STATISTICAL ANALYSIS PLAN

Title	An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH)
Protocol:	UX023-CL304
Investigational Product:	KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])
Indication:	X-linked Hypophosphatemia (XLH)
IND Number:	76,488
Phase:	3
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
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ABBREVIATIONS

$1,25[OH]_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxy vitamin D
6MWT	6-Minute Walk Test
AE	Adverse event
ALP	Alkaline phosphatase
AUC	Area under the curve
BALP	Bone-specific alkaline phosphatase
BFI	Brief fatigue inventory
BFR	Bone formation rate
BPI	Brief Pain Inventory
CFB	Change from Baseline
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Carboxy terminal cross-linked telopeptide of type I collagen
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	Estimated glomerular filtration rate
FGF23	Fibroblast growth factor 23
GEE	Generalized Estimating Equation
GFR	Glomerular filtration rate
HAHA	Human anti-human antibody
iPTH	Intact parathyroid hormone
ISR	Injection site reactions
KRN23	Investigational product, an anti-FGF23 antibody
LVH	Left ventricular hypertrophy
mAb	Monoclonal antibody
MAR	Mineral apposition rate
MLt	Mineralization lag time

MedDRA	Medical Dictionary for Regulatory Activities
MS/BS	Mineralization surface/bone surface
OS/BS	Osteoid surface/bone surface
O.Th	Osteoid thickness
OV/BV	Osteoid volume/bone volume
P1NP	Procollagen type 1 N-propeptide
PD	Pharmacodynamics
PHEX	Phosphate-regulating gene with Homologies to Endopeptidases on the X-chromosome
PK	Pharmacokinetics
QTc	Corrected QT interval
SAE	Serious adverse event
SC	Subcutaneous
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 reabsorption of phosphate
WHO	World Health Organization
XLH	X-Linked Hypophosphatemia

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses planned for data collected under Ultragenyx Pharmaceutical Inc. Protocol UX023-CL304 titled "An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH)." This SAP covers the original protocol and its two amendments, the latest of which was dated 07October 2016. Since the study protocol is a companion document to this SAP, aspects in the protocol unrelated to statistical issues (e.g., patient eligibility criteria and descriptions of clinical materials) are not repeated here. For all statistical matters, this SAP takes priority over any related statements on statistical matters within the protocol in the event there are any inconsistencies.

2 STUDY OBJECTIVES

2.1 Primary Efficacy Objective

Establish the effect of KRN23 treatment on improvement in XLH-associated osteomalacia as determined by osteoid volume (osteoid volume/bone volume, OV/BV)

2.2 Secondary Efficacy Objectives

The key secondary efficacy objective is to establish the effect of KRN23 treatment on increasing serum phosphorus levels in adults with XLH

Other secondary efficacy objectives are to establish the effect of KRN23 treatment in adults with XLH on:

- Changes from baseline in additional histomorphometric parameters – including osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and mineralization lag time (MLt)
- Changes from baseline in parameters of bone mineralization including mineral apposition rate (MAR), mineralizing surface (MS/BS), bone formation rate (BFR), and others
- Additional pharmacodynamics (PD) markers reflecting the status of phosphorus homeostasis and renal function
- Bone remodeling as assessed by bone turnover markers

2.3 Exploratory Efficacy Objectives

- Examine the effect of KRN23 treatment in adults with XLH on pseudofracture healing
- Patient reported outcomes (PROs) assessing skeletal pain and fatigue

2.4 Pharmacokinetics Objective

Assess the PK of KRN23 throughout the dosing cycle following the first doses and steady state

2.5 Safety Objective

Establish the safety and tolerability profile of KRN23 in the treatment of adults with XLH including adverse events (AEs), ectopic mineralization risk, cardiovascular effects, and immunogenicity profile

3 STUDY DESIGN

3.1 Overall Study Design and Plan

This is a Phase 3 open-label, single-arm, multicenter study to establish the effects of KRN23 on bone quality and osteomalacia associated with XLH. A total of 14 adult subjects with a diagnosis of XLH supported by typical clinical and biochemical features who have not received oral phosphate and vitamin D therapy in the past two years have been enrolled. To ensure a level of gender balance, at least 3 subjects of each sex have been enrolled. Iliac crest bone biopsies will be performed at baseline and 48 weeks. Baseline histologic and histomorphometric assessments of the bone biopsy specimens will be performed as each biopsy is completed to assess sample quality and confirm the presence of osteomalacia in at least 8 subjects. If a subject is determined not to have osteomalacia at the time of the initial biopsy, that subject will continue on study but will not undergo the second bone biopsy procedure at Week 48. All other assessments will be completed as scheduled. The goal of the study is to assess changes in bone quality. Histologic and histomorphometric evaluation of iliac crest bone biopsies will be supported by changes in serum phosphorus and biochemical markers of bone turnover and additional PD markers associated with FGF23-mediated processes. Pseudofractures and PROs will provide additional information on KRN23 efficacy. Safety, immunogenicity, and PK of KRN23 will also be evaluated.

KRN23 will be administered via subcutaneous (SC) injections monthly (Q4W, 28 days) for 48 weeks. Subjects who complete the 48 weeks of the Open-Label Treatment Period will then continue into an additional 48-week Treatment Extension Period. A Safety Follow-up Phone Call will be conducted 12 weeks (± 5 days) after the last dose of study drug.

All subjects will receive 1.0 mg/kg KRN23 monthly (Q4W, 28 days), rounded to the nearest 10 mg. The amount of drug administered will be calculated based on baseline weight and a 1.0 mg/kg KRN23 dose level (rounded to the nearest 10 mg) up to a maximum dose of 90 mg. The dose will remain fixed for the duration of the study, provided serum phosphorous levels do not exceed 5.0 mg/dL (1.61 mmol/L) at any time or 4.5 mg/dL (1.45 mmol/L) on two occasions. The dose will be recalculated if body weight changes by more than 20% from the baseline measurement.

Subjects will receive study drug via SC injection to the abdomen, upper arms, or thighs; the injection site will be rotated with each injection. No more than 1.5 mL may be administered to a single injection site. If the dose requires more than 1.5 mL, multiple injections must be administered, each at a different injection site.

If serum phosphorus increases above 5.0 mg/dL (1.61 mmol/L) at any time the actual dose will be decreased by half. If serum phosphorous increases above the ULN (4.5 mg/dL; 1.45 mmol/L) but does not exceed 5.0 mg/dL (1.61 mmol/L), the dose will be adjusted only if a second serum phosphorus result exceeds the ULN. Following a downward dose adjustment, the investigator together with the medical monitor should determine how and when to dose titrate up. Unscheduled serum phosphorus assessments may be necessary.

Based on the totality of the data from studies INT-001 and INT-002 over a period of 16 months in which most subjects were treated with 1.0 mg/kg KRN23 and no subject experienced an elevation of serum phosphorus that approached the 4.5 mg/dL (1.45 mmol/L) threshold, it is considered unlikely that dose adjustment will be necessary.

A complete schedule of events is included in Appendix 5.

3.2 Blinding and Randomization Methods

All subjects receive KRN23 on an open-label basis. Blinding and randomization are not applicable to this study design.

3.3 Stratification Factors

Not applicable.

3.4 Determination of Sample Size

The study will enroll approximately 14 adult subjects with XLH; baseline histologic and histomorphometric assessments of the bone biopsy specimens will be performed as each biopsy is completed to assess sample quality and confirm the presence of osteomalacia in at least 8 subjects. To ensure a level of gender balance, at least 3 subjects of each sex will be enrolled. At least 6 paired biopsy specimens are expected at the end of the study. A reduction in excess osteoid is expected to be shown in all subjects with paired biopsies with an estimated [redacted] reduction from baseline in osteoid thickness. The sample size and study duration are believed to be sufficient to enable characterization of KRN23 effects on bone tissue and skeletal health.

Information will be used to support the findings of UX023-CL303 study which is a larger Phase 3 confirmatory efficacy and safety study, where it is adequately powered to evaluate increases in serum phosphorus levels across the entire dosing interval and to describe the treatment effect on select patient reported outcomes.

3.5 Primary and Final Analyses

The primary efficacy analysis will be performed after all subjects have completed Week 48 or discontinued from the study prior to week 48 and completed the post-baseline Bone Biopsy test for those who has been determined to have the osteomalacia at the baseline.

The final analysis will be performed after all subjects have completed the Week 96 assessments and the Safety Follow-up or discontinued from the study.

Administrative analyses during the Open Label Treatment Period and Treatment Extension Periods may be performed to support regulatory activities.

3.6 Data Monitoring Committee

An independent DMC that includes two clinicians with expertise in metabolic bone disease and one statistician will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial. A review of safety data will be conducted by the DMC periodically. Ad hoc meetings will be held if indicated based on observed events. The roles and responsibilities of the DMC will be defined in the DMC Charter.

4 STUDY CLINICAL OUTCOMES AND COVARIATES

4.1 Primay Efficacy Endpoint

The primary endpoint is the percent change from baseline in osteoid volume/bone volume (OV/BV) at Week 48 based on analysis of iliac crest bone biopsies

4.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the mid-point of the dose interval (i.e., Weeks 2, 6, 14, and 22), as averaged across dose cycles between baseline and Week 24.

4.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints will compare the effects of treatment with KRN23 on the following:

- Percent changes from baseline in additional histomorphometric parameters – including osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and mineralization lag time (MLt) at Week 48
- Changes from baseline in MAR, MS/BS, BFR and additional measures of bone formation and remodeling at Week 48
- Additional measures to assess serum phosphorus levels between baseline and Week 24 include:
    - Proportion of subjects achieving mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L] at the end of the dosing cycle (4 weeks after dosing), as averaged across dose cycles
    - Mid-point of dosing cycle: mean change from baseline, and percent change from baseline averaged across dose cycles
    - End of dosing cycle: mean change from baseline, and percent change from baseline averaged across dose cycles
    - Cumulative exposure: time-adjusted area under the curve (AUC)
- Change from baseline over time in serum phosphorus, serum intact FGF23, serum $1,25(OH)_2D$, urinary phosphorus, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), tubular reabsorption of phosphate (TRP), and fractional excretion of phosphorus (FEP)

- Change and percent change from baseline over time in serum bone turnover markers, including procollagen type 1 N-propeptide (P1NP), carboxy-terminal cross-linked telopeptide of type I collagen (CTx), and bone-specific alkaline phosphatase (BALP)

4.4 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be examined:

- The number of active pseudofractures as defined by skeletal survey at baseline and the number and percentage of the baseline active pseudofractures which healed, partially healed, were unchanged or worsened at post-baseline visits
- The number of subjects with baseline active pseudofractures and the number of those subjects who have changes from baseline to healed, partially healed, unchanged and worsened at post-baseline visits
- Change from baseline over time in Brief Pain Inventory (BPI) Q3 – Worst Pain
- Change from baseline over time in BPI Pain Severity Score
- Change from baseline over time in Pain Interference scores
- Change from baseline over time in Brief Fatigue Inventory (BFI) Q3 – Worst Fatigue scores
- Change from baseline over time in BFI Global Fatigue Score, calculated by averaging all 9 items on the BFI

4.5 PK Endpoints

Serum KRN23 concentrations will be obtained from all subjects at time points reflecting peak and trough drug concentration.

4.6 Safety Endpoints

Safety will be evaluated by the incidence, frequency and severity of AEs and serious adverse events (SAEs), including clinically significant changes from baseline to scheduled time points in the following safety variables:

General safety variables include:

- Vital signs and weight
- Physical examinations
- Estimated glomerular filtration rate (eGFR)

- Chemistry, hematology, and urinalysis, including additional KRN23/XLH biochemical parameters of interest (creatinine, calcium, and intact parathyroid hormone [iPTH])
- Immunogenicity (human anti-human antibodies; HAHA)
- Concomitant medications

Ectopic Mineralization Safety Assessments:

- Renal ultrasound
- Echocardiogram (ECHO) and electrocardiogram (ECG)

5 DEFINITIONS AND DERIVED EFFICACY VARIABLES

5.1 Baseline

Baseline is defined as the last non-missing measurement taken prior to or on the first dose of Investigational Product (IP) administered in the study.

5.2 Duration of Exposure

Duration of exposure to IP in days is defined as the following:

For the primary analysis or other specified analysis before final analysis,

- The date at milestone visit (e.g. week 48) – first date of IP + 1 day for the subjects completing the corresponding milestone visit
- Last date of IP – first date of IP + 28 days for the subjects early discontinued

For final analysis:

- Last date of IP – first date of IP + 28 days

5.3 Study Day

Study Day 1 is the first date of IP.

- For visit date that is after Study Day 1, Study Day is calculated as the visit date – the first date of IP +1.
- For visit date that is prior to Study Day 1, Study Day is calculated as the first date of IP – the visit date.

5.4 Fractional Excretion of Phosphorus

Fractional excretion of phosphorus (FEP) is defined as 100%*(2-hour urine phosphorus*serum creatinine)/(2-hour urine creatinine * serum phosphorus).

5.5 Iliac Crest Bone Biopsy

A bone biopsy of the iliac crest will be performed to assess OV/BV, O.Th, OS/BS, MLt as well as other parameters. Subjects will receive two courses of tetracycline (or demeclocycline) label prior to biopsy associated with the Baseline and Week 48 (or Early Termination if it occurs between the Week 24 and Week 48) visits. Bone biopsy of the trans-iliac crest will be performed by a physician trained and experienced in the procedure. Baseline bone biopsies will be qualitatively analyzed in real time to assess the presence of osteomalacia. If a subject is determined not to have osteomalacia at the time of the initial

biopsy, that subject will continue on study but will not undergo the second bone biopsy at Week 48/ET.

Primary and secondary efficacy endpoints derived from these assessments are provided in Section 8.8.

5.6 Brief Pain Inventory

The short-form Brief Pain Inventory (BPI) is an 11-question, self-reported, pain-specific questionnaire with a recall period of 24 hours that may allow a detailed characterization of the pain experienced by patients with XLH. The BPI will be administered at pre- and post-treatment time points as indicated in the Schedule of Events (Appendix 2) to assess pain severity and the impact of pain on daily functioning as measured by subject self-report.

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 the extent to which pain interfered with daily activities in the last 24 hours.

5.7 Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) is a self-reported questionnaire consisting of 9 items related to fatigue that are rated on a 0 to 10 numerical rating scale with a recall period of 24 hours. As with the BPI, two dimensions are measured: fatigue and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life).The BFI will be administered at pre- and post-treatment time points as indicated in the Schedule of Events (Appendix 3) to assess fatigue severity and the impact of fatigue on daily functioning as measured by subject self-report.

The BFI endpoints to be analyzed are as follows:

- Worst fatigue, defined as the answer to question 3 (fatigue at its worst in the last 24 hours)
- BFI Global Fatigue score, defined as the average of all 9 items (questions 1 through 3 and questions 4A through 4F) on the BFI as recorded on the day of the study visit.

5.8 Targeted Radiography and Skeletal Survey

A radiographic skeletal survey will be conducted at baseline to assess healing or resolution of current pseudofractures, determine areas of osteomalacia and enthesopathy, and identify the number of pre-existing fractures/pseudofractures. Standard radiographs will be obtained of the chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot.

During the 48-week long Open-Label Treatment Period, targeted radiography at locations identified by the skeletal survey will be taken at Weeks 12, 24, 36, and 48 to monitor frequency and healing of pseudofractures. During the Treatment Extension Period, targeted radiographs will only be taken at clinic visits following newly diagnosed fractures.

Post-baseline radiographs will be compared to baseline radiographs using a pre-defined list of abnormalities by a trained central reader who is blinded to subject data. Existing and new pseudofractures will be graded as not healed, partially healed, or fully healed.

5.9 Time-Adjusted Area Under the Curve (AUC)

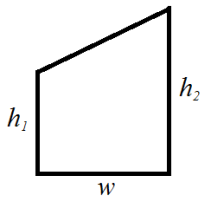
The trapezoidal rule is a numerical method that approximates the value of a definite integral.

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

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

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

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



Each pair of consecutive response assessment times t_1 and t_2 form the width of a trapezoid with $w_1 = t_2 - t_1$. The heights h_1 and h_2 are the response values at times t_1 and t_2, respectively. AUC is the sum of trapezoidal areas across specified time point.

$$\int_a^b f(x)dx \approx w_1\left(\frac{h_1 + h_2}{2}\right) + w_2\left(\frac{h_2 + h_3}{2}\right) + \cdots + w_{n-1}\left(\frac{h_{n-1} + h_n}{2}\right)$$

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

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

5.10 Adverse 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 mineralization related AE: There is no available SMQ. Ectopic mineralization related AE is defined using a MedDRA search of 'calcification'.

Restless leg syndrome AE:. Defined by PTs "Restless legs syndrome", "Restlessness", "Akathisia", "Sensory disturbance", "Psychomotor hyperactivity", "Limb discomfort", "Neuromuscular pain", "Formication".

See search criteria in Appendix 4.

5.11 Prior medication and Concomitant medication

Prior medication is defined as any medications start before the date of the first dose of IP.

Concomitant medication is defined as any medications that start before, on, or after the first dose of IP and continue into the treatment period.

6 ANALYSIS POPULATIONS

6.1 Primary Analysis Set

The primary analysis set will include enrolled subjects with baseline and follow-up (Week 48/ET) bone biopsy data.

6.2 Full Analysis Set

The full analysis set for efficacy is defined as all enrolled subjects who receive at least one dose of study drug. This analysis set will be used for the analyses of efficacy endpoints.

6.3 Safety Analysis Set

The safety analysis set consists of all enrolled subjects who receive at least one dose of study drug. This analysis set will be used for the analyses of all safety endpoints.

6.4 Treatment Extension Analysis Set

The treatment extension analysis set consists of all enrolled subjects who continued after the Open-Label Treatment Period and received at least one dose during the Treatment Extension Period. This analysis set will be used for the analyses of efficacy and safety endpoints after Week 48 analysis in additional to the full analysis set and safety analysis set.

6.5 Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis set is the subset of subjects in the Safety analysis set who have at least 1 evaluable KRN23 concentration. The PK analysis set will be used for the analysis of the PK endpoints at each specific analysis milestone.

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 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.

7.1.1 Non-Responder Imputation

If no serum data is available to evaluate the key secondary endpoint, the subject will be considered as not achieving a serum phosphorus level above the LLN.

7.1.2 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.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of IP 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.

Missing Stop Dates

- 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.

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

7.1.3 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 double-blind investigational product, a causality of yes 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.

7.1.4 Missing Data in Bone Biopsy Parameter MLt

1. If the MLt data is missing due to low quality of the bone biopsy sample (i.e. no bone biopsy parameters are available for that sample), the MLt parameter is set to missing for the sample. If the MLt data is missing due to very little label uptake because of the mineralization defect (i.e. there is at least one bone biopsy parameter available for that sample), the MLt will be imputed as O.Th/(MAR*MS/OS), where MAR is imputed as 0.3 µm/day, using O.Th, MS and OS from the same visit of the same subject (Dempster et al. 2013). If any of O.Th, MS or OS at that visit for the subject is missing, MLt will be set as missing.

7.2 Unscheduled or Early Termination Visits

For an unscheduled visit occurring after the first dose date of IP, the unscheduled visit will be mapped into the closest post-baseline study scheduled visit for the assessment based on the study day of the unscheduled visit, and the target study day of the scheduled visit of the assessment in the protocol. If the unscheduled visit has the equal distance to the 2 study scheduled visits, it will be mapped to the later one.

The unscheduled visit will be only mapped to the study visit within each study period during which it occurs. If an unscheduled visit occurs during the Open-Label Treatment Period (from the first dose date to the dose date at week 48), it should be mapped to the study visit in the Open-Label Treatment Period. If an unscheduled visit occurs after the dose date at week 48 and in the Treatment Extension Period, it should be mapped to the study visit in the Treatment Extension Period.

When there is more than one measurement mapped to the same scheduled visit (including the original measurement taken from the 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 more than one visit has the equal distance 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 follow the same rule for unscheduled visit as described above.

The bone biopsy taken in the early termination visit will not be mapped to the study scheduled visit as the bone biopsy will be only taken either on week 48 or at the early termination visit post-baseline used in the analysis.

7.3 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 by number of subjects, mean, standard deviation (SD), standard error (SE), median, Q1, Q3, minimum, and maximum. Categorical variables will be summarized by number and percentages of subjects. No imputation on missing data will be made, unless stated otherwise.

When the sample size and number of observations allow, the change from baseline 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 number of observations are insufficient for analyses using a GEE model, a t-test will be performed for continuous variables and a 95% confidence interval (CI) of the proportion will be provided for binary variables.

8.2 Subject Accountability

The number of subjects screened and enrolled, and the number and percentage of subjects in each analysis set will be summarized. The number and percentage of subjects who complete each treatment period and of subjects who prematurely discontinue during each treatment period and the study will be summarized. The reasons for study discontinuation will also be summarized. A subject disposition listing will be provided for individual subjects.

8.3 Protocol Deviations

Major and minor protocol deviations will be summarized separately by type for the Full analysis set. The protocol deviations recorded in the CRF will be listed.

8.4 Demographics and Baseline Characteristics

Demographic characteristics and other baseline characteristics will be summarized descriptively for the Full Analysis Set and listed by subject including the following.

- Demographics: age, sex, race, ethnicity, height, weight, BMI, country and region
- Baseline Characteristics: baseline PD (serum phosphorus, etc.), renal ultrasound scores, baseline BPI-Q3, baseline skeletal survey radiographs measures, PHEX mutation

The summary of demographics and baseline characteristics will also be provided for the Primary Analysis Set when the number of subjects in the Primary Analysis Set is significantly fewer than the Full Analysis Set.

8.5 Disease Characteristics and Medical History

8.5.1 Medical History / XLH Medical History

Medical history will be summarized by body system for the Full Analysis set and will also be listed by subject. Fracture history will be summarized by reported term for the Full Analysis set and will also be listed by subject.

8.5.2 XLH Treatment History

The subjects' past XLH treatment with phosphates and vitamin D metabolites or analogs will be listed for the Full Analysis set if there is any reported XLH treatment history. 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.

8.6 Efficacy Analysis

The primary efficacy analysis and other bone biopsy analysis (e.g. MAR, MS/BS, BFR, etc.) will be performed on the Primary Analysis set. All other efficacy analysis will be performed on the Full Analysis set at each milestone analysis. The treatment Extension Analysis Set might also be used for efficacy analysis at the final analysis.

8.6.1 Primary Efficacy Endpoint

The primary endpoint is the percent change from baseline at Week 48 in osteoid volume (osteoid volume/bone volume, OV/BV).

OV/BV at baseline, Week 48, both change from baseline, and percent change from baseline at Week 48 will be summarized. Change from baseline at Week 48 will be tested using a t-test if the normality assumption is valid. If the normal assumption is not met, a sign test will be used. The p-value from the statistical tests will be reported. A listing will be provided.

8.6.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the proportion of subjects achieving mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L]) at the mid-point of the dose interval (i.e., Weeks 2, 6, 14, and 22), as averaged across dose cycles between baseline and Week 24.

The number and proportion of subjects achieving mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L]) will be summarized and the two-sided 95% confidence interval will be provided for the proportion. The Wilson score method (Wilson 1927) will be

applied to estimate the confidence interval. The p-value for testing the proportion of subjects achieving the mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L]) against 0% from the binomial test will also be provided.

8.6.3 Secondary Efficacy Endpoints

8.6.3.1 Additional bone biopsy endpoints

Analysis for the following parameters will use the same analysis method for the primary endpoint:

- Additional histomorphometric parameters – including osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and mineralization lag time (MLt)

The observed, change from baseline, and percent change from baseline values over time for the following parameters will be summarized.

- MAR, MS/BS, BFR and additional measures of bone formation and remodeling

A listing of the bone biopsy parameters will be provided.

A sensitivity analysis for bone biopsy parameters based on the bone osteomalacia severity at baseline may also be explored. A shift analysis from baseline to post-baseline for the bone osteomalacia severity based on the category reported in the EDC may also be performed.

8.6.3.2 Key PD

Descriptive summaries of the following secondary PD endpoints will be provided.

- Proportion of subjects achieving mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L]) at the end of the dosing cycle (4 weeks after dosing), as averaged across dose cycles between baseline and week 24.

- Mean change from baseline and percent change from baseline in serum phosphorus at each mid-point of dosing cycle, as averaged across dose cycles between baseline and week 24.

- Mean change from baseline and percent change from baseline in serum phosphorus at each end of dosing cycle, as averaged across dose cycles between baseline and week 24.

- Time-adjusted area under the curve (AUC) of serum phosphorus between baseline and week 24.

Observed values and change from baseline, serum intact FGF23, percent change from baseline over time in serum phosphorus, $1,25(OH)_2D$, and urinary phosphorus, TRP, TmP/GFR, and FEP will be summarized at each milestone analysis.

The change from baseline over time for key PD will be analyzed using the GEE model as described in Section 8.1, if the model converges.

A listing for the PD parameters will be provided.

Mean (±SE) PD-time plots may be presented for the PD parameters.

8.6.3.3 Bone turnover markers

Observed values, change and percent change from baseline over time in serum ALP and biochemical markers of bone turnover, including BALP, CTx, and P1NP, will be summarized at each milestone analysis. A listing will be provided for the biochemical markers of bone turnover.

The change from baseline over time for biomarkers will also be analyzed using the GEE model as described in Section 8.1, if the model converges.

Correlations may be used to assess the relationship between bone turnover markers and selected histomorphometric indices.

8.6.4 Exploratory Efficacy Endpoints

The number of active (non-healed) pseudofractures and/or fractures as defined by skeletal survey at baseline and the number and percentage of the baseline active pseudofractures/fractures which healed, partially healed, were unchanged or worsened at post-baseline visits will be summarized. New active pseudofractures and/or fractures identified at post-baseline visits will also be summarized.

The number of the subjects with baseline active pseudofractures and/or fractures and the number of those subjects who have changes from baseline to healed, partially healed, unchanged and worsened at post-baseline visits will be summarized. The number of subjects with new active pseudofractures and/or fractures at post-baseline visits will also be summarized.

For BPI (worst pain, pain severity and pain interference), BFI (worst fatigue, and global fatigue score), the observed values, change from baseline over time will be summarized. The change from baseline over time will also be analyzed using the GEE model as described in Section 8.1, if the model converges. Listings for the patient-reported outcomes will be provided.

8.7 PK Analysis

All PK analyses will be performed for subjects in the PK Analysis set with evaluable serum PK samples. Serum KRN23 will be summarized descriptively at each time point.

8.8 General Safety Analysis

All safety analyses will be performed on the Safety Analysis set at each milestone analysis. The treatment Extension Analysis Set might also be used for safety analysis at the final analysis. General safety will include dosing summary, AEs, treatment related AEs, SAEs, events to monitor, prior and concomitant medication, laboratory measurements including chemistry, hematology, and urinalysis parameters, GFR, amylase, HAHA, pregnancy test and vital signs. No hypothesis testing is planned for safety data.

8.8.1 Dosing Summary

The total dose administered and the subjects with dose adjustment and the reasons for dose adjustment will be summarized by treatment groups by visits for the safety analysis set.

8.8.2 Adverse Events

Reported adverse event (AE) terms are coded to MedDRA (version 18.1). All reported events will appear in AE listings, however only TEAEs will be summarized. TEAEs are defined as AEs occurring or worsened in severity on or after the first dose date of IP.

The following AEs will be summarized at each milestone analysis:

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

The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT). Events to monitor will be summarized by PT. Injection site reactions (ISR) will be listed for PT, seriousness, severity, outcome, relationship to study drug, and onset time from IP administration.

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

8.8.3 Prior and Concomitant Medications

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug dictionary, version 2015 September or newer.

Prior medication will be summarized by therapeutic class and preferred term at week 48 analysis.

At each specific milestone analysis, concomitant medications will be summarized by therapeutic class and preferred term.

8.8.4 Safety Lab Parameters

The descriptive statistics will be provided for lab safety parameters (chemistry, hematology, and urinalysis parameters, serum 25(OH)D, FGF23, lipase, amylase, eGFR). Observed values and change from baseline will be presented.

In addition, a shift table will be provided for amylase. The following categories will be used for serum amylase:

- No Grade
- Grade 1: >ULN to 1.5 x ULR
- Grade 2: >1.5 to 2 x ULR
- Grade 3: >2 to 5 x ULR
- Grade 4: > 5 x ULR

Individual and mean (±SE) over time plots may be presented for selected safety lab parameters.

Listings of the lab safety parameters will be provided.

8.8.5 HAHA

Antibody (human anti-human antibody [HAHA]) results will be summarized by the baseline and post-baseline testing results. Each subject positive for antibody will be listed with titer (if available), the cumulative dose of KRN23 up to the time of the positive antibody test, the time since the first exposure to KRN23, and the latest dose of KRN23 before the positive antibody test.

8.8.6 Physical Examination

Physical exam results will include the assessment of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatology, lymphatic, respiratory, gastrointestinal, musculoskeletal, genitourinary, neurological systems. All physical examination assessments will be listed.

8.8.7 Pregnancy Test

A subject level listing for pregnancy test results will be created for those who had a positive pregnancy test.

8.8.8 Vital Signs

Systolic blood pressure, diastolic blood pressure, temperature, respiratory rate and heart rate and their changes from baseline over time will be summarized. If the subject has taken 2 measurements of BP separated by 15 min at the same scheduled visit per the protocol amendment 1, the mean of the 2 measurements of the blood pressure at the visit will be used for analysis.

8.9 Ectopic Mineralization Safety Analysis

Ectopic mineralization safety data includes renal ultrasound, ECG, ECHO, serum calcium, phosphorus, intact parathyroid hormone (iPTH), urinary calcium and creatinine.
The observed values and changes from baseline in the ectopic mineralization labs (serum calcium etc.) will be summarized. Listings containing the ectopic mineralization safety parameters will be provided.

8.9.1 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 cortical collecting duct 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 cortical collecting duct and the radiologist's comments will also be provided.

8.9.2 ECG

Summary statistics for the absolute measurements and changes from Baseline for selected ECG parameters including the following intervals: QT, QTcF - Fridericia's Correction Formula, the time elapsed from the onset of atrial depolarization to the onset of ventricular depolarization (PR), RR duration, and time elapsed for depolarization of the ventricles (QRS) will be provided.

ECG parameters will also be summarized by the maximum post-baseline value and maximum change from baseline using the following categories based on International Conference on Harmonisation (ICH) E14 (ICH 2005).

Categories for ECG Results

ECG Parameter	Categories for Baseline and Maximum Post-Baseline Value	Categories for Maximum Change from Baseline Value
QTcF	≤450, >450-≤480, >480-≤500 and >500 msec	≤30, >30-≤60 and >60 msec

The normality or abnormality of the ECG tracing will be summarized using shift tables of numbers of subjects who have a normal/abnormal ECG tracing by visits.

8.9.3 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. The categorical summaries for the subjects with change from baseline >=2 in ectopic mineralization score will be performed. 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 also be created.

9 REFERENCES

Dempster, DW, Compston, JE, Drezner, MK, Glorieux, FH, Kanis, JA, Malluche, H, Meunier, PJ, Ott, SM, Recker, RR, and Parfitt, AM. 2013. "Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee." *J Bone Miner Res* 28 (1):2-17.

ICH. *The International Conference on Harmonisation. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* 2005.

Wilson, E. B. (1927). Probable inference, the law of succession, and statistical inference. Journal of the American Statistical Association 22: 209–212

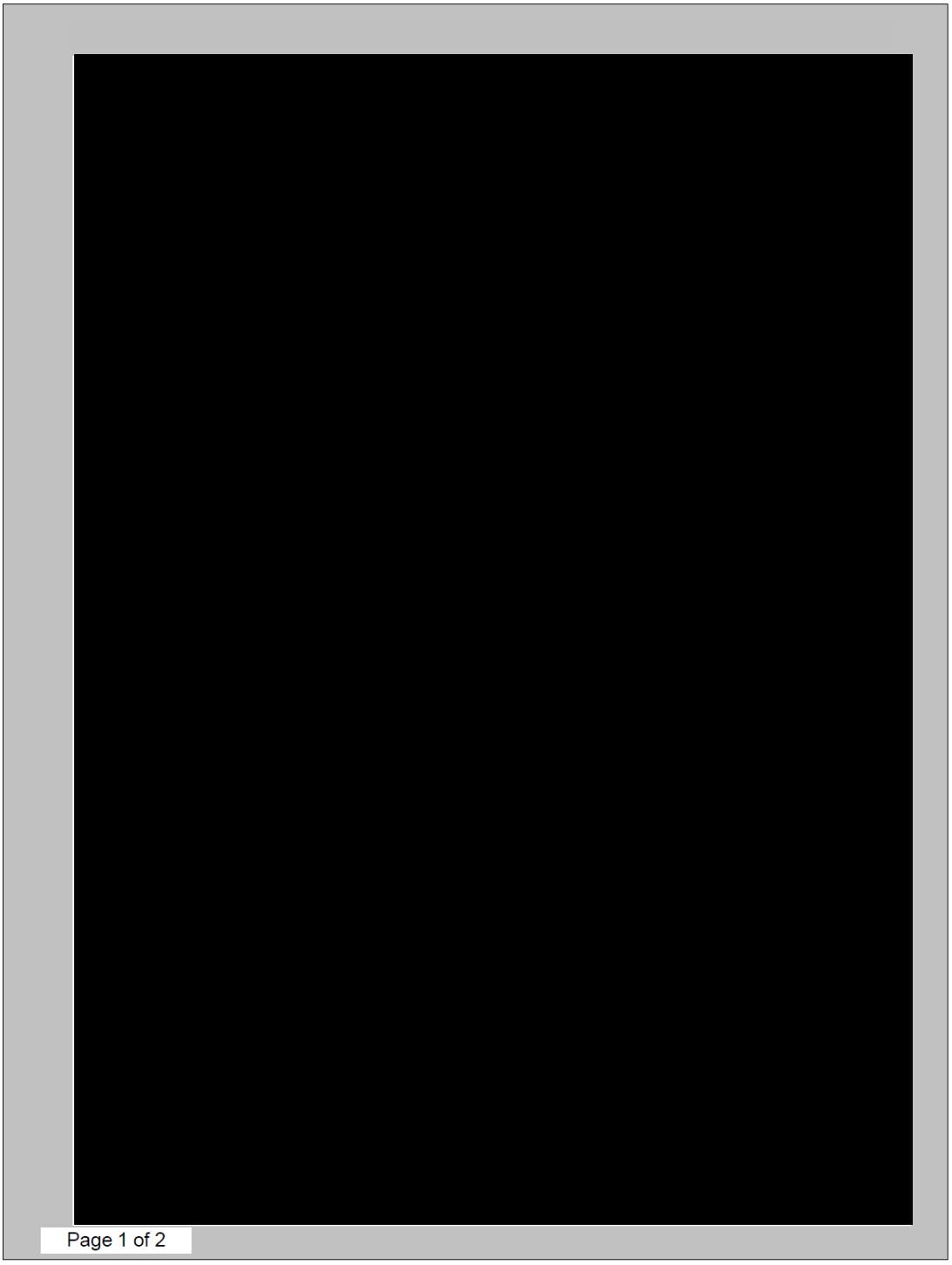
10 APPENDICES

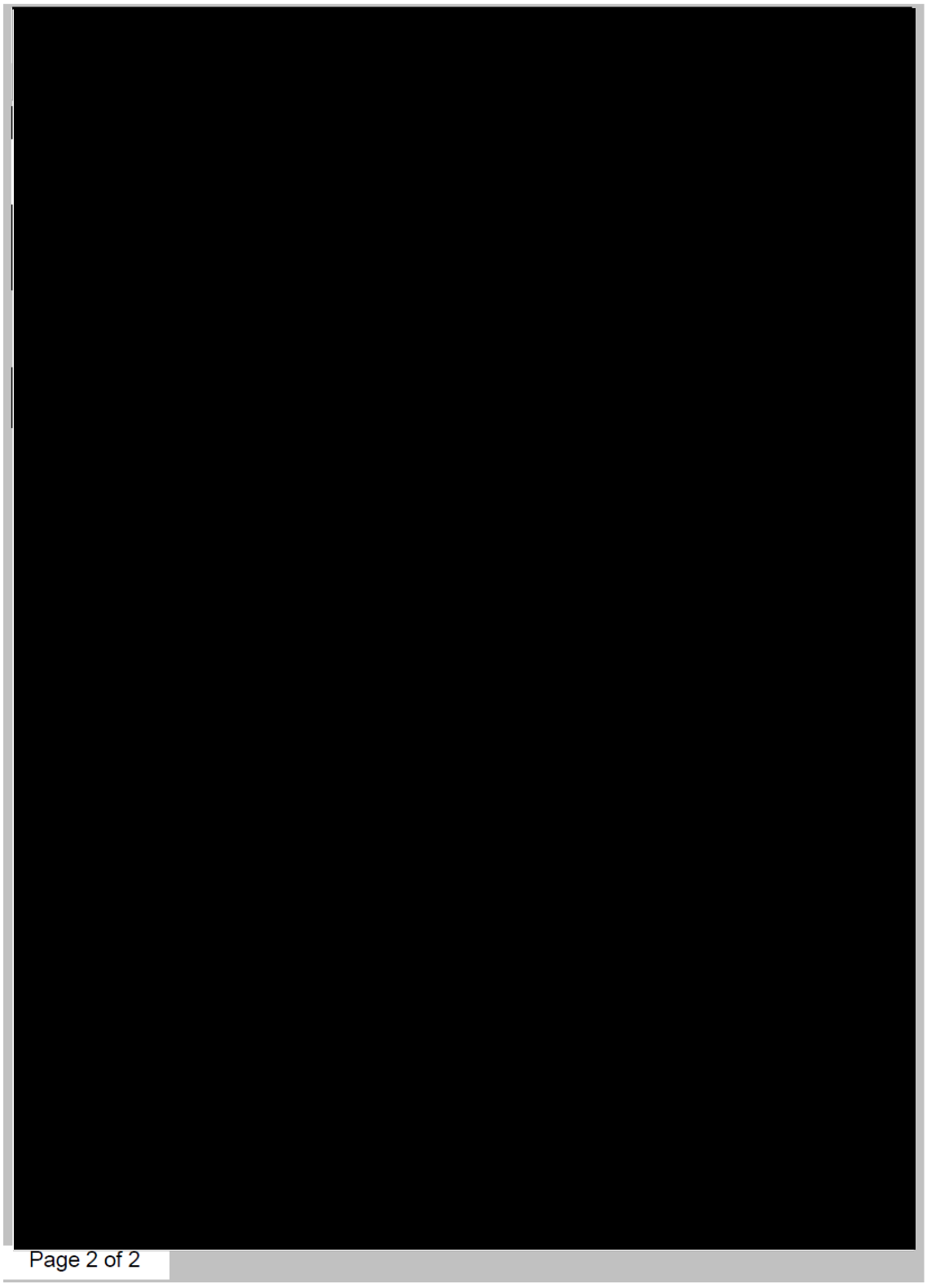
Appendix 1: Summary of Efficacy Endpoint and Analysis

Test / Instrument	Endpoint	Type	Time points for Assessment	Statistical Analysis
Bone Biopsy	The primary endpoint is the percent change from baseline in osteoid volume/bone volume (OV/BV) at Week 48 based on analysis of iliac crest bone biopsies.	Primary Efficacy Endpoints	Baseline, 48/ET	Descriptive Summary and T-Test (or Sign Test)
Serum Phosphorus	The proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL at the mid-point of the dose interval as averaged across dose cycles between baseline and Week 24.	Key Secondary Efficacy Endpoints	Screening, Baseline, Week 1, 2, 4, 6, 12,14,20,21, 22, 24,28, 36, 48, 60, 70, 72, 84, 94, 96, ET.	Descriptive Summary and Wilson Confidence Interval
Bone Biopsy	Percent changes from baseline in additional histomorphometric parameters – including osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and mineralization lag time (MLt)	Secondary Efficacy Endpoints	Baseline, 48/ET	Descriptive Summary and T-Test (or Sign Test)
Bone Biopsy	Changes from baseline in MAR, MS/BS, BFR and additional measures of bone formation and remodeling	Secondary Efficacy Endpoints	Baseline, 48/ET	Descriptive Summary
Serum Phosphorus	Proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL at the end of the dosing cycle, as averaged across dose cycles	Secondary Efficacy Endpoints	Screening, Baseline, Week 1, 2, 4, 6, 12,14,20,21, 22, 24,28, 36, 48, 60, 70, 72, 84, 94, 96, ET.	Descriptive Summary
	Mid-point of dosing cycle: mean change from baseline and percent change from baseline averaged across dose cycles through Week 24	Secondary Efficacy Endpoints		Descriptive Summary
	End of dosing cycle: mean change from baseline averaged across dose cycles	Secondary Efficacy Endpoints		Descriptive Summary
	Cumulative exposure: Time Adjusted area under the curve (AUC)	Secondary Efficacy Endpoints		Descriptive Summary

Test / Instrument	Endpoint	Type	Time points for Assessment	Statistical Analysis
PD	Change from baseline over time in serum intact FGF23, ALP, 1,25(OH)2D; and urinary phosphorus, TRP,TmP/GFR, and FEP	Secondary Efficacy Endpoints	Screening, Baseline, Week 1, 2, 4, 12,20,21, 22, 24,36, 48, 60, 72, 84, 94, 96, ET.	Descriptive Summary , GEE Model
Biomarker	Change and percent change from baseline over time in bone biomarker, including BALP, CTx, P1NP, and osteocalcin	Secondary Efficacy Endpoints	Baseline, week 12, 24, 48, 72, 96 and ET.	Descriptive Summary , GEE Model
X-Ray	Number of post-baseline healed, partial healed pseudofractures from baseline active pseudofractures; Number of subjects who have active pseudofractures at baseline and healed, partial healed post-baseline pseudofractures	Exploratory Efficacy Endpoints	Baseline, week 12, 24, 36, 48 and ET.	Descriptive Summary , GEE Model
BPI	Change from baseline in:	Exploratory Efficacy Endpoints	Screening, Baseline, week 12, 24, 36, 48, 72, 96 and ET.	Descriptive Summary , GEE Model
	Worst Pain			
	Pain Severity			
	Pain Interference			
BFI	Change from Baseline in:	Exploratory Efficacy Endpoints	Screening, Baseline, week 12, 24, 36, 48, 72, 96 and ET.	
	Worst Fatigue			
	Global Fatigue Score			

Appendix 2: Brief Pain Inventory





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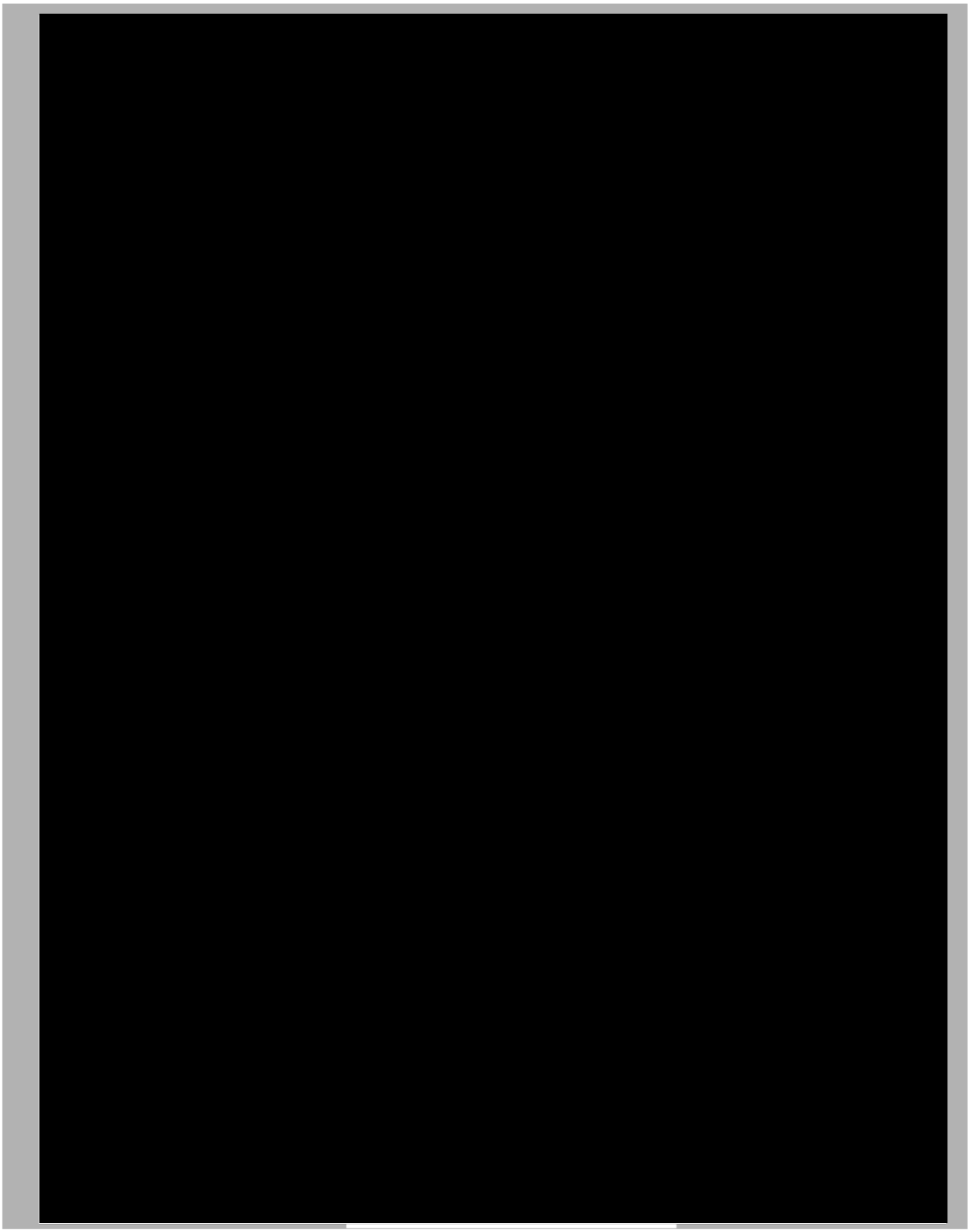
Appendix 3: Brief Fatigue Inventory



Appendix 4: 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

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 5: Schedule of Events

Screening and Baseline Visits

	Screening[1]			Baseline[1]		
VISIT TYPE/NUMBER		**TC 1**	**TC 2**	**V1**		
STUDY WEEK or DAY	**Week −4**	**Week −3**	**Week −1**	**Day -2**	**Day -1**	**Day/Wk 0**
Informed Consent, Inclusion/Exclusion Criteria	X					
Medical History, Demographics, Height [2]	X					
PHEX Mutation Analysis [3,4]				X		
Tetracycline HCl or Demeclocycline Label [5]		X	X			
Bone Biopsy [1]					X	
Bone Turnover Markers [6]				X		
Serum Phosphorus, Calcium, iPTH, Creatinine/eGFR [6]	X			X		
Serum $1,25(OH)_2D$ [6]				X		
Serum iFGF23	X[4]			X		
2-hr Urine [6,7]	X			X		
24-hr Urine [6,7]				X		
BPI, BFI [8,9]	X			X		
Skeletal survey [10]				X		
Anti-KRN23 (HAHA)						X
Vital Signs [11]	X			X	X	X
Physical Examination	X			X		
Weight[12]				X		
Renal Ultrasound [1]	X					
ECHO, ECG [1]				X		
Chemistry, Hematology (with PT/PTT), Urinalysis/pregnancy test[6, 13, 14]	X			X		
Concomitant Medications	X			X	X	X
Adverse Events	X			X	X	X
KRN23 ADMINISTRATION						**X**

Open Label Treatment Period (Weeks 1 – 48)

VISIT TYPE/NUMBER[15]	HH V2	V3	V4	HH V5	HH V6	V7	HH V8	HH V9	HH V10	HH V11	V12	V13	HH V14	HH V15	V16	HH V17	HH V18	TC 3	TC 4	V19[1]	
WEEK	1	2	4	6	8	12	14	16	20	21	22	24	28	32	36	40	44	45	47	48[1] Day 1	48[1] Day 2
Tetracycline HCl or Demeclocycline Label[5]																		X	X		
Bone Biopsy [1]																					X[16]
Bone Turnover Markers [6]						X						X								X	
Serum Phosphorus, Calcium [6]	X	X	X	X		X	X		X	X	X	X	X		X					X	
Serum $1,25(OH)_2D$ [6]	X	X	X						X	X	X	X								X	
iPTH[6]	X	X	X						X	X	X									X	
Serum iFGF23[6]												X								X	
Serum Creatinine/eGFR[6]		X	X			X					X	X								X	
2-hr Urine [6,7]		X	X			X					X	X								X	
24-hr Urine [6,7]						X						X			X					X	
BPI, BFI [8,9]						X						X			X					X	
Targeted Radiography [10]						X						X			X					X	
KRN23 PK	X	X	X							X	X	X								X	
Anti-KRN23 (HAHA)			X									X								X	
Vital Signs [11]			X			X						X			X					X	
Weight [12]						X						X			X					X	
Physical Examination						X						X			X					X	
Renal Ultrasound												X								X	
ECHO, ECG												X								X	
Chemistry, Hematology (with PT/PTT), Urinalysis [6, 13]			X			X						X			X					X	
Urine Pregnancy Test [14]			X		X	X		X	X			X	X	X	X	X	X			X	

VISIT TYPE/NUMBER[15]	HH V2	V3	V4	HH V5	HH V6	V7	HH V8	HH V9	HH V10	HH V11	V12	V13	HH V14	HH V15	V16	HH V17	HH V18	TC 3	TC 4	V19[1]	
WEEK	1	2	4	6	8	12	14	16	20	21	22	24	28	32	36	40	44	45	47	48[1]	
																				Day 1	Day 2
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
KRN23 ADMINISTRATION			X		X	X		X	X			X	X	X	X	X	X			X	

Treatment Extension Period (Weeks 49-96), Early Termination, and Safety Follow-up

	Treatment Extension Period														Early Termination				Safety Follow-up
VISIT TYPE/NUMBER[15]	HH V20	HH V21	V22	HH V23	HH V24	HH V25	V26	HH V27	HH V28	V29	HH V30	HH V31	HH V32	V33[1]	ET[1]				Follow-up Phone Call[18]
WEEK	52	56	60	64	68	70	72	76	80	84	88	92	94	96	TC 5 Week -3	TC 6 Week -1	ET Day 1	ET Day 2	12 weeks after Final Dose[18]
Bone Biopsy[1]																		X[16]	
Tetracycline HCl or Demeclocycline Label[5, 16]															X	X			
Bone Turnover Markers [6]							X							X			X		
Serum Phosphorus, Calcium [6]			X			X	X			X			X	X			X		
Serum 1,25$(OH)_2$D [6]			X			X	X			X			X	X			X		
iPTH[6]			X			X	X			X			X	X			X		
Serum iFGF23[6]														X			X		
Serum Creatinine/eGFR[6]			X				X			X				X			X		
2-hr Urine [6,7]			X				X			X				X			X		
24-hr Urine [6,7]							X							X			X		
BPI, BFI [8,9]							X							X					
Targeted Radiography [10]	Only at clinic visits following a newly diagnosed fracture[17]																		
Anti-KRN23 (HAHA)							X							X			X		
KRN23 PK						X	X							X			X		
Vital Signs [11]			X				X			X				X			X		
Weight [12]							X							X			X		
Physical Examination							X							X			X		
Renal Ultrasound							X							X			X		
ECHO, ECG							X							X			X[17]		
Chemistry, Hematology (with PT/PTT), Urinalysis [6, 13]			X				X			X				X			X[13]		
Urine Pregnancy Test [14]	X	X	X	X	X		X	X	X	X	X	X		X			X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X

	Treatment Extension Period														Early Termination				Safety Follow-up
VISIT TYPE/NUMBER[15]	HH V20	HH V21	V22	HH V23	HH V24	HH V25	V26	HH V27	HH V28	V29	HH V30	HH V31	HH V32	V33[1]	ET[1]				Follow-up Phone Call[18]
WEEK	52	56	60	64	68	70	72	76	80	84	88	92	94	96	TC 5 Week -3	TC 6 Week -1	ET Day 1	ET Day 2	12 weeks after Final Dose[18]
KRN23 ADMINISTRATION	X	X	X	X	X		X	X	X	X	X	X							

Footnotes to Table 2.1, Table 2.2, and Table 2.3

1 The Baseline visit should occur no more than 31 days following the Screening visit. The bone biopsy must be completed on a day with no other procedures, and prior to dosing on Day 0. Renal ultrasound, ECHO, ECG, and x-rays may be performed within 3 days of indicated clinic visit to accommodate scheduling availability. The Baseline, Week 48, and Week 96 (or Early Termination; ET) assessments may be completed in any reasonable order (except where indicated) to allow for flexibility in scheduling. However, all Screening/Baseline assessments and inclusion/exclusion criteria must be satisfied prior to dosing.

2 Medical history will include any available previous *PHEX* mutation analysis results for the subject or relevant family members with appropriate X-linked inheritance pattern. Height (in meters) will be obtained using a stadiometer (without shoes).

3 *PHEX* mutation analysis will be performed for all qualified subjects. If the Baseline result for *PHEX* mutation analysis is negative or inconclusive (i.e., No Mutation, Likely Benign, Variant of Uncertain Significance, or Possibly Pathogenic), and informed consent is provided by the subject, reflexive genetic testing will be performed to assess additional genes associated with phenotypes overlapping with XLH. A new blood sample for genetic analysis may be collected if necessary.

4 For patients without prior *PHEX* mutation analysis who fail screening on the basis of the Kainos iFGF23 assay, *PHEX* analysis may be conducted before the baseline visit

5 Available test results related to eligibility will be communicated to the subject within 1 week of the Screening visit by telephone call (TC1). If eligible, tetracycline HCl (or demeclocycline) will be provided to the subject with instructions for administration. The bone biopsy should be performed 5 days after the last dosing day for tetracycline or demeclocycline: The first dose should be given on days -20, -19, and -18 following TC1, and the second dose given on days -8, -7, and -6 following a second telephone call (TC2). The same instructions apply to TC3 and TC4 prior to the Week 48 (or TC5 and TC6 prior to ET if applicable) bone biopsy.

6 Blood and urine to be collected after a minimum overnight fasting time of 8 hours and prior to drug administration (if applicable).

7 Both 2-hr and 24-hr urine will be used for measurements of urinary phosphorus, creatinine and calcium; 2-hr urine will be used for the derivation of TmP/GFR and TRP.

8 Only the BPI Question 3 (Worst Pain) will be administered at Screening for eligibility. The complete short-form BPI and BFI will be administered at all other indicated visits.

9 Administer BPI first followed by BFI. The BPI and BFI should be administered prior to the performance of any invasive procedures.

10 X-rays will be taken at locations pre-determined by skeletal survey (chest, lateral spine, right and left hand/wrist, right and left humerus, right and left radius/ulna, right and left femur/pelvis, right and left tibia/fibula, and right and left foot). If active pseudofracture(s) detected at baseline, targeted X-rays at

that location will be obtained as indicated. During the Extension Period, targeted x-rays will only be performed at clinic visit(s) to follow healing of any newly diagnosed fractures.

[11] Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg; 2 measurements separated by 15 minutes), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of the visit before any additional assessments are completed

[12] Weight will be recorded in kilograms. Dose of study drug must be adjusted if weight increases by more than 20% from baseline.

[13] Serum chemistry panels may include PD parameters (i.e. serum phosphorus), and safety parameters of interest (i.e. calcium) to avoid duplication of testing. Screening and Week 48 Day1 hematology will include Prothrombin time/Partial thromboplastin time (PT/PTT). ET hematology will include PT/PTT if a bone biopsy is also scheduled (if a subject discontinues the study between 24 and 48 weeks)

[14] Urine pregnancy test for women of childbearing potential only. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result.

[15] During the Open-Label Treatment Period (Weeks 1 – 48) and Treatment Extension Period (Weeks 49-96) subjects will return to the clinic and/or have home health (HH) visits as indicated (± 5 days). HH visits may also be conducted at the clinic depending on subject proximity to the investigational site and local availability of home health care resources.

[16] Bone biopsies will not be performed at Week 48 (or at ET) for subjects who do not have evidence of osteomalacia on the initial biopsy. Bone biopsies will not be performed at the ET Visit if the subject discontinues within 6 months of the baseline biopsy or if the subject terminates the study after 48 weeks. Prior to ET biopsy, tetracycline HCl (or demeclocycline) will be provided to the subject with instructions for administration. The bone biopsy should be performed 5 days after the last dosing day for tetracycline or demeclocycline The first dose should be given on days -20, -19, and -18 following TC5, and the second dose given on days -8, -7, and -6 following a second telephone call (TC6) prior to the ET biopsy (if eligible).

[17] Targeted X-rays and ECHO will not be performed at ET if the assessment was conducted within 3 months of termination. Targeted X-rays will not be taken at ET if the subject terminates the study after 48 weeks.

[18] To be completed only for subjects who complete the study and choose not to enroll in a planned extension study under a separate protocol or subjects who discontinue the study early. This call is not required for subjects who are eligible and choose to participate in the separate extension study. The site personnel will initiate this safety follow-up telephone call 12 weeks ± 5 days after a subject's last dose of study drug to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.