# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Title** | **A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Subjects with Tumor-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS) – associated Osteomalacia** |
| **Protocol:** | **UX023T-CL201** |
| **Investigational Product:** | **KRN23 (Recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 [FGF23])** |
| **Indication:** | **Treatment of tumor-induced osteomalacia (TIO) and epidermal nevus syndrome (ENS) - associated osteomalacia** |
| **IND Number:** | **123878** |
| **Phase:** | **2** |
| **Sponsor:** | **Ultragenyx Pharmaceutical Inc.<br>60 Leveroni Court<br>Novato, CA, USA 94949** |
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| **Date:** | **04 May 2016** |
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## ABBREVIATIONS

| | |
|---|---|
| 1,25[OH]$_2$D | 1,25-dihydroxyvitamin D |
| 25(OH)D | 25-hydroxy vitamin D |
| 6MWT | 6-Minute Walk Test |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| BALP | Bone-specific alkaline phosphatase |
| BFI | Brief fatigue inventory |
| 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 |
| DLT | Dose-limiting toxicity |
| DXA | Dual-energy X-ray absorptiometry |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eGFR | Estimated glomerular filtration rate |
| ENS | Epidermal nevus syndrome |
| FGF23 | Fibroblast growth factor 23 |
| GEE | Generalized Estimating Equation |
| GFR | Glomerular filtration rate |
| HAHA | Human anti-human antibody |
| HHD | Hand-held dynamometry |
| iPTH | Intact parathyroid hormone |
| ISR | Injection site reactions |
| KRN23 | Investigational product, an anti-FGF23 antibody |
| LVH | Left ventricular hypertrophy |
| mAb | Monoclonal antibody |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| MVIC | Maximum voluntary isometric contraction |
| 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 |
| SF-36 | 36-item Short Form Health Survey |
| SMQ | Standardised MedDRA Query |
| SSRT | Study safety review team |
| STS | Sit-to-stand (test) |
| TEAE | Treatment-emergent adverse event |
| TIO | Tumor-induced osteomalacia (also known as oncogenic osteomalacia) |
| TmP/GFR | Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate |
| TRP | Tubular reabsorption of phosphate |
| WAL | Weighted arm lift (test) |
| 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 UX023T-CL201 Protocol Amendment 3, dated 17 February 2016. The data collected in this study will evaluate the efficacy and safety of KRN23 in adult subjects with tumor-induced osteomalacia (TIO) or epidermal nevus syndrome (ENS)-associated osteomalacia.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objectives

The primary objectives of this study are to evaluate the following:

- Effect of KRN23 treatment on increasing serum phosphorus levels in adults with TIO or ENS-associated osteomalacia
- Effect of KRN23 treatment on improvement in TIO/ENS-associated osteomalacia as determined by the following histomorphometric indices:
    - Osteoid Thickness (O.Th)
    - Osteoid surface/Bone surface (OS/BS)
    - Osteoid volume/Bone volume (OV/BV)
    - Mineralization lag time (MLt)

## 2.2 Secondary Objectives

Secondary objectives of the study are to evaluate the following:

- The pharmacodynamics (PD) profile of KRN23 as assessed by changes from baseline over time in additional measures of serum phosphorus, serum FGF23, alkaline phosphatase (ALP), and $1,25(OH)_2D$, TRP, and TmP/GFR (the ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate)
- Effects of KRN23 on bone turnover markers, including bone-specific ALP (BALP), carboxy terminal cross-linked telopeptide of type I collagen (CTx), procollagen type 1 N-propeptide (P1NP), and osteocalcin
- Functional outcomes including upper and lower extremity muscle strength, walking and reaching ability, mobility
- Patient-reported outcomes including self-reported pain, disability, and quality of life

## 2.3 Exploratory Objectives

Exploratory objectives of the study are to evaluate the following:

- Changes in additional histomorphometry parameters in trans-iliac crest bone biopsies including both structural and dynamic measures

- Changes in underlying skeletal disease/osteomalacia as assessed by standard radiographs, dual-energy X-ray absorptiometry (DXA), 99mTc-labelled bone scan, and high-resolution peripheral quantitative CT (XtremeCT; where available).

### 2.4 Pharmacokinetics Objectives

The pharmacokinetics (PK) objective of the study is to:

- Determine the PK profile of repeat SC injections of KRN23 at baseline (Weeks 0, 2, and 4) and 6 months (Weeks 20, 22, and 24) in subjects with TIO or ENS-associated osteomalacia.

### 2.5 Safety Objectives

The safety objective of the study is to:

- Assess the safety of KRN23 administration in subjects with TIO or ENS-associated osteomalacia, based on adverse events (AEs), vital signs, laboratory assessments, cardiac imaging, renal ultrasound and immunogenic response.

## 3 STUDY DESIGN

### 3.1 Overall Study Design and Plan

This study will be conducted over 144 weeks to determine the efficacy, safety, PD and PK of repeat subcutaneous (SC) injections of KRN23 every 4 weeks from Week 0 through Week 140 in adult subjects with TIO or ENS-associated osteomalacia.

All enrolled subjects will begin treatment with KRN23 at a starting dose of 0.3 mg/kg (Week 0). Doses of KRN23 will then be titrated in an effort to achieve a target fasting serum phosphorus range of 2.5 to 4.0 mg/dL. If the subject's peak serum phosphorus level at Week 2 remains below the target range, the subject's dose may be increased at Week 4 to 0.6 mg/kg, at the discretion of the investigator. Doses will then continue to be titrated in increments of 0.2 mg/kg at Weeks 8, 12, and 16 in individual subjects to achieve the target peak serum phosphorus range. Doses may be titrated at later visits, at the discretion of the investigator, if there are concerns about safety or sub-optimal efficacy. The maximum dose allowed in this protocol is 2.0 mg/kg. If needed, the final dose adjustment increment may be less than 0.2 mg/kg to reach the 2.0 mg/kg maximum dose.

A complete schedule of events is included in Appendix 10.6.

### 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

NA

### 3.4 Determination of Sample Size

Assuming the proportion of subjects with a phosphorus level above the lower limit of normal at 2 weeks after dosing, as averaged across dose cycles between baseline and Week 24 is 60%, a sample size of 15 subjects will provide a 95% confidence interval with the half width no greater than 24.8%. A reduction in excess osteoid is expected to be shown in all subjects with paired biopsies, with an estimated ≥ 50% reduction from baseline in osteoid thickness. The sample size and study duration are believed to be sufficient to enable characterization of KRN23 effects on serum phosphorus levels, excess osteoid histomorphometric indices and the safety profile of KRN23.

### 3.5 Interim Analyses

Administrative analyses may be performed to support regulatory activities or product development per Sponsor's decision. The primary analysis will be conducted when subjects complete the Week 48 assessments.

### 3.6 Data Monitoring Committee

An independent data monitoring committee will not be used. Safety will be continuously monitored by Ultragenyx.

## 4 STUDY CLINICAL OUTCOMES AND COVARIATES

### 4.1 Primay Efficacy Endpoints

The study has co-primary endpoints:

- The proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL (0.81 mmol/L) at the mid-point of the dose interval (2 weeks after dosing), as averaged across dose cycles between baseline and Week 24 (i.e. serum phosphorus levels at Weeks 2, 6, 10, 14 and 22).
- The change from baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using the following histomorphometric indices:
    - O.Th
    - OS/BS
    - OV/BV
    - MLt

## 4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Additional measures to assess serum phosphorus levels over time include:
  - Proportion of subjects achieving mean serum phosphorus levels above 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
  - Mid-point of dosing cycle: mean change from baseline and percent change from baseline averaged across dose cycles between baseline and Week 24
  - End of dosing cycle: mean change from baseline and percent change from baseline averaged across dose cycles between baseline and Week 24
  - Cumulative exposure: time-adjusted area under the curve (AUC) between baseline and Week 24
- Change from baseline over time in serum FGF23, ALP, $1,25(OH)_2D$; and urinary phosphorus, TRP, TmP/GFR, and fractional excretion of phosphorus (FEP)
- Change and percent change from baseline over time in serum biochemical markers of bone turnover, including BALP, CTx, P1NP, and osteocalcin
- Change from baseline in muscle strength assessed by HHD, STS test, WAL test, and 6MWT
- Change from baseline in BPI, BFI, and SF-36 over time

## 4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Changes in other measures of structural and dynamic histomorphometry in trans-iliac crest bone biopsies
- Changes in bone condition and healing of prior long bone and pseudo-fractures as assessed by $^{99m}$Tc-labelled bone scan
- Changes in bone mineral density and bone mineral content as measured by DXA
- Changes in complications of osteomalacia, such as fractures, pseudo-fractures or suspicion of delayed fracture healing as assessed by standard radiographs
- Changes in bone geometry, and microarchitecture in the cortical and trabecular compartments of the radius and tibia as measured by XtremeCT (when available)

## 4.4 PK Endpoints

Serum KRN23

### 4.5 Safety Endpoints

Safety and tolerability will be evaluated by the incidence, frequency and severity of treatment-emergent adverse events (TEAEs) and SAEs, including clinically significant changes from baseline to scheduled time points.

General safety variables include:

- Vital signs and weight
- Physical examinations
- eGFR
- Serum calcium, phosphorus, intact parathyroid hormone (iPTH), and urinary calcium and creatinine
- Chemistry, hematology, and urinalysis, including additional KRN23/TIO biochemical parameters of interest (serum 25-hydroxy vitamin D [25(OH)D], lipase, amylase, creatinine, and FGF23)
- Tumor imaging (TIO) or dermatologic assessment of skin lesions (ENS-associated osteomalacia)
- Anti-KRN23 antibody testing
- Dose-limiting toxicities, defined as:
    - Unexpected SAEs occurring during treatment considered to be either probably or possibly related to the investigational product.
    - A confirmed serum phosphorus level of ≥6.5 mg/dL (defined as hyperphosphatemia) at any time after dosing.
- Concomitant medications
- Urine pregnancy testing

Ectopic Mineralization Safety Assessments include:

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

# 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 investigational drug administration in the study.

## 5.2 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).

## 5.3 Hand-Held Dynamometry

Hand-held-dynamometry (HHD) will be administered pre- and post-treatment as indicated in the Schedule of Events (Appendix 10.6) to assess muscle strength. The maximum voluntary isometric contraction (MVIC) against a dynamometer will be used to measure bilateral strength, defined as the average of the left and the right scores, in the following muscle groups: elbow flexors, elbow extensors, knee flexors and knee extensors. If only one of the right and left raw values is missing, the average scores of left and right measurements will be replaced with the non-missing value. If both left and right raw values are missing, the average score will be set to missing. Absolute values will be recorded, and the predicted normal values for each group will be derived using published normative data as outline in Table 1. Percent of predicted normal HHD values for the individual muscle groups will be calculated as (Raw strength value/Predicted normal strength value)*100%.

Table 1. Regression Equations for predicted normal values

| **Muscle Action** | **Equation** |
|---|---|
| Right Elbow Flexion | - (age * 0.13) + (gender * 11.24) + ((weight/height$^2$) * 0.07) + 22.78 |
| Left Elbow Flexion | - (age * 0.11) + (gender * 10.63) + ((weight/height$^2$) * 0.05) + 19.66 |
| Right Elbow Extension | - (age * 0.08) + (gender * 8.33) + ((weight/height$^2$) * 0.16) + 12.37 |
| Left Elbow Extension | - (age * 0.07) + (gender * 8.18) + ((weight/height$^2$) * 0.17) + 11.32 |
| Right Knee Flexion | -(age * 0.16) + (gender * 8.78) + ((weight/height$^2$) * 0.08) + 22.47 |
| Left Knee Flexion | -(age * 0.17) + (gender * 7.67) + ((weight/height$^2$) * 0.14) + 21.10 |
| Right Knee Extension | - (age * 0.38) + (gender * 18.44) + ((weight/height$^2$) * 0.62) + 34.41 |
| Left Knee Extension | - (age * 0.38) + (gender * 17.68) + ((weight/height$^2$) * 0.62) + 33.61 |

Normal Isometric Strength Data (NIMS) Database Consortium. Muscular Weakness Assessment: Use of Normal Isometric Strength Data. Arch Phys Med Rehabil. 1996;77:1251-5

Strength prediction results in kilograms (kg)
Age = years; gender: male = 1, female = 0; weight = kg; height = meters

Age, height and weight values collected at the baseline visit will be used for the calculation of predicted normal values for all study time points.

### 5.4 Sit-To-Stand

The sit-to-stand (STS) test will be administered pre- and post-treatment as indicated in the Schedule of Events (Appendix 10.6) to assess lower extremity strength and mobility. Absolute values for number of sit-to-stand repetitions will be recorded.

### 5.5 Weighted Arm Lift

The weighted arm lift (WAL) test will be administered pre- and post-treatment as indicated in the Schedule of Events (Appendix 10.6) to assess upper extremity strength, mobility and reaching ability. The bilateral average of the number of repetitions performed will be recorded. If only one of the right and left raw values is missing, the bilateral average will be replaced with the non-missing value. If both left and right raw values are missing, the bilateral average will be set to missing.

### 5.6 Six-Minute Walk Test

The six-minute walk test (6MWT) will be administered pre- and post-treatment as indicated in the Schedule of Events (Appendix 10.6) by a trained clinician (preferably a licensed physical therapist) in accordance with general principles set forth in the American Thoracic Society guidelines (ATS 2002). Subjects will be instructed to walk the length of a pre-measured course for six consecutive minutes. The total distance walked at the end of six minutes will be recorded in meters. The percent predicted values for the 6MWT will be calculated using published normative data based on age, gender, and height (Gibbons et al. 2001). Assistive devices may be used; any use will be noted on the CRF.

To calculate the percent predicted 6MWT value, the following formula will be applied.

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

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 Brief Pain Inventory

The Brief Pain Inventory (BPI) will be administered at pre- and post-treatment time points as indicated in the Schedule of Events (Appendix 10.2) 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.

### 5.7.1 BPI Pain Responder definition

The BPI pain responder definition 1 is defined as greater than or equal to 30% reduction in worst pain from baseline. Only subjects with baseline worst pain > 0 will be evaluated for response.

The BPI pain responder definition 2 is defined as greater than or equal to 2 points reduction in worst pain from baseline. Only subjects with baseline worst pain ≥ 2 will be evaluated for response.

## 5.8 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 10.3) 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)
- Fatigue severity, defined as the average of questions 1 through 3
- Fatigue interference, defined as the average of questions 4A through 4F regarding "fatigue interfered" in the last 24 hours.
- Global fatigue score, defined as the average of the nine questions.

## 5.9 SF-36 Health Survey version 2

The SF-36v2 is a self-reported survey of general health-related quality of life (HRQL) with a 4-week recall period. It will be administered at pre- and post-treatment time points as indicated

in the Schedule of Events (Appendix 10.6) to assess physical and mental health based on summary and subscale scores. 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 10.4) 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.

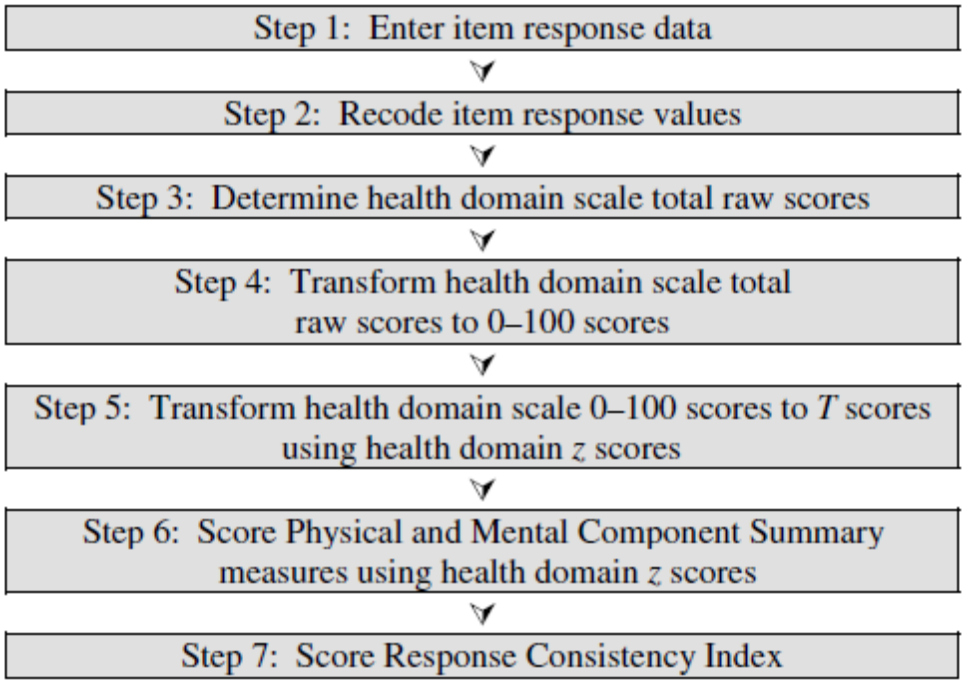
Scoring the SF-36 version 2 is accomplished using T-score Based scoring software from QualityMetric Inc. (Lincoln, RI). T-score Based scoring is standardized across the SF family of adult tools using the means and standard deviations from the 2009 U.S. general

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 50 can be interpreted as below the U.S. general population t-score and scores above 50 can be interpreted as 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




### 5.9.1 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.

For each individual SF36-v2 scale, the responders are the subjects with the change from baseline greater than or equal to the corresponding MIC.

### 5.10 $^{99m}$Tc-labelled Bone Scan

Whole body bone scans will be performed to evaluate bone condition and areas of bone damage, including current or prior long bone fractures and the presence of pseudo-fractures. Scans will be performed pre- and post-treatment as indicated in the Schedule of Events (Appendix 10.6), and pre- and post-treatment scans will be compared by a central reader who is blinded to time point and subject data.

### 5.11 Dual-energy X-ray Absorptiometry

Bone mineral density and content of the lumbar spine, and hip will be assessed by dual-energy X-ray absorptiometry (DXA) at pre- and post-treatment time points as indicated in the Schedule of Events (Appendix 10.6).

### 5.12 Standard Radiographs

Complications of osteomalacia, such as fractures, pseudo-fractures or suspicion of delayed fracture healing will be assessed by standard radiographs at pre- and post-treatment time points as indicated in the Schedule of Events (Appendix 10.6).

### 5.13 XtremeCT

XtremeCT scan of the radius and tibia will be performed (when available) pre- and post-treatment as indicated in the Schedule of Events (Appendix 10.6). As an exploratory efficacy measure, XtremeCT will be used to assess bone mineral density and content at the cortical and trabecular compartment.

### 5.14 Time-Adjusted Area Under the Curve (AUC)

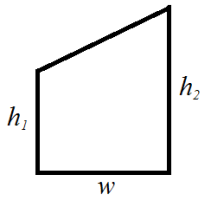
The trapezoidal rule is a numerical method that approximates the value of a definite integral.

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

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

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

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




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

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

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

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

### 5.15 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'.

**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 10.5.

# 6 ANALYSIS POPULATIONS

## 6.1 Biopsy Analysis Set

The biopsy analysis set will include enrolled subjects with baseline and follow-up (either Week 48 or early termination prior to Week 48) bone biopsy data.

## 6.2 Full Analysis Set

All efficacy (except bone biopsy endpoints), safety and PK/PD analyses will be performed on the set of all subjects who receive at least 1 dose of investigational product.

# 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.

## 7.2 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:
        I. If the year matches the first dose date year, then impute the month and day of the first dose date.
        II. Otherwise, assign ‘January’.
    3) If the day is unknown, then:

I. If the month and year match the first dose date month and year, then impute the day of the first dose date.

II. 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.

### 7.3 Missing Data in Bone Biopsy Parameter MLt

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, with 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.

### 7.4 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 that 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 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.

### 7.5 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 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 number of observations are insufficient for analyses using a GEE model, for continuous variables, a t-test will be performed; for binary variables, a 95% confidence interval (CI) of the proportion will be provided.

## 8.2 Subject Accountability

The number of subjects screened and enrolled, and the number and percentage of subjects in each analysis set (Biopsy and Full) will be summarized. The number and percentage of subjects who complete the treatment period and of subjects who prematurely discontinue will be summarized. The reasons for premature discontinuation from treatment period as recorded on electronic case report forms (eCRFs) will be summarized. A subject disposition listing will be provided for individual subject.

## 8.3 Protocol Deviations

Deviations from the protocol that are related to study inclusion and exclusion criteria, conduct of the trial, subject management or subject assessment will be summarized descriptively. A table and a data listing to document protocol deviations for the Full Analysis set will be provided.

## 8.4 Demographics and Baseline Characteristics

Demographic characteristics (age, height, weight, BMI, sex, race, and ethnicity) and other baseline characteristics will be summarized descriptively for the Full Analysis set and listed by subject. If the number of subjects in the Biopsy Analysis set differs quite a lot from the Full Analysis set, the same summary will be provided for the Biopsy Analysis set.

## 8.5 Disease Characteristics and Medical History

### 8.5.1 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 TIO/ENS History

TIO/ENS medical history will be summarized by number and percentage for each category for the Full Analysis set and will also be listed by subject. Subjects' past TIO/ENS treatment (including medications and therapies) will be summarized and listed for the Full Analysis set.

## 8.6 Dosing Summary

The weight-based dose level and total dose administered will be summarized and listed by study visit for the Full Analysis set.

## 8.7 Efficacy Analysis

All efficacy analysis (except bone biopsy analysis) will be performed on the Full Analysis set. The bone biopsy analysis will be performed on the Biopsy Analysis set.

### 8.7.1 Primary Efficacy Endpoints

The co-primary efficacy parameters will be the proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL (0.81 mmol/L) at the mid-point of the dose interval (2 weeks after dosing), as averaged across dose cycles between baseline and Week 24 (i.e. serum phosphorus levels at Weeks 2, 6, 10, 14 and 22) and the change from baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using the following histomorphometric indices: O.Th, OS/BS, OV/BV and MLt.

The number and proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL 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.

Histomorphometric indices O.Th, OS/BS, OV/BV and MLt 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 invalid, a sign test will be used. The p-value from the statistical tests will be reported. A listing will be provided for these parameters.

### 8.7.2 Secondary Efficacy Endpoints

<u>Additional measures to assess serum phosphorus levels over time</u>

The number and proportion of subjects achieving mean serum phosphorus levels above 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, will be provided, along with the two-sided 95% confidence interval of the proportion.

The serum phosphorus change from baseline and percent change from baseline at the end of the dosing cycle, as averaged across dose cycles between baseline and Week 24, will be summarized.

In addition, the serum phosphorus change from baseline and percent change from baseline at the mid-point of dosing cycle, averaged across dose cycles between baseline and Week 24 will also be summarized.

Additional analyses of serum phosphorus including observed, change from baseline, percent change from baseline values over time and time-adjusted area under the curve (AUC) between baseline and Week 24 will be summarized.

The number and % of subjects with post-dose serum phosphorus levels will be summarized over time by the following ranges: ≤2.5, >2.5 but ≤4.0, and >4.0 mg/dL (1.13 mmol/L).

Pharmacodynamics (PD) profile of KRN23

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

A listing for the PD parameters will be provided.

Individual and mean (±SE) PD-time plots may be presented for the PD parameters.

Effects of KRN23 on 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, P1NP, and osteocalcin, will be summarized. A listing will be provided for the biochemical markers of bone turnover.

Functional outcomes

For HHD (observed values and the percent of predicted normal values for four muscle groups as defined in Section 5.2), STS test (number of sit-to-stand repetitions), WAL test (bilateral average of the number of arm lifts performed) ), the observed values, change from baseline over time will be summarized. Listings for the functional outcomes will be provided.

6MWT was removed from the protocol at protocol amendment 1 and then added back as an assessment at protocol amendment 2. Therefore, there are very few subjects with baseline 6MWT data collected. A listing for the 6MWT data will be provided.

Patient-reported outcomes

For BPI (Worst Pain, Pain Severity and Pain Interference), BFI (Worst Fatigue, Global Fatigue Score), and SF-36 (PCS score and the PF, RP, BP and GH subscales that contribute the most to PCS; MCS score and the MH, RE, SF, and VT subscales that contribute the most to MCS) scores, the observed values, change from baseline over time, and the proportion of

responders (for BPI and SF-36) over time, will be summarized. Listings for the patient-reported outcomes will be provided.

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

### 8.7.3 Exploratory Efficacy Endpoints

For all the other parameters of structural and dynamic histomorphometry in trans-iliac crest bone biopsies, the observed, change from baseline, and percent change from baseline values over time will be summarized. A listing of the bone biopsy parameters will be provided.

For bone condition and areas of bone damage assessed by $^{99m}$Tc-labelled bone scan, the observed and change from baseline values over time will be summarized. A listing containing the details of the bone scan parameters will be provided.

For bone mineral density and content of the lumbar spine and hip, assessed by DXA, the observed values and percent change from baseline over time for bone mineral density will be summarized. A listing containing all the DXA parameters will be provided.

For complications of osteomalacia assessed by standard radiographs, the observed and change from baseline values over time will be summarized and listed.

For bone geometry, and microarchitecture in the cortical and trabecular compartments of the radius and tibia as measured by XtremeCT (when available), the observed values will be listed.

## 8.8 PK Analysis

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

## 8.9 General Safety Analysis

All safety analyses will be performed on the Full Analysis set. 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, tumor imaging or dermatologic assessment of skin lesions, concomitant medications, physical exams, pregnancy test and vital signs. No hypothesis testing is planned for safety data.

### 8.9.1 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
- TEAE by severity
- Events to monitor:
    - Injection site reactions
    - Immunogenicity
    - Hyperphosphataemia
    - Ectopic mineralization
    - Gastrointestinal events
    - 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 investigational product administration.

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

### 8.9.2 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 amylase:

- Normal
- 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.

### 8.9.3 HAHA

The HAHA data will be summarized and listed. In addition, shift tables will be provided for HAHA.

### 8.9.4 Concomitant Medications

Each medication will be coded to a preferred name and an Anatomic Therapeutic Classification (ATC) code using WHO Drug. The number and percentage of subjects taking each concomitant medication will be displayed by preferred name. 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.

### 8.9.5 Physical Examination

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

### 8.9.6 Pregnancy Test

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

### 8.9.7 Vital Signs

Observed and change from baseline values over time in vital signs, including systolic blood pressure, diastolic blood pressure and heart rate, will be summarized by descriptive statistics. Individual subject listing of vital signs will be provided.

## 8.10 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.

### 8.10.1 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.

### 8.10.2 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.

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 at each scheduled time of assessment.

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

### 8.10.3 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 also be created.

### 8.10.4 Tumor Imaging

For subjects with TIO, if the tumor is visible and localized at screening, it will be imaged at Screening and every 6 months using the same radiologic imaging technique (either CT scan or MRI) used initially to identify the tumor. Screening images will be used as baseline. In cases where the tumor was initially identified using another imaging technology, a baseline CT scan or MRI (whichever is more clinically appropriate) will be performed. During follow up, the same imaging technique (CT scan or MRI) that was used at Screening will be utilized

to assess tumor size. The radiologist will indicate whether tumor size and volume have changed over time. Tumor imaging data will be listed.

### 8.10.5 Dermatological Assessment

ENS-associated osteomalacia is characterized by skin lesions. Serial photographs of skin lesions will be taken at baseline and post-treatment to assess progress in the skin lesions over time in subjects with ENS-associated osteomalacia only. Dermatological data will be listed.

## 9 REFERENCES

1. The National Isometric Muscle Strength (NIMS) Database Consortium. Muscular Weakness Assessment: Use of Normal isometric Strength Data. Arch Phys Med Rehabil 1996;77:1251-5.

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

3. 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.

4. Dempster, D. W., Compston, J. E., Drezner, M. K., Glorieux, F. H., Kanis, J. A., Malluche, H., … Parfitt, A. M. (2013). Standardized Nomenclature, Symbols, and Units for Bone Histomorphometry: A 2012 Update of the Report of the ASBMR Histomorphometry Nomenclature Committee. Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research, 28(1), 2–17.

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

# 10 APPENDICES

## 10.1 Summary of Endpoint and Analysis

| Type | Endpoint | Statistical Analysis |
|---|---|---|
| Primary Efficacy Endpoints | 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. | Descriptive Summary and Wilson Confidence Interval |
| Primary Efficacy Endpoints | The percent change from baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using the following histomorphometric indices: O.Th, OS/BS. OV/BV, MLt. | Descriptive Summary and T-Test (or Sign Test) |
| Secondary Efficacy Endpoints | 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 | Descriptive Summary and Confidence Interval |
| Secondary Efficacy Endpoints | Mid-point of dosing cycle: mean change from baseline and percent change from baseline averaged across dose cycles through Week 24 | Descriptive Summary |
| Secondary Efficacy Endpoints | End of dosing cycle: mean change from baseline averaged across dose cycles | Descriptive Summary |
| Secondary Efficacy Endpoints | Cumulative exposure: area under the curve (AUC) | Descriptive Summary |
| Secondary Efficacy Endpoints | Change from baseline over time in serum FGF23, ALP, 1,25(OH)2D; and urinary phosphorus, TRP,TmP/GFR, and FEP | Descriptive Summary , GEE Model |
| Secondary Efficacy Endpoints | Change and percent change from baseline over time in bone biomarker, including BALP, CTx, P1NP, and osteocalcin | Descriptive Summary , GEE Model |
| Secondary Efficacy Endpoints | Change from baseline in muscle strength assessed by HHD, STS test, WAL test, and 6MWT | Descriptive Summary , GEE Model |
| Secondary Efficacy Endpoints | Change from baseline in BPI, BFI, and SF-36 over time | Descriptive Summary , GEE Model |
| Exploratory Efficacy Endpoints | Changes in other measures of structural and dynamic histomorphometry in trans-iliac crest bone biopsies | Descriptive Summary |
| Exploratory Efficacy Endpoints | Changes in bone condition and healing of prior long bone and pseudo-fractures as assessed by $^{99m}$Tc-labelled bone scan | Descriptive Summary |
| Exploratory Efficacy Endpoints | Changes in bone mineral density and bone mineral content as measured by DXA | Descriptive Summary |
| Exploratory Efficacy Endpoints | Changes in complications of osteomalacia, such as fractures, pseudo-fractures or suspicion of delayed fracture healing as assessed by standard radiographs | Descriptive Summary |
| Exploratory Efficacy Endpoints | Changes in bone geometry, and microarchitecture in the cortical and trabecular compartments of the radius and tibia as measured by XtremeCT (when available) | Descriptive Summary |
| PK Endpoints | Serum KRN23 | Descriptive Summary |
| Safety Endpoints | Adverse events, vital signs, physical examinations | Descriptive Summary |
| Safety Endpoints | eGFR | Descriptive Summary |
| Safety Endpoints | Serum calcium, phosphorus, intact parathyroid hormone (iPTH), and urinary calcium and creatinine | Descriptive Summary |

| Type | Endpoint | Statistical Analysis |
|---|---|---|
| Safety Endpoints | Chemistry, hematology, and urinalysis, including additional KRN23/TIO biochemical parameters of interest (serum 25-hydroxy vitamin D [25(OH)D], lipase, amylase, creatinine, and FGF23) | Descriptive Summary |
| Safety Endpoints | Concomitant medications, urine pregnancy testing | Descriptive Summary |
| Safety Endpoints | Anti-KRN23 antibody testing | Descriptive Summary |
| Safety Endpoints | Tumor imaging (TIO) or dermatologic assessment of skin lesions (ENS-associated osteomalacia) | Descriptive Summary |
| Safety Endpoints | Echocardiogram (ECHO), electrocardiogram (ECG), and renal ultrasound | Descriptive Summary |

## 10.2 Brief Pain Inventory

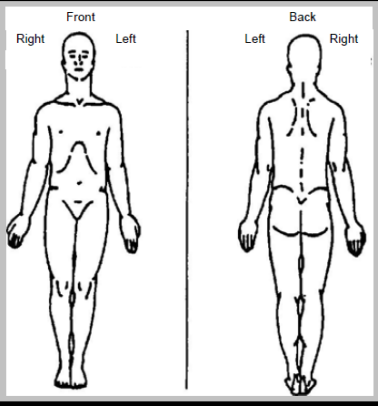
### Brief Pain Inventory (Short Form)

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 |

Page 1 of 2

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

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

**A. General Activity**

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

**B. Mood**

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

**C. Walking Ability**

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

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

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

**E. Relations with other people**

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

**F. Sleep**

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

**G. Enjoyment of life**

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



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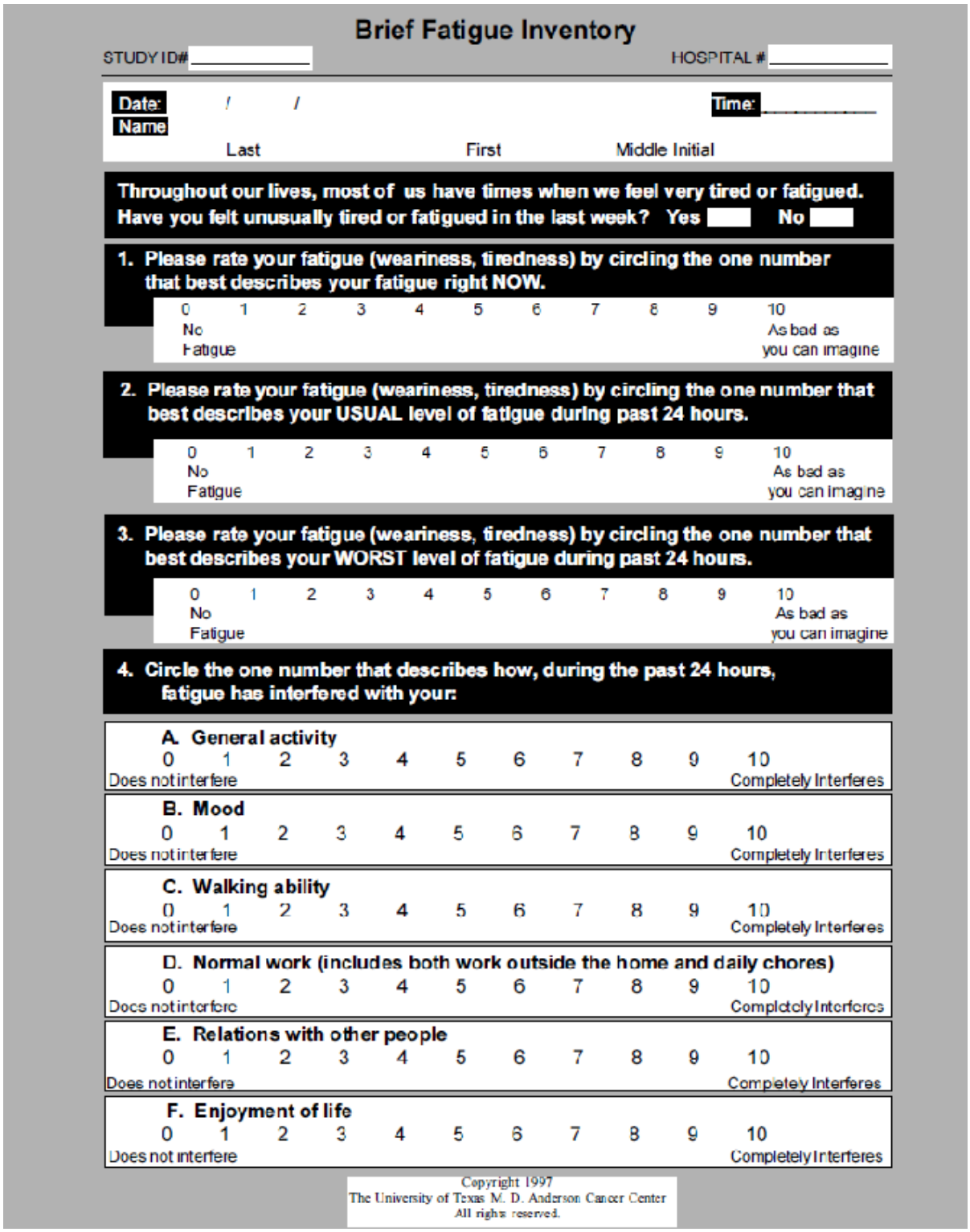
## 10.3 Brief Fatigue Inventory



**Brief Fatigue Inventory**

STUDY ID# _____ HOSPITAL # _____

**Date:** / / **Time:** _____

**Name**

Last First Middle Initial

**Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐**

**1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.**

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

**2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.**

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

**3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.**

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

**4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:**

**A. General activity**
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

**B. Mood**
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

**C. Walking ability**
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

**D. Normal work (includes both work outside the home and daily chores)**
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

**E. Relations with other people**
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

**F. Enjoyment of life**
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

### 10.4 SF-36

# 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!***

## 10.5 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 |

## 10.6 Schedule of Events

| STUDY VISIT | Screening | Baseline[2] | | | | | |
|---|---|---|---|---|---|---|---|
| | Screening Visit | TC1[1] | TC2[1] | Visit 1[3] | | | |
| STUDY WEEK or STUDY DAY | Week −4 | Week −3 | Week −1 | Day −3 | Day −2 | Day −1 | Week / Day 0[4] |
| Informed Consent | X | | | | | | |
| Inclusion/Exclusion Criteria | X | | | X | | | |
| Medical History & Demographics | X | | | | | | |
| **PHARMACODYNAMICS** | | | | | | | |
| Serum Phosphorus[5] | X | | | X | | | |
| Serum FGF23[5] | X | | | X | | | |
| Serum ALP[6] | | | | X | | | |
| Serum Creatinine[5,6] | X | | | X | | | |
| $1,25(OH)_2D$[5] | | | | X | | | |
| 2-Hour Urine [5,6] | X | | | X | | | |
| Bone turnover markers[5,7] | | | | X | | | |
| **EFFICACY** | | | | | | | |
| $^{99m}$Tc Bone Scan[8] | | | | | X | | |
| DXA[8] | | | | | X | | |
| Standard Radiographs[9] | X | | | | | | |
| Xtreme CT of Radius and Tibia[10] | X | | | | | | |
| Bone Biopsy[11] | | | | | | X | |
| BPI, BFI, SF36[12] | X | | | | X | | |
| HHD, STS, WAL, 6MWT[12] | X | | | | X | | |

| STUDY VISIT | Screening | Baseline[2] | | | | | |
|---|---|---|---|---|---|---|---|
| | Screening Visit | TC1[1] | TC2[1] | Visit 1[3] | | | |
| STUDY WEEK or STUDY DAY | Week −4 | Week −3 | Week −1 | Day −3 | Day −2 | Day −1 | Week / Day 0[4] |
| **PHARMACOKINETICS** | | | | | | | |
| Serum KRN23 | | | | | | | X |
| **SAFETY** | | | | | | | |
| Vital Signs[13] | | | | X | X | X | X |
| Weight | X | | | | X | | |
| Height | X | | | | | | |
| Physical Examination | X | | | X | | | |
| Concomitant Medications | X | | | X | | | |
| Adverse Events | | | | X | | | |
| Chemistry[14], Hematology[15] | X | | | X | | | |
| Anti-KRN23 Antibody[16] | | | | | | | X |
| Serum Calcium[4] | X | | | X | | | |
| Serum iPTH[4] | X | | | X | | | |
| 25(OH)D | X | | | | | | |
| Urinalysis | X | | | X | | | |
| 24-hour Urine[17] | | | | X | | | |
| ECHO, ECG[8] | | | | X | | | |
| Renal Ultrasound[18] | X | | | | | | |
| Tumor Imaging[19] | X | | | | | | |
| Photographs for Dermatologic Assessment[20] | | | | X | | | |

| STUDY VISIT | Screening | Baseline[2] | | | | | |
|---|---|---|---|---|---|---|---|
| | Screening Visit | TC1[1] | TC2[1] | Visit 1[3] | | | |
| STUDY WEEK or STUDY DAY | Week −4 | Week −3 | Week −1 | Day −3 | Day −2 | Day −1 | Week / Day 0[4] |
| Urine Pregnancy Test[21] | X | | | X | | | |
| **DRUG ADMINISTRATION** | | | | | | | |
| Tetracycline Labeling | | X | X | | | | |
| KRN23[22] | | | | | | | X |

[1] TC1 will be a telephone call to the subject within 1 week of the Screening visit to communicate test results related to eligibility. If eligible for the study, the subject will be instructed to begin taking a tetracycline (e.g., tetracycline HCl and demeclocycline) on Days −21, −20, and −19 prior to the Baseline visit. TC2 will be a second telephone call to the subject and should be conducted at least 7 days prior to the Baseline visit to instruct the subject to begin taking a tetracycline on Days −7, −6, and −5 prior to the Baseline visit. Tetracycline will be provided to the subject once eligibility has been determined.

[2] At the discretion of the investigator, Baseline Day −3 and Day −2 assessments may be completed in any order to allow for flexibility in scheduling. All assessments from Days −3 and −2 must be completed prior to the bone biopsy, which must be completed on its own day with no other assessments and 1 day prior to dosing on Day 0.

[3] Visit 1 may include overnight stay if deemed necessary by the Investigator. Discharge will occur approximately 24 hours after the first dose of KRN23 but may occur later in cases of prolonged recovery from the bone biopsy procedure

[4] All Day 0 assessments must be performed prior to administration of the first dose of KRN23.

[5] Blood and urine to be collected after a minimum overnight fasting time of 8 hours and prior to drug administration.

[6] Fasting 2-hour urine collections for TmP/GFR, TRP, and urinary calcium. Blood draw for serum creatinine should occur at 1 hour into the urine collection.

[7] Bone turnover markers will include serum measures of CTx, P1NP, BALP, and osteocalcin.

[8] May be completed within ± 5 days of the projected visit date to accommodate scheduling.

[9] At Screening, 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 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(s).

[10] May be performed any time after the subject has enrolled in the study (after meeting all eligibility criteria) until Baseline.

[11] A bone biopsy of the trans-iliac crest will be performed using general or local anesthesia as per institution practice(s) and performed by a physician trained and experienced in the procedure. The bone biopsy is not required at the Baseline visit if a previous bone biopsy taken within 12 months of screening confirmed the diagnosis of osteomalacia, the subjects' clinical manifestations have not changed significantly since the time of the previous biopsy/diagnosis, and the tissue collected at that biopsy is made available for testing for this protocol. BPI, BFI, SF36, HHD, STS, WAL, and 6MWT may be completed within ± 5 days of the projected visit date to accommodate scheduling.

[12] Vital sign measurements consist of seated systolic/diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate (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 and after the subject has rested for 5 minutes.

[13] This comprehensive metabolic profile will include serum Na, K, Cl, bicarbonate, BUN, creatinine, glucose, hepatic transaminases (ALT and AST), calcium, total protein, albumin, total bilirubin, indirect bilirubin.

[14] Complete blood count, differential, and platelet count.

[15] If anti-KRN23 antibodies are identified in a given subject, additional samples may be obtained to perform further testing.

[16] 24-hour urine collections for urinary phosphorus, calcium, creatinine, and eGFR; fasting 2-hour urine collections for TmP/GFR, TRP, and urinary calcium/creatinine ratio.

[17] Screening results will be treated as Baseline data.

[18] If visible, the tumor will be imaged at screening using the same radiologic imaging technique (e.g. computed tomography [CT] or magnetic resonance imaging [MRI]) used to identify the tumor. In cases where the tumor was initially identified using another imaging technology, a Baseline CT scan or MRI (whichever is more clinically appropriate) will be performed. During follow up, the same imaging technique (CT scan or MRI) that was used at Baseline will be utilized.

[19] Serial photographs of skin lesions will be taken in subjects with ENS-associated osteomalacia only. Photographs will be acquired using a standardized photo-imaging service

[20] For women of childbearing potential only, a serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test.

[21] All enrolled subjects will begin treatment with KRN23 at a starting dose of 0.3 mg/kg (Week 0, Day 0, and no sooner than the day after the bone biopsy is performed)

| VISIT TYPE/NUMBER[1] | V1 | HH V1 | HH V2 | V3 | HH V4 | V5 | HH V6 | V7 | HH V8 | V9 | HH V10 | HH V10.1 | HH V11 | V12[2] | HH V13 | HH V14 | V15 | HH V16 | HH V17 | TC3[3] | TC4[3] | V18[4] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Day 1 | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 20 | 21 | 22 | 24 | 28 | 32 | 36 | 40 | 44 | 45 | 47 | 48 | |
| | | | | | | | | | | | | | | | | | | | | | | D1 | D2 |
| **PHARMACODYNAMICS** | | | | | | | | | | | | | | | | | | | | | | | |
| Serum Phosphorus[5] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | |
| Serum FGF23[5] | X | | | X | | | | X | | X | | | | X | | | X | | | | | X | |
| Serum ALP[5] | | | | | | | | X | | X | | | | X | | | X | | | | | X | |
| Serum Creatinine[5,6] | | | | X | | X | | X | | X | | | | X | | | X | | | | | X | |
| $1,25(OH)_2D$[5] | | X | X | | | | | X | | X | | X | | X | | | X | | | | | X | |
| 2-Hour Urine[5,6] | | | | X | | X | | X | | X | | | | X | | | X | | | | | X | |
| Bone Biomarkers[5,7] | | | | | | | | | | X | | | | X | | | | | | | | X | |
| **EFFICACY** | | | | | | | | | | | | | | | | | | | | | | | |
| $^{99m}$Tc Bone Scan[8] | | | | | | | | | | | | | | X | | | | | | | | X | |
| DXA[8] | | | | | | | | | | | | | | X | | | | | | | | X | |
| Standard Radiographs[9] | | | | | | | | X | | | | | | X | | | X | | | | | X | |
| XtremeCT of Radius and Tibia[8] | | | | | | | | | | | | | | | | | | | | | | X | |
| Bone Biopsy[10] | | | | | | | | | | | | | | | | | | | | | | | X |
| BPI, BFI, SF36[11] | | | | | | | | X | | | | | | X | | | | | | | | X | |
| HHD, STS, WAL, 6MWT[11] | | | | | | | | X | | | | | | X | | | | | | | | X | |
| **PHARMACOKINETICS** | | | | | | | | | | | | | | | | | | | | | | X | |
| Serum KRN23 | X | | X | X | | X | | | | X | X | | X | X | | X | X | X | | | | | |
| **SAFETY** | | | | | | | | | | | | | | | | | | | | | | | |
| Vital Signs[12] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | |

| VISIT TYPE/NUMBER[1] | V1 | HH V1 | HH V2 | V3 | HH V4 | V5 | HH V6 | V7 | HH V8 | V9 | HH V10 | HH V10.1 | HH V11 | V12[2] | HH V13 | HH V14 | V15 | HH V16 | HH V17 | TC3[3] | TC4[3] | V18[4] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **STUDY WEEK** | **Day 1** | **1** | **2** | **4** | **6** | **8** | **10** | **12** | **14** | **16** | **20** | **21** | **22** | **24** | **28** | **32** | **36** | **40** | **44** | **45** | **47** | **48** | |
| | | | | | | | | | | | | | | | | | | | | | | **D1** | **D2** |
| Weight | | | | | | X | | | | X | | | | X | | | X | | | | | X | |
| Physical Examination | | | | | | X | | | | X | | | | X | | | X | | | | | X | |
| Concomitant Medications | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | |
| Chemistry,[13] Hematology[14] | | | | X | | X | | X | | X | X | | | X | X | X | X | X | X | | | X | |
| Anti-KRN23 Antibody[15] | | | | | | X | | | | X | | | | X | | | X | | | | | X | |
| Serum Calcium[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | |
| Serum iPTH[5] | X | | | | | X | | | | X | | | | X | | | X | | | | | X | |
| 25(OH)D | | | | | | | | | | | | | | X | | | | | | | | X | |
| Urinalysis | | | | X | | X | | | | X | | | | X | | | | | | | | X | |
| 24-hour Urine[16] | | | | | | X | | | | X | | | | X | | | X | | | | | X | |
| ECHO, ECG[8] | | | | | | | | | | | | | | X | | | | | | | | X | |
| Renal Ultrasound[8],[17] | | | | | | | | | | | | | | X | | | | | | | | X | |
| Tumor Imaging[8],[18] | | | | | | | | | | | | | | X | | | | | | | | X | |
| Photographs for Dermatologic Assessment[19] | | | | | | | | X | | | | | | X | | | X | | | | | X | |
| Urine Pregnancy Test[20] | | | | X | | X | | X | | X | X | | | X | X | X | X | X | X | | | X | |

| VISIT TYPE/NUMBER[1] | V1 | HH V1 | HH V2 | V3 | HH V4 | V5 | HH V6 | V7 | HH V8 | V9 | HH V10 | HH V10.1 | HH V11 | V12[2] | HH V13 | HH V14 | V15 | HH V16 | HH V17 | TC3[3] | TC4[3] | V18[4] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | Day 1 | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 20 | 21 | 22 | 24 | 28 | 32 | 36 | 40 | 44 | 45 | 47 | 48 | |
| | | | | | | | | | | | | | | | | | | | | | | D1 | D2 |
| **DRUG ADMINISTRATION** | | | | | | | | | | | | | | | | | | | | | | | |
| Tetracycline Labeling | | | | | | | | | | | | | | | | | | | | X | X | | |
| KRN23[21] | | | | X | | X | | X | | X | X | | | X | X | X | X | X | X | | | X | |
| Dose Adjustment (as needed) | | | | X | | X | | X | | X | | | | | | | | | | | | | |

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

[2] The Week 24 visit may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days.

[3] TC3 will be a telephone call to the subject to instruct the subject to begin taking a tetracycline (e.g., tetracycline HCl and demeclocycline) on Days −21, −20, and −19 prior to the Week 48 Day 2 visit. TC4 will be a second telephone call to the subject and should be conducted at least 7 days prior to the Week 48 Day 2 visit to instruct the subject to begin taking a tetracycline on Days −7, −6, and −5 prior to the Week 48 Day 2 visit when the bone biopsy will be performed. Tetracycline will be given to the subject at the clinic during the Week 36 visit.

[4] The Week 48 visit (if applicable) may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days. The bone biopsy must be completed on its own day with no other assessments.

[5] Blood and urine to be collected after a minimum overnight fasting time of 8 hours and prior to drug administration.

[6] Fasting 2-hour urine collections for TmP/GFR, TRP, and urinary calcium. Blood draw for serum creatinine should occur at 1 hour into the urine collection.

[7] Bone biomarkers will include serum measures of CTx, P1NP, BALP, and osteocalcin.

[8] May be completed within ± 5 days of the projected visit date to accommodate scheduling.

[9] Standard radiographs will be completed in the anatomical location where a fracture or pseudo-fracture is identified at Screening every 12 weeks (at weeks 24, 36, and 48) until resolution. Unscheduled radiographs will be completed for any new fractures or pseudo-fractures identified during the Treatment Period approximately every 12 weeks from the date of fracture until resolution.

[10] A bone biopsy of the trans-iliac crest will be performed using general or local anesthesia as per institution practice(s) and performed by a physician trained and experienced in the procedure.

[11] BPI, BFI, SF36, HHD, STS, WAL, and 6MWT may be completed within ± 5 days of the projected visit date to accommodate scheduling.

[12] Vital sign measurements consist of seated systolic/diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate (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 and after the subject has rested for 5 minutes.

[13] This comprehensive metabolic profile will include serum Na, K, Cl, bicarbonate, BUN, creatinine, glucose, hepatic transaminases (ALT and AST), calcium, total protein, albumin, total bilirubin, indirect bilirubin.

[14] Complete blood count, differential, and platelet count.

[15] If anti-KRN23 antibodies are identified in a given subject, additional samples may be obtained to perform further testing.

[16] 24-hour urine collections for urinary phosphorus, calcium, creatinine, and eGFR; fasting 2-hour urine collections for TmP/GFR, TRP, and urinary calcium/creatinine ratio.

[17] Screening results will be treated as Baseline data.

[18] Subjects with a TIO diagnosis only. If visible at screening, the tumor will be imaged every 6 months using the same radiologic imaging technique (e.g. CT scan or MRI) used to identify the tumor.

[19] Serial photographs of skin lesions will be taken in subjects with ENS-associated osteomalacia only. Photographs will be acquired using a standardized photo-imaging service

[20] For women of childbearing potential only, a serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test.

[21] After the starting dose, doses of KRN23 will be titrated in an effort to achieve a target fasting serum phosphorus range of 2.5 to 4.0 mg/dL. If the subject's peak serum phosphorus level at Week 2 remains below the target range, the subject's dose may be increased at Week 4 to 0.6 mg/kg, at the discretion of the investigator. Doses will then be titrated in increments of 0.2 mg/kg at Weeks 8, 12, and 16 in individual subjects to achieve a target peak serum phosphorus range. If needed, the final dose adjustment increment may be less than 0.2 mg/kg to reach the 2.0 mg/kg maximum dose. Doses may be titrated at later visits, at the discretion of the investigator, if there are concerns about safety or sub-optimal efficacy.

| VISIT TYPE/NUMBER[2] | HH V19 | HH V20 | HH V21 | HH V22 | HH V23 | V24 | HH V27 | V30[4] | HH V33 | V36 | HH V39 | HH V41 | V42[3] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | 52 | 56 | 60 | 64 | 68 | 72 | 84 | 96 | 108 | 120 | 132 | 140 | 144/ET | |
| | | | | | | | | | | | | | D1 | D2 |
| **PHARMACODYNAMICS** | | | | | | | | | | | | | | |
| Serum Phosphorus[4] | | | X | | | X | X | X | X | X | X | | X | |
| Serum FGF23[4] | | | | | | X | | X | | X | | | X | |
| Serum ALP[4] | | | | | | X | | X | | X | | | X | |
| Serum Creatinine[4,5] | | | | | | X | | X | | X | | | X | |
| $1,25(OH)_2D$[4] | | | | | | X | | X | | X | | | X | |
| 2-Hour Urine[4,5] | | | | | | X | | X | | X | | | X | |
| Bone Biomarkers[4,6] | | | | | | X | | X | | X | | | X | |
| **EFFICACY** | | | | | | | | | | | | | | |
| $^{99m}$Tc Bone Scan[7] | | | | | | | | X | | | | | X | |
| DXA[7] | | | | | | | | X | | | | | X | |
| Standard Radiographs[8] | | | | | | X | | X | | X | | | X | |
| XtremeCT of Radius and Tibia[7] | | | | | | | | X | | | | | X | |
| BPI, BFI, SF36[9] | | | | | | X | | X | | X | | | X | |
| HHD, STS, WAL, 6MWT[9] | | | | | | X | | X | | X | | | X | |
| **PHARMACOKINETICS** | | | | | | | | | | | | | | |
| Serum KRN23 | | | X | | | | | X | | | | | X | |
| **SAFETY** | | | | | | | | | | | | | | |
| Vital Signs[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Weight | | | | | | X | | X | | X | | | X | |
| Physical Examination | | | X | | | X | X | X | X | X | X | | X | |

| VISIT TYPE/NUMBER[2] | HH V19 | HH V20 | HH V21 | HH V22 | HH V23 | V24 | HH V27 | V30[4] | HH V33 | V36 | HH V39 | HH V41 | V42[3] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY WEEK | 52 | 56 | 60 | 64 | 68 | 72 | 84 | 96 | 108 | 120 | 132 | 140 | 144/ET | |
| | | | | | | | | | | | | | D1 | D2 |
| Concomitant Medications | 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 | |
| Chemistry,[11] Hematology[12] | | | X | | | X | X | X | X | X | X | | X | |
| Anti-KRN23 Antibody[13] | | | | | | X | | X | | X | | | X | |
| Serum Calcium[4] | | | X | | | X | X | X | X | X | X | | X | |
| Serum iPTH[4] | | | X | | | X | X | X | X | X | X | | X | |
| 25(OH)D | | | | | | X | | X | | X | | | X | |
| Urinalysis | | | | | | X | | X | | X | | | X | |
| 24-hour Urine[14] | | | | | | X | | X | | X | | | X | |
| ECHO, ECG[7] | | | | | | X | | X | | X | | | X | |
| Renal Ultrasound[7],[15] | | | | | | X | | X | | X | | | X | |
| Tumor Imaging[7],[16] | | | | | | X | | X | | X | | | X | |
| Photographs for Dermatologic Assessment[17] | | | | | | X | | X | | X | | | X | |
| Urine Pregnancy Test[18] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| **DRUG ADMINISTRATION** | | | | | | | | | | | | | | |
| KRN23 | X | X | X | X | X | X | X | X | X | X | X | X | | |

[1] During the Treatment Extension Period (Weeks 49-144), clinic visits will occur at approximately 24-week intervals

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

[3] The Week 144 or Early Termination (ET) visit (if applicable) may be up to 2 days in duration due to the volume of testing; required blood draws may be split across the 2 days. $^{99m}$TC bone scan, DXA, XtremeCT, , HHD, STS, WAL, 6MWT, and ECHO will not be performed at the ET Visit if the assessment was conducted within 3 months of termination or if the subject discontinues prior to Week 96.

[4] Blood and urine to be collected after a minimum overnight fasting time of 8 hours and prior to drug administration.

[5] Fasting 2-hour urine collections for TmP/GFR, TRP, and urinary calcium. Blood draw for serum creatinine should occur at 1 hour into the urine collection.

[6] Bone biomarkers will include serum measures of CTx, P1NP, BALP, and osteocalcin.

[7] May be completed within ± 5 days of the projected visit date to accommodate scheduling.

[8] Standard radiographs will be completed in the anatomical location where a fracture or pseudo-fracture is identified at Screening every 24 weeks (at weeks 72, 96, 120, and 144) until resolution.

[9] BPI, BFI, SF36, HHD, STS, WAL, and 6MWT may be completed within ± 5 days of the projected visit date to accommodate scheduling.

[10] Vital sign measurements consist of seated systolic/diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate (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 and after the subject has rested for 5 minutes.

[11] This comprehensive metabolic profile will include serum Na, K, Cl, bicarbonate, BUN, creatinine, glucose, hepatic transaminases (ALT and AST), calcium, total protein, albumin, total bilirubin, indirect bilirubin.

[12] Complete blood count, differential, and platelet count.

[13] If anti-KRN23 antibodies are identified in a given subject, additional samples may be obtained to perform further testing.

[14] 24-hour urine collections for urinary phosphorus, calcium, creatinine, and eGFR; fasting 2-hour urine collections for TmP/GFR, TRP, and urinary calcium/creatinine ratio.

[15] Screening results will be treated as Baseline data.

[16] Subjects with a TIO diagnosis only. If visible at screening, the tumor will be imaged every 6 months using the same radiologic imaging technique (e.g. CT scan or MRI) used to identify the tumor.

[17] Serial photographs of skin lesions will be taken in subjects with ENS-associated osteomalacia only. Photographs will be acquired using a standardized photo-imaging service

[18] For women of childbearing potential only, a serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test.