STATISTICAL ANALYSIS PLAN

Title	**A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH)**
Protocol:	**UX023-CL203**
Investigational Product:	**KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])**
Indication:	**X-linked Hypophosphatemia (XLH)**
IND/EudraCT Number:	**076488**
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STATISTICAL ANALYSIS PLAN AMENDMENT

SUMMARY OF CHANGES

UX023-CL203 Amendment 1

27 April 2016

The UX023-CL203 statistical analysis plan (dated 15 January 2016) has been amended. Important changes in Amendment 1 are summarized below:

1. **Interim Analysis Timing**: Section 3.6 has been updated to reflect the timing of the interim analysis to support regulatory submission.

2. **Events to Monitor**: Section 8.6.1 has been updated so that the events to monitor categories are consistent with the product identified or potential risks.

3. **Analysis of Vital Signs**: Section 8.6.6 has been updated to reflect the standard descriptive analysis for vital signs.

4. **Analysis of ECG**: Section 8.7.2 has been updated to remove the normality or abnormality analysis of the ECG tracing because the overall interpretation of ECG is not collected for the study.

5. **6-Minute Walk Test**: Section 8.8.2.3 has been updated to remove the graph display of 6-minute walk test data because there is only one post-baseline time point (Week 24).

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ABBREVIATIONS

$1,25[OH]_2D$	1,25-dihydroxyvitamin D
3MSCT	3-Minute Stair Climb Test
6MWT	6-Minute Walk Test
AE	Adverse event
ALP	Alkaline phosphatase
BALP	Bone-specific alkaline phosphatase
BMI	Body mass index
BPI	Brief Pain Inventory
CFB	Change from Baseline
CTx	Carboxy terminal cross-linked telopeptide of type I collagen
FGFR1	Fibroblast growth factor receptor 1
FGF23	Fibroblast growth factor 23
GEE	Generalized Estimating Equations
GFR	Glomerular filtration rate
HAHA	Anti-KRN23 antibody
HQRL	Health-related quality of life
iPTH	Intact parathyroid hormone
ISR	Injection site reactions
LVH	Left ventricular hypertrophy
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
P1NP	Procollagen type 1 N-terminal propeptide
PD	Pharmacodynamic
PHEX	Phosphate-regulating gene with Homologies to Endopeptidases on the X-chromosome
PRO	Subject-reported outcome
QOL	Quality of life
QTc	Corrected QT interval
SAE	Serious adverse event
SC	Subcutaneous
SF-36	36-item Short Form Health Survey
SMQ	Standardised MedDRA Query
TEAE	Treatment-emergent adverse event
TmP/GFR	Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate
TRP	Tubular resorption of phosphate
TUG	Timed up and go
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-Linked Hypophosphatemia

1 INTRODUCTION

The purpose of this statistical analysis plan is to provide details of the statistical analyses that have been outlined within the original UX023-CL203 Protocol dated 05 September 2014. The data collected in this study will evaluate the safety and pharmacodynamics of KRN23 in adult subjects with X-Linked Hypophosphatemia.

2 STUDY OBJECTIVES

2.1 Primary Safety and Pharmacodynamics

The primary objectives of this study are to:

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

2.2 Efficacy

The efficacy objectives of this study are to:

- Evaluate changes in underlying skeletal disease by standard radiographs of the legs, feet, and lateral spine as well as any location(s) where the subject is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (< 3 months) fracture
- Evaluate changes in subject-reported outcomes (PROs) and physical function outcomes including:
  - Subject-reported pain – Brief Pain Inventory (BPI)
  - Disability – Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
  - Quality of life (QOL) scores – 36-item Short Form Health Survey (SF-36)
  - Walking ability – 6-Minute Walk Test (6MWT)
  - Balance and agility – Timed Up and Go (TUG) Test

Due to the inability to standardize the number of stairs used for testing at all study sites, the 3MSCT was not collected in this study and is excluded from the final and interim analyses.

3 STUDY DESIGN

3.1 Overall Study Design and Plan

This study is a Phase 2b, open-label, long-term extension study of the completed studies KRN23-INT-001 and KRN23-INT-002 in adult subjects with XLH. The study population will consist of approximately 25 eligible subjects who participated in Kyowa Hakko Kirin Pharma, Incorporated's study KRN23-INT-001 or study KRN23-INT-002 (received at least 2 doses of KRN23). Subjects who were discontinued from KRN23-INT-001 or KRN23-INT-002 due to a TEAE classified as possibly or probably related to treatment may be eligible for participation in this study based on the clinical judgment of the investigator with agreement from the sponsor. The study will be conducted over 72 weeks to assess the long-term safety, immunogenicity, PD, and clinical efficacy of KRN23.

The starting dose of KRN23 at Baseline (Week 0) in this study will be individual for each subject, i.e., the same as a subject's last dose in studies KRN23-INT-001 or KRN23-INT-002 (0.30, 0.60, or 1.0 mg/kg). Dosing will occur at the clinic and the volume will be based on the weight obtained on Day 0.

Up to Week 12, individual subjects who have not reached serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL) at the end of the dose interval may have their doses titrated every 4 weeks to a maximum dose of 1.0 mg/kg based on fasting trough serum phosphorus levels. Doses may be titrated downward if at any point the serum phosphorus level increases above the upper limit of normal (ULN; 4.5 mg/dL). KRN23 injections will be repeated every 4 weeks for the duration of the study (from Week 0 through Week 68), and weight will be reassessed periodically for dose volume adjustments as needed.

A complete schedule of events is included in Appendix 6.

3.2 Study Duration

The planned duration of treatment in this study will be 72 weeks.

3.3 Randomization and Blinding Method of Assigning Subjects to Treatment Groups

All subjects received KRN23 on an open-label basis. Randomization and blinding are not applicable in this study.

3.4 Stratification Factors

Not applicable.

3.5 Determination of Sample Size

The rationale for the sample size for this open-label extension study is based on practical considerations to obtain the needed information to meet study objectives. The sample size of this study is based on the number of subjects who have satisfactorily completed studies KRN23-INT-001 and/or KRN23-INT-002, along with the other eligibility criteria, and have agreed to participate in this long-term extension study. Approximately 25 subjects may be enrolled in this study. Subjects who were enrolled in the KRN23-INT-002 bone sub-study and who received KRN23 are also eligible. Since this is an exploratory study, no formal statistical power and sample size estimation methods were used to determine the sample size; therefore, the current study design is not powered to assess a pre-defined statistical difference in any endpoint.

3.6 Week 24 Analysis

Week 24 analysis will be conducted after all subjects have completed the Week 24 visits or discontinued the study. The purpose of this analysis is to potentially provide supporting data to any regulatory filings of UX023 in XLH.

Additional interim analyses may be conducted if deemed necessary.

3.7 Data Monitoring Committee

Based on the open-label study design, safety will be monitored by Ultragenyx.
An independent data monitoring committee will not be used.

4 STUDY CLINICAL OUTCOMES AND COVARIATES

4.1 Safety Endpoints

Safety assessments will be summarized at Baseline and at each observed time that they are collected. In addition to the incidence and frequency of AEs, the following endpoints will be examined as CFB:

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

4.2 Pharmacodynamics Endpoints

The primary pharmacodynamics endpoints are:

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

4.3 Efficacy Endpoints

The exploratory efficacy endpoints are:

- Change from baseline in pain and health-related QoL as measured by changes in the WOMAC, BPI, and SF-36 scores
- Healing of prior or existing fractures or other disease-related skeletal abnormalities as viewed on standard radiographs
- Change from baseline in walking ability as measured by change in the distance walked on the 6MWT in meters and percent predicted normal values
- Change from baseline in transitions during ambulatory activity that incorporates strength, agility, and dynamic balance as measured by the time required to complete the TUG test.

5 DEFINITIONS AND DERIVED EFFICACY VARIABLES

5.1 Baseline

Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug administration in CL203 study.

Note that all subjects enrolled in this study received at least 2 doses of KRN23 in Kyowa Hakko Kirin Pharma, Incorporated's study KRN23-INT-001 or study KRN23-INT-002; however, since a minimum of 21 months separated the last dose in KRN23-US-001/002 studies and the first dose in this study, values measured in KRN23-INT-001 or KRN-INT-002 studies will not serve as baseline values for this study.

5.2 First KRN23 Dose Date

First KRN23 dose date refers to the first dose of KRN23 given in UX023-CL203 study. First dose date will not take into account KRN23 doses given in studies KRN23-US-02, KRN23-INT-001 or KRN23-INT-002.

5.3 BPI

The BPI will be completed by subjects to assess pain severity and the impact of pain on daily functioning.

The BPI endpoints to be analyzed are as follows:

- Worst pain, defined as the answer to question 3 (pain at its worst in the last 24 hours)
- Pain severity, defined as the average of questions 3 through 6
- Pain interference, defined as the average of questions 9A through 9G regarding "pain interfered" in the last 24 hours.

Appendix 2 includes the complete text of the BPI. Of note, subjects enrolled in this study were not asked questions 7 and 8, therefore the answers to these questions are not used for analysis in this study.

5.4 WOMAC

The WOMAC will be completed by subjects to assess pain, stiffness, and physical function. The WOMAC consists of 24 items divided into 3 subscales:

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

bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties.

The 24-question self-reported WOMAC evaluates the condition of the knee, hip, and other joints in osteoarthritis, measuring three dimensions: Pain, Stiffness, and Physical Functioning (Table 1) over the previous 48 hours.

Table 1: WOMAC Scales, Number of Questions in Each Scale, and Scores from a General Population

		Normative values from general population[1]	
Scale Name	Number of WOMAC questions combined into scale score	Mean*	Standard Deviation*
Pain	5	14.1	19.7
Stiffness	2	20.1	23.6
Physical Functioning	17	15.4	20.2

* The published values are on a 0-10 scale and were converted here to a 0-100 scale by multiplying by 10.

All questions are measured on a 5-point Likert scale: none (0), mild (1), moderate (2), severe (3), and extreme (4). Scoring is a simple sum, so Pain scores could range from 0 to 20, Stiffness from 0 to 8, and Physical Functioning from 0 to 68, with higher numbers indicating worse condition. Scores are then normalized to a 0-100 metric representing the percent of the maximum score, where 0 was the best health state and 100 the worst.

WOMAC scores are not norm-based, so they cannot be interpreted directly as difference from a population mean. However, mean WOMAC scores from a large population-based sample of healthy adults have been published (Bellamy et al. 2011), giving benchmark values for comparison (Table 1).

Appendix 3 includes the complete text of the WOMAC as it appears to subjects in the study.

5.4.1. MPCI for WOMAC Scales and Responder definition

The minimum perceptible clinical improvement (MPCI) for WOMAC scales are defined according to the WOMAC User Guide (Bellamy 2012) as follows:

- WOMAC Pain: 9.7 nu (normalized units)
- WOMAC Stiffness: 10.0 nu
- WOMAC Physical Functioning: 9.3 nu

For each of the three WOMAC scales the responders are the subjects with the decrease from baseline greater than or equal to the corresponding MPCI.

5.5 SF-36 Health Survey version 2

The SF-36v2 is a self-reported survey of general HRQL with a 4-week recall period. Its 36 questions measure eight underlying health domains, and responses to sets of questions are combined and scored to yield scale scores for each domain, as shown in Table 2.

Table 2: SF-36v2 Scales and Number of Questions in Each Scale

Scale Name	Acronym	Number of SF-36v2 questions combined into scale score
Physical Functioning	PF	10
Role Limitations due to Physical Health	RP	4
Bodily Pain	BP	2
General Health Perceptions	GH	5
Vitality	VT	4
Social Functioning	SF	2
Role Limitations due to Emotional Problems	RE	3
Mental Health	MH	5

Note: The health transition question (item 2 on the SF-36v2, as shown in Appendix 4) is not used in the calculation of SF-36v2 scales.

Additionally two summary component scores are calculated from domain scores (Physical Component Summary Scale [PCS] and the Mental Component Summary Scale [MCS]). They each draw information from all eight scales, with weights derived from the population-based sample. The PCS depends most heavily on the PF, RP, BP and GH scales, while the MCS mainly reflects the MH, RE, SF, and VT scales.

Raw scores range from 0 to 100 with higher scores indicating better health. Domain scores are calculated from raw scores such that domain scores have a mean of 50 and SD of 10. The PCS and MCS summary component scores also have mean of 50 and SD of 10 to allow comparisons with domain scores.

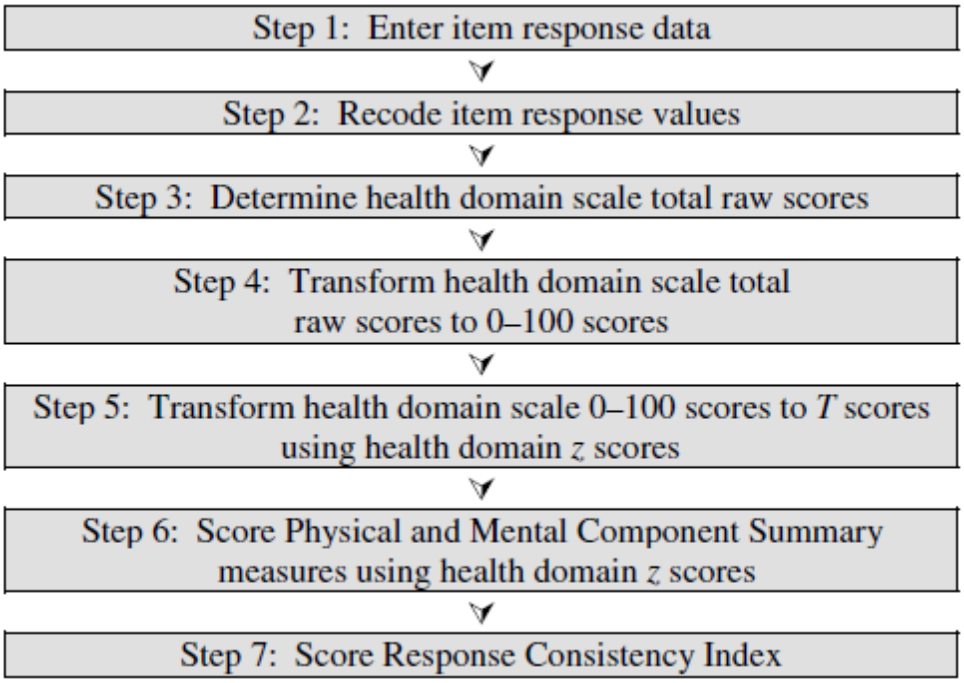
Scoring the SF-36 version 2 is accomplished using T-score Based scoring software from QualityMetric Inc (Maruish 2011). T-score Based scoring is standardized across the SF family of adult tools using the means and standard deviations from the 2009 U.S. general population. The T-score Based scores in the U.S. general population have a mean of 50 and a standard deviation of 10. The PCS and MCS are both expressed as norm-based scores on the

same metric as the scales, and can be interpreted in the same manner. The scoring process is summarized in Figure 1.

The main advantage of T-score Based scoring of the adult SF tools is easier interpretation. By using the T-score Based scoring method, the data are scored in relation to U.S. general population t-scores. Therefore, all scores obtained that are below 40 can be interpreted as 1 standard deviation below the U.S. general population t-score and scores above 60 can be interpreted as 1 standard deviation above the U.S. general population t-score. Because the standard deviation for each scale is 10, it is easier to see exactly how far above or below the mean a score is in standard deviation units (10 points = 1 standard deviation unit).

Appendix 4 includes the complete text of the SF-36 as it appears to subjects in the study.

Figure 1: Process for scoring SF-36v2 Health Domain Scales and Component Summary Measures



5.5.1 MIC for SF-36v2 Scales and Responder definition

The Minimally Important Change (MIC) is the smallest change over time in an individual patient's score that represents a clinically significant change in their health status. Using a distributional approach with a US general population sample, MICs have been established for the SF-36v2 as: PF, 3.5 points; Role-Physical, 3.2; Bodily Pain, 4.5; General Health, 5.7; Vitality, 5.5; Social Functioning, 5.0; Role-Emotional, 3.8; Mental Health, 5.5; PCS, 3.1; and MCS, 3.8.

5.6 Percent of Predicted 6-Minute Walk Test Distance

To calculate the percent predicted 6MWT value, the following formula will be applied (Gibbons et al. 2001).

$$X_i = \frac{X_{0i}}{868.8 - (2.99 \times Age) - (74.7 \times Gender)} * 100$$

where X_i is the percent predicted 6MWT result at time i for subject X, X_{0i} is the 6MWT result (in meters) at time i for subject X, and Gender is equal to 0 if the subject is male or 1 if the subject is female. Age at the study visit will be used for the calculation for the duration of the study.

5.7 Events To Monitor

Injection Site Reaction (ISR): 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".

See search criteria in Appendix 5.

6 ANALYSIS POPULATIONS

6.1 Safety Analysis Set

The safety analysis population will consist of all enrolled subjects who receive at least 1 dose of KRN23 (full or partial injection) during the study.

6.2 Pharmacodynamic Analysis Set

The pharmacodynamic (PD) analysis set consists of all subjects who receive at least 1 dose of study drug and who have evaluable plasma/serum data.

6.3 Efficacy Analysis Set

All efficacy analyses (other than the PD analyses) will be performed on all subjects who receive at least 1 dose of study drug and who have at least one pre- and post-treatment measurement.

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.

For all analyses, missing data will be treated as missing, unless otherwise specified. When a change from baseline is assessed, only subjects with a baseline and at least one post-baseline measurement will be included in the analysis.

Depending on the number of discontinuations and missed visits from the study, a sensitivity analysis might be conducted for the pharmacodynamics and the efficacy endpoints analyses, where missing data will be imputed using mBOCF (modified Baseline Observation Carried Forward) defined as follows:

- for discontinuations due to AE or death use the worst between BOCF (Baseline Observation Carried Forward) and LOCF (Last Observation Carried Forward)
- otherwise use LOCF.

7.2 Missing data in WOMAC questionnaire

For computing the domain scores at each visit for each subject, the WOMAC missing data algorithm is as follows:

1. If two or more Pain items, both Stiffness items, or four or more Physical Functioning items are missing, then the corresponding scale score is set to missing.
2. Otherwise, any missing item is replaced with the mean of the other items in its scale, and scales are then calculated normally.

7.3 Missing data in SF36 questionnaire

The SF-36v2 missing data algorithm for computing the domain scores from responses to individual items is property of QualityMetric, and is not available for further description.

7.4 Missing Date Imputation Rules

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. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

1. Start Dates

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

2. Stop Dates
    1. If the year is unknown, then the date will not be imputed and will be assigned a missing value.
    2. If the month is unknown, then assign 'December.'
    3. If the day is unknown, then assign the last day of the month.

7.5 Unscheduled or Early Termination Visits

In general, data collected by study visit will be summarized using the visit number specified in the database. Outcomes scheduled at a planned study visit but are collected during an unscheduled visit or early termination visit will be mapped into the closest study visit based on the study day of the unscheduled visit or early termination visit, and the schedule of assessment in the protocol.

For outcomes where both the planned study visit and an unscheduled visit or early termination visit corresponding to that study visit are both available, the planned study visit measurement will be used for the analysis.

All safety data including the planned study visits and unscheduled/early termination visits will be included in the shift tables.

All data will be included in the data listings and outcomes measured during unscheduled visits and early termination visits will be marked as acquired during an unscheduled visit.

7.6 Software

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

8 STATISTICAL METHODS OF ANALYSIS

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, standard errors, 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.

The Week 24 analysis will be performed when all patients enrolled in the study have completed the Week 24 visit or have discontinued the study. The final analysis will be conducted when all patients enrolled in the study have completed the Week 72 visit or have discontinued the study.

8.1.1 Repeated Measure Model: General Estimating Equations

When the sample size and number of observations allow it, the change from baseline over time and the binary endpoints over time will be analyzed using a generalized estimation equation (GEE) model that includes time as the categorical variable and adjusted for baseline measurement. The covariance structure that will be used for the GEE model is compound symmetry which specifies constant variance for the assessments and constant covariance between the assessments over time. If the compound symmetry 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 and corresponding 95% confidence intervals will also be provided along with p-values for assessing statistical significance.

The p-value for testing the statistical significance of the change from the baseline to week 24 (for the interim analysis) and to week 72 (for the final analysis) assessments will be provided for changes from baseline in primary PD endpoints, selected safety endpoints (eGFR, creatinine, amylase), PRO endpoints (BPI, WOMAC, SF-36) and clinical outcomes endpoints (6MWT, percent predicted 6MWT, TUG).

For week 24 analysis, only measurements up to week 24 will be included in the model. For final analysis (week 72), all measurements will be included in the model.

If the number of observations are insufficient for analyses using a GEE model, a descriptive summary will be provided, and analyses using observations at a single time point, such as paired t-test or nonparametric methodologies, will be considered.

8.1.2 Graphic Displays and Study Results

Graphical displays of study endpoints will be completed and include both observed study data and modeled analyses, where applicable. Arithmetic means, least square means (where applicable), and appropriate measure of dispersion (e.g., standard deviation, standard error) or confidence intervals may be displayed in figures. In general, graphical displays will accompany each planned analysis to present study results.

8.1.3 Direction of Effects for the PRO Endpoints

The three PRO endpoints for the study are not scaled in the same directions. In the SF-36v2 a higher score indicated better health whereas in the BPI and WOMAC higher scores indicate worse health. They are presented as-is, with reminders that improvements in health appear as positive numbers for the SF-36v2 and BPI scales and as negative numbers for the WOMAC scales.

8.2 Demographics and Baseline Characteristics

Summaries of demographic characteristics will include descriptive statistics for age, height, weight, BMI, renal ultrasound scores, baseline skeletal survey radiographs measures (mean, standard deviation, median, minimum and maximum values) and for sex, race, ethnicity, PHEX mutation, radiograph location (number and percentage of subjects in each category).

8.3 Disease Characteristics and Medical History

8.3.1 Medical History / XLH Medical History

Medical history will be summarized by body system and will also be listed by subject.

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, dihydrotachysterol) therapy will be presented.
Use of calcimimetics or the treatment of hyperparathyroidism will also be reported.
For subjects receiving standard of care therapy for XLH (phosphate and/or vitamin D) the drug name, duration of treatment, dose and frequency of administration will be listed.
A summary of currently used walking devices will be included.

8.4 Subject Accountability

Subject disposition summaries will include the number of subjects who received study medication, the number of subjects who completing the study, and the reasons for study discontinuation. The number of subjects included in the safety, pharmacodynamics and efficacy analysis, respectively, will be presented.

8.5 Dosing Summary

The total dose administered, weight-based dose will be summarized by study visit for the Safety Population. Study medication dispensing and treatment compliance will be summarized in individual subject listings.

8.6 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, AE of injection site reaction (grouped by High-Level Group Term), laboratory measurements including chemistry, hematology, and urinalysis parameters, GFR, amylase, HAHA, concomitant medications, physical exams, pregnancy test and vital signs. No hypothesis testing is planned for safety data.

8.6.1 Adverse Events

Reported adverse event (AE) terms are coded to MedDRA (version 18.1). All reported events will appear in AE listings, however only TEAE will be summarized. TEAEs are defined as AEs with onset on or after the time of initiation of study drug administration.

The following AEs will be summarized:

- All TEAEs
- Related TEAEs
- Events to monitor:
  - Injection site reactions
  - Gastrointestinal events
  - Immunogenicity
  - Ectopic mineralization
  - Hyperphosphatemia
  - Restless legs syndrome
- Grade 3/4 TEAEs
- Serious TEAEs
- Serious related TEAEs
- TEAEs resulting in discontinuation
- Fatal TEAEs.

Summaries of TEAEs will show incidence rates for each MedDRA primary SOC and PT.

All TEAEs will be tabulated in the following manner: by system organ class/preferred term in descending order, by system organ class/preferred term/relationship to study drug, and by system organ class/preferred term/severity. Additionally, treatment-emergent SAEs and TEAEs related to investigational drug will be tabulated by system organ class/preferred term in descending order.

Injection site reactions (ISR) will be listed for PT, seriousness, severity, outcome, relationship to study drug, and onset time from investigational product administration.

8.6.2 Safety Lab Parameters

The descriptive statistics will be provided for lab safety parameters (chemistry, hematology, and urinalysis parameters, GFR, HAHA). In addition, shift tables will be provided for HAHA (with categories Yes/No) and for amylase. For amylase, the following categories will be used:

- Normal
- Grade 1: 1 - 1.5 x ULR
- Grade 2: 1.5 – 2 x ULR
- Grade 3: 2 – 5 x ULR
- Grade 4: > 5 x ULR.

8.6.3 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 preferred name. This display will be created for the safety analysis set. A concomitant medication listing will also be made. Prior medications, i.e. medications that were used within 30 days before the Screening visit will also be listed.

8.6.4 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, musculoskeletal, genitourinary, neurological systems All physical examination assessments will be listed.

8.6.5 Pregnancy Test

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

8.6.6 Vital Signs

Systolic blood pressure, diastolic blood pressure and heart rate etc. and their changes from baseline over time will be summarized by descriptive statistics including mean, standard error etc. Individual subject listing of vital signs will be provided.

8.7 Ectopic Mineralization Safety

Ectopic mineralization safety data includes renal ultrasound, ECG, ECHO, serum calcium, creatinine, GFR, iPTH, 24-hr urinary calcium excretion rate, fasting 2-hr urinary calcium/creatinine. The observed values and changes from baseline in the ectopic mineralization safety data will be summarized and listed by individual subjects.

8.7.1 Renal Ultrasound

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

The number and percentage of subjects with nephrolithiasis observed in the kidney will be summarized by time point. A shift table summarizing changes from baseline by time point will be created.

A listing of renal ultrasound nephrocalcinosis scores, the presence or absence of nephrolithiasis in the kidney and the radiologist's comments will also be provided.

8.7.2 ECG

Descriptive statistics for the absolute measurements and changes from Baseline for selected ECG parameters will be reported. These include the following intervals: QT, QT corrected for heart rate, 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 the QTc interval will be summarized according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTc post dose values according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized.

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

8.7.3 ECHO

ECHO data will be centrally read 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 index, etc.) will be at the scheduled time points and will include the change from baseline value. The summary of

the descriptive statistics will be displayed by visit. Shift tables will be provided for categorical ECHO measurements (e.g. ectopic mineralization score, aortic and mitral valve regurgitation). A listing of all ECHO parameters will be provided.

8.8 Endpoints

8.8.1 Pharmacodynamic Endpoints

The number and proportion of subjects with serum phosphorus level in the normal range (≥ 2.5 and < 4.5) at each time point will be provided, along with the two-sided 95% confidence intervals, obtained using the GEE model described in Section 8.1.1. An overall summary of the number and proportion of patients who ever reached the normal range over the duration of the study will also be provided. Additional analyses of serum phosphorus including observed values, change from baseline, percent change from baseline over time will be summarized.

For the final analysis, the primary PD endpoints at all post-baseline visits will be compared to baseline using the GEE model described in Section 8.1.1, and the primary statistical comparison will be between the levels at baseline and week 72.

For the interim analysis, the primary PD endpoints at all post-baseline visits prior or at week 24 for all patients will be compared to baseline using the GEE model, and the primary statistical comparison will be between the levels at baseline and week 24.

For all primary PD endpoints descriptive statistics of observed values and of changes from baseline at each visit will be provided.

Graphs showing the change over time in key PD parameter for both observed measure and the change from baseline will be provided. The relationship between various PD parameters as well as KRN23 concentrations may be examined.

8.8.2 Efficacy Endpoints

8.8.2.1 PRO Endpoints

BPI (Worst Pain, Pain Severity and Pain Interference), WOMAC (the three domains) and SF-36 (the eight domains and the two components) scores and the proportion of responders at each study time point will be evaluated using descriptive statistics. The binary endpoints (responder/non-responder to treatment) and the changes from baseline to week 24 (interim analysis) and week 72 (final analysis) will be analyzed using the GEE model described in Section 8.1.1. Listings containing the answers to each question and each of the scores over time will also be provided. In addition, the cumulative distribution functions (CDF) based on change from baseline and percent change from baseline of worst Pain score will be provided.

8.8.2.2 X-Ray Endpoints

The number, the change from baseline and the location of the active pseudofractures or other disease-related skeletal abnormalities as viewed on standard radiographs at each visit will be evaluated using descriptive statistics. A listing containing the X-Ray endpoints details will also be provided.

8.8.2.3 6-Minute Walk Test and Percent Predicted 6-Minute Walk Test

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. Changes from baseline to week 72 will be analyzed using the GEE model described in Section 8.1.1. Changes from baseline to week 24 will be analyzed using paired t-test.
A listing containing the 6MWT details will also be provided.

8.8.2.4 Timed Up and Go Test

The TUG will be used to evaluate changes in transition time during ambulatory activity that incorporates strength, agility, and dynamic balance. TUG results will be evaluated using descriptive statistics. Changes from baseline to week 72 will be analyzed using the GEE model described in Section 8.1.1. Changes from baseline to week 24 will be analyzed using paired t-test.

A listing containing the TUG details and graphs showing change from baseline in TUG results will be provided.

8.8.2.5 Subgroup Analyses

Summary tables for the actual values and change from baseline in:

- BPI scores at each study time point for the subgroups of patients with worst pain score at baseline <4 and ≥ 4
- SF-36 scores and the proportion of responders at each study time point for the subgroups of patients with baseline PCS T-scores ≤ 40 and > 40
- total distance walked and percent of predicted 6MWT for the subgroup of patients with percent predicted 6MWT at baseline $\leq 80\%$ and $> 80\%$

will be provided.

9 REFERENCES

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Gibbons, WJ, Fruchter, N, Sloan, S, and Levy, RD. 2001. "Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years." *J Cardiopulm.Rehabil.* 21 (2):87-93.

Maruish, M. 2011. *User's manual for the SF-36v2 Health Survey (3rd ed.)*: Lincoln, RI: QualityMetric Incorporated.

10 APPENDICES

Appendix 1: UX023-CL203 Efficacy Endpoint Summary Table

Test / Instrument	Eligible Study Population	Endpoint	Pharmacodynamics, efficacy or safety endpoint	Timepoints for Assessment	Statistical approach at week 24 analysis	Statistical approach at week 72 analysis
PD	PD Analysis Set	Change from baseline in serum phosphorus	Pharmacodynamics	Baseline, Weeks 2, 4, 6, 8, 10, 12, 24, 26, 28, 36, 38, 40 48, 50, 52, 60, 72/ET	GEE Model	GEE Model
PD	PD Analysis Set	Percent change from baseline in serum phosphorus	Pharmacodynamics	Baseline, Weeks 2, 4, 6, 8, 10, 12, 24, 26, 28, 36, 38, 40 48, 50, 52, 60, 72/ET	GEE Model	GEE Model
PD	PD Analysis Set	Proportion of subjects with serum phosphorus level in the normal range	Pharmacodynamics	Baseline, Weeks 2, 4, 6, 8, 10, 12, 24, 26, 28, 36, 38, 40 48, 50, 52, 60, 72/ET	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in iPTH	Pharmacodynamics	Baseline, Weeks 12, 24, 36, 48, 72	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in Total FGF23	Pharmacodynamics	Baseline, Weeks 4, 8, 12, 24, 28, 36, 40, 48, 72	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in Free FGF23	Pharmacodynamics	Baseline, Weeks 4, 8, 12, 24, 28, 36, 40, 48, 72	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in $1,25(OH)_2D$	Pharmacodynamics	Baseline, Weeks 12, 24, 36, 48, 72	GEE Model	GEE Model

Test / Instrument	Eligible Study Population	Endpoint	Pharmacodynamics, efficacy or safety endpoint	Timepoints for Assessment	Statistical approach at week 24 analysis	Statistical approach at week 72 analysis
PD	PD Analysis Set	Change from baseline in 2-hr urine parameters (TmP/GFR, calcium, creatinine, calcium/creatinine ratio, phosphorus)	Pharmacodynamics	Baseline, Weeks 12, 24, 36, 48, 72	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in 24-hr urine parameters (calcium, calcium/creatinine ratio, creatinine, phosphorus, phosphorus/creatinine ratio)	Pharmacodynamics	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in fractional excretion of phosphorus	Pharmacodynamics	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
PD	PD Analysis Set	Change from baseline in bone biomarkers (ALP, BALP, CTx, P1NP)	Pharmacodynamics	Baseline, Weeks 24, 48, 72/ET	Paired t-test	GEE Model
PD	Safety Analysis Set	Change from baseline in serum calcium	Safety	Baseline, Weeks 2, 4, 6, 8, 10, 12, 24, 26, 28, 36, 38, 40 48, 50, 52, 60, 72/ET	GEE Model	GEE Model
PD	Safety Analysis Set	Change from baseline in serum creatinine	Safety	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
PD	Safety Analysis Set	Change from baseline in amylase	Safety	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model

Test / Instrument	Eligible Study Population	Endpoint	Pharmacodynamics, efficacy or safety endpoint	Timepoints for Assessment	Statistical approach at week 24 analysis	Statistical approach at week 72 analysis
PD	Safety Analysis Set	Change from baseline in GFR	Safety	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
BPI	Efficacy Analysis Set	Change from baseline in: • Worst Pain • Pain Severity • Pain Interference	Efficacy	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
WOMAC	Efficacy Analysis Set	Change from baseline in: • Pain • Stiffness • Physical Functioning	Efficacy	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
SF36	Efficacy Analysis Set	Change from baseline in: • PF, RP, BP, GH, MH, RE, SF,VT scales • MCS and PCS summary component scores	Efficacy	Baseline, Weeks 12, 24, 36, 48, 72/ET	GEE Model	GEE Model
6MWT	Efficacy Analysis Set	Change from baseline in distance traveled during 6 minutes (meters)	Efficacy	Baseline, Weeks 24, 36, 48, 72/ET	Paired t-test	GEE Model
6MWT	Efficacy Analysis Set	Change from baseline in percent predicted of the distance traveled during 6 minutes	Efficacy	Baseline, Weeks 12, 24, 36, 48, 72/ET	Paired t-test	GEE Model
TUG	Efficacy Analysis Set	Change from baseline in TUG	Efficacy	Baseline, Weeks 12, 24, 36, 48, 72/ET	Paired t-test	GEE Model

Test / Instrument	Eligible Study Population	Endpoint	Pharmacodynamics, efficacy or safety endpoint	Timepoints for Assessment	Statistical approach at week 24 analysis	Statistical approach at week 72 analysis
PD	PD Analysis Set	Change from baseline in chemistry lab parameters (ALT, AST, bilirubin -direct and total, BUN, uric acid, CO_2, total cholesterol, triglycerides, GGT, glucose, LDH, Potassium, Protein -albumin and total, sodium)	Safety	Baseline, Weeks 12, 24, 36, 48, 72/ET	Descriptive statistics	Descriptive statistics
PD	PD Analysis Set	Change from baseline in hematology lab parameters (hematocrit, hemoglobin, platelet, RBC, WBC, MCV, MCH, MCH concentration)	Safety	Baseline, Weeks 12, 24, 36, 48, 72/ET	Descriptive Summary	Descriptive Summary
PD	PD Analysis Set	Change from baseline in urinanalysis parameters (pH, ketones, protein, glucose)	Safety	Baseline, Weeks 12, 24, 36, 48, 72/ET	Descriptive Summary	Descriptive Summary
ECG	Safety Analysis Set	Change from baseline in ECG parameters (PR, QT, QTc, QRS)	Safety	Baseline, Weeks 24, 48, 72/ET	Descriptive Summary	Descriptive Summary

Appendix 2: BPI Questionnaire

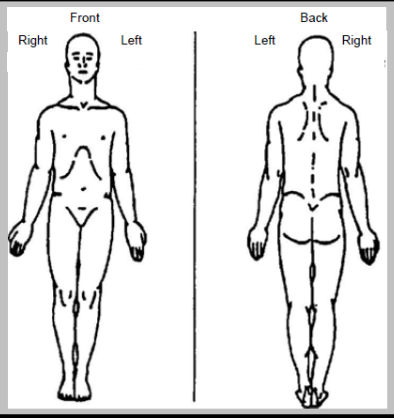
Brief Pain Inventory (Short Form)

SUBJECT ID: __ __ __ - __ __ __ VISIT DATE: __ __/ __ __ __/ __ __ __ __

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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SUBJECT ID: __ __ __ - __ __ __ VISIT DATE: __ __ / __ __ __ / __ __ __ __

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

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Appendix 3: WOMAC Questionnaire

WOMAC OSTEOARTHRITIS INDEX VERSION LK3.1

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions are asked in the following format. Please select the circle for your response.

EXAMPLES:

1. If you fill in the circle on the far left as shown below,

none	mild	moderate	severe	extreme
●	○	○	○	○

then you are indicating that you feel **no** pain.

2. If you fill in the circle on the far right as shown below,

none	mild	moderate	severe	extreme
○	○	○	○	●

then you are indicating that you feel **extreme** pain.

Please note:

a) that the further to the right you select, the **more** pain you feel.
b) that the further to the left you select, the **less** pain you feel.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Which lower extremity joint has been most bothersome and/or has given you the most difficulty in the last 48 hours? [ ]

Think about your _____ when answering the questions. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your _____.

Section A
PAIN

Think about the pain you felt in your _____ caused by your arthritis during the last 48 hours.					
Question: **How much pain have you had.....**	None	Mild	Moderate	Severe	Extreme
1. when walking on a flat surface?	○	○	○	○	○
2. when going up or down stairs?	○	○	○	○	○
3. at night while in bed? (that is - pain that disturbs your sleep)	○	○	○	○	○
4. while sitting or lying down?	○	○	○	○	○
5. while standing?	○	○	○	○	○

Section B
STIFFNESS

Think about the stiffness (not pain) you felt in your _____ caused by arthritis during the last 48 hours. Stiffness is a sensation of **decreased** ease in moving your joint.					
	None	Mild	Moderate	Severe	Extreme
6. How **severe** has your stiffness been **after you first woke up** in the morning?	○	○	○	○	○
7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**?	○	○	○	○	○

Section C
DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ _____during the last 48 hours.
By this we mean **your ability to move around and take care of yourself.**

Question: **How much difficulty have you had....**	None	Mild	Moderate	Severe	Extreme
8. when going down the stairs?	○	○	○	○	○
9. when going up the stairs?	○	○	○	○	○
10. when getting up from a sitting position?	○	○	○	○	○
11. while standing?	○	○	○	○	○
12. when bending to the floor?	○	○	○	○	○
13. when walking on a flat surface?	○	○	○	○	○
14. getting in or out of a car, or getting on or off a bus?	○	○	○	○	○
15. while going shopping?	○	○	○	○	○
16. when putting on your socks or panty hose or stockings?	○	○	○	○	○
17. when getting out of bed?	○	○	○	○	○
18. when taking off your socks or panty hose or stockings?	○	○	○	○	○
19. while lying in bed?	○	○	○	○	○
20. when getting in or out of the bathtub?	○	○	○	○	○
21. while sitting?	○	○	○	○	○
22. when getting on or off the toilet?	○	○	○	○	○
23. while doing heavy household chores?	○	○	○	○	○
24. while doing light household chores?	○	○	○	○	○

Appendix 4: SF-36 Questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 5: 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

Category	PT
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
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

Category	PT
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
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

Category	PT
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
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

Category	PT
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
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

Category	PT
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
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
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

Category	PT
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: 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
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

Category	PT
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
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

Appendix 6: Schedule of Events

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

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

VISIT TYPE / NUMBER	HH[3] 18	19	HH[3] 20	HH[3] 21	HH[3] 22	HH[3] 23	HH[3] 24	HH[3] 25	26
WEEK[4]	44	48	50	52	56	60	64	68	72/ EoT[15]
Informed Consent									
Inclusion/Exclusion Criteria									
Medical History & Demographics[5]									
Renal Ultrasound		X							X
Chemistry[6], Hematology[7], Urinalysis		X							X
2-hr and 24-hr Urine		X							X
Urine Pregnancy Test[8]	X	X		X	X	X	X	X	X
Vital Signs[9]	X	X	X	X	X	X	X	X	X
Height		X							X
Physical Examination		X							X
PHEX mutation analysis									
Anti-KRN23 antibody (HAHA)[10]		X							X
Serum Phosphorus[11]		X	X	X		X			X
Serum Calcium		X	X	X		X			X
Serum Creatinine		X							X
Serum iPTH		X							X
Serum FGF23		X							X
Serum $1,25(OH)_2D$		X							X
Bone Biomarkers[12]		X							X
ECHO, ECG		X							X

VISIT TYPE / NUMBER	HH[3] 18	19	HH[3] 20	HH[3] 21	HH[3] 22	HH[3] 23	HH[3] 24	HH[3] 25	26
WEEK[4]	**44**	**48**	**50**	**52**	**56**	**60**	**64**	**68**	**72/ EoT[15]**
WOMAC, BPI, SF36[13]		X							X
6MWT, 3MSCT, TUG		X							X
X-Ray[14]		X							X
Interval History		X							X
Prior and Concomitant Medications	X	X		X	X	X	X	X	X
Adverse Events	X	X		X	X	X	X	X	X
Weight		X							X
Drug Administration	X	X		X	X	X	X	X	

1,25(OH)$_2$D= 1,25-dihydroxy vitamin D; 3MSCT = stair climb test; 6MWT = 6-minute walk test; BL = Baseline; ECG = electrocardiogram; ECHO = echocardiogram; EoT = end of treatment; FGF23 = fibroblast growth factor 23; HAHA = Human Anti-Human Antibody (immunogenicity testing assay); HH = home health; HIV = human immunodeficiency virus; hr = hour; iPTH = intact parathyroid hormone; PHEX = phosphate regulating gene with homology to endopeptidases located on the X chromosome; Scr = Screening; TmP/GFR = the ratio of phosphorus tubule maximum (TmP) to glomerular filtration rate (GFR), or tubular resorption of phosphate; TUG = timed up and go (test)

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

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

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

4 The visit window for visits 3 through 25 is ± 3 days. The visit window for the EoT visit at Week 72 is is ± 5 days.

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

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

7 Complete blood count, differential, and platelet count.

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

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

[10] If the 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.

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

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

[13] Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Brief Pain Inventory (BPI), and SF-36 self-reported patient-reported outcomes (PROs) tools.

[14] Standard radiographs will be customized by patient and will be repeated every 3 months or until specified lesions are healed.

[15] Those subjects who terminate the study early will be asked to come back to the clinic for a final assessment. Every reasonable effort should be made to have subjects return to the clinic for the final assessment; however, subjects who are unable to return to the clinic for the final assessment will be given the option of providing blood and urine samples as part of a HH visit.