Study Title:	An Open Label Trial to Assess the Safety and Efficacy of KRN23, an Investigational Antibody to FGF23, in a Single Pediatric Patient with Epidermal Nevus Syndrome (ENS) and Associated Hypophosphatemic Rickets
Protocol Number:	
Investigational Product:	KRN23
Indication:	Epidermal Nevus Syndrome with Associated Hypophosphatemic Rickets
IND Number:	
Sponsor:	**University of Alabama at Birmingham**
Principal Investigator:	Hussein Abdullatif, MD
Sub-Investigator:	Bhuvana Sunil, M.D
Protocol Version Date:	Version - 1 December, 5th 2018
Study Site:	University of Alabama at Birmingham Department of Pediatric Endocrinology

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1.0 STUDY OBJECTIVES

1.1 Primary Objective

The effect of KRN23 treatment on normalizing age-adjusted fasting serum phosphorous levels in a single pediatric patient with Epidermal Nevus Syndrome associated hypophosphatemic rickets

1.2 Secondary Objectives

1. The PD profile of KRN23 as assessed by changes from baseline over time 1,25(OH)2D, iPTH, Serum Calcium, TRP and TmP/GFR (the ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate)
2. Changes in underlying skeletal disease/rickets as assessed by standard radiographs utilizing the Radiographic Global Impression of Change (RGI-C) rating scales
3. Effects of KRN23 on biochemical markers of bone turnover that reflect rickets severity, alkaline phosphatase (ALP)
4. Walk test to be done if safe.

Commented [JM1]: 6MWT and PROs are included in the table of assessments. Since the patient is wheelchair dependent for all mobility, the 6MWT would not be safe. It may be that the patient can safely walk but requires a wheelchair for longer distances. We suggest the walk test should be listed under secondary endpoints if safe. Alternatively, the TUG test may be more appropriate. We suggest to include the PROs as secondary or exploratory objectives.

1.3 Exploratory Objective

1. Dual-energy X-ray absorptiometry (DXA)

1.4 Safety Objective

Assess the safety of KRN23 administration in a single patient with ENS-associated hypophosphatemic rickets, based on adverse events (AEs), laboratory assessments, cardiac imaging and renal ultrasound.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Disease Background

Epidermal nevus syndrome (CSHS formerly known as ENS) is a rare congenital syndrome characterized by the presence of epidermal nevi in association with one or more other developmental abnormalities of other organ systems including the nervous, skeletal, cardiovascular, and ocular systems. The epidermal nevi are non-neoplastic overgrowth of various components of skin cells (e.g., sebaceous cells- linear sebaceous nevus), which are usually distributed linearly along the lines of Blaschko, corresponding to the movement of skin cells during embryogenesis. While these epidermal nevi may be limited to the skin, the additional systemic abnormalities almost exclusively occur in the setting of extensive skin surface area involvement (10%-60% of the body surface area) consistent with early embryonic somatic mutation in multipotent progenitor cells. Specific genetic defects and timing of mutation during fetal development influence the varied phenotypes of ENS (Lim et al. 2014).

Hypophosphatemia may rarely be one of the skeletal manifestations of ENS presenting in children primarily as rickets and in adults as osteomalacia. In all ENS-associated osteomalacia

cases in which serum FGF23 levels were assessed, they were found to be elevated. The source of the excess FGF23 in ENS-associated osteomalacia is unclear. While early studies suggested it may be from the skin lesions themselves, more recent studies suggest it may be skeletally derived. Compared with TIO, complete resection and surgical cure leading to removal of the source of excess FGF23 is less likely. Nonetheless, published case reports of ENS-associated osteomalacia indicate improvement with skin debridement surgery in some cases. In many cases, improvement, if any, is modest and transient. In ENS-associated osteomalacia when surgery is not curative or feasible, medical treatment comprises oral phosphate and/or vitamin D replacement. Efficacy of these treatments is often limited; it does not treat the underlying disease; and its benefits must be balanced with monitoring for potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism.

There are no approved therapies for the treatment of ENS associated hypophosphatemic rickets. The current standard therapy involves oral replacement of phosphate and supplementation with vitamin D metabolites (e.g.,

calcitriol), which can improve some aspects of the bone disease, but is often associated with poor compliance. Oral phosphate therapy provides limited benefit by increasing the intake of phosphate into the body, but does not treat the underlying cause (Costa et al. 1981), (Carpenter 2012). The treatment regimen requires balancing the benefits of treatment with complicated monitoring and potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism (Carpenter et al. 2011), (Ruppe 2012). Treatment with oral phosphate may also enhance FGF23 production and cause worsening symptoms of enthesopathy and other problems (Carpenter 2012), (Karaplis et al.2012). High FGF23 levels may also cause direct effects on bone and cartilage which are not treated by oral phosphate (Kawai et al. 2013). By targeting inappropriately elevated FGF23 levels, the reabsorption of phosphate could potentially be improved by normal pathways, reducing urinary phosphate loss and naturally increasing 1,25(OH)2D production in a feedback-regulated manner, offering a potentially more effective and safe treatment option for this pediatric ENS patient.

2.2 Supporting Previous Studies

Commented [VW2]: Per Monica Yost (UGNX Safety):

Section is significantly lagging behind to reflect the current development program and approve. We suggest to reference our current version (13) of the Investigator Brochure.

Burosumab (previously referred to as KRN23) is a fully human monoclonal antibody (mAb) designed to bind, and thereby inhibit the excess biological activity of fibroblast growth factor 23 (FGF23). Burosumab is being investigated for the treatment of X-linked hypophosphatemia (XLH), and tumor-induced osteomalacia (TIO) (also known as oncogenic osteomalacia), and the osteomalacia resulting from epidermal nevus syndrome (ENS). These conditions are diseases of bone hypomineralization caused by urinary phosphate wasting due to elevated levels of FGF23.

Burosumab (Crysvita®) was approved by the United States Food & Drug Administration (FDA) on 17 April 2018 for the treatment of XLH in adult and pediatric patients 1 year of age and older. The European Commission granted conditional marketing authorization for burosumab on 19 February 2018 for the treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons. Conventional therapy for XLH, TIO, or ENS-associated osteomalacia involves oral replacement of phosphate and supplementation with active vitamin D metabolites (eg, calcitriol), but does not treat the underlying pathophysiology of these conditions.

Conventional therapy can improve some aspects of the bone disease, but is often associated with poor compliance and potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism (Carpenter et al. 2011), (Ruppe 2012). Treatment with oral phosphate may also enhance FGF23 production and cause worsening symptoms of enthesopathy and other problems, including direct effects on bone and cartilage which are not treated by oral phosphate (Kawai et al. 2013), (Karaplis et al. 2012).

By inhibiting FGF23, burosumab restores renal phosphate reabsorption, and increases the production of 1,25(OH)2D in a feedback-regulated manner, which enhances intestinal absorption of phosphate. The resulting improved serum phosphorus levels improve bone mineralization, and reduce the bone and non-bone manifestations associated with hypophosphatemia in XLH patients; similar effects are expected to be seen in patients with

TIO/ENS-associated osteomalacia.

As of the last data cutoff date among the clinical studies presented in this Investigator's Brochure (13 April 2018), 4 early phase clinical studies of burosumab in adults with XLH have been completed, 5 Phase 2/Phase 3 clinical studies are ongoing in pediatric subjects with XLH, and 4 Phase 2/Phase 3 clinical studies are ongoing in adult subjects with XLH. Two Phase 2 studies are ongoing in adult subjects with TIO/ENS-induced osteomalacia (Table 2).

Results from clinical studies to date, in both children and adults, demonstrate that burosumab improves phosphate homeostasis by restoring tubular reabsorption of phosphate (as indicated by increased serum phosphorus levels and increased TmP/GFR) and increasing serum 1,25(OH)2D. In children, burosumab treatment substantially improved rickets, growth, physical function, and pain. In adults, burosumab treatment resulted in an improvement in skeletal health, including osteomalacia, and improved healing of fractures and pseudofractures, and physical function, and reduced subject-reported stiffness and pain.

2.3 Protocol Rationale

KRN23 is a fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23), leading to an increase in serum phosphorus levels. There are multiple disorders (each with a unique underlying cause) that result in unusually high circulating levels of FGF23, which in turn result in renal phosphate wasting and reduced (or aberrantly normal in relationship to elevated FGF23) levels of 1,25-dihydroxy vitamin D (1,25[OH]2D). Across these disorders the clinical symptoms are similar and often include osteomalacia (and, in children, rickets), muscle weakness, fatigue, bone pain, and fractures. KRN23 has been studied in one of these disorders, X-linked hypophosphatemia (XLH). In single- and repeat-dose clinical studies in subjects with XLH, subcutaneous (SC) administration of KRN23 consistently increased and sustained serum phosphorus levels and tubular reabsorption of phosphate (TRP) without a major impact on urine

calcium levels or vitamin D metabolism. Positive results were also observed in a nonclinical pharmacology model of XLH. It is hypothesized that KRN23 may provide clinical benefit in this patient due to the common underlying feature in this patient and in patients with XLH – abnormally elevated FGF23 in the context of low age –adjusted serum phosphorous levels.

3.0 STUDY DESIGN

Open-label, 52-week study designed to assess the efficacy, safety and pharmacodynamics (PD) of KRN23 in a single subject with ENS-associated hypophosphatemic rickets.

3.1 Number of Subjects Planned

Study will enroll a single 13 year old male pediatric ENS patient with associated hypophosphatemic rickets.

3.2. Study Timeline

Patient will be seen at Screening visit, Baseline visit and every 2wks from that point forward until the end of the 52 week period. (See Table 1 for list of tasks per visit). Subjects who complete treatment through Week 52 may have the option to continue KRN23 treatment. If this is warranted based on preliminary efficacy, the current protocol will be amended to allow for an extension.

4.0 Selection and Enrollment of the Subject

4.1 Inclusion Criteria

1. Patient has confirmed ENS by physician diagnosis
2. Patient has confirmed FGF23 elevations in the context of low serum phosphorous < 4.1 mg/dL
3. Patient able to tolerate KRN23 treatment
4. Have a corrected serum calcium level < 10.8mg/dL
5. Have an eGFR >60 ml/min
6. Must be willing in the opinion of the investigator, to comply with study procedures and schedule
7. Provide written informed consent by a parent after the study has been explained and prior to any research related procedures begin

4.2 Exclusion Criteria

1. Patient should not use CRYSVITA with Oral phosphate or active Vitamin D analogs.
2. Patient and investigator should not initiate CRYSVITA if Phosphorus level is within or above normal.
3. CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.
4. The use or enrollment in studies using other investigational therapies including

Commented [VW3]: Per Monica Yost (UGNX Safety):

Suggest to include the contraindications in the Product Insert (PI). Language in the PI:
"Do not use CRYSVITA with oral phosphate and active vitamin D analogs.

Do not initiate CRYSVITA treatment if serum phosphorus is within or above the normal range for age.

CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism."

other monoclonal antibodies

5. Subject and their Parent not willing or not able to give written informed consent
6. In the Investigators opinion, the subject may not be able to meet all the requirements for study participation
7. Subject has a history of hypersensitivity to KRN23 excipients that in the opinion of the investigator, places the subject at an increased risk of adverse effects
8. Subject has a condition that in the opinion of the investigator could present a concern for subject safety or data interpretation.

4.3 Consent Procedure

Informed consent/assent will be obtained following an informed consent /assent conference wherein the principal investigator/sub PI or their IRB-approved designee will discuss with the subject and parent the purpose of the study, procedures to be followed, the duration of participation, alternate modes of treatment, and the risks and benefits of participation, as described in the consent form.

Signed consent / assent forms will be obtained from the subject and parent. The signed original consent / assent documents will become a part of the permanent medical record and copies will be provided to the subject and their parent.

This study will be conducted in compliance with all United States Federal and local laws, regulations, and guidelines for the conduct of research in a vulnerable population.

5.0 Methods

5.1 Recruitment of Subject

Patient is previously known to, and is under the routine care of, the Sponsored Investigator

5.2 Source of Research Material

KRN23 is a fully human IgG1monoclonal antibody that binds to and inhibits the activity of FGF23, leading to an increase in serum phosphorus levels. Ultragenyx is developing KRN23 as a potential therapeutic candidate for the treatment of XLH, Tumor-Induced Osteomalacia (TIO), and the rickets/osteomalacia resulting from Epidermal Nevus Syndrome (ENS). All of these conditions are diseases of bone hypomineralization, caused by urinary phosphate wasting due to elevated levels of FGF23.

5.2.1 Mechanism of Action

Through direct binding, KRN23 neutralizes the functions of FGF23, thereby preventing signal transduction from the FGF23/α-Klotho/FGFR complex. By blocking FGF23 actions, KRN23 restores normal phosphate reabsorption in the proximal kidney tubules and increases the production of 1,25(OH)2D that enhances intestinal absorption of phosphate (Razzaque etal. 2007); (Fukumoto 2008); (Yamazaki et al. 2008). KRN23 increases phosphate reabsorption in the kidney and increases serum phosphorus levels. The consequent improved serum phosphorus levels are expected to improve bone mineralization, heal rickets & osteomalacia, and reduce the diverse bone and non-bone manifestations associated with hypophosphatemia. Nonclinical studies demonstrated KRN23 possesses high binding affinity to the N-terminal domain of FGF23. KRN23 binds to FGF23 from humans, monkeys and rabbits, but not to other species tested. KRN23 increases phosphate reabsorption in the kidney and increases serum phosphorus levels. KRN23 also increases serum 1,25(OH)2D levels.

5.2.2 Dose and Mode of Administration

KRN23 is supplied as a sterile, clear, colorless and preservative-free solution in single-use 5 mL vials containing 1 mL of KRN23 at a concentration of 30 mg/mL. KRN23 should be securely stored at 2°C to 8°C and protected from light. It should not be shaken or frozen. KRN23 is intended for administration by the subcutaneous (SC) route.

The chosen starting dose of KRN23 will be 0.3 mg/kg given SQ Q2W. Alternating sites of administration (abdomen, upper arm, thigh) may be utilized to minimize potential injection site

Commented [LW4]: Need to be consistent with below starting dose in Sec. 5.2.3.

reactions. Subsequent KRN23 titrations to achieve normal, age adjusted serum phosphorous levels will be allowed (see “Titration of KRN23”). Data from an ongoing pediatric Phase 2 study helped establish the dose regimen and provided information for the design of this trial for a single pediatric ENS patient. Interim data suggested KRN23, administered Q2W at approximately 0.8 mg/kg for 40 weeks, increased serum phosphorus by an average of 0.7 mg/dL; increases of > 0.5 mg/dL were seen in 83.3% of subjects. Serum 1,25(OH)2D concentrations and TmP/GFR levels also increased, demonstrating overall improved phosphorus homeostasis. The increases in serum phosphorus and 1,25(OH)2D were sufficient to provide substantial healing of rickets. No previous subjects have experienced serum phosphorus levels above the upper limit of normal. Additionally, the Q2W dosing regimen was chosen because it appeared to produce a more stable and consistent increase in serum phosphorus levels with less fluctuation over time than a Q4W dosing regimen

which was also previously evaluated. The Q2W regimen had a safety profile that was not substantially different from the Q4W dosing regimen in the pediatric population.

5.2.3 Titration of KRN23

The starting dose will be 0.3 mg/kg to be given every 2 weeks.

Commented [SK5]: Is dose being started at 0.2mg/kg due to safety concern? Are you aware of the 0.3mg/kg results?

If required dose may be titrated with increments of 0.1 mg/kg/dose every 4 weeks up to a maximum of dose of 2.0mg/kg (not to exceed 90mg per dose) until phosphorus level is WNL.

Serum phosphorous level will be obtained within 48 hours prior to each regularly scheduled office visit following Baseline visit.

- Any visit at which the serum phosphorous level is shown to be below LLN the dose given at that visit will be up titrated to the next level as long as 4 weeks have passed since the last dose adjustments. Dose will be titrated upwards by increments of 0.2 mg/ kg/dose.

- Any visit at which the serum phosphorus level is shown to be in WNL dose given at that visit will remain the same as the previous dose.

- Any visit at which serum phosphorus level is shown to be above ULN that visit's dose will be withheld.

  - The visit following a visit with no dose given:

    - If the serum phosphorus level continues to be above ULN no dose will be given at that visit and subject will have serum phosphorus re-checked weekly until it decreases to the normal range.

    - Once serum phosphorus is shown to be WLN or below LLN range, restart dosing at ½ the previous dose prior to the serum phosphorus exceeding the normal range, per the Investigator's discretion.

    - The restarting dose will be repeated at the next visit (2 weeks later per protocol visit schedule), as long as the serum phosphorus remains WLN. If the serum Phosphorus falls below the LLN at the next visit, the Investigator may titrate the dose upward by 0.1 mg/kg.

    - Dose titration may occur in increments of 0.1 mg/kg not sooner than 4 weeks from the previous dose adjustment.

    - If the serum phosphorus becomes close to the ULN or LLN during the study and the Investigator feels that based on the change trends that the serum phosphorus will be out of range at the next follow up appointment, the dose may be titrated at the discretion of the Investigator.

Patient will receive study drug via SC injection to the abdomen, upper arms, thighs, or buttocks; the injection site will be rotated with each injection. If the dose level exceeds 1.5 mL in volume, the dose should be administered at two injection sites.

5.3 Duration of Treatment

Duration of treatment is 52 weeks. Subjects that complete treatment through week 52 may have the option to continue KRN23 treatment. If this is warranted based on preliminary efficacy, the current protocol will be amended to allow for an extension.

5.4 Study Procedure

Two weeks prior to Baseline visit (B), patient and parent will attend a screening visit to discuss and sign informed consent / assent. Once Informed consent / assent is obtained subject will be instructed to discontinue oral phosphate and active Vitamin D treatment in preparation for first dose of study drug at baseline visit.

Baseline Assessments (B) will entail Physical Exam, Radiographs, labs, DXA scan, Renal Ultrasound, ECHO, ECG, Functional & Quality of Life assessments and first dose of KRN23. These events may occur over the course of several visits pending scheduling and patient's ability to complete. Administration of the first dose of KRN23 will be given as the final part of the baseline visit and will initiate the timing for the next visit.

There will be a total of 28 visits to the clinic. A screening visit not less than two weeks prior to Baseline visit, and, every 2 weeks thereafter over the 52-week study period.

Commented [VW6]: If DXA is listed as an exploratory objective, please list DXA assessment here for consistency.

We suggest including DXA as there was significant improvement in DXA seen in our ENS clinical trial patient

Table 1

FGF23 levels 1																											

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Study Visit (wk) S= screening visit B= Baseline Visit	S	B	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
(Appointment Window)	All Appointments from week 2 - week 52 are =/-3 days																											
Informed Consent/Assent	X																											
Physicial Exam		X						X							X						X							X
Vital Signs & Weight		X						X							X						X							X
KRN23 Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel		X	X	X	X	X	X	X							X						X							X
Non-Standard labs (iPTH, $1,25(OH)_2$ D, Amylase, Blilirubin direct, GGT, LDH, Lipase, Uric Acid		X	X	X	X	X	X	X							X						X							X
Serum Phosphorus [3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X							X						X							X
Urinalysis		X	X	X	X	X	X	X							X						X							X
2 hr Urine Collection (Ca, Cr, PO_4)		X	X	X	X	X	X	X													X							
TmP GFR		X																										
Concominant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FGF23 levels		X																										
Whole body X-ray [1]		X																										
LFT																												
Functional (6MWT) & PRO (PROMIS & FPS-R)		X													X													X
Renal Ultrasound [1]		X													X													X
Echo [1] & ECG [1] (safety)		X																										X

Commented [LW7]: Following assessments are not consistent with section 5.5 Assessment schedule. Please review for consistency.
- Whole body x-ray – week 52 missing?
- 6MWT – confirm assessment.
- Echo & ECG – Week 26 missing?
- 24-hour Urine collection – missing.

Commented [VW8]: Per Monica Yost (UGNX Safety):

Suggest to add adverse event collection.

Commented [VW9]:

Commented [KL10R9]: We suggest including DXA as there was significant improvement in DXA seen in our ENS clinical trial patient

LFTs are not marked on SOE. Are LFTs part of the Chemistry panel that will be done?

2 hour urine: If the 24-hour urine is removed, will all tests normally done on the 24 hour urine be done on the 2 hours urine (Table 2)

Footnotes

1. May be completed within ± 5 days of the projected visit date to accommodate scheduling
2. *Non-standard labs: iPTH,* 1,25$(OH)_2$D, Amylase, LDH, Lipase, Uric Acid, 25 (OH) D.
3. *In office titration of study drug dose is based on lab value of Serum Phosphate. Subject will have this lab drawn up to 2 days prior to next appointment.*

5.5 Assessment Schedule

5.5.1 Physical Assessment & Vital Signs

Complete physical examinations will be performed at Baseline (B), Weeks 12, 26, 38 and 52. Physical examination will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, , musculoskeletal, and neurologic systems.

5.5.2 Concomitant Medications/Therapies

Concomitant medications and therapies will be reviewed and recorded in the subject's CRF at each study visit to the investigational site Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to baseline visit will be reviewed and recorded. Therapies (physical therapy, occupational therapy as well as mobility and walking devices, including ankle-foot orthosis, braces, cane, crutches, walker, wheelchair etc.) utilized during the 30 days prior to Baseline will also be reviewed and recorded. At each subsequent visit, change in medications and therapies since the previous visit will be recorded.

5.5.3 Radiographs

Standard radiographs will be obtained at Baseline and Week 52.
*S*tandard radiographs of the lateral spine, AP chest, 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 other location where the patient is currently experiencing tenderness or pain that may reflect underlying pathology, or where the subject has a history of recent (< 3months) fracture(s), or in bones where the bone scan suggests the presence of pseudo-fracture, non-vertebral fracture, vertebral fracture or other finding likely deemed related to rickets and/or osteomalacia, During follow up, if the patient develops new symptoms of hip pain, rib pain or leg/femur pain, targeted x-rays will be ordered to assess for the presence of new fractures or pseudo-fractures. Follow-up standard radiographs will be completed in the anatomical location where a fracture or pseudo-fracture is identified every 12 weeks during the 52-week study period. Radiographs will be interpreted locally for the identification of new abnormalities.

5.5.4 Laboratory

Blood and urine samples will be collected throughout the study beginning at the Baseline visit. All baseline visit labs will be drawn prior to subject receiving initial dose of KRN23.
Prior to every office visit subject will have the required blood work done after no less than an 8 hour fast. (See Table 1, page 12 for specific lab requirements for each visit)
Visits for week 2, 4, 6, 8, 10, 12 will require a 2-hr urine collection in addition to blood labs. The following procedure will be followed for these urine collections:

- Subject will fast overnight – minimum of 8 hours. Upon rising subject will void bladder (do not collect this sample)
- Subject will arrive to the laboratory approximately 1 hour after initial discarded void. At this time blood samples will be drawn.
- Subject will stay at laboratory site an additional hour to complete 2-hr urine collection.

5.5.5 Renal Ultrasound

Renal ultrasounds will be conducted at the Baseline, week 26 and Week 52 visit. Baseline and post-treatment renal ultrasounds will be evaluated to detect changes in calcifications and all other renal abnormalities from baseline. Ultrasonographic findings of nephrocalcinosis will be graded on a 5-point scale (Patriquin, H, and Robitaille, P. 1986. "Renal calcium deposition in children: sonographic demonstration of the Anderson-Carr progression." *AJR Am J Roentgenol* 146 (6):1253-6.").

5.5.6 Electrocardiogram

A standardized 12-lead ECG will measure PR, QRS, QT, and QTc at Baseline, Week 26 and Week 52.
The goal is to evaluate both for LVH changes, as well as for changes in conductivity and intervals.
The ECG results will be assessed for any clinically significant abnormality or relevant changes from baseline.

5.5.7 Fibroblast Growth Factor 23

FGF23 concentrations will be measured at Baseline

5.5.8 Echocardiogram

ECHO will be performed at Baseline, Week 26 and Week 52. The goal is to assess for evidence of ectopic mineralization in the heart and aorta. Additional tests may be performed if any abnormalities are detected or if medically indicated.

5.5.9 Walking Ability

The Six Minute Walk Test (6MWT) will be administered at the Baseline, Week 26 and Week 52 if patient is able and willing to walk

5.5.10 Patient Reported Outcomes

PROMIS-The Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference, patient is capable of completing those surveys. Physical Function Mobility, and Fatigue measurements will be administered at Baseline, Week 26 and 52. FPS-R-The Faces Pain Scale – Revised will be administered at Baseline, Week 26 and Week 52.

5.5.11 KRN23 Administration

KRN23 will be administered SQ in clinic, every 2 weeks for the duration of the 52-week study. Initial dose given at baseline will be 0.3mg/kg. Subsequent Q2W doses may be titrated according to the titration schedule with the goal of achieving a normal fasting serum phosphorous level for females 5 to 13 years old within the range of 4.1-5.9 mg/dL

Commented [JM11]: Same comment as previous page:

6MWT and PROs are included in the table of assessments. Since the patient is wheelchair dependent for all mobility, the 6MWT would not be safe. It may be that the patient can safely walk but requires a wheelchair for longer distances. We suggest the walk test should be listed under secondary endpoints if safe. Alternatively, the TUG test may be more appropriate. We suggest to include the PROs as secondary or exploratory objectives.

Commented [JM12]: Please confirm if the patient will complete the PRO themselves or if a proxy version is needed.

Commented [LW13]: Please review of consistency with other starting dose references (Sec. 5.2.2 & 5.2.3)

6.0 Observations and Measurements

6.1 Pharmacodynamic

A comprehensive serum metabolic panel (Chem-20), complete blood count, and urinalysis (Table 2) will be used to assess safety as well as for the primary efficacy parameter of normalization of serum phosphorous. Additional biochemical parameters of interest include serum 1,25(OH)2D, calcium, creatinine, and iPTH; and urinary phosphorus, calcium, and creatinine. In the event of elevated amylase levels on Chem-20, reflexive isoenzyme testing will be conducted.

Fasting for a minimum of 8 hours (overnight) is required prior to each blood draw.
Twenty-four-hour urine collection is required to assess urinary phosphorus: creatinine and calcium: creatinine ratios; urinary phosphorus, a PD parameter will also be obtained from 24-hour urine samples.

Commented [LW14]: 24 hour urine collection is not listed in the Table of assessments.

Same comment as above:
If the 24-hour urine is removed, will all tests normally done on the 24 hour urine be done on the 2 hours urine (Table 2)? Please provide detail here.

Table 2.0

Chemistry	Hematology	Urinalysis
1,25(OH)₂D	Hematocrit	Appearance
Alanine aminotransferase (ALT)	Hemoglobin	Color
Alkaline phosphatase (ALP)	Platelet count	pH
Amylase	Red blood cell (RBC) count	Specific gravity
Aspartate aminotransferase (AST)	White blood cell (WBC) count	Ketones
Bilirubin (direct and total)	Mean corpuscular volume (MCV)	Protein
Blood urea nitrogen (BUN)	Mean corpuscular hemoglobin (MCH)	Glucose
Calcium (total)	MCH concentration	
Chloride		
Cholesterol (total)	**24-hour Urine**	
Creatinine	Calcium	
Gamma-glutamyl transpeptidase (GGT)	Calcium/creatinine ratio	
Glucose	Creatinine	
Intact parathyroid hormone (iPTH)	Phosphorus	
Lactate dehydrogenase (LDH)	Phosphorus/creatinine ratio	
Lipase		
Phosphorus	**2-hour Urine**	
Potassium	Calcium	
Protein (albumin and total)	Creatinine	
Sodium	Phosphorus	
Uric acid		

6.2 Radiographic

6.2.1 Radiograph Global Impression of Change (RGI-C)
Pairs of wrist, knee and standing long leg images from the patient will be presented to an independent radiologist, with the Baseline image on the left and the later image (Week 52) on the right. The rater will be asked to assess change in rickets severity in the wrists and knees and extent of bowing in the legs using a 7-point ordinal RGI-C scale score ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets).

6.3 Functional

6.3.1 Six Minute Walk Test
The 6MWT will be administered 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 of predicted normal values will be calculated using published normative data based on age, gender, and height (Geiger et al. 2007). This test will be done only if the patient is able and willing to do it. Patient is wheel chair bound.

6.4 Patient Reported Outcomes

6.4.1 PROMIS
The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). The domain-specific approach is based on the idea that health attributes, such as pain and physical function are not unique to a specific disease. The PROMIS contains a bank of questions from which relevant items can be extracted and used to create a custom form. To assess these health domains, items from the Pediatric Pain Interference, Physical Function Mobility, and Fatigue item banks (Version 2.0) were extracted to develop this self- report form.. Patient is very capable of self reporting.

6.4.2 FPS-R
The Faces Pain Scale – Revised (FPS-R) is a self-reported measure of pain intensity developed for children (Hicks et al. 2001). It was adapted from the Faces Pain Scale (Bieri et al. 1990) to make it possible to score the sensation of pain on the widely accepted 0-to-10 metric. The FPS-R has been validated for use in children 5 to 16 years of age. The FPS-R graphically depicts pain intensity using faces with scores chosen from 0, 2, 4, 6, 8, and 10 (0=no hurt; 10=hurts worst).

7.0 Criteria for Evaluation

7.1 Safety

Safety will be evaluated by the incidence, frequency and severity of AEs and serious adverse events (SAEs), including clinically significant changes from baseline to scheduled time points in vital signs, weight, interval history and physical examination, GFR, clinical laboratory evaluations (including additional KRN23/XLH biochemical parameters of interest), and concomitant medications.

Known KRN23 adverse drug reactions, i.e., possibly related to study drug, include injection site reactions (erythema, swelling, rash).Other events that have been reported reported in patients with X linked Hypophosphatemia who received CRYSVITA, not necessarily causally related, include pain in extremity, Vitamin D deficiency, arthralgia and myalgia. Monitoring of these and other potential adverse events will occur throughout the duration of the study. Baseline and 52-week ECHO, Renal ultrasound and ECG will monitor for ectopic mineralizations during KRN23 administration. There are no adverse effects noticed with TIO/ ENs subjects and so the above side effects are unexpected.

Commented [LW15]: See comment above.

Commented [JM16]: See my comments above as well

Commented [JM17]: As above, please confirm if subject is able to self-report

Commented [VW18]: Per Monica: No ADRs are established for TIO/ENS. These are adverse reactions for XLH. We suggest to remove or to state that all events are unexpected.

7.2. Efficacy

7.2.1 Pharmacodynamically

Achieving a normal, age adjusted fasting serum phosphorous levels over time is the primary efficacy parameter and will be ascertained through fasting blood and urine samples as described in the Table 1, Schedule of Assessments.

7.2.2 Radiographically

Healing of rickets as measured by X-rays.
Healing of rickets in the wrists and knees as measured X-rays and the 7-point RGI-C scale.

7.2.3 Functionally

Improved walking ability as measured by change in the distance walked on the 6MWT in meters and percent predicted normal values at Baseline compared to Week 26 and 52 if patient is capable and willing to walk.

Commented [LW19]: See comment above.

7.2.4 Patient Reported Outcomes

PROMIS and FPS-R scales will be scored at Baseline, Week 26 and 52 and compared to report on any changes in pain, fatigue and physical functioning as result of KRN23 administration

Commented [JM20]: Helpful to list the domains measures as PROMIS is not specific enough to explain what is administered. PROMIS customized questionnaire assessing Mobility, Fatigue and Pain Interference domains.

8.0 Criteria for Removal of Patient from Therapy

1. Occurrence of an Adverse Event(AE), collection of unassociated AEs, or a pattern of AE which in the opinion of the PI make further participation in the trial an unacceptable risk of harm to the patient
2. An illness that in the opinion of the PI/Sub PI might place the patient at risk
3. At the request of the patient/guardian or PI/Sub PI

9.0 Potential Risks and Potential Benefits

KRN23 is an investigational fully human IgG monoclonal antibody to FGF23 that is currently being developed as a
The risks of burosumab in the treatment of CSHS are unknown. The risks of burosumab in the treatment of pediatric and adult patient with XLH are provided in the *the Crysvita™ Package Insert (Revised 04/2018). The burosumab investigator's brochure (dated 15Jun2018) provided by Ultragenyx Pharmaceutical Inc. also provides detailed information regarding potential side effects or adverse drug reactions of burosumab.*

The most common adverse drug reactions reported in paediatric patients treated with burosumab for XLH during clinical trials were injection site reactions (57%), headache (54%), pain in extremity (42%), vitamin D decreased (28%), rash (23%), toothache (18%), tooth abscess (14%), myalgia (14%), and dizziness (11%).

The most common adverse drug reactions reported in adult patients treated with burosumab for XLH during clinical trials were back pain (15%), headache (13%), tooth infection (13%), restless legs syndrome (12%), vitamin D decrease (12%) and dizziness (10%).

In addition to the common adverse drug reactions, the following are potential risks to the participant that may occur based on the mechanism of action of burosumab, the inherent risks with the subcutaneous administration of monoclonal antibodies, and data from nonclinical and clinical studies of burosumab to date: hyperphosphatemia, ectopic mineralization. hypersensitivity, injection site reactions, and anti-drug antibodies.

Hyperphosphatemia is a potential risk of burosumab due to its mechanism of action. Based on the role that FGF23 plays in the maintenance of phosphate homeostasis, careful attention should be paid to serum levels of phosphorus and other related factors, such as serum calcium, creatinine, BUN, 1,25(OH)2D, and iPTH, as well as urinary calcium. Ectopic mineralization risks are mitigated by careful, detailed, and controlled monitoring of serum phosphorus levels and other biochemically-related factors including serum calcium, 1,25(OH)2D, and iPTH as well as urinary calcium. In addition, surveillance and monitoring via imaging modalities (i.e., renal ultrasound) are used to mitigate any further risks for the subject.

Hypersensitivity events (rash, injection site rash, and urticaria*) and injection site reactions (erythema, rash, swelling, bruising, pain, pruritus, urticaria, and hematoma) are also a potential risk and monitoring for these will occur throughout the duration of the study.*

10.0 Data Collection and Adverse Event Reporting

10.1 Clinical Data Collection

Data to be collected will include demographic, ENS medical history, genetic (PHEX), laboratory values, PD parameters, FGF23 levels, prior and current medications, prior procedures and interventions. Data for AE's will also be collected.

10.2 Case Report Form

The investigator is required to initiate and maintain an adequate and accurate case history that records all observations and other data related to the study for this subject. All information recorded on CRFs for this study must be consistent with the subject's source documentation. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records.

10.3 Data Management & Storage

Site shall maintain complete and accurate records related to the Study in accordance with Code of Federal Regulations Title 21, section 312.62.

10.4 Site Monitoring

Site monitoring will be completed by internal The University of Alabama IRB office. The functions of the internal monitoring will include the review of timelines and provision of data, the collection of internal and updated regulatory documents and the frequency of identified and resolved issues as it pertains to this 52-week trial.

10.5 Adverse Event Reporting

All AEs (i.e. any new or worsening in severity or frequency of a pre-existing condition) will be recorded from the time the informed consent is signed through 90 days following the last dose of investigational product. In addition, any AE that occurs after this time period that is considered to have a reasonable possibility of being associated with the investigational product will be recorded. Details of the event to include severity, relationship to investigational product, duration, action taken, and outcome.

All AEs that are considered related to investigational product will be followed to resolution or stabilization if improvement is not expected. AEs which completely resolve and then recur will be recorded as a new AE. AEs continuing at 90 days following the last dose of the investigational product will have a comment that the event has recovered, recovered with sequelae, stabilized, or is not expected to improve. The severity of all AEs will be graded using the NCI CTCAE (version 5.0).

- *Mild (Grade 1):* Awareness of signs or symptoms, but easily tolerated and of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- *Moderate (Grade 2):* Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- *Severe (Grade 3):* Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
- *Life-threatening (Grade 4):* Events that place the participant at immediate risk of death or are disabling.
- *Death (Grade 5):* Events that result in death.

10.5.1 Medical Safety Monitor
All SAE's must be reported within 24 hours to the IRB

10.5.2 Safety Report
Copy of all reports will be stored in the Study File. All SAEs will be reported to the IRB and Ultragenyx.

Commented [VW21]: Investigator is obligated to follow the Serious Adverse Event reporting instructions per the IST contract.

Please include a statement that states the safety reporting instructions and timing will be referred to Exhibit B: Serious Adverse Event Reporting of the IST Agreement.

10.5.3 Protocol Deviations
Protocol deviations are events that are inconsistent with the protocol to the point that they may impact subject safety and /or to the extent of impacting the study outcome. Protocol deviations will be reported to the IRB in accordance with their reporting guidelines.

11.0 Statistical Considerations

11.1 Safety Analysis
Safety data will be reviewed on a regular basis by both PI and Sub PI. For the safety analysis, the numbers (frequency) and incidence rates of AEs and SAEs will be summarized during exposure to KRN23 throughout the study. The analyses of safety time frame will encompass both the 52-week study period and subsequent safety extension period if applicable.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), relationship to study drug, and severity. A complete listing of AEs and SAEs will be provided for the patient at the end of the study

Clinical laboratory data will be summarized by the type of laboratory test. The frequency of abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for Baseline and all subsequent scheduled visits during which laboratory measurements were obtained. Changes from Baseline to the treatment visits will also be provided. Descriptive statistics of vital signs and concomitant medications will be provided in a similar manner.

11.2 Efficacy Analysis

11.2.1 Pharmacodynamic
Serum phosphorous levels taken throughout the 52-week period will be compared to the baseline value. Serum $1,25(OH)_2$ D levels taken throughout the 52-week period will be compared to the baseline value. Phosphate reabsorption defined as the ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) will be assessed throughout the 52-week period and compared to the baseline value.
Alkaline Phosphatase(ALP) levels taken throughout the 52-week period will be compared to the baseline value

11.2.2 Bone Health

Severity of rickets and epiphyseal (growth plate) abnormalities will be assessed at baseline and 52-weeks.
Lower extremity deformity assessed by intercondylar distance and intermalleolar distance. Specific abnormalities related to lower extremity deformity and bowing observed on standing long leg films will also be evaluated using the qualitative RGI-C scoring system

11.2.3 Functional

Six Minute Walk Test (6MWT) total distance and percent of predicted normal distance walked will be assessed and compared at baseline, 26 weeks and at 52-weeks if patient is able and willing to walk.

Commented [LW22]: See comments above.

11.2.4. Patient Reported Outcomes

The PROMIS and FPS-R tools will be administered and compared at baseline, 26 and 52-weeks.

Commented [JM23]: T-scores are generated for the PROMIS domains through scoring software available at the HealthMeasures site and can be compared to baseline. Useful to specify PROMIS domain T-scores here.

12.0 Human Subject

12.1 Institutional Review Board Review and Informed Consent

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB. A signed consent form will be obtained from the parent for this subject. A signed informed assent will also be obtained from the subject.

12.2 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the sponsor, the FDA or other government agencies as part of their duties to ensure research subjects are protected

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