Abbreviated Title: Burosumab for FD

NIH IRB #: 000798

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Title: A phase 2 Study of Burosumab For Fibroblast Growth Factor-23 Mediated Hypophosphatemia in Fibrous Dysplasia

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Investigational Agents:

Drug Name:	Burosumab
IND Number:	161576
Sponsor:	NIDCR
Manufacturer:	Kyowa Kirin Co. Ltd.

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

Title: A Phase 2 Study of Burosumab For Fibroblast Growth Factor-23 Mediated Hypophosphatemia in Fibrous Dysplasia

Study Description: This will be a phase 2, open-label, single-arm study to evaluate the safety and efficacy of burosumab to normalize serum phosphate levels in subjects with fibrous dysplasia (FD) and fibroblast growth factor 23 (FGF23)-mediated hypophosphatemia.

Objectives:

Primary Objective:

- Evaluate the efficacy of burosumab to normalize serum phosphate levels in subjects with FD and FGF23-mediated hypophosphatemia at 48 weeks.

Secondary Objectives:

- Evaluate the efficacy of burosumab to normalize serum phosphate levels in subjects with FD and FGF23-mediated hypophosphatemia at 24 weeks.
- Evaluate the safety and tolerability of burosumab in patients with FD.
- Evaluate the effect of burosumab on increasing serum phosphate and additional mineral markers.
- Evaluate the impact of burosumab on FD lesion activity.
- Evaluate the effect of burosumab on functional parameters.
- Evalua9te the effect of burosumab on pain and health-related quality of life.

Endpoints:

Primary Endpoint:

- The proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 48.

Secondary Endpoints:

- Proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 24.
- Adverse events and clinical safety laboratory tests for up to 4 weeks after the final burosumab dose (48 weeks for adult subjects, 50 weeks for pediatric subjects).
- Change and percent change from baseline to post-baseline visits in serum phosphate, serum 1,25(OH)2D, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR).
- Change in FD lesion activity using 18F-NaF PET/CT total lesion activity from baseline to 48 weeks
- Change and percent change in serum bone turnover markers, including procollagen 1 N-terminal propeptide (P1NP), beta crosslaps C-telopeptides (CTX), osteocalcin, and bone-specific alkaline phosphatase from baseline to 48 weeks.
- Change in FD lesion histology and cell proliferation as assessed by minimally invasive bone biopsies from baseline to 48 weeks (adults with capacity to consent only) from baseline to 48 weeks
- Skeletal changes assessed on skeletal survey at baseline and 48 weeks
- Change from baseline to 48 weeks in:
    - Muscle strength

	○ Range-of-motion ○ Walking speed (9-minute walk) Change from baseline to 48 weeks in patient reported outcomes measures: • SF36: adults • SF10: children • PROMIS Pain Intensity: Pediatric and Parent Proxy version 1.0, Adult version 2.0 • PROMIS Pain Interference: Pediatric and Parent Proxy v 2.0, Adult v 1.1 • PROMIS Mobility: Pediatric and Parent Proxy version 2.0, Adult Mobility Lower Extremity v 1.0 • PROMIS Fatigue: Pediatric and Parent Proxy v 2.0, Adult FACIT 13a v1.0 • Activities of Daily Living Questions: adults and children
Study Population:	Up to 15 subjects with FD and FGF23-mediated hypophosphatemia
Phase:	2
Description of Sites/Facilities Enrolling Participants:	National Institutes of Health (NIH) Clinical Center (CC)
Description of Study Intervention:	Burosumab is an injectable solution in single use vials at concentrations of 30 mg/mL
Study Duration:	Estimated time from when the study opens to enrollment until completion of data analyses is approximately 20 months.
Participant Duration:	Up to 50 weeks (2 week washout period + 48 week treatment period + final adverse event review)

1.2 Schema

NIH evaluation											NIH evaluation												NIH evaluation
-2	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Washout period	**Burosumab Treatment**																								

Subjects will be treated with burosumab for 48 weeks following a 2-week washout period. Evaluations will be performed at the NIH Clinical Center at baseline, 24, and 48 weeks. Between visits burosumab will be administered locally, and subjects will be monitored remotely with outpatient labs.

1.3 Schedule of Activities (SoA)

Procedures	**Weeks -12 to -1** [1]	**Weeks -2 to 0: Washout period for subjects on therapy** [2]	**Baseline Visit (NIH CC)** [3]	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**Week 20**	**Week 22**	**Week 24 Visit (NIH CC)** [3]
Informed consent	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics			X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history			X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Physical exam (including height, arm span, and weight)	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Vital signs	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Injection teaching	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Functional parameters [4]	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
NIH lab tests [5]	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Outpatient lab tests [6]	-		-	X	X	X	X	X	X	X	X	-	X	-	X	-	-
Pregnancy test [7]	-		X	-	-	-	X	-	X	-	X	-	X	-	X	-	X
Bone biopsy [8]	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Imaging assessment [9]	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient reported outcomes [10]	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Burosumab administration (pediatric subjects) [11]	-		X	-	X	-	X	X	X	X	X	X	X	X	X	X	X
Burosumab administration (adult subjects) [11]	-		X	-	-	-	X	-	X	-	X	-	X	-	X	-	X
Adverse event collection, review and evaluation	-		←													→	

Procedures	**Week 26**	**Week 28**	**Week 30**	**Week 32**	**Week 34**	**Week 36**	**Week 38**	**Week 40**	**Week 42**	**Week 44**	**Week 46**	**Week 48 Visit (NIH CC)** [3]	**Week 50**
Informed consent	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	-	-	-	-	-	-	-	-	-	-	-	X	-
Physical exam (including height, arm span, and weight)	-	-	-	-	-	-	-	-	-	-	-	X	-
Vital signs	-	-	-	-	-	-	-	-	-	-	-	X	-
Injection teaching	-	-	-	-	-	-	-	-	-	-	-	-	-
Functional parameters [4]	-	-	-	-	-	-	-	-	-	-	-	X	-
NIH lab tests [5]	-	-	-	-	-	-	-	-	-	-	-	X	-
Outpatient lab tests [6]	-	X	-	X	-	X	-	X	-	X	-	-	-
Pregnancy test [7]	-	X	-	X	-	X	-	X	-	X	-	X	
Bone biopsy [8]	-	-	-	-	-	-	-	-	-	-	-	X	-
Imaging assessment [9]	-	-	-	-	-	-	-	-	-	-	-	X	-
Patient reported outcomes [10]	-	-	-	-	-	-	-	-	-	-	-	X	-
Burosumab administration (pediatric subjects) [11]	X	X	X	X	X	X	X	X	X	X	X	-	-
Burosumab administration (adult subjects) [11]	-	X	-	X	-	X	-	X	-	X	-	-	-
Study close-out teleconference (pediatric subjects) [12]													X
Adverse event review and evaluation [12]	←											→	

[1] Informed consent will be obtained by telephone or in person prior to the baseline visit.

[2] Subjects receiving supplemental phosphate, active vitamin D metabolites, or current burosumab treatment will discontinue these medications for 2 weeks prior to screening.

[3] Visits will be conducted in the NIH Clinical Center in the inpatient, day hospital, or clinic settings as appropriate. All visits will occur within a window of +/- 5 days from the planned timepoint.

[4] Muscle strength, range-of-motion, 9-minute walk test.

[5] Serum sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, albumin, total protein, calcium, magnesium, phosphate, parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, osteocalcin, procollagen type 1 N-terminal propeptide, Beta-CrossLaps C-telopeptides, intact FGF23 (baseline visit only), C-terminal FGF23 (baseline visit only), research blood, anti-drug antibodies, neutralizing antibodies (in samples testing positive for neutralizing antibodies only), and burosumab concentration. 24-hour urinary calcium, creatinine, phosphate (toilet trained subjects), random urinary calcium, creatinine, phosphate (non-toilet trained subjects), and TmP/GFR.

[6] Serum calcium, phosphate, creatinine, and alkaline phosphatase. Random urine calcium, creatinine, and phosphate. Urine pregnancy test (girls and women of childbearing potential only). Outpatient labs will be obtained 3 +/-2 days and reviewed prior to burosumab administration. Subsequent elements on the Schedule of Events will be dictated by the timing of the previous injection.

[7] To be performed in girls and women of childbearing potential only. Female subjects of child-bearing potential must be non-pregnant and non-nursing. Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result or can be performed if pregnancy test by urine is not feasible.

[8] To be performed only in adult subjects with capacity to consent.

[9] ^{18}Sodium fluoride-PET/CT scan, skeletal survey, renal ultrasound. Will accept outside or internal imaging for ^{18}Sodium fluoride-PET/CT scan, and/or skeletal survey as baseline study imaging if obtained within 6 months prior to Week 0/Baseline visit, as a means of reducing unnecessary repeated exposure to radiation

[10] SF36 (adults), SF10 (children), PROMIS Pain Intensity (Pediatric and Parent Proxy version 1.0, Adult version 2.0), PROMIS Pain Interference (Pediatric and Parent Proxy v 2.0, Adult v 1.1), PROMIS Mobility (Pediatric and Parent Proxy version 2.0, Adult Mobility Lower Extremity v 1.0), PROMIS Fatigue (Pediatric and Parent Proxy v 2.0, Adult FACIT 13a v1.0), Activities of Daily Living Questionnaire (adults and children).

[11] Burosumab is administered every 2 weeks in children age <18 years, and every 4 weeks in adults age ≥18 years. The initial dose will be administered at the NIH CC, and subsequent doses will be self/caregiver administered under the observation of the study team. If the target range is not reached for patients >18 year and older, dosing may be administered at every 2-week dosing intervals at the discretion of the PI.

[12] Final adverse event review will be performed 4 weeks +/- 5 days after the final dose: at the 48 week NIH CC visit for adult subjects, and at a teleconference at 50 weeks for pediatric subjects, or adult subjects who have been on every 2-week dosing interval.

2 INTRODUCTION

2.1 Study Rationale

Fibrous dysplasia (FD) is a rare, mosaic disorder of $G\alpha_s$ activation in which normal bone and marrow are replaced with fibro-osseous tissue. Disease may involve one bone or many, and may occur in association with extraskeletal features, termed McCune-Albright syndrome (MAS) [1]. $G\alpha_s$ mutation-bearing skeletal stem cells produce excess amounts of the phosphaturic hormone fibroblast growth factor-23 (FGF23). This leads to hyperphosphaturia in most patients, and those with a high FD tissue burden may develop frank hypophosphatemia. Because FD tissue is inherently poorly mineralized and structurally unsound, it is likely at increased vulnerability to the deleterious effects of hypophosphatemia compared to typical bone. Therefore, in addition to sequelae of rickets/osteomalacia, patients with FGF23-mediated hypophosphatemia present with increased FD-related morbidity, including progressive skeletal deformities, fractures, bone pain, and functional impairment [2-4].

Like other disorders of FGF23 excess, management of hypophosphatemia in FD has traditionally focused on repletion with oral phosphate and active vitamin D analogs. However, this regimen is complicated by dose-limiting side effects, including gastrointestinal intolerance and renal toxicity. Normalization of serum phosphate is therefore not a practical goal with conventional treatment, placing patients with FD at continued risk of skeletal complications from persistent hypophosphatemia. Burosumab, a human recombinant monoclonal antibody to FGF23, represents a new, targeted treatment approach. Multiple clinical trials have demonstrated safe, efficacious use of burosumab in FGF23-mediated disorders such as X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO), leading to improved serum phosphate levels and skeletal outcomes without adverse gastrointestinal or renal side effects. While the underlying pathophysiology of FGF23 excess is shared between these conditions, there is no literature regarding the use of burosumab in FD.

Given the known limitations of conventional therapy, burosumab is an intuitive choice for management of hypophosphatemia in FD. However, additional research into the safety and efficacy of burosumab is needed before it can be used routinely in this population. The potential for FD tissue effects is an important consideration; it is unknown whether burosumab may impact skeletal stem cell proliferation or other drivers of FD lesion growth and activity. Given the increased vulnerability of FD to deleterious effects of hypophosphatemia, investigation is needed to determine if targeting a mid-normal serum phosphate level (typically unachievable with conventional therapy) is a safe and effective therapeutic goal in patients with FD. Burosumab is labeled as a subcutaneous injection administered by healthcare professionals; however, the option of self-administration would offer many benefits in the FD population, including improved accessibility, cost, and convenience. Studies are needed to determine the feasibility of this approach.

2.2 Background

Burosumab has been studied extensively in clinical trials of pediatric and adult patients with X-linked hypophosphatemia (XLH), an X-linked dominant disorder of FGF23 overproduction. An open label phase 2 study of 52 children age 5-12 years, burosumab treatment at 2-week intervals led to sustained improvements in serum phosphate levels and radiographic measures of rickets severity [5]. A subsequent phase 3 study in 61 children age 1-12 years compared burosumab to

conventional treatment, showing significantly greater improvements in rickets severity, growth, and biochemistries [6]. A randomized placebo-controlled study of adults with XLH treated with burosumab at 4-week intervals reported improvements in serum phosphate, patient-reported physical outcomes, and healing of osteomalacia-related insufficiency fractures [7 8]. A subsequent open-label adult phase 3 study evaluated transiliac bone biopsies after 48 weeks of burosumab, demonstrating improvement in histomorphometric indices related to osteomalacia [9]. Based on these studies, burosumab has received approval from the Food and Drug Administration (FDA) for treatment of XLH in adults and children age 6 months and older.

Burosumab has been studied in adults with tumor-induced osteomalacia (TIO), a rare paraneoplastic process in which acquired phosphaturic mesenchymal tumors produce high levels of FGF23. In an open-label phase 2 study of 14 adults, burosumab treatment at 4-weeks intervals was associated with improved serum phosphate levels, fracture healing, and histomorphometric indices of osteomalacia [10]. Similar findings were reported in a second open-label study in adults (n=13) [11]. Based on these studies, burosumab was approved by the FDA for treatment of TIO in patients age 2 years and older.

Burosumab is currently approved for administration by healthcare professionals via subcutaneous injection every 2 weeks for children and every 4 weeks for adults. In the clinical development program of burosumab, self-administration by either patient or caregiver was permitted and monitored in two open-label studies of XLH in Japan and South Korea, KRN23-003 (NCT03233126) and KRN23-004 (NCT04308096). Based on this data, the Pharmaceuticals and Medical Devices Agency in Japan approved self- and/or caregiver administration of burosumab in December 2020. Self- and/or caregiver administration was temporarily allowed by the FDA due to the COVID-19 pandemic. Self- and/or caregiver-administration was also approved by the European Medicines Agency in 2021, if suitable and if performed by an individual who has been trained in injection techniques.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

There are no known risks of burosumab in the target population of patients with FD. The potential risks and adverse reactions for burosumab are based on the approved indications XLH and TIO [12].

Adverse Reactions in Clinical Trials of Burosumab-Treated Pediatric Patients with XLH

The following data reflect safety data from burosumab treatment in 3 pediatric clinical trials of XLH: Study 1 is a randomized, open-label phase 3 study in children ages 1 to 12 years, who were randomized to treatment with burosumab or conventional treatment (burosumab n=29, control n=32). Study 2 is an open-label phase 2 study in children ages 5 to 12 years (n=52). Study 3 is an open-label phase 2 study in children ages 1 to less than 5 years (n=13). Overall, the patient population was 1-12 years (mean age 7.0 years), 49% male, and 88% white.

In Study 1, burosumab-treated patients received a mean dose of approximately 0.90 mg/kg (range 0.8-1.2 mg/kg) every 2 weeks. All patients in this group and the active control group completed 64 weeks of treatment. Adverse reactions occurring in ≥10% of subjects in the burosumab group, with higher frequency than in the subjects in the control group, through the 64-week treatment period in Study 1 are shown in the below **Table 1**:

Table 1. Adverse Reactions in ≥10% of Burosumab-Treated Pediatric Patients and with Higher Frequency Than the Active Control Group in Study 1

Adverse Reaction	Burosumab Treatment (n=29), n (%)	Active Controls (n=32), n (%)
Pyrexia	16 (55%)	6 (19%)
Injection site reaction	15 (52%)	0 (0%)
Cough	15 (52%)	6 (19%)
Vomiting	12 (41%)	8 (25%)
Pain in extremity	11 (38%)	10 (31%)
Headache	10 (34%)	6 (19%)
Tooth abscess, infection, and/or toothache	10 (34%)	4 (13%)
Dental caries	9 (31%)	2 (6%)
Diarrhea	7 (24%)	2 (6%)
Decreased vitamin D levels	7 (24%)	1 (3%)
Constipation	5 (17%)	0 (0%)
Rash	4 (14%)	2 (6%)

In Study 2, 26 patients received burosumab at a mean dose of 1.05 mg/kg (range 0.4 – 2.0 mg/kg) every 2 weeks at Week 64; the other 26 patients received burosumab every 4 weeks. The mean duration of exposure in Study 2 was 124 weeks. In Study 3, patients received burosumab at a mean dose of 0.90 mg/kg (range 0.8 – 1.2 mg/kg) every 2 weeks at Week 40. The mean duration of exposure in Study 3 was 45 weeks. Adverse reactions occurring in ≥10% of burosumab -treated patients from Studies 2 and 3 are shown in the below **Table 2**:

Table 2.Adverse Reactions in ≥10% of Burosumab-Treated Pediatric Patients in Studies 2 and 3.

Adverse Reaction	Study 2 (n=52), n (%)	Study 3 (n=13), n (%)	Overall (n=65), n (%)
Headache	38 (73%)	1 (8%)	39 (60%)
Injection site reaction	35 (67%)	3 (23%)	38 (59%)

Adverse Reaction	Study 2 (n=52), n (%)	Study 3 (n=13), n (%)	Overall (n=65), n (%)
Vomiting	25 (48%)	6 (46%)	31 (48%)
Pyrexia	23 (44%)	8 (62%)	31 (48%)
Pain in extremity	24 (46%)	3 (23%)	27 (42%)
Decreased vitamin D levels	19 (37%)	2 (15%)	21 (32%)
Rash	14 (27%)	1 (8%)	15 (23%)
Tooth abscess, toothache	20 (38%)	5 (38%)	25 (40%)
Myalgia	9 (17%)	1 (8%)	10 (15%)
Dizziness	8 (15%)	0 (0%)	8 (12%)

Hypersensitivity reactions: In Study 1 (n=29), the most frequent hypersensitivity reactions were rash (10%), injection site rash (10%) and injection site urticaria (7%). In Studies 2 and 3 (n=65), the most frequent hypersensitivity reactions were rash (22%), injection site rash (6%), and urticaria (5%).

Hyperphosphatemia: No events of hyperphosphatemia were reported in pediatric studies.

Injection Site Reactions: In Study 1, 52% of patients had a local injection site reaction (injection site urticaria, erythema, rash, swelling, bruising, pain, pruritus, and hematoma). In Studies 2 and 3, approximately 58% of the patients had a local injection site reaction. Injection site reactions were generally mild, occurred within 1 day of injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Adverse Reactions in Clinical Trials of Burosumab-Treated Adult Patients with XLH

The following data reflect safety data from burosumab treatment in adult patients with XLH in a 24-week randomized, double-blind, placebo-controlled study (Study 4) of 134 patients, age 20-63 years (mean age 41 years). Most were white (81%) and female (65%). A total of 68 and 66 patients received at least one dose of burosumab or placebo, respectively. The mean dose of burosumab was 0.95 mg/kg (range 0.3 – 1.2 mg/kg) subcutaneously every 4 weeks. Adverse reactions reported in ≥5% of burosumab-treated patients, and ≥2 patients greater than the placebo group are shown in the following **Table 3**:

Table 3. Adverse Reactions Occurring in ≥5% of Burosumab-Treated Adult Patients, and in at ≥2 Patients More Than with Placebo in the 24-Week Placebo-Controlled Period of Study 4

Adverse Reaction	Burosumab Treatment (n=68), n (%)	Placebo Group (n=66), n (%)
Back pain	10 (15%)	6 (9%)
Headache	9 (13%)	6 (9%)
Tooth infection	9 (13%)	6 (9%)
Restless leg syndrome	8 (12%)	5 (8%)
Decreased vitamin D levels	8 (12%)	3 (5%)
Dizziness	7 (10%)	4 (6%)
Muscle spasms	5 (7%)	2 (3%)
Constipation	6 (9%)	0 (0%)
Hyperphosphatemia	4 (6%)	0 (0%)

Hypersensitivity Reactions: Approximately 6% of patients in both the burosumab and placebo groups experienced a hypersensitivity event, which were mild-moderate and did not require study discontinuation.

Hyperphosphatemia: Six percent of patients in the burosumab group experienced hyperphosphatemia meeting the protocol-specified criteria for dose reduction (either a single serum phosphate greater than 5.0 mg/dL or serum phosphate greater than 4.5 mg/dL [upper limit of normal] on two occasions). A single patient required a second dose reduction for continued hyperphosphatemia.

Injection Site Reactions: Approximately 12% of patients in both the burosumab and placebo groups had a local reaction (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 Legs Syndrome: Approximately 12% of the burosumab group had worsening of baseline or new onset of restless legs syndrome of mild to moderate severity; these events did not lead to dose discontinuation.

Adverse Reactions in Clinical Trials of Burosumab-Treated Adult Patients with TIO

The following data reflect pooled safety data from burosumab treatment in adult patients with TIO in two open-label trials (Studies 5 and 6) that enrolled a total 27 patients. Patients ranged from 33-73 years of age and 14 (52%) were male. The mean dose of burosumab was 0.77 mg/kg every 4 weeks and the mean duration of exposure was 121 weeks. Adverse reactions from both studies are shown below in **Table 4**:

Table 4. Adverse Reactions Reported in Adult Patients with TIO in Study 5 and Study 6

Adverse Reaction	**Overall (n=27), n (%)**
Tooth abscess	5 (19%)
Muscle spasm	5 (19%)
Dizziness	4 (15%)
Constipation	4 (15%)
Injection site reaction	4 (15%)
Rash	4 (15%)
Headache	3 (11%)
Vitamin D deficiency	2 (7%)
Hyperphosphatemia	2 (7%)
Restless leg syndrome	2 (7%)

Hypersensitivity reactions: 22% of patients experienced a hypersensitivity reaction. The most frequent hypersensitivity reactions were eczema (11%) and rash (15 %), and reactions were mild-moderate in severity.

Hyperphosphatemia: 2 patients (7%) experienced hyperphosphatemia which was managed with dose reduction.

Injection Site Reactions: The frequency of injection site reactions was 15% (injection site reaction, injection site pain, and injection site swelling). Reactions were generally mild in severity, required no treatment and resolved in all cases.

Restless Leg Syndrome: 2 patients (7%) experienced symptoms of restless legs syndrome, which were mild and did not require treatment interruption.

Immunogenicity

There is potential for immunogenicity with all therapeutic proteins. In XLH clinical studies, none (0/13) of the 1 to 4-year-old patients, 19% (10/52) of the 5- to 12-year-old patients, and 15% (20/131) of the adult patients tested positive for anti-drug antibodies after receiving burosumab. Three 5- to 12-year-old patients tested positive for neutralizing antibodies. Anti-drug antibodies were not associated with clinically-relevant changes in pharmacokinetics, pharmacodynamics, efficacy, or safety. In one TIO clinical study, 14% (2/14) of the adult patients tested positive for anti-drug antibodies after receiving burosumab, and one of these patients tested positive for neutralizing antibodies. In another TIO clinical study, none of the 13 adult patients tested positive for anti-drug antibodies.

Additional Important Potential Risks

Pregnancy and Lactation

There are no available data on burosumab use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. *In utero*, burosumab-twza exposure in cynomolgus monkeys did not result in teratogenic effects. Adverse effects such as late fetal loss and preterm birth were observed in pregnant cynomolgus monkeys, however, these effects are unlikely to indicate clinical risk because they occurred at a drug exposure that was 15-fold higher, by AUC, than the human exposure at the maximum recommended human dose of 2 mg/kg every 2 weeks and were accompanied by maternal hyperphosphatemia and placental mineralization. Currently, Women of child-Bearing Potential (WOCBP) will be consented to receive pregnancy testing prior to burosumab initiation and at intervals throughout the trial and required to utilize contraception and agree to avoid pregnancy during the experimental treatment. There is no information regarding the presence of burosumab in human milk, or the effects on milk production or the breastfed infant. Women who are breastfeeding will therefore be excluded from participating in this study.

Ectopic Mineralization

In rabbits and cynomolgus monkeys, ectopic mineralization in multiple tissues and organs was observed at doses of burosumab-twza that resulted in supra-physiologic serum phosphate levels. In a study in wild type and hypophosphatemic Hyp mice, a murine model of XLH, ectopic mineralization was markedly less in Hyp mice. In clinical trials of XLH and TIO no clinically meaningful changes related to potential ectopic mineralization were observed. Although ectopic mineralization is a known risk related to XLH disease, and is exacerbated by the current standard of care consisting of oral phosphate and/or active vitamin D supplementation, burosumab does not appear to be associated with progression of cardiac or renal ectopic mineralization beyond the natural course of pre-existing disease.

Hyperphosphatemia

Increases in serum phosphate to above the upper limit of normal may be associated with an increased risk of nephrocalcinosis. For this reason, dose interruption and/or dose reduction may be required based on a patient's serum phosphate. In clinical trials of TIO, 7% of patients experienced events of hyperphosphatemia, which were managed with dose reduction. In the double-blind period of Study 4 in patients with XLH, 6% of patients in the treatment group experienced hyperphosphatemia, which was managed with dose reduction. A single patient required a second dose reduction for continued hyperphosphatemia. To date, no dose-limiting toxicity of hyperphosphatemia (ie, a serum phosphate value of $\geq$ 6.5 mg/dL) has been seen in the pediatric studies of burosumab in XLH.

Burosumab Effects on FD Lesion Activity

There are no known risks of burosumab on FD lesion growth or metabolic activity. However, because FD is a benign neoplastic process, it is important to consider potential metabolic effects of any novel therapy. Burosumab does not have tumoricidal activity, and the natural history of FD lesions is to progress slowly. Reports of lesion progression may be seen, and therefore lesion metabolic activity will be monitored.

Alternative Therapies to Burosumab for Patients with FD and FGF23 excess

Should patients elect not to participate in the study, they may be treated with oral active vitamin D analogs (calcitriol or alfacalcidiol) in combination with supplemental phosphate, termed conventional therapy. This approach is the current mainstay of treatment in patients with FD. Because FGF23 impairs 1α-hydroxylase activity, administration of active vitamin D analogs is necessary to maintain mineral metabolism and prevent secondary hyperparathyroidism. However, because these analogs increase calcium absorption, they carry a dose-related risk of hypercalciuria, nephrocalcinosis, and nephrolithiasis [13 14]. Oral phosphate supplements are short-acting and typically require administration 3-5 times daily, making adherence to therapy challenging. They are also associated with often dose-limiting gastrointestinal irritation [13 14]. Conventional therapy may partially ameliorate the metabolic effects of excess FGF23, however dose-related toxicities make normalization of serum phosphate an impractical goal, placing patients at risk for complications of persistent hypophosphatemia.

Potential Risks Associated with Study Procedures

Multiple blood and urine collections will occur introducing known common risks (discomfort, bruising) for blood draws and/or intravenous catheter placement introducing smaller risks of complications including fainting (usually a vasovagal response to sight or insertion of needles) or inflammation of the insertion site (including potentially pain and swelling) and the potential for infection or venous thrombosis.

Bone biopsies in adult subjects may cause discomfort and pain for several days and can be treated safely with acetaminophen or more potent analgesics as needed. Bleeding and infection at the site of biopsy are possible but rare. Subjects may experience some transient anesthesia-related symptoms such as nausea, vomiting, decreased appetite, fatigue, and decreased blood pressure. Subjects may undergo a routine pre-anesthesia consult and be asked to sign a separate surgical consent form prior to the procedure. Only biopsies judged to be minimally invasive according to the judgement of the PI and surgeon will be performed. A bone biopsy will not be done if there is no site containing FD that allows a minimally invasive procedure with minimal risk of fracture.

At baseline and 48 weeks the following radiologic procedures will be performed: 1) ^{18}Sodium fluoride-PET/CT scan to evaluate metabolic activity of FD lesions, 2) skeletal survey to include x-rays of the arms, legs, pelvis, skull, and lateral spine to evaluate for skeletal deformities and metaphyseal irregularities, and 3) CT-guided bone biopsy (adults with capacity to consent only). This radiation exposure is not necessary for medical care and is for research purposes only. The effective dose that participants will receive from participation in this research study is 2.1 rem for adults with capacity to consent; 1.7 rem for adults without capacity to consent, 1.8 rem for children ages 4-17; and 0.6 rem for children ages 1-4.

2.3.2 Known Potential Benefits

There are no known definitive benefits of burosumab in the target population of patients with FD and FGF23-mediated hypophosphatemia. However, potential benefits may be inferred from studies of XLH and TIO, which share excess FGF23 production as a common etiology. In clinical trials of XLH, burosumab achieved normalization of serum phosphate without increasing urinary calcium levels, drastically reducing the risk of renal complications. Benefits of phosphate normalization included improved skeletal mineralization, as evidenced by radiographic improvement in rachitic features, and improved histomorphometric markers on transiliac bone

biopsies. In a child with FD who was unable to be managed with conventional therapy, clinically-indicated burosumab treatment was associated with marked improvements in serum phosphate and other metabolic indices [15]. As a once to twice monthly injection, burosumab has the benefit of markedly superior convenience compared to conventional therapy, which requires oral medications 3-5 times daily. Burosumab is also better-tolerated than conventional therapy, without the frequent dose-limiting gastrointestinal side effects.

2.3.3 Assessment of Potential Risks and Benefits

Taken together, available data support investigation of burosumab as a potential therapy targeted to excess FGF23 production in patients with FD. Current standard of care, which includes oral phosphate and active vitamin D supplementation, is complicated by an undesirable safety and tolerability profile, resulting in suboptimal therapeutic effects. Because FD tissue is inherently poorly mineralized and structurally unsound, patients are at extremely high risk for fractures and progressive deformities; these complications occur with increasing frequency and severity in the setting of hypophosphatemia [2-4]. Burosumab is the first therapy that offers the possibility of normalizing serum phosphate in patients with FD.

The study is designed to minimize known potential risks (as described above) while maximizing therapeutic treatment to increase the probability of establishing a definitive proof-of-concept of the potential utility of burosumab as a treatment for FGF23-mediated hypophosphatemia in patients with FD.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the efficacy of burosumab to normalize serum phosphate levels in subjects with FD and FGF23-mediated hypophosphatemia at 48 weeks	The proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 48	Serum phosphate is the primary driver of skeletal complications in patients with FGF23-mediated hypophosphatemia and has been correlated with poor clinical outcomes in patients with FD
Secondary		
Evaluate the efficacy of burosumab to normalize serum phosphate levels in subjects with FD and FGF23-mediated hypophosphatemia at 24 weeks	Proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 24	Serum phosphate is the primary driver of skeletal complications in patients with FGF23-mediated hypophosphatemia and has been correlated with poor clinical outcomes in patients with FD

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Evaluate the safety and tolerability of burosumab in patients with FD	Adverse events and clinical safety laboratory tests for up to 48 weeks	Safety endpoints for expected and unexpected adverse events
Evaluate the effect of burosumab on increasing serum phosphate and additional mineral markers	Change and percent change from baseline to post-baseline visits in serum phosphate, serum 1,25(OH)2D, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR)	Safety endpoint for monitoring metabolic impact of burosumab in patients with FD
Evaluate the impact of burosumab on FD lesion activity	• Change in FD lesion activity using 18F-NaF PET/CT total lesion activity from baseline to 48 weeks • Change and percent change in serum bone turnover markers, including procollagen 1 N-terminal propeptide (P1NP), beta crosslaps C-telopeptides (CTX), osteocalcin, and bone-specific alkaline phosphatase from baseline to 48 weeks. • Change in FD lesion histology and cell proliferation as assessed by minimally invasive bone biopsies from baseline to 48 weeks (adults with capacity to consent only) from baseline to 48 weeks • Skeletal changes assessed on skeletal survey at baseline and 48 weeks.	Safety endpoints to determine if burosumab impacts metabolic activity of FD lesions, which are a benign neoplastic process
Evaluate the effect of burosumab on functional parameters	Change from baseline to 48 weeks in: • Muscle strength • Range-of-motion • Walking speed (9-minute walk)	Outcome measures that reflect activities of daily living
Evaluate the effect of burosumab on pain and health-related quality of life	Change from baseline to 48 weeks in patient reported outcomes measures: • SF36: adults • SF10: children • PROMIS Pain Intensity: Pediatric and Parent Proxy version 1.0, Adult version 2.0 • PROMIS Pain Interference: Pediatric and Parent Proxy v 2.0, Adult v 1.1 • PROMIS Mobility: Pediatric and Parent Proxy version 2.0, Adult Mobility Lower Extremity v 1.0 • PROMIS Fatigue: Pediatric and Parent Proxy v 2.0, Adult FACIT 13a v1.0 • Activities of Daily Living Questions: adults and children	Outcome measures to determine pain and health-related quality of life

4 STUDY DESIGN

4.1 Overall Design

This is a single center, single-arm, open-label study to evaluate the efficacy and safety of burosumab treatment for FGF23-mediated hypophosphatemia in patients with FD/MAS. All subjects will be co-enrolled and screened through Screening and Natural History protocol 98-D-0145, a longstanding natural history study of FD/MAS protocol 98-D-0145. Up to 15 subjects will be enrolled, with the goal of a minimum 10 subjects receiving 48 weeks of burosumab treatment with week 50 for a final adverse event review. Research activity will be conducted at the NIH Clinical Center, with outpatient laboratory monitoring and burosumab self- and/or caregiver administration between NIH visits. Study subjects will be evaluated weekly on weeks 1-4 and then every two weeks for weeks 6-50.

4.2 Scientific Rationale for Study Design

An open-label study is proposed because: 1) the target population for this intervention is extremely small, making sufficient recruitment for a larger placebo-controlled study infeasible. FD/MAS is estimated to occur in approximately 1/100,000 – 1/1,000,000 individuals, and patients with clinically significant hypophosphatemia comprise only 15-30% of the overall FD/MAS population. 2) The primary endpoint of serum phosphate is an objective, quantifiable, and well-established surrogate marker that is relatively resistant to outcome assessment bias. 3) Burosumab has been well-studied in phase 2 and 3 studies in other conditions and has an overall well-established safety profile. The current study design is well-equipped to capture potential adverse effects that are specific to the FD/MAS population.

4.3 Justification for Dose

Dosing for pediatric and adult subjects will be based on current FDA-approved regimens for XLH and TIO. Doses will be adjusted to target a serum phosphate level between -1 and +2 standard deviations for age and sex. The justification for targeting a mid-high normal phosphate level is based on the following rationale: FD bone is inherently structurally unsound and poorly mineralized, and patients with FD have an overall high prevalence of skeletal morbidity compared to other FGF23 excess disorders. Even mild degrees of hypophosphatemia have been associated with increased fractures and deformities in patients with FD [1-4]. It is therefore feasible that patients with FD may experience clinical benefit from maintaining a higher therapeutic target for serum phosphate levels. The current study provides an important opportunity to investigate the safety and efficacy of this approach in patients with FD and is supported by the well-established and favorable safety profile of burosumab in phase 2 and 3 studies.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Confirmed diagnosis of fibrous dysplasia
2. Serum phosphate <10th percentile for age and sex, AND intact serum FGF23 ≥30 pg/mL[16]
3. Age ≥1 year
4. Provision of signed and dated informed consent/assent form

5. Stated willingness of subject or Legally Authorized Representative (LAR) to comply with all study procedures and availability for the duration of the study
6. For females of reproductive potential: agreement to use highly effective contraception for during study participation. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study the vasectomized male partner should be the sole partner for that participant.
    - Combination of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
7. For males of reproductive potential: use of condoms or other methods described above to ensure effective contraception with partner
8. Minimum body weight of 7.5 kilograms

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy or lactation
2. Known allergic reactions to burosumab or drug component
3. Treatment with another investigational drug within 30 days of screening
4. Treatment with burosumab within 30 days of screening
5. Have any condition which in the opinion of the PI could present a concern for subject safety or difficulty with data interpretation
6. Severe renal impairment or end stage renal disease, defined as: pediatric patients with estimated glomerular filtration rate (eGFR) 15 mL/min/1.73m2 to 29 mL/min/1.73m2 or end stage renal disease (eGFR < 15 mL/min/1.73m2), adult patients with creatinine clearance (CLcr) 15 mL/min to 29 mL/min or end stage renal disease (CLcr < 15 mL/min)

5.3 Inclusion of Vulnerable Participants

5.3.1 Children

Children ≥1 year will be included in this study. Burosumab has been well-studied in children with good safety and tolerability in phase 2 and 3 studies. Children with FD have higher incidence of hypophosphatemia compared to adults [17], and are at increased risk for growth-related and skeletal complications.

5.3.2 Adults who Lack Capacity to Consent to Research Participation

Adults who lack capacity to consent may be included in this study. Due to the likelihood of direct benefit from burosumab, and the favorable safety profile of burosumab in phase 2 and 3 studies, exclusion of this population is not appropriate. Adults who lack capacity to consent will be excluded from pre- and post-treatment bone biopsies, which entail more than minimal risk without the possibility of direct benefit.

For adult subjects, the study team will do a clinical assessment to determine if they have capacity. In situations where the clinical assessment determines that the capacity is in question, an assessment by ACAT (Ability to Consent Assessment Team) will be initiated. In the situation where the subject is known not to have capacity, this study will allow a Legally Authorized Representative (LAR) to sign consent providing the legal paperwork is filed with the Admissions Department per policy (i.e., legal guardianship, durable power of attorney, next of kin, etc). Oversight for the provisions of protection for adults unable to consent will be informed by the PI. The PI will be responsible for proper implementation of the HRPP Policy 403 - Research with Subjects Lacking Capacity to Consent.

5.4 Inclusion of Pregnant Women, fetuses or neonates

Not applicable

5.5 Lifestyle Considerations

Subject will need to commit weekly and bi-weekly research procedures as well as contraception requirements.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any Serious Adverse Event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an insufficiently low serum phosphate or low FGF23 level may be rescreened up to 3 times. Rescreened individuals should be assigned the same subject number as for the initial screening.

5.7 Strategies for Recruitment and Retention

Subjects will be recruited from the existing cohort of subjects enrolled in the protocol, Screening and Natural History of Patients with Polyostotic Fibrous Dysplasia and the McCune-Albright Syndrome (98-D-0145), and new referrals. All potentially eligible subjects enrolled onto protocol 98-D-0145 will be invited to participate in the burosumab study. The study will also be posted on ClinicalTrials.gov. Additional recruitment may proceed through referrals from worldwide clinical and research experts involved in this specialized area of mineral metabolism. Outreach through patient advocacy organizations worldwide will also be pursued. Written flyers may be distributed at patient advocacy events. Subjects may be self-referred and/or referred by the Patient Recruitment and Public Liaison Office however, prior to enrollment onto the burosumab study all subjects will need to be enrolled and screened through protocol 98-D-0145.

5.7.1 Costs

Subjects will not be billed for any research or related clinical care that participants will receive at the NIH Clinical Center for this study. The NIH Clinical Center will provide short-term medical care for any injury resulting from participation in this clinical trial.

5.7.2 Compensation

There will be no financial compensation given for participation in this study. Air/train/bus travel will be arranged by the NIH travel agency unless there are extenuating circumstances requiring the participant to book his/her own travel. For minor subjects and adults who lack capacity for consent, travel and Children's Inn/hotel accommodation will also be provided for 1 parent or LAR. Miscellaneous out-of-pocket travel expenses (e.g., baggage receipts, airport parking, taxis) will be reimbursed if a receipt is provided. Subjects traveling by car from > 50 miles will be reimbursed mileage per NIH policies. Subject copays or co-insurance for local laboratories will be paid or reimbursed if an invoice or receipt is provided.

6 STUDY INTERVENTION

6.1 Study Interventions Administration

This is an open-label study of burosumab. All subjects will receive burosumab for 48 weeks according to regimens described in the Section **6.1.2, Dosing and Administration**.

6.1.1 Study Intervention Description

Burosumab is supplied in sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution in single-dose vials containing 30 mg/mL concentrations. Burosumab should be securely stored at 2 to 8°C and protected from light. It should not be frozen. Burosumab will be administered subcutaneously without dilution in the abdomen, upper arm, or thigh. The site of injection will be rotated. No more than 1.5 mL will be administered in a single injection. If a subject needs more than 1.5 mL per administration, multiple injections must be administered, and a different site must be used for each injection.

6.1.2 Dosing and Administration

Burosumab initiation for pediatric and adult subjects will be based on currently approved regimens for XLH and TIO.

For pediatric subjects (age < 18 years) who weigh less than 10 kg, the starting dose is 1 mg/kg of body weight, rounded to the nearest 1 mg, administered every 2 weeks. For pediatric subjects who weigh 10 kg and greater, the starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every 2 weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. For adults (age 18 years and older) the starting dose regimen is 0.5 mg/kg body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every 4 weeks.

After burosumab administration, doses will be titrated in an effort to achieve a target fasting peak serum phosphate level between –1 and +2 standard deviations for age and sex (**Table 5**). If the subject's peak serum phosphate level at week 2 remains below the target range, the subject's dose may be increased at week 4 by 0.2 to 0.5 mg/kg at the discretion of the Investigator. Doses will then continue to be titrated in increments of 0.2 to 0.5 mg/kg at 4-week intervals in individual subjects to achieve the target peak serum phosphate range. If the target range is not reached for patients >18 year and older, dosing may be administered at every 2-week dosing

intervals at the discretion of the PI and adjusted in increments of 0.2 to 0.5 mg/kg to a maximum dose of 90 mg every 2 weeks.

Table 5. Burosumab Target Phosphate Ranges for Pediatric and Adult Subjects

Age (years)	Normal Phosphate Range (mg/dL)	Target Peak Serum Phosphate Range (Z-score –1 to +2; mg/dL)
1 to <5	4.3 - 6.8	4.9 - 6.8
5 to <13	4.1 - 5.9	4.6 - 5.9
13 to <16 (girls)	3.2 - 5.5	3.8 - 5.5
13 to <16 (boys)	3.5 - 6.2	4.2 - 6.2
16-18	2.9 – 5	3.4 - 5
>18	2.5 - 4.5	3 - 4.5

From: summary of age and sex-partitioned reference intervals from the CALIPER study, including thousands of healthy children and adolescents from a multiethnic population and measured using the Abbot Architect analyzer [18].

Following this initial dose titration phase, doses may be titrated at later weeks at the discretion of the PI, if there are concerns about safety, suboptimal efficacy, or if a subject has not yet achieved the target range of serum phosphate. To optimize serum phosphate levels throughout the dose cycle, Investigators may increase the dose of burosumab in 0.5 mg/kg increments in those subjects whose trough serum phosphate level (just prior to the next dose) is below the lower limit of the target range on 2 consecutive measurements performed at 4-week intervals (**Table 6**).

Table 6. Burosumab Dose Titration Scheme

Study Week	Serum Phosphate Level Z-score [1]	Dose Adjustment
Week 2	Less than –1	Increase the dose by 0.2 to 0.5 mg/kg at next dose
Week 2 6, 10 (adults) Week 1, 2, 3 (pediatrics)	> +2 [3]	Decrease the dose by 0.2 to 0.5 mg/kg
Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44	Less than –1 [2]	Increase the dose by 0.2 to 0.5 mg/kg
	–1 to +2	Continue the current dose
	> +2 [3]	Skip dose

[1] See **Table 5** for target phosphate levels according to age and sex-adjusted Z-scores

[2] If phosphate levels are below –1 standard deviation on 2 consecutive measurements, the burosumab dose may be increased by 0.5 mg/kg

[3] If phosphate is Z-score > +2, withhold the next dose and reassess the serum phosphate level in 2 weeks. Once serum phosphate is in target range or less than Z-score –1, treatment may be restarted at 0.2 mg/kg less than prior administered dose. If more than 2 sequential phosphate measurements are > +2 Z-score range, the patient may be considered for study discontinuation.

6.1.2.1 Dose Limiting Toxicity

A dose limiting toxicity is defined as the occurrence of any of the following:

- A Grade ≥ 3 toxicity that is probably or possibly related to the investigational product, defined according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- A confirmed serum phosphate level of ≥ 8 mg/dL for pediatric subjects, or ≥ 6.5 mg/dL for adult subjects (defined as hyperphosphatemia) at any time after dosing.

  If a subject experiences a dose limiting toxicity, the planned dosing for that subject will be evaluated by the Investigators. The outcome of this investigation will determine the subject's continuation or withdrawal from the study, as described in the Section Discontinuation of Study Intervention.

The following laboratory abnormalities will necessitate discontinuation of study drug:

- Documented decline in estimated glomerular filtration rate (eGFR) to <30 mL/min/1.73m2 for pediatric patients, or <30 mL/min for adults

6.1.2.2 Dose Modifications

See the Section **6.1.2**, **Dosing and Administration** for dose modification criteria in response to serum phosphate.

6.1.2.3 Drug Administration

For the initial NIH visit, the NIH pharmacy will dispense the burosumab vial(s) directly to the NIH Patient Care Unit responsible for administering the drug. Subjects and/or caregivers will receive injection teaching from a study team member at the initial NIH visit, which will include verbal and written instructions (see Appendix 2). The subject and/or caregiver's proficiency will be assessed by observation of injection of normal saline into a teaching model device. All home injections will be supervised by the study team via telehealth appointment. A study team member will travel to home sites for the second dose to observe patient home administration and verify proficiency and injection teaching and inspection of burosumab storage and handling at home.

Subjects will receive an additional proficiency check and injection teaching at Week 24. If in the opinion of the PI, caregivers are not suitably proficient to administer injections, a study team member who is a licensed medical professional will travel to subject's home location and administer the medication to prevent interruption of therapy. Subjects may also return to NIH for injections. Federal, state and local policies, procedures and regulations dictate practice related to the safe transportation of the medication and handling of waste in/from the subjects' homes. For

subjects receiving home injections, the NIH Pharmacy will ship the study drug and supplies to the subject's home. The drug will be shipped on ice, and subjects will be instructed to store the drug in a refrigerator until time of use. Subjects will also be instructed on safe disposal of needles after use.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

The site research pharmacist or delegated personnel will maintain an accurate record of the receipt of the burosumab (shipped by Kyowa Kirin), including the date and quantity received. In addition, an accurate drug disposition record will be kept that specifies the amount to be administered to each participant, the date of dispensation, and any amount returned. Subjects will be instructed to return any unused drug during the final study visit. This inventory record must be available for inspection at any time. The NIH pharmacy in collaboration with the PI is responsible for keeping accurate records of the amount of drug dispensed, returned and remaining at the conclusion of the study.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Burosumab will be provided as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution. Single-dose vials will be dispensed in 10 mg/mL, 20 mg/mL, and/or 30 mg/mL concentrations. Burosumab is manufactured by Kyowa Kirin, Inc, Bedminster, NJ, U.S. License No. 2077

6.2.3 Product Storage and Stability

Kyowa Kirin, Inc will provide drug supplies to the study center. Burosumab vials will be stored under refrigerated conditions at 36°F to 46°F (2°C to 8°C). Reuse of vials is not permitted after the seal is broken. The expiration date is labeled and use of burosumab after the expiration date is not permitted.

6.2.4 Preparation

Not applicable

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable

6.4 Study Intervention Compliance

Outpatient burosumab administration will be directly observed and documented by a member of the study team via telehealth assessment. Participants will return any unused burosumab vials at their next designated NIH visit, which will be reviewed for accountability and an estimate of compliance.

6.5 Concomitant Therapy

At screening and enrollment, the study staff at NIH will question each subject specifically on the use of all concomitant medications and record the medication, dosage, and duration of use in the appropriate CRF. In general, upon admission and throughout the study, site staff will monitor, record, and administer all concomitant medications during the NIH stay. Investigators may

prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

All subjects who are receiving conventional therapy at screening will be instructed to stop taking pharmacologic vitamin D metabolites or analogs (e.g., calcitriol, alfacalcidiol, doxercalciferol, and paricalcitol) and oral phosphate supplements on Week -2. These medications will remain prohibited throughout the conduct of the study. Any subject who resumes or requires the use of any of these medications will be discontinued from the study. Patient safety during this washout time period will be monitored and adverse events will be reported as described in Section **10.5**.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Study Intervention Discontinuation

Discontinuation from burosumab does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment (including, but not limited to changes from baseline), the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation for subjects who prematurely discontinue burosumab will include the following, as described in detail in Section **10.8**:

- NIH lab tests
- Physical Medicine and Rehabilitation evaluation
- Administration of questionnaires for patient-reported outcomes
- Activities of Daily Living questionnaires

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Completion of study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion
- Positive pregnancy test
- Subject unable to receive burosumab for 12 weeks

7.2 Participant Discontinuation/Withdrawal from the Study

If subjects discontinue participation or are terminated early from the study, they should be converted back to their outpatient conventional therapy regimen of oral phosphate and active vitamin D analogs. Subjects will be instructed to undergo outpatient laboratory testing of their blood phosphate within 1-7 days of discontinuing study medication and to have those results sent to NIH investigators for review. A telephone contact should be arranged for the investigative staff to review the lab results and advise on optimizing their outpatient clinical management.

All subjects who received burosumab and terminated early from the study, regardless of cause, should undergo a 30-day (± 7 days) follow-up telephone call after the last dose of burosumab. The reason for early termination from the study will be reflected in the CRF. If a subject terminates early from the study because of an AE, the PI/study staff must record the AE as the reason for discontinuation.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she missed at least 3 documented phone calls, followed by no response after a registered letter to the participant's last known mailing address is received.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening Procedures

Screening for this protocol will be done under protocol 98-D-0145 (NCT00001727).

Screening process:

New subjects participating in protocol 98-D-0145 will have an evaluation as part of that study to confirm the diagnosis of FD/MAS, obtain routine and bone-specific blood work (per that protocol) and to characterize the extent of disease. Subjects diagnosed with FD/MAS will be offered enrollment into the burosumab protocol.

Subjects already enrolled into protocol 98-D-0145 with confirmed FD/MAS and hypophosphatemia will be offered enrollment into the burosumab protocol. If the subject is interested in enrollment and hasn't had a recent visit for the 98-D-0145 protocol, the subject will be asked to come back to NIH for an evaluation to obtain an updated history, physical exam and blood work as part of protocol 98-D-0145.

Identifiable subject data will be shared between protocol 98-D-0145 and this study. The data captured on 98-D-0145 that will be shared and used to demonstrate eligibility for this study includes the diagnosis of FD/MAS, results of laboratory, imaging and other measures that define and characterize the scope of the disease. The outcome results of the following procedures/tests from the protocol 98-D-0145 will be evaluated as screening tests to determine eligibility into the burosumab protocol: imaging studies, serum phosphate, and serum FGF23 levels.

Subjects who have lab work returned that fulfill all eligibility and no exclusion criteria will be scheduled for an NIH visit. Visits will be conducted in the NIH Clinical Center in the inpatient, day hospital, or clinic settings as appropriate. If the subject is eligible for the burosumab protocol based on the screening tests performed within protocol 98-D-0145 and is interested, the protocol will be explained to them and the consent process implemented. If willing to participate in the study, the subject or LAR will be asked to sign informed consent. Consent for participation in the burosumab protocol will be obtained before any study specific procedures are performed. If a subject declines to participate in the burosumab protocol, they have the option to remain in protocol 98-D-0145.

8.2 Study Evaluations & Procedures

All subjects who are currently receiving active vitamin D analogs and oral phosphate supplements will be asked to discontinue these medications at week -2 prior to baseline visit.

The following procedures and imaging assessments will occur according to Section **1.3**, **Schedule of Activities (SoA)** in order to support determination of efficacy, as per the primary and secondary objectives:

Serum phosphate concentrations: Samples will be collected and tests performed at the NIH Clinical Center. Between NIH visits, samples will be collected and evaluated at outpatient laboratories near subjects' homes.

Physical Medicine and Rehabilitation evaluation: 9-minute walk/run test (ambulatory patients), range-of-motion testing, activity of daily living assessment, and manual muscle testing. Standardized and validated measures of functional status used routinely by the Clinical Center Rehabilitation Department will be obtained.

Administration of questionnaires for patient-reported outcomes

Patients will be asked to complete questionnaires to assess change from baseline to 48 weeks in patient reported outcomes measures. Adults will be asked to complete the patient-reported 36-item Short Form Health Survey (SF-36). Pediatric patients age 5-18 will be asked to complete the SF-10™ Child Health Survey. The following PROMIS questionnaires will be administered:

- PROMIS Pain Intensity: Pediatric and Parent Proxy version 1.0 (children), Adult version 2.0 (adults)
- PROMIS Pain Interference: Pediatric and Parent Proxy v 2.0 (children), Adult v 1.1 (adults)
- PROMIS Mobility: Pediatric and Parent Proxy version 2.0 (children), Adult Mobility Lower Extremity v 1.0 (adults)
- PROMIS Fatigue: Pediatric and Parent Proxy v 2.0 (children), Adult FACIT 13a v1.0 (adults)

Pediatric questionnaires will be administered to subjects age 8-17 years, and Parent Proxy questionnaires will be administered to caregivers of subjects age 7 years and younger. Parent Proxy questionnaires may be administered to caregivers of subjects age 8 years and older at the discretion of the PI if considered developmentally appropriate.

8.2.1 Activities of Daily Living Questions

Patients and/or caregivers will be asked during the Baseline clinical visit to provide a list of 3 activities of daily living that are affected by FD skeletal features at home or school/work (e.g., mobility, climbing stairs, dressing, playing with peers, catching a bus, etc) and to estimate the extent of impact upon their activity level (see Appendices). These activities will then be reassessed at Week 24 and Week 48 for the level of change since Baseline on the extent of the impact upon these 3 activities.

8.2.2 Biospecimen Evaluations

NIH lab tests: The following laboratory evaluations will be obtained and performed at the NIH Clinical Center according to Section **1.3**, **Schedule of Activities (SoA)**. For some tests, the NIH Clinical Center may contract and send samples to specialized outside laboratory facilities.

- Serum sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, albumin, total protein, calcium, magnesium, phosphate, parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcin, procollagen type 1 N-terminal propeptide, Beta-CrossLaps C-telopeptides, intact FGF23, C-terminal FGF23, and TmP/GFR.
- 24-hour urinary calcium, creatinine, phosphate.

Outpatient lab tests: The following laboratory evaluations will be obtained at outside laboratory facilities close to subjects' homes:

- Serum calcium, phosphate, creatinine, alkaline phosphatase.
- Random urine calcium, creatinine, phosphate.

The following laboratory evaluations will be performed at BioAgilytix Labs, LLC and Toray Research Center, Inc, specialty lab services that have been previously contracted by Ultragenyx:

- Anti-burosumab antibodies, and burosumab concentration. If anti-burosumab antibodies are detected, these samples will subsequently be evaluated for the presence of neutralizing antibodies.

Clinical Safety lab tests:

- Serum sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase
- Random urine calcium, creatinine, phosphate
- Anti-burosumab antibodies, neutralizing antibodies (in samples with detectable anti-burosumab antibodies), and burosumab concentration

The total amount of blood to be drawn over this study is 203 mL. The maximum amount drawn over an 8-week period is 67.5 mL. This is below the maximum safety threshold for adults of 550 mL over an 8-week period determined by the NIH Clinical Center. Based on the minimum weight requirement for this study (7.5 kg), this corresponds to a maximum potential blood draw volume of 9 mL/kg over an 8-week period for pediatric patients. This is below the maximum safety threshold of 9.5 mL/kg over an 8-week period determined by the NIH Clinical Center.

The maximum amount of blood drawn in a single day will not exceed 5 mL/kg for pediatric subjects. Bone tissue from a minimally invasive biopsy pre- and post-treatment will be obtained in adult subjects at the NIH. Tissue will be limited to 1-4 cores from standard bone biopsy needles.

8.2.3 Correlative Studies for Research/Pharmacokinetic Studies

Not applicable

8.2.4 Samples for Genetic/Genomic Analysis

8.2.4.1 Description of the scope of genetic/genomic analysis

Not applicable, genetic/genomic analysis will not be performed in this study.

8.2.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

All subject data in this clinical trial will be anonymized using the same system, each subject's identity will remain anonymous in the clinical trial database.

The clinical trial database, which may be shared with appropriate regulatory agencies, in addition to access from the pharmaceutical collaborators and investigators, will contain clinical/demographic data on subject's age, ethnicity, sex, diagnosis, treatment, response to treatment, adverse events as per the standards of human clinical research, however, all the data will be anonymized without any link to individual identifying information.

8.2.4.3 Management of Results

The results of all clinical documentation and laboratory data performed at the NIH Clinical Center will be available to subjects through the NIH online patient portal and through NIH medical records on request. Clinical documentation and laboratory data will be shared with subjects' home clinicians on request. Subjects will be encouraged to inform their home clinicians about participation in the study, and the Investigators will maintain close communication with home clinicians regarding any clinically relevant issues.

8.2.4.4 Genetic counseling

Not applicable, genetic counseling will not be performed in this study.

8.3 Safety and Other Assessments

8.3.1 Physical Examination

At the times detailed in the Section **1.3**, **Schedule of Activities (SoA)**, subjects will undergo a complete physical examination (PE), which is to be completed by a physician or an appropriately trained health professional. Any abnormal physical examination finding that is deemed clinically important (i.e., is associated with symptoms and/or requires medical intervention) and is changed from baseline will be recorded as an AE as described in Section **8.4**.

8.3.2 Vital Signs

Vital signs will be assessed in accordance with times and details indicated in the Section **1.3**, **Schedule of Activities (SoA)**. Any abnormal vital sign that is deemed clinically significant (i.e.,

is associated with symptoms and/or requires medical intervention) will be recorded as an AE as described in Section **8.4**.

8.3.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the times detailed in the Section **1.3**, **Schedule of Activities (SoA)**. Samples will be collected for evaluation of anti-burosumab antibodies at NIH visits according to the Section **1.3**, **Schedule of Activities (SoA)**. Samples will be sent to BioAgilytix Labs, LLC and Toray Research Center, Inc, specialty lab services that have been previously contracted by Kyowa Kirin to evaluate for the development of anti-burosumab antibodies, burosumab concentration, and neutralizing antibodies, respectively. At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page and defined according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Samples will be collected, processed, and stored according to the instructions provided in the Laboratory Manual.

The investigator or qualified sub-investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (i.e., is associated with signs and symptoms and/or requires medical intervention) will be recorded as an AE as described in Section **8.4**.

8.3.4 ^{18}F-sodium fluoride PET/CT bone scan

Because FD is a benign neoplastic process, ^{18}F-NaF PET/CT scans will be performed at NIH visits on Weeks 0 and 48 to evaluate for any potential deleterious effects of burosumab on FD lesion activity. Subjects will receive intravenous 18F-Sodium Fluoride via a placed catheter. Images will be obtained 1 hour after injection and will last approximately 1 ½ hours. Only subjects who can hold still without requiring sedation will undergo scanning.

8.3.5 Renal Ultrasound

Renal ultrasounds to assess for nephrocalcinosis will be performed at NIH visits on Weeks 0 and 48.

8.3.6 Skeletal Survey

Plain film x-rays of the arms, legs, pelvis, ribs, and lateral spine will be obtained at Weeks 0 and 48 to evaluate for the development or progression of skeletal deformities, and to assess for rachitic metaphyseal changes in growing children.

8.3.7 Bone Biopsy

Percutaneous core needle bone biopsies will be performed in adult subjects with capacity to consent at Weeks 0 and 48. Because FD is a benign neoplastic process, biopsies will be performed to evaluate for any potential deleterious effects of burosumab on FD tissue. This will include evaluation of tissue histology for changes in cell proliferation and neoplastic bone content. The first biopsy will be performed prior to burosumab therapy (baseline) and the second at the same site following completion of therapy (post treatment). The biopsies will be performed

by a licensed, credentialed practitioner in Interventional Radiology or the operating room of the NIH Clinical Center under local anesthesia with sedation. The biopsies will be performed from areas containing FD. The PI and the surgeon will jointly determine which sites are to be biopsied. All subjects will be evaluated by an anesthesiologist, who will determine the level of anesthesia needed based on clinical evaluation of the patient and planned procedure. Only biopsies judged to be minimally invasive (i.e. percutaneous procedures that allow bone to be removed via a core needle) will be performed. A bone biopsy will not be done if there is no site containing FD that allows a minimally invasive procedure with minimal risk of fracture.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32 (a)). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a pre-existing condition is considered an AE.

Any abnormal laboratory test results (hematology, clinical chemistry, or urine) or other safety assessments (e.g., vital sign measurements), including those that worsen from Screening/baseline that are felt to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs. Elective surgeries to correct or prevent skeletal deformities are considered standard treatment for FD [19], and will not be reported as AE's. These events will be recorded as part of the medical history at each NIH visit, according to the Schedule of Activities.

8.4.2 Definition of Serious Adverse Events (SAE)

A serious adverse event (SAE) is an AE that meets any of the following criteria in the view of either the Investigator, Ultragenyx, or Kyowa Kirin:

- Death
- Life-threatening
  - A life-threatening AE is an event that places the patient or subject at immediate risk of death. It does not include events that if it had occurred in a more serious or severe form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.
- Inpatient hospitalization or prolongation of existing hospitalization
  - Hospitalization is defined as a full admission to hospital for a period of 24 hours or longer for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization. Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Preplanned or elective procedures prior to study enrollment (e.g., outpatient surgery)
- Protocol procedures

– Hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

– AEs requiring hospitalization should be considered SAEs. Hospitalization planned prior to study enrollment (eg, for elective surgery or routine clinical procedures) that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to seriousness criteria described above.

- Disability/Incapacity
  – An AE is disabling or incapacitating if it results in substantial and/or permanent disruption of the subject’s ability to carry out normal life functions.
- Congenital anomaly/birth defect not present at screening
- Important Medical Events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the criteria listed in the definition. Examples of such events are:
  – Intensive treatment in an emergency room or at home for allergic bronchospasm
  – Blood dyscrasias that do not result in inpatient hospitalization
  – Development of drug dependency or drug abuse

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

The Investigators will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the participant’s CRF. The severity of all AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.4.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the subject based on temporal relationship and their clinical judgment and the information provided in the Reference Safety Information. Treatment-

related conditions must be distinguished from disease-related conditions. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related**: The available evidence suggests there is a reasonable possibility that the study drug caused the adverse. For example, a temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the subject's clinical state, concurrent disease or concomitant therapies. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
- **Not related**: The available evidence suggests an unrelated AE is one for which there is not a reasonable possibility that the drug caused the AE. The adverse event is most likely related to factors other than the administration of the study drug. Such other factors may include the underlying disease state, comorbidities, an intercurrent illness, concomitant medication(s) or procedures.

A causality assessment should include, for example, assessment of temporal relationship, physiologic plausibility, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, and presence (or absence) of a more likely cause. The PI may change the causality assessment at any time based on new accumulated information.

Note: The Investigator's assessment of causality for individual AEs is part of the study documentation process and will be recorded in the CRF and SAE form, if applicable. AEs recorded without the Investigator's assessment of the relationship to study drug will be followed up until causality is assigned.

8.4.3.3 Expectedness

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed or is not consistent with the risk information described in the general investigational plan. The sponsor will evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction. The suspected adverse reaction will then be reported expeditiously in an IND safety report if it also meets the definitions of serious and unexpected (21 CFR 312.32(c)(1)(i)).

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline, recorded as patient medical history, and not recorded as an AE. However, if the subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 4 weeks after the last burosumab dose. Events will be followed for outcome information until resolution or stabilization.

8.4.5 Adverse Event Reporting

Any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment, treatment, or posttreatment period are to be considered AEs (and SAEs if appropriate), and consequently recorded and reported as such.

Subjects are to be queried regarding any AEs or SAEs at the time of each vital sign assessment, as well as at each visit, according to the Schedule of Activities (Section 1.3). Subjects will be asked to volunteer information with a nonleading question such as, "How do you feel?" Study center personnel will then record all pertinent information in the subject's CRF.

All AEs and SAEs reported by the subject (or subject's legal representative) or observed or otherwise identified by the investigator (or other study center personnel) at a defined study visit or during any communication with the subject (or subject's legal representative) occurring outside a defined study visit (from the time the subject signs the ICF to 30 ± 7 days after the last dose of burosumab) must be documented.

All AEs must be recorded on the appropriate AE reporting page of the subject's CRF whether or not they are considered causally related to the burosumab.

For every AE, the investigator must:

- Provide an assessment of the severity, causal relationship to burosumab, and seriousness of the event (i.e., whether it is a SAE)
- Document all actions taken with regard to burosumab
- Detail any other treatment measures taken for the AE
- Document resolution of the AE (with or without sequelae); ongoing; or lost to follow-up.

8.4.6 Serious Adverse Event Reporting

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of all adverse events and shall report the results of such evaluation to the NIH Institutional Review Board (IRB) as per Policy 801.

All SAEs will be reported to the NIDCR Office of the Clinical Director within 7 days of investigator awareness. The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any

other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.4.7 Reporting of Serious Adverse Events to Kyowa Kirin Pharmacovigilance

In addition to any IND reporting requirements to the FDA, all serious adverse events (regardless of causality) must be reported to Kyowa Kirin via a MedWatch 3500A Form or equivalent form within 24 hours of knowledge of the event to: drugsafety@kyowakirin.com.

8.4.8 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem or is new information that might affect the willingness of subjects on the NIH study to enroll or remain in the study will need to be reported to the NIH Intramural IRB.

8.4.9 Events of Special Interest

Not applicable

8.4.10 Reporting of Pregnancy and other Special Situations

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of investigator awareness to Kyowa Kirin at drugsafety@kyowakirin.com. The reporting period for pregnancies is the period from the signing of the ICF until 30 ± 7 days after the last dose of burosumab. Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information. Pregnancies in subjects or partners will be reported to the NIDCR Office of the Clinical Director within 7 days of investigator awareness.

In addition, the following other special situations arising with the use of burosumab whether or not associated with an adverse event must be reported to Kyowa Kirin drugsafety@kyowakirin.com within 24 hours of knowledge of the event:

- Overdose, defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol
- Suspected or confirmed transmission of infectious agents via product (must always itself be considered an SAE)

8.4.11 Safety Updates from Kyowa Kirin to NIH

During the course of the study, Kyowa Kirin will report to the investigator any safety related major issues (issues potentially leading to major impact on the risk-benefit balance of a product/compound and/or on patients' or public health including health hazard or lawsuits, which may require regulatory actions such as product recall, product withdrawals, removal of approved indications, failure to obtain product registration renewal due to safety reason, termination of studies, label changes, or prompt communication to patients and healthcare professionals) or any new information about the study product, that does not fall within the definition of an IND safety report, that poses a significant health or safety risk to study

participants or affects the willingness of study participants to continue their participation in the study.

8.5 Unanticipated Problems

8.5.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related 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
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

This single-arm open-label trial is to gather preliminary information on the effectiveness and safety of burosumab in FD patients. Estimates for the primary and secondary endpoints will be provided.

- Primary Endpoint: The proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 48.
- Secondary Endpoints:
    - Proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 24
    - Adverse events and clinical safety laboratory tests for up to 4 weeks following the final burosumab dose (48 weeks for adults, 50 weeks for children).
    - Proportion of subjects achieving mean serum phosphate levels above the target range (Z-score >+2), as averaged across dose cycles between Baseline and Week 48
    - Change and percent change from baseline to post-baseline visits in serum phosphate, serum 1,25(OH)2D, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR)
    - Change in FD lesion activity using ^{18}F-NaF PET/CT total lesion activity from baseline to 48 weeks

- Change and percent change in serum bone turnover markers, including procollagen 1 N-terminal propeptide (P1NP), beta crosslaps C-telopeptides (CTX), osteocalcin, and bone-specific alkaline phosphatase from baseline to 48 weeks
- Change in FD lesion histology and cell proliferation as assessed by minimally invasive bone biopsies from baseline to 48 weeks (adults with capacity to consent only) from baseline to 48 weeks
- Change from baseline to 48 weeks in muscle strength, range-of-motion, and walking speed (9-minute walk)
- Change from baseline to 48 weeks in patient reported outcomes measures: SF36 (adults), SF10 (children), Brief Pain Inventory (adults and children), Brief Fatigue Inventory (adults and children)

9.2 Sample Size Determination

For the primary endpoint, the proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 48, we will use the Clopper-Pearson exact method to calculate the confidence interval of the proportion. Table 7 below shows different widths achieved assuming different true proportions. Calculations were done using the statistical software PASS (Power Analysis and Sample Size, NCSS). With a sample size of 10, we will be able to provide a two-sided 95% confidence interval (CI) with a width of no more than 0.44 when the true proportion is 0.9 (which we expect to be most likely). A total of 15 subjects will be recruited to ensure that 10 of them will have at least 48 weeks of follow-up time.

Table 7. Confidence interval widths achieved assuming different true proportions (N=10)

True proportion	0.5	0.6	0.7	0.8	0.9	0.95
CI width	0.63	0.62	0.59	0.53	0.44	0.38
95% CI	(0.19, 0.81)	(0.26, 0.88)	(0.35, 0.93)	(0.44, 0.97)	(0.55, 1)	(0.62, 1)

9.3 Populations for Analyses

- Safety Analysis Dataset: This will include participants who took at least one dose of burosumab.
- Efficacy Analysis Dataset: This will include all participants who received at least one dose of burosumab and have sufficient post-baseline assessment data to enable analyses of study endpoints. For the proportions evaluated at week 48 (the primary endpoint and some secondary endpoints), subjects who have completed 48 weeks of therapy and returned for the week 48 assessment will be included in the analysis.

9.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with burosumab.

9.3.2 Evaluable for objective response

Not applicable.

9.3.3 Evaluable Non-Target Disease Response

Not applicable.

9.4 Statistical Analyses

9.4.1 General Approach

We will report summary statistics such as means, standard deviation, median and interquartile range for continuous variables, and frequencies and proportions for categorical variables. The strength of statistical evidence throughout the study will be assessed using point estimates, confidence intervals, together with *p* values in drawing conclusions. For this small disease population trial, we will make all efforts to minimize the occurrence of missing data. For longitudinal continuous data, linear mixed effects models will handle the missing data under the assumption that values are missing at random. All analyses will be conducted in SAS (version 9.4, SAS Institute, Cary NC).

9.4.2 Analysis of the Primary Endpoints

The 95% Clopper-Pearson exact confidence interval will be calculated for the proportion of subjects achieving serum phosphate levels within the target range (Z-score -1 to +2) at Week 48. The primary endpoint will be evaluated in the Efficacy Analysis Dataset.

9.4.3 Analysis of the Secondary Endpoint(s)

The 95% Clopper-Pearson exact confidence interval will be provided for the proportions listed in the secondary endpoints. P-values will be calculated. This will be done in the Efficacy Analysis Dataset. If data is missing for categorical outcomes, it will be imputed by either carrying the last observation forward or assuming non-response.

For change from baseline type of secondary endpoints, baseline scores and change over time scores will be summarized by mean, standard deviation, median, and interquartile range. Linear mixed models will be used to analyze the longitudinal change scores collected at multiple post baseline visits if normality assumption is met. The confidence interval will be calculated for change scores at Week 48 based on these models. P-values will be provided as well. All subjects with any data at post baseline visits will be included in these models. For outcomes variables that are collected only at Week 48 post baseline, a 95% confidence interval and the p value from the one-sample t test will be reported for the change score (from baseline to Week 48)

If the normality assumption is violated when fitting the linear mixed effects models to the raw data, other common transformation methods (such as log or square-root transformation will be explored. If no suitable transformation method is found, p-values will be reported by using the exact Wilcoxon signed rank test.

9.4.4 Safety Analyses

Adverse events will be coded as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and each AE will be counted once only for a given participant. The severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. Each AE will be report will include start date, stop date, severity, relationship, expectedness, outcome, and duration. Summaries of AEs, AEs leading to premature discontinuation from the study intervention, treatment-related AEs, and

serious treatment-emergent AEs will be presented in a separate table. Safety analyses will be conducted in the Safety Analysis Dataset.

9.4.5 Baseline Descriptive Statistics

All baseline descriptive characteristics, including demographics, clinical, and laboratory variables will be summarized descriptively for the burosumab treated subjects. Descriptive statistics will include means, standard deviation, median and interquartile range for continuous variables, and frequencies and proportions for categorical variables.

9.4.6 Planned Interim Analyses

There is no planned interim analysis.

9.4.7 Sub-Group Analyses

Not applicable

9.4.8 Tabulation of Individual Participant Data

Not applicable

9.4.9 Exploratory Analyses

Not applicable

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 Informed Consent Process

10.1.1 Consent/Assent Procedures and Documentation

Standard Consent Procedures: The informed consent document will be provided as a physical or electronic document to the subject or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain, either in-person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) the procedures and tests involved in this study, and the associated risks, discomforts, and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the subject/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. When in person, consenting investigators and subject/consent designee, will be located in a private area (e.g., clinic consult room or private inpatient room). When consent is conducted remotely, the subject/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If consent is obtained remotely, subjects and investigators will view individual copies of the approved consent document at their respective locations.

For electronic consent: The study team will confirm with the subject that they are comfortable using the electronic consenting before proceeding with obtaining consent. If not, other methods

will be utilized. When an electronic document with a digital signature is used for the documentation of consent, this study will use the iMedConsent™ platform which is 21 CFR, Part 11 compliant to obtain the required signatures. During the consent process, subjects/LARs and investigators will view the same approved consent document simultaneously in their respective locations. The identity of the subject will be determined by verifying a government issued identification card via the telehealth platform, prior to obtaining the signature. Electronic signature with a timestamp will be provided by required parties through system prompts. Once the completed consent has been saved, it will post to CRIS within a few minutes. All consents completed in iMedConsent™ will post to both the Documents tab and the Consents tab in CRIS. If the research participant has a FollowMyHealth™ account a copy of the completed consent will be posted to their account within two business days. The study team will provide the research participant with a printed copy of the signed document.

Assent Procedures for Minors: Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Assent procedures for minors may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303). Children under the age 7 will not be required to provide assent as they typically do not have the ability to fully understand the nature of research. Verbal assent will be obtained from minor participants age 7-12 who are old enough to understand the nature of the study and its implications but are too young to provide a signature. Written assent will be obtained from minors age 13 years and older whenever possible using a similar procedure as outlined in the above Standard Consent Procedures section. Dissent will be respected in children of all ages. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. If any enrolled subjects reach the age of 18 while enrolled in the trial, they will be contacted to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

Privacy measures as described in the section titled Confidentiality and Privacy will be implemented for all minor in-person and remote consent process. During the remote consent process, minors with their parents/legal guardians and designated study investigators will view individual copies of the approved consent document at their respective locations. The assent process will be documented in the medical record.

Consent Procedures from Parents/Legal Guardians for Minors: Parental permission will be obtained in line with NIH policies regarding child custody.

10.1.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained.

If reconsent is not feasible, we request waiver of informed consent to continue to use data and/or specimens for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116(f)(3):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(3) As the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.
    a. Though the purpose of future studies cannot yet be known, they often involve the correlation of clinical outcomes and clinical interventions with laboratory studies. Such information would be unavailable if access to medical record numbers was unavailable.
(4) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

10.1.3 Consent of Subjects who are, or become, decisionally impaired

For adult subjects, the study team will do a clinical assessment to determine if they have capacity. In situations where the clinical assessment determines that the capacity is in question, an assessment by ACAT (Ability to Consent Assessment Team) will be initiated. In the situation where the subject is known not to have capacity, this study will allow a Legally Authorized Representative (LAR) to sign consent providing the legal paperwork is filed with the Admissions Department per policy (i.e., legal guardianship, durable power of attorney, next of kin, etc.) Oversight for the provisions of protection for adults unable to consent will be informed by the PI. The PI will be responsible for proper implementation of the NIH guidance SOP 403, Research Involving Adults Who Are or May Be Unable to Consent. The legally authorized representative and adult subject will be included in all discussions about the trial and cognitively appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Verbal assent will be obtained from subjects who understand the nature of the study and its implications but are unable to provide a signature. Dissent will be respected in all subjects. The consent process will be documented in the subject's medical record, including the assessment of the subject's ability to provide verbal assent as applicable.

It is possible but unlikely that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the

subjects will remain in the study at the discretion of the PI because of the likelihood of direct benefit associated with study participation. If subjects will remain in the study, a legally authorized representative will be identified consistent with Policy 403 and informed consent obtained as described above.

10.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to subjects, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities, as appropriate. If the study is prematurely terminated or suspended, the PI will promptly inform subjects, the Institutional Review Board (IRB), FDA, and Ultragenyx and Kyowa Kirin and will provide the reason(s) for the termination or suspension. Subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the investigators, IRB, and the FDA.

10.3 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators. This confidentiality is extended to cover testing of biological samples and clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the investigators.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All subjects' records will only be identified by subject number. Subjects' names are not to be transmitted to Ultragenyx and Kyowa Kirin. The investigator will keep a master subject list on which the subject number and the full name, address, and telephone number of each subject are listed. The subject's contact information will be securely stored at NIH Clinical Center for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or the Sponsor requirements.

Data collection will involve the use of a 21 CFR part 11 compliant EDC system, only authorized personnel will have access to the EDC system.

All data collected in the context of this study will be stored in a secure location and evaluated according to regulatory requirements and applicable guidance for electronic records. Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents) will be retained at the NIH Clinical Center, along with adequate source documentation, according to local regulatory requirements and ICH requirements.

The investigator must retain a copy of all records that support CRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, drug dispensing records) for a period of at least 15 years after study completion unless local regulations or NIH Clinical Center policies require a longer retention period.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study center or to a suitably qualified and responsible third party.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.4 Future use of Stored Specimens and Data

A unique subject code, as opposed to personal identifiers, will be used on the CRFs, and in the study database. A subject code log that links the names to identification numbers will be securely maintained at the NIH.

Data collected for this study will be analyzed and transmitted to Ultragenyx and Kyowa Kirin via a secure, encrypted Internet connection and stored on a secure server.

All stored samples are coded and do not have personal identifiers. The codes for identifiers are contained in a subject code log that is maintained in secure research files at the NIH. Samples received for anti-burosumab antibody evaluation by Ultragenyx and Kyowa Kirin from subjects consented to this protocol will be destroyed after use.

With the participant's approval and as approved by the IRB, identified biological samples will be stored at the NIH. These samples could be used to research the causes of FGF23 excess in FD, its complications and other conditions for which individuals with FD are at increased risk, and to improve treatment.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological sample storage may not be possible after the study is completed.

10.5 Safety Oversight

The PI will be responsible for monitoring the data and accruing safety information. Serious adverse event (SAE) monitoring will be supported by an independent medical monitor as determined by the PI in collaboration with the Office of Clinical Director and the Office of Clinical Trials Operations and Management (OCTOM), NIDCR.

The investigator will be responsible for monitoring the data and accruing safety information. The investigator is responsible for monitoring the study progress and study data. The investigator will also maintain responsibility for ensuring the accuracy, completeness, timeliness, and legibility of the data. The investigator and associate investigators are also required to keep accurate and timely records to ensure that the conduct of the study is fully documented. The investigator will review individual study participant data upon each patient encounter. Trends will be discussed with the NIH, Ultragenyx, and Kyowa Kirin study teams to ensure participant safety; study compliance and recruitment goals are met.

This study will be monitored by an NIDCR Division of Intramural Research Data and Safety Monitoring Committee (DSMC). Assessment and recommendations by the DSMC in relation to the study will be made to the NIDCR Clinical Director. The DSMC will include members with expertise in a broad range of areas, including human subjects' protection, biostatistics, clinical trial implementation, pediatrics, and medical bone and mineral metabolism. The PI and NIDCR OCD will receive assessments and recommendations from the DSMC following interval meetings. These assessments and recommendations will be submitted to the IRB at the time of Continuing Review, or as needed if safety concerns arise.

An independent study monitor on contract with NIDCR, NIH will review data and safety parameters of the study. Independent study monitors are qualified by training and experience to monitor the progress and safety of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct. The PI and NIDCR OCD will receive reports from the independent study monitor following interim monitoring visits. The results will be summarized for the DSMC at interval meetings and for the IRB at Continuing Review, or as needed if safety concerns arise.

10.6 Clinical Monitoring

The independent study monitor will routinely monitor the progress of the study by conducting on-site or virtual/remote visits thereafter. The monitor will also be able to review query statuses remotely, which may warrant more frequent communication with the NIH investigator and study staff. The investigator will make available to the study monitor the source documents, the signed consent forms, and all other study-related documents. The investigator will be responsible for reviewing eCRFs, resolving data queries generated by the study monitor via the system, providing missing or corrected data, approving all changes performed on the data, and endorsing the participants data within the EDC system.

Following written Standard Operating Procedures (SOPs), the clinical trial monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). Additional details of

monitoring (including Clinical, Safety, Data, Quality, and overall Trial monitoring) will be available in designated monitoring plan documents.

Additional details of the processes and procedures for clinical study research site monitoring will be documented in the clinical monitoring plan prepared by the NIDCR Clinical Research Operations and Management Support (CROMS) contractors, in collaboration with the OCD and OCTOM

10.7 Quality Assurance and Quality Control

Internal quality assurance activities will include study team meetings, where the protocol team will review any new consents, unanticipated problems, and adverse events, and quarterly reporting of quality assurance/quality improvement activities to the NIDCR Office of the Clinical Director Clinical Operations Manager and NIDCR-OCTOM.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

10.8 Data Handling and Record Keeping

10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies or electronic copies of the study visit and outpatient lab results will be provided for use as source document worksheets for recording data for each subject enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into electronic data capture system that is 21 CFR Part 11-compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered into the electronic data capture system directly from the source documents.

10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, and as per the NIH Intramural Records Retention Schedule.

10.9 Protocol Deviations and Non-Compliance

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801.

10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any change, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

10.10 Publication and Data Sharing Policy

10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study is conducted in collaboration with Ultragenyx, Inc and Kyowa Kirin and publications of data from this study will be in alignment with the NIH, Kyowa Kirin, and Ultragenyx Inc Clinical Trials Agreement.

National Institutes of Health (NIH) Public Access Policy ensures that the public has access to the published results. NIH funded research requires that NIH scientists submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Results from this trial will be made available 12 months after the primary study completion date. Results from this study may also be shared at scientific conferences. Investigators from NIH and Ultragenyx and Kyowa Kirin will consider requests from qualified researchers for access to clinical data.

10.10.2 Genomic Data Sharing Compliance

Not applicable

10.11 Collaborative Agreements

10.11.1 Agreement Type

The NIDCR investigator(s), Kyowa Kirin, and Ultragenyx will sign the protocol and Clinical Trials Agreement to confirm agreement. The investigator(s) will not implement any amendment (deviation or changes of the protocol) without agreement by the Ultragenyx and Kyowa Kirin and IRB approval, except where necessary to eliminate immediate hazard(s) to subjects, or when change(s) involve only logistical or administrative aspects of the study. Any logistical or

administrative changes will be done in agreement with Ultragenyx and Kyowa Kirin and documented within 30 days on implementation.

10.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH, NIDCR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 Abbreviations

AE	Adverse Event
CC	Clinical Center
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Forms
FD	Fibrous dysplasia
FDA	Food and Drug Administration
FGF23	Fibroblast growth factor 23
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MAS	McCune-Albright syndrome
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

TIO	Tumor-Induced Osteomalacia
UP	Unanticipated Problem
US	United States
XLH	X-linked hypophosphatemia

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