secondary Efficacy Endpoints

8.8.3.1 RGI-C

The efficacy analyses evaluating RGI-C scores will be performed at Week 40 and Week 64. The GEE model will be applied to each RGI-C score type (wrist, knee, global and lower limb deformity) separately to obtain 95% CIs and p-values. Baseline RSS score will be included as a covariate in the model; age may also be included as covariate in the model.
As sensitivity analysis, t test will be performed for RGI-C scores at Week 40 and Week 64. In the case when model assumption is not met, analyses using alternative methods such as non-parametric tests will be performed.

Descriptive statistics for all RGI-C scores will be provided in both continuous and categorical summary. RGI-C responder rate will be calculated. Summary of abnormality at baseline and change in abnormality at Week 40 and Week 64 will also be presented.

8.8.3.2 RSS

The efficacy analyses evaluating change from Baseline of RSS scores will be performed at Week 40 and Week 64. The GEE model will be applied to each RSS score type (wrist, knee and total) separately to obtain 95% CIs and p-values. Baseline RSS score and age may be included as covariate in the model. As sensitivity analysis, t test will be performed for RSS scores at Week 40 and Week 64. In the case when the model assumption is not met, analyses using alternative methods such as non-parametric tests will be performed.

Descriptive statistics for all RSS scores and change from baseline in RSS score will be provided in both continuous and categorical summary.

8.8.3.3 Growth

Growth in standing height/recumbent length and weight will be summarized over time in observed value, Z-score and percentile. Individual subject growth curves will be plotted with CDC growth charts as reference. Historical growth records may be used to evaluate change in growth velocity from pre- to post-baseline.

For standing height/recumbent length Z-score, the GEE model will be applied to obtain 95% CIs and p-values on all scheduled visits. Baseline Z score, age and gender may be included as covariate in the model.

8.8.4 Other Pharmacodynamics Parameters

Other PD parameters such as ALP, $1,25(OH)_2D$ and urine phosphorus will be summarized descriptively. Summary statistics will be provided for observed value, change from baseline and percentage of change from baseline at each visit. Graphic display will be provided to show the change in PD parameters over time.

8.9 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. The listing of serum KRN23 will also be provided.

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

8.10 Safety Analysis

The safety analysis will be performed using the Safety Analysis Set. The safety parameters will include adverse events (AEs) and clinical laboratory, vital sign, physical examination, renal ultrasounds, and electrocardiographic (ECG) parameters.

8.10.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the MedDRA version 18.1 or the latest version at the time of snapshot/database lock. An AE (classified by preferred term) will be considered as a treatment emergent adverse event (TEAE) if it occurred on or after the first dose and was not present prior to the first dose, or it was present at the first dose but increased in severity during the study.

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 from study or from study drug treatment 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.

Subject incidence of 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. In addition, 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 to assess the trend over time. The summary of incidence over time may also be explored for other events to monitor categories.

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

8.10.2 Safety Lab Parameters

Clinical laboratory data will be summarized by the type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Shift table for iPTH at each scheduled visit will be provided to assess to the normality over time. The frequency and percentage of subjects who experience abnormal clinical laboratory results and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

8.10.3 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, and neurological systems. The number and percentage of subjects with Normal/Abnormal assessment for each body system will be summarized by visit. All physical examination assessments will be listed.

8.10.4 Vital Signs

Blood pressure measurements will be obtained only in children aged 3 and 4 years of age and will only be obtained at clinic visits. The blood pressure will be summarized by study visit in mmHg and percentile to assess the blood pressure change over time. The average of the triple measurements will be used in the summary.

Heart rate and heart rate percentile category will also be summarized by study visit.

8.10.5 Renal Ultrasound

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, a grade shift table summarizing changes from Baseline by time point will also be created.

8.10.6 Electrocardiogram

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

ECG parameters will be summarized by the maximum post-baseline value and maximum change from baseline using the following categories based on FDA guidance (FDA 2015) listed in Table 8.10.6.1.

Table 8.10.6.1: Criteria for ECG Results

ECG Parameter	Categories for Baseline and Maximum Post-Baseline Value	Categories for Maximum Change from Baseline Value
PR Interval	≤200 and >200 msec	≤20 and >20 msec
QRS Interval	≤110 and >110 msec	≤10 and >10 msec
QTc Interval	≤450, >450-≤480, >480-≤500 and >500 msec	≤30, >30-≤60 and >60 msec

.

9 REFERENCES

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10 APPENDICES

Appendix 1: Efficacy Endpoint Summary Table

Endpoints	Scale	Analysis Set	Comparisons	Data Time Points	Week 40 Analysis	Week 64 Analysis
Serum phosphorus	Continuous	PK/PD	Baseline vs. Post-baseline	Refer to Schedule of Events (Appendix 3)	GEE Descriptive Statistics	GEE Descriptive Statistics
RGI-C wrist, knee, global and lower limb deformity scores	Continuous Categorical	Efficacy	Baseline vs. Post-baseline	Baseline, Week 40, 64	GEE Descriptive Statistics	GEE Descriptive Statistics
RSS knee, wrist and total scores	Continuous	Efficacy	Baseline vs. Post-baseline	Baseline, Week 40, 64	GEE Descriptive Statistics	GEE Descriptive Statistics
Growth (standing height/recumbent length)	Continuous	Efficacy	Baseline vs. Post-baseline	Baseline, Week 12, 24, 40, 64	GEE Descriptive Statistics	GEE Descriptive Statistics
Other PD parameters	Continuous	PK/PD	Baseline vs. Post-baseline	Refer to Schedule of Events (Appendix 3)	Descriptive Statistics	Descriptive Statistics

Appendix 2: Clinical Laboratory Assessments for Safety

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

Chemistry	Hematology	Urinalysis[1]
Potassium		Phosphorus
Protein (albumin and total)		
Sodium		
Uric acid		

[1]Urinalysis to be conducted if possible based on urine volume collected.
[2]Also designated as a PD/efficacy parameter

Appendix 3: Schedule of Events

Table 10.1: Schedule of Events – Screening, Baseline, and Treatment Period Weeks 1-30

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

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

See footnotes after Table 10.2

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

	Treatment Period[3]																	Safety Visit[13]
Visit Type/Number	**V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**V27**	**HH V28**	**HH V29**	**HH V30**	**V31**	**HH V32**	**HH V33**	**HH V34**	**V35**	**V36**
Week	**W 32**	**W 34**	**W 36**	**W 38**	**W 40**	**W 42**	**W 44**	**W 46**	**W 48**	**W 50**	**W 52**	**W 54**	**W 56**	**W 58**	**W 60**	**W 62**	**W64/ ET[12]**	**W 76**
PD MEASURES																		
Serum Phosphorus [6]	X				X				X				X				X	X
$1,25(OH)_2$ D [6]	X				X				X				X				X	X
Spot urine [6,7]	X				X				X				X				X	X
ALP only [6]					X												X	
EFFICACY MEASURES																		
Growth (length/standing height)					X												X	
Bilateral AP knee X-rays [2]					X												X	
Bilateral PA hand/wrist X-rays [2]					X												X	
Standing long leg X-ray [2]					X												X	
PHARMACOKINETICS																		
Serum Pre-Dose KRN23[6]					X													
SAFETY																		
Vital Signs [8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X				X				X				X					
Physical Examination					X												X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Treatment Period[3]																	Safety Visit[13]
Visit Type/Number	**V19**	**HH V20**	**HH V21**	**HH V22**	**V23**	**HH V24**	**HH V25**	**HH V26**	**V27**	**HH V28**	**HH V29**	**HH V30**	**V31**	**HH V32**	**HH V33**	**HH V34**	**V35**	**V36**
Week	**W 32**	**W 34**	**W 36**	**W 38**	**W 40**	**W 42**	**W 44**	**W 46**	**W 48**	**W 50**	**W 52**	**W 54**	**W 56**	**W 58**	**W 60**	**W 62**	**W64/ ET[12]**	**W 76**
Renal Ultrasound [2]					X												X	
ECG [2]					X												X	
Chemistry, Hematology, Urinalysis [6,7,10]					X				X				X				X	X
Serum 25(OH)D[6]					X												X	
Serum Calcium [6]	X				X				X				X				X	X
Serum Creatinine [6]	X				X				X				X				X	
Serum iPTH [6]					X												X	
Serum FGF23[6]																	X	
Anti-KRN23 antibody (HAHA) [6, 11]					X													
DRUG ADMINISTRATION	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

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

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

3 Subjects will return to the clinic for site visits at approximately 4-week intervals from Baseline to Week 24 and at 8-week intervals from Week 24 to Week 64. The visit window is ± 3 days

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

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

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

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

[8] At site visits, vital sign measurements consist of seated systolic/diastolic blood pressure (BP) measured in millimeters of mercury (mm Hg), heart rate (HR; beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Blood pressure will only be obtained for subjects age 3 or 4 years. Obtain HR, respiration rate, and temperature at the beginning of each visit before any additional assessments are completed. At the Screening Visit BP should be measured 3 times, 30 seconds apart at the beginning of each visit; 3 additional BP measurements, 30 seconds apart, should be obtained at the end of the study visit after all procedures have been performed. At baseline and post-baseline visits, 3 BP measurements 30 seconds apart, should be obtained at the beginning of the study visit.

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

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

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

[12] Radiography (x-rays) will not be performed at the early termination (ET) visit if the assessment was conducted within 3 months of termination.

[13] An additional safety visit will take place 12 weeks ±1 week after the date of the last study drug administration for those subjects who discontinue treatment, or 12 weeks ±1 week after the Week 64 visit for subjects who complete the study and choose not to enroll immediately in an extension study. This visit is not required for subjects who are eligible and choose to take part in an extension study. Every reasonable effort should be made to have required subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic for the final safety visit will be given the option of providing blood and urine samples as part of a HH visit.

Appendix 4: 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 5: RGI-C Data Collection Form

REGIONAL RATING OF RICKETS

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

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

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

PA HAND/WRIST SINGLE ABNORMALITY RATING

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

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

REGIONAL RATING OF RICKETS

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

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

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

AP KNEES SINGLE ABNORMALITY RATING

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

AP KNEES SINGLE ABNORMALITY RATING

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

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

GLOBAL RATING OF RICKETS

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

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

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

RATING OF LOWER LIMB DEFORMITY

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

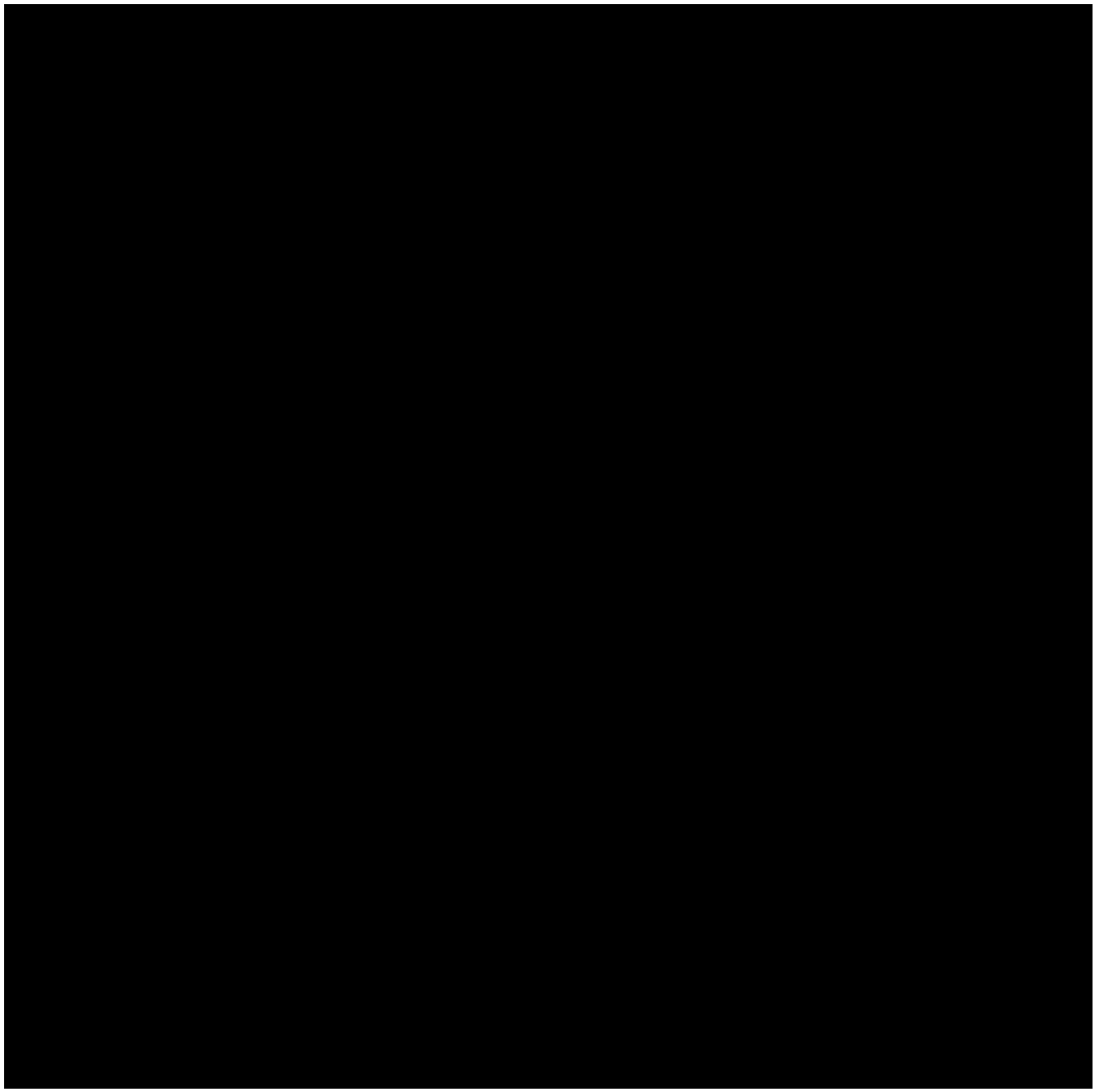
−3	−2	−1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

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

SINGLE ABNORMALITY RATING

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

Appendix 6: Blood Pressure Percentiles by Gender, Age and Height (NHLBI 2005)



Appendix 7: Heart Rate Percentiles by Gender and Age

Appendix 8: 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 urticarial
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

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

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

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

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

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

Hyperphosphatemia: based on selected PTs below

Category	PT
Hyperphosphatemia	Hyperphosphatemia
Hyperphosphatemia	Blood phosphorus increased
Hyperphosphatemia	Blood phosphate abnormal

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

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

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

Restless legs syndrome

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