HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Examining the Effect of Burosumab on Muscle Function Using MR Spectroscopy

Principal Investigator: Karl Insogna, MD

Version Date: October 1, 2021

(*If applicable*) Clinicaltrials.gov Registration #: NCT04146935

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   The main objective of the study will be to test the hypothesis that reduced muscle ATP flux may underlie the myopathy seen in patients with X-linked hypophosphatemia (XLH).

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   2.5 years from start up to completion

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   X-linked hypophosphatemia is a skeletal dysplasia. The mineralized tissue complications of XLH have been the focus of investigative studies seeking to understand its pathogenesis, as well as studies directed at new therapies. However, in addition to their skeletal complaints, patients with XLH have among their most frequent symptoms, fatigue and weakness, which manifest as both a generalized sense of a lack of energy as well as a more specific feeling that their muscular function is impaired. Objectively, patients complain of fatigue after exertion, when otherwise they do not think they should expect to feel so spent. These symptoms occur in individuals who otherwise have good cardiovascular and respiratory health, so co-morbidities are unlikely to explain these pervasive complaints. Anecdotally, our open-label trial data using KRN23 suggest that these symptoms are dramatically ameliorated by treatment with the drug. In a recent study[1], we found that when stressed by a low-phosphate diet, rates of insulin-stimulated myocyte ATP flux were reduced by 50% in an experimental model of systemic hypophosphatemia (the NaPi2a knockout mouse). Moreover, ATP synthetic flux correlated directly with cellular and mitochondrial phosphate uptake in two rodent myocyte cell lines, as well as in freshly isolated myocyte mitochondria. As direct evidence that these preclinical findings are relevant to human hypophosphatemic genetic syndromes we studied a patient with Heredity Hypophosphatemic Rickets with Hypercalciuria (HHRH) who was not being treated at the time of our experiment. In this patient who had a 50% reduction in serum phosphate, muscle ATP content was also significantly reduced [1]. Both of these parameters normalized completely with oral phosphate repletion [1]. These data strongly support the hypothesis that reduced muscle ATP flux may underlie the myopathy seen in our patients with XLH. We propose to directly test this hypothesis, in patients about to begin treatment with Crysvita®.

4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   We will only recruit patients who the PI and his two physician-collaborators have decided, based on their clinical exam and review of the potential subject's history, biochemical and radiographic studies, qualify for Crysvita® therapy. Patients will only be invited into the study because they are planning to start Crysvita for clinical indications. While the participants are enrolled in the study, Ultragenyx will provide drug for the 3 injections that will be administered during the study. Once a subject enrolls in the study we plan to obtain approval for Crysvita® from their insurers so that at study end, their treatment will not be interrupted. If there is a delay in obtaining approval from the insurer, Ultragenyx has a program that provides drug at no cost to the subject while the dermination process moves forward.

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Eligible study subjects receiving therapy with supplemental phosphate and calcitriol will be asked to stop both medications 2 weeks prior to enrollment.

Muscle tissue phosphorus concentration and ATP flux rates will be assessed in the right gastrocnemius of the lower leg using ^{31}P-NMR spectroscopy. Phosphate spectra will be obtained in the NMR center at Yale, under the direction of Dr. Kitt Petersen, using previously published methods [2-4]. Subjects are maintained in the supine position within an ORS-Bruker NMR spectrometer (1-meter bore, 4.0 Tesla). The gastrocnemius muscle of the right leg is positioned appropriately within the magnetic field, and placed on top of a surface coil probe. Motion of the leg is minimized with Velcro straps and a foam foot holder. Study participation requires approximately 120 minutes for this part. Our findings would be correlated with the changes in serum phosphorus, TmP/GFR, $1,25(OH)_2$vitamin D, pain scores, dynamometry and most importantly the results of the six-minute walk test.

The study protocol involves five visits, 1-5. There are three visits that involve MR Spectroscopy. Those are MRS1, MRS2 and MRS3. There are three dosing visits. The Crysvita® will be prescribed at the recommended adult dose of 1 mg/kg body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg. The Crysvita prescribing information will be followed. Depending on the patient's lab work at the following visits and from other clinical data their dose may be adjusted during the course of the study. The first coincides with Visit 1 denoted Dose1. The second and third doses occur 4 weeks after the first dose denoted Dose 2 and Dose 3. MR spectroscopy studies are performed at Visit 1 before the 1st dose of Crysvita® is given, (MRS1), the second MR study is 2 weeks after Dose 3 (Visit 4 at the peak of Crysvita's® action), denoted MRS2) and the final MR study occurs 4 weeks after Dose 3 (at Visit 5 denoted MRS3).

Table 1: Schedule of Procedures

Visit number/time	**1 (month 0)**	**2 (month 1)**	**3 (month 2)**	**4 (2 weeks after visit 3)**	**5 (4 weeks after visit 3)**
Consent	X (or at clinic before visit)				
Inclusion/Exclusion criteria	X (or at clinic before visit)				
Vital signs	X	X	X	X	X
Medical History	X				
Urine pregnancy	X	X	X	X	X
Height/Weight	X				
Physical exam	X (full)	X (limited)	X (limited)	X (limited)	X (limited)
Serum phos[2] & Calcium		X	X		
Renal US	X				
Full blood work	X[1]			X	X
Spot urine for Ca, Cr and Phos	X			X	X
MR Spectroscopy	X (MRS 1)			X (MRS 2)	X (MRS 3)
Functional testing & KOOS,PROMIS	X			X	X
Crysvita dosing	X (Dose 1)	X (Dose 2)	X(Dose 3)		
Adverse Event reporting	X	X	X	X	X

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[1]FGF23 will be drawn at this visit in addition to the other full blood work detailed below
[2]Serum Phos will be measured by the clinical physican (standard of care) 2 weeks post dose after the first 2 doses of Crysvita/burosumab. After the 3rd dose of Crysvita/burosumab peak serum phos will be measured in the study and results shared with the clinical physician.

The visits that incorporate MR Spectroscopy (visits 1, 4 and 5) involve blood work that includes fasting serum calcium, phosphate, creatinine, PTH, 25-hydroxyvitamin D, 1,25 dihydroxyvitamin D, and bone-specific alkaline phosphatase, On the other visits (Visits 2 and 3) only a serum phosphate and a serum calcium will be measured. A fasting serum FGF23 will be drawn only at Visit 1.

A full physical exam, vital signs, height and weight and renal ultrasound will be done at baseline. For all subsequent visits, vital signs and a limited physical exam will occur.

Spot fasting urine creatinine, phosphate, and calcium will be collected at the three MR Spectroscopy visits and TmP/GFR calculated at each of these visits. A urine pregnancy text will be done at each visit prior to the MR Sprectroscopy or dosing and patients will not participate if pregnant.

All samples for blood and urine will be processed on the Hospital Research Unit (HRU) and sent for analysis at the YCCI core lab in batches. Calcium and phosphorus samples will be sent to the YNHH Chemistry department for analysis since these data will need to be reviewed promptly for Crysvita dosing. For the batch samples, samples will be run as patients complete the study to avoid any inter-assay variability.

Functional testing will occur after each MR spectroscopy analysis. The study coordinator(s) will be trained by YNHH Physicial therapy (PT) staff and monitored at the start to ensure the positioning of the patient and the testing is being done correctly. The following tests of physical function will be conducted at visits 1,4 and 5.

- Comprehensive dynamometry for both UE's (handrip) andLE's(knee extension and flexion, hip flexion, extension and abduction)
- Weighted arm
- Heel rises
- Six-minute walk test
- Timed Up and Go (TUG)
- 30-second Sit to Stand Test

Finally, the KOOS and PROMIS questionnaires to measure pain, stiffness, fatigue and physical function will be employed at each MR study visit.

References Cited:

1. Pesta DH, Tsirigotis DN, Befroy DE, et al. Hypophosphatemia promotes lower rates of muscle ATP synthesis. FASEB J 2016;30:3378-87.
2. Rothman DL, Shulman RG, Shulman GI. 31P nuclear magnetic resonance measurements of muscle glucose-6-phosphate. Evidence for reduced insulin-dependent muscle glucose transport or phosphorylation activity in non-insulin-dependent diabetes mellitus. J Clin Invest 1992;89:1069-75.
3. Lebon V, Dufour S, Petersen KF, et al. Effect of triiodothyronine on mitochondrial energy coupling in human skeletal muscle. J Clin Invest 2001;108:733-7.

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4. Befroy DE, Petersen KF, Dufour S, Mason GF, Rothman DL, Shulman GI. Increased substrate oxidation and mitochondrial uncoupling in skeletal muscle of endurance-trained individuals. Proc Natl Acad Sci U S A 2008;105:16701-6.
5. Carpenter TO, Imel EA, Ruppe MD, et al. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. J Clin Invest 2014;124:1587-97.
6. Imel EA, Zhang X, Ruppe MD, et al. Prolonged Correction of Serum Phosphorus in Adults With X-Linked Hypophosphatemia Using Monthly Doses of KRN23. J Clin Endocrinol Metab 2015;100:2565-73.
7. Hershberger S. Hodges-Lehmann estimators. In: Lovric M, ed. International Encyclopedia of Statistical Science. Berlin, Germany: Springer-Verlag; 2011:635-6.
8. Han L, Merch & Co, Inc., North Wales, PA. Calculating the point estimate and confidence interval for Hodges-Lehmann's median using SAS software. SESUG Proceedings, SESUG, Inc. 2018, at http://www.sesug.org); https://analytics.ncsu.edu/sesug/2008/ST-154.pdf.

5. Genetic Testing N/A ☒

A. Describe
   i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
   ii. the plan for the collection of material or the conditions under which material will be received *Write here*
   iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
   iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
C. Is widespread sharing of materials planned? *Write here*
D. When and under what conditions will materials be stripped of all identifiers? *Write here*
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
F. Describe the provisions for protection of participant privacy *Write here*
G. Describe the methods for the security of storage and sharing of materials *Write here*

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
We are planning to recruit 10 patients age 18-65 years with an established diagnosis of XLH who qualify for Crysvita® therapy based on their clinical data.

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children ☐ Healthy ☐Fetal material, placenta, or dead fetus

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☐Non-English Speaking ☐ Prisoners ☐Economically disadvantaged persons
☐Decisionally Impaired ☐ Employees ☐Pregnant women and/or fetuses
☐Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?
   Inclusion criteria will include:
   1. 18-65 years of age
   2. Diagnosis of XLH
   3. eGFR ≥ 50
   4. Corrected serum calcium ≤ 10.5 mg/dl
   5. Phosphate ≤ 2.5 mg/dl
   6. Deemed clinically appropriate for starting therapy with Crysvita®(based on the treating physician's evaluation) or re-starting Crysvita if the subject has previously received fewer than 3 doses of the drug with the last dose given more than a year ago.
   7. Deemed appropriate for MR Spectroscopy

   Exclusion criteria will include:
   1. Patients with fixed skeletal abnormalities which would prevent them from successfully completing study-related functional assessments
   2. Patients unwilling to stop therapy with supplemental phosphate and calcitriol 2 weeks prior to enrollment.
   3. Patients who have undergone an orthopaedic procedure with the previous 6 months involvd ing implanation of metal hardware.

9. How will eligibility be determined, and by whom? Eligibility will be determined by Drs. Insogna, Carpenter, Bergwitz.or Petersen (expert in MR spectroscopy). Laboratory assessments and medical history used for determining eligibility will be obtained at a clinic visit prior to the study start within the last 6 months.
   Write here
10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

    1. Blood sampling: May cause slight discomfort when the sample is drawn. There is the potential for slight bruising at the needle site; infection or swelling rarely occurs. These risks are minimized through the use of trained personnel to perform the blood draw. The amount of blood to be drawn at each visit (visit 1-25 ml, visits 2 and 3- 5ml each and visits 4 and 5- 20 ml each totaling 75 ml) and over the course of the study does not pose a risk. This amounts to 5 tablespoons over the course of 3 months.

    2. MR Spectroscopy and ^{31}P MRS : In order to monitor muscle ATP synthesis the subject's leg will be placed in a 4T MR Spectrometer to obtain ^{31}P-spectra from the gastrocnemius muscle. The radio frequency power and magnetic field strength to be used for the MRS in this study present no known hazards to human subjects without ferro-magnetic metals in or on their body. Special care will be taken to exclude subjects with these type of objects. The subjects will be under continuous surveillance while in the magnet. A physician will be immediately available at all

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times. All subjects will fill out the standard YNHH-MRI metal screen questionnaire prior to being placed in the magnet.

MR spectroscopy: The radio frequency and magnetic fields to be used for the ^{31}P MR spectroscopy in this study present no known hazards to human subjects without ferromagnetic metals or pacemakers. Special care will be taken to exclude these subjects from the study. There are no known long-term risks associated with MR spectroscopy or imaging (MRI).
Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

Consent is obtained in a private setting in the MRRC (Magnetic Resonance Research Center) or during the HIC study on the HRU prior to any study related procedures. Any subject with concerns about participation or who may have any of the issues listed under exclusion criteria will not be enrolled. Dr. Petersen's (Professor of Medicine Endocrinology at Yale specializing in MR Sprectroscopy) study record over the years shows that they are very careful and rather will not study a subject than take any chances. The subjects will be under continuous surveillance while in the magnet. A physician will be immediately available at all times. All subjects will fill out the standard YNHH-MRI metal screen questionnaire prior to being placed in the magnet.

The subjects will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens, the subject may ask to stop the study at any time and we will take him/her out of the MR scanner. On rare occasions, some people might feel dizzy or get an upset stomach. These sensations usually go away quickly but the subjects will be instructed to tell us if they occur.

If the patient has a history of anxiety or lying still is a known concern, Ativan 0.5-1.0 mg (a routinely used mild sedative and anti-anxiety) will be prescribed for the patient to take prior to each MR study as needed. If Ativan is used, we will ensure the patient has transportation to and from the study visit and they are monitored by study personnel throughout the course of the study. The Ativan would be prescribed by Dr. Insogna and filled by the patient at their pharmacy outside of the study. Common side effects of Ativan include drowsiness, dizziness, headache, nausea, blurred vision or loss of coordination. Since only a low dose (0.5-1.0 mg Ativan) would be prescribed, we anticipate side effects to be very mild and temporary if they do occur at all and to resolve prior to the patient returning home.

There are some risks with an MR study for certain people. Subjects with a pacemaker or some metal objects inside the body may not be in this study because the strong magnets in the MR scanner might harm them. Another risk is the possibility of metal objects being pulled into the magnet and hitting people. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once the subject is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

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We want the subjects to read and answer very carefully the questions on the MR Safety Questionnaire related to personal safety. We willask them to take a moment now to be sure that they have read the MR Safety Questionnaire and to tell us any information he/she thinks might be important.

This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on a scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact the subject, inform him/her of the finding, and recommend that he/she seeks medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with the subject and his/her physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment received based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

Female subjects of childbearing potential will require urine pregnancy testing prior to enrollment in the protocol. Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, young women who would not be comfortable with pregnancy testing or sharing the results of such testing can "opt out" of the study at the time of the initial consent, without having to declare specific reasons.

Minimizing Risks of MRI**:** By carefully screening each individual including but not limited to the MRRC official metal screening questionnaires and use of the metal detector in the MRRC. All subjects are asked to change into scrubs and to remove all personal items (including piercings and jewelry) before the study.

3. Urine sampling: There is no associated risk although it may be inconvenient

4. Comprehensive dynamometry for both UE's and LE's, weighted arm, sit to stand and heel rises: Subjects could potentially experience muscle strain if they exert themselves excessively during these tests. A trained coordinator or PT will instruct study subjects in the appropriate execution of these tests to mitigate this risk.

5. Six-minute walk test and Timed Up and Go: Patients may find the exertion associated with this test a barrier to completing it successfully. Patients will be constantly monitored by trained staff while completing the 6 Minute Walk Test and the Timed Up and Go test. Subjects will be asked before and after the tests whether they have any symptoms of dizziness, shortness of breath, chest pain, or extreme fatigue. If they are to develop any of these symptoms during the 6 Minute Walk Test or the Timed Up and Go test they will be asked to stop the test and a nurse on the HRU or the study doctor will be contacted if necessary.

6. KOOS (Knee Injury and Osteoarthritis Outcome Score) and PROMIS: these are questionnaires and there are no foreseeable risks.

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7. Crysvita (Burosumab-twza):

Adverse Reactions in Adult Patients with XLH

The safety data described below reflect exposure to CRYSVITA in 68 adult XLH patients, age 20-63 years (mean age 41 years), of whom most were white/Caucasian (81%) and female (65%). These patients were enrolled in a randomized, double-blind, placebo-controlled Phase 3 study in adults with XLH (68 patients received Crysvita for the first 24 week and 66 patients received Placebo), The mean Crysvita dose was 0.95 mg/kg (range 0.3 – 1.2 mg/kg) subcutaneously every 4 weeks. At Week 24 the subjects in the Placebo arm crossed over to Crysvita therapy for the next 24 weeks; and those in the Crysvita arm continued on Crysvita for 24 weeks.
Adverse reactions reported in more than 5% of CRYSVITA-treated patients and 2 patients or more than with placebo from the 24-week placebo-controlled portion of Study 3 are shown in Table 2.

Table 2: Adverse Reactions Occurring in More Than 5% of CRYSVITA-Treated Adult Patients and in at Least 2 Patients More Than with Placebo in Phase 3 study

Adverse Reaction	Crysvita (N=68) n(%)	Placebo (N=66) n(%)
Back Pain	10 (15)	6 (9)
Headache[1]	9 (13)	6 (9)
Tooth infection[2]	9 (13)	6 (9)
Restless legs syndrome	8 (12)	5 (8)
Vitamin D decreased[3]	8 (12)	3 (5)
Dizziness	7 (10)	4 (6)
Constipation	6 (9)	0 (0)
Blood phosphorus increased[4]	4 (6)	0 (0)

n = number of patients with an event; N = total number of patients who received at least one dose of CRYSVITA or placebo
1 Headache includes: headache, and head discomfort
2 Tooth infection includes: tooth abscess, and tooth infection
3 Vitamin D decreased includes: vitamin D deficiency, blood 25-hydroxycholecalciferol decreased, and vitamin D decreased
4 Blood phosphorus increased includes: blood phosphorus increased, and hyperphosphatemia

Hypersensitivity Reactions

In the double-blind period of Study 3, approximately 6% of patients in both the CRYSVITA and placebo treatment groups experienced a hypersensitivity event. The events were mild or moderate and did not require discontinuation.

Hyperphosphatemia

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In the double-blind period of Study 3, 7% of patients in the CRYSVITA treatment group experienced hyperphosphatemia meeting the protocol-specified criteria for dose reduction (either a single serum phosphorus greater than 5.0 mg/dL or serum phosphorus greater than 4.5 mg/dL [the upper limit of normal] on two occasions). The hyperphosphatemia was managed with dose reduction. The dose for all patients meeting the protocol-specified criteria was reduced 50 percent. A single patient required a second dose reduction for continued hyperphosphatemia.

Injection Site Reactions (ISR)

In the double-blind period of Study 3, approximately 12% of patients in both the CRYSVITA and placebo treatment groups had a local reaction (e.g. injection site reaction, erythema, rash, bruising, pain, pruritus, and hematoma) at the site of the injection. Injection site reactions were generally mild in severity, occurred within 1 day of injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Restless Leg Syndrome (RLS)

In the double-blind period of Study 3, approximately 12% of the CRYSVITA treatment group had worsening of baseline restless leg syndrome (RLS) or new onset RLS of mild to moderate severity; these events did not lead to dose discontinuation. Non-serious RLS has also been reported in other repeat dose adult XLH studies; in one case, worsening baseline RLS led to drug discontinuation and subsequent resolution of the event.

Spinal Stenosis

Spinal stenosis is prevalent in adults with XLH and spinal cord compression has been reported. In the CRYSVITA phase 2 and phase 3 studies of adults with XLH (total N=176), a total of 6 patients underwent spinal surgery. Most of these cases appeared to involve progression of a pre-existing spinal stenosis. It is unknown if CRYSVITA therapy exacerbates spinal stenosis or spinal cord compression.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to burosumab-twza may be misleading. Pre-existing anti-drug antibodies (ADA) have been detected in up to 10% of patients in clinical studies. ADA was not detected in patients who were antibody negative at the start of treatment. However, the assay used to measure ADA is subject to interference by serum burosumab-twza, possibly resulting in an underestimation of the incidence of antibody formation. Due to the limitation of the assay conditions, the potential clinical impact of antibodies to burosumab-twza is not known.

Allergic reaction

An allergic-type reaction to Crysvita® is possible. Allergic-type reactions may be serious or life threatening. The study doctor or nurse will monitor the patient during and after the administration of the study drug. If the participant does develop an allergic reaction, the study doctor or nurse will give them medicines to stop or lessen the allergic reaction. Some things that could be a sign or symptom of an allergic reaction (including more severe allergic reactions such as anaphylaxis) are:

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- Skin reactions such as rash, hives, itching
- Swelling around the mouth, throat or eyes
- Trouble breathing
- Weak and fast pulse
- Nausea, vomiting or diarrhea
- Drop in blood pressure (making you feel dizzy or lightheaded)
- Fever
- Chills

Local reactions to the injections

Crysvita® injections are done under the skin in the abdominal (belly) area, upper arms or thighs. The area of the body used for injections will be changed from injection to injection. The injections may cause the following at or around the site of injection:

- Pain
- Itching
- infection
- bleeding
- Rash, including Hives
- Redness
- Bruising
- Scarring

Reproductive Risks and Contraceptive Measures

Crysvita® has not been studied in pregnant or breast feeding women or in the sperm of men taking Burosumab. It should not be taken if a woman is pregnant or planning to become pregnant during the study. The study drug may involve risks to the patient or to the unborn baby or breast fed infant which are currently unknown.

It is recommended that sexually active females of childbearing potential use a highly effective method of contraception during sex throughout the study period.

1. Established use of hormonal contraceptives, such as the contraceptive pill, injection or implant
2. Intrauterine device (IUD) or intrauterine system (IUS), a small device with hormones that goes inside the uterus
3. Male sterilization, also called vasectomy
4. Complete abstinence, which means not having sex because you choose not to.

Sexually active males must use one of the highly effective methods of contraception above (such as complete abstinence) or a condom with spermicide during sex throughout the study period

We plan to obtain urine pregnancy tests in all females of child-bearing potential at each study visit prior to the MR spectroscopy or Crysvita dosing. Pregnant females will be exclused from the study.

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8. As noted to participate in this study subjects will need to discontinue conventional therapy (if they are taking it) for two weeks before beginning Crysvita therapy.

9. The risks of Crysvita® will be minimized by carefully following the prescribing information and monitoring of the patient. Drs. Insogna, Carpenter and Bergwitz have been safely using this drug in clinical trials over the last several years and have been prescribing it to their clinic patients since April 2018 when it was first approved.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
See above under each risk.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here +for
        i. Minimal risk
        ii. Greater than minimal

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with the MR spectroscopy and Crysvita ®, the FDA approved medication for X-linked hypophosphatemia, as minimal risks.
2. Given the now established good safety profile for and efficacy of Crysvita, as well as the long, published track record Dr. Petersen has safely using MR spectroscopy, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

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3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Karl Insogna, MD according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The common terminology criteria for adverse events (CTCAE) version 5.0 scale will be used in grading the severity of adverse events noted during the study or the following scale when CTCAE criteria is not available:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience
3. in-patient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant disability or incapacity;
5. A congenital anomaly or birth defect; OR
6. Any other important medical event i.e an adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

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2. Is related (definitely, probably or possibly related) to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.
4. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related (definitely, probably or possibly) adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above, which are, 1, **unexpected 2, assessed as definitely, probably, or possibly related to the study and 3,** suggests that the research places subjects or others at greater risk of harm.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
□ National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
X Study Sponsor- Ultragenyx Inc.
□ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator (*Karl Insogna)* will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Please note: For any study that may be considered high risk, the IRB will be more focused on the safety requirements for the study and a DSMB will likely be required.

For more guidance on Adverse Event reporting and DSMPs, see **IRB Policy 710 Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events**

d. For multi-site studies for <u>which the Yale PI serves as the lead investigator</u>: N/A

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
ii. What provisions are in place for management of interim results? *Write here*
iii. What will the multi-site process be for protocol modifications? *Write here*

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Sample Size Estimate (note references cited are included at the end of Section I above

Serum Phosphate:
Using previously published studies [1,5,6,] a sample size of 10 paired observations, with a within-person correlation in the range of 10-50%, achieves greater than 90% power to detect a statistically significant increase at alpha of 0.05 in the expected mean serum phosphate level from around 1.7-2.0 mg/dL at baseline to at least 3.0 mg/dL at 6-month follow up. These results are based on 2000 Monte Carlo samples from the null distribution, with the standard deviation of serum phosphate in the range of 0.3 to 0.6 mg/dL

V_{ATP}:
Similarly, using previously published studies [1,5,6] ,a sample size of 10 paired observations, with a within-person correlation in the range of 10-50%, achieves greater than 90% power to detect a statistically significant increase at alpha of 0.05 in the expected mean muscle V_{ATP} flux rates from 3.5 micro-mol/g/min at baseline to at least 5.5 micro-mol/g/min at 6-month follow up. These results are based on 2000 Monte Carlo samples from the null distribution, with the standard deviation of V_{ATP} in the range of 0.7 to 1.3 micro-mol/g/min.

Analytical Approach
Patient characteristics will be summarized using mean (standard deviation) and median (range) for continuous variables, and using counts and percents for categorical variables. The distributions of the primary outcomes of interest (serum phosphate level and V_{ATP}) at each evaluation will be presented visually using box-plots. The primary analysis of the comparison of baseline and 3-month follow up distributions of the two outcomes will be performed using the Wilcoxon signed rank test. Medians will be compared using the Hodges-Lehmann estimator 7,8. If the outcomes are normally distributed, we will also use the paired t-test to compare the means at baseline and 6 months. Confidence intervals for the differences in the medians and the means of the outcomes will be obtained using the Hodges-Lehmann's estimator and the t-distribution, respectively, and all estimates will be bootstrapped. Significance will be established at alpha of 0.05. Secondary analyses will involve examining the longitudinal trajectories of the two outcomes over time, with baseline and 3 months as the time points of interest. We will utilize the linear mixed-effects approach as well as the quantile regression for panel data to test for the effect of time on the levels of each outcome. Individual trajectories as well as the observed and estimated means (95%CIs) and medians (95%CIs) will be plotted over time using the spaghetti plot. Analyses will be performed using SAS 9.4 (Cary, NC) and R statistical software.

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SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒

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4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Burosumab (Crysvita®) was approved by the Unites 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.
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). Overall the results from the clinical trials indicate a very favorable benefit-risk profile. We plan to prescribe the drug as indicated in the prescribing information. We do not anticipate the side effects of the drug to be any greater in the research subjects than what is known about the drug. An IND application is therefore not required.

3. Source: Identify the source of the drug or biologic to be used. *Write here*

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom? Ultragenyx Pharmaceutical Inc.

4. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
CRYSVITA (burosumab-twza) injection for subcutaneous administration is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution. The product is available as one single-dose vial per carton in the following strengths:10 mg/mL, 20 mg/mL or 30 mg/mL. CRYSVITA vials must be stored in the original carton until the time of use under refrigerated conditions at 36°F to 46°F (2°C to 8°C). CRYSVITA vials will be stored in the original carton to protect from light until time of use. Vials are not to be frozen or shaken and are to be used before the expiration date stamped on the carton. CRYSVITA vials are single-dose only and all unused product should be discarded. The YNHH IDS has previously handled this medication for the clinical trials.

Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

5. Use of Placebo: ☒Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

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a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study.
Write here

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Write here

d) Describe the procedures that are in place to safeguard participants receiving placebo.
Write here

6. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☒ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. The clinician will plan to submit a start form for a prescription for Crysvita at the start of the study. This will provide sufficient time to have the study subject approved through their insurance to continue receiving Crysvita after the study is completed.

☐ **NO** If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

***If Yes, please be aware of the following requirements*:**

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
Write here
3. **Source:**
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: 10 subjects
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☒ Other: Current patients of Drs. Insogna, Carpenter or Bergwitz or patients being referred to one of these doctors for clinical care		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. **Recruitment Procedures:**
a. Describe how potential subjects will be identified. In the clinics of Drs. Insogna, Bergwitz and Carpenter or advertising through the XLH network
b. Describe how potential subjects are contacted. In clinic at the time they are considering the use of Crysvita® for their care they will be offered participation in the study
c. Who is recruiting potential subjects? Drs. Insogna, Bergwitz and Carpenter

4. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

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☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship. These subjects will all be known to the doctors in the study or will be referred to them for treatment of XLH.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
   Choose one:
   ☐ For entire study
   ☒ For recruitment/screening purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

   i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: Preliminary contact may be made with a potential study participant over the phone or via e-mail especially if they live at a distance to the study site

   ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: N/A

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   The consenting personnel will explain the purpose of the study as well a detailed description of the schedule of the procedures. They will explain the study procedures and the risks involved. Consent will be obtained from the subject either prior to or upon arrival to the HRU at the first visit. Because the subjects will be greater than 18 years of age, they will consent for the study themselves by signing the consent forms.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   After describing the study to the subjects, they will be asked if they have any questions and if they understand the purpose of the study. They will also be asked if they understand the schedule of procedures required of them throughout the study.
8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

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We do not anticipate any non-English speaking subjects.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☒ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? We will be collecting blood and urine results that may become part of the patient's medical record. The MR Spectroscopy results, strength assessment and KOOS and PROMIS testing will only be included in the patient's research record. We will also obtain information that identifies the study subjects including name, address, phone number and date of birth in our research records.

2. How will the research data be collected, recorded and stored?

   The paper data files will be stored in designated locked file cabinets in the principal investigator's or the study coordinator's office. The digital data will be stored on password protected Yale University computers. Any identifiable data will be stored on the shared drive dedicated to our XLH projects.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   The file cabinets will be locked. Only the principal investigator and research personnel approved to work on the study will have access to the shared drive. Also, the data will be immediately de-identified, where the identifying information will be replaced with a code that does not directly identify the research subjects when possible. Research staff will be instructed to limit their access of the study participants' medical record to only those portions relevant to the current study. All computers used to access the identifiable data will be encrypted as per the University Policy.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

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5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Research files will be stored for 7 years after the completion of the study. After 7 years, the identifiable data will be destroyed or de-identified. The PI will maintain a list of those who participated in the study. The data that is part of the MR will remain as per hospital policy.

6. If appropriate, has a Certificate of Confidentiality been obtained? N/A

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
There is no direct benefit to participating in this study although it will improve our understanding of how Crysvita affects muscle function.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   Patients may continue on conventional treatment or if they are not on treatment they can begin conventional therapy or start treatment Crysvita® without participating in the study.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Stipends: Participants will receive a stipend in the amount of $100 for their time and inconvenience for each of visits 1, 4 and 5 (visits with MR Spectroscopy) and a stipend in the amount of $50 for each of visits 2 and 3. A stipend will only be provided for those visits completed.

   Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   All study related tests detailed in the protocol will be covered by the study with no cost to the patient. Patients will receive reimbursement of out of pocket travel expenses.. This may include the cost for transportation and/or a hotel stay the night before or after the study visit depending on visit time and travel schedule. The study medication will be provided at no cost during the course of the study.

3. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? Yes

b. Where and from whom may treatment be obtained? YNHH
c. Are there any limits to the treatment being provided? No
d. Who will pay for this treatment? The study subjects through their insurance
e. How will the medical treatment be accessed by subjects? The YCCI HRU is within YNHH

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☒ No ☐

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By

submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

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