CRYSVITA®
burosumab-twza

Injection for subcutaneous use

UltraCare™

UPON ENROLLMENT, AN ULTRACARE GUIDE WILL:

- Partner with and remain dedicated to your patient throughout the treatment journey
- Contact the patient or caregiver to review insurance coverage and support programs
- Assess the patient's eligibility for available financial assistance programs

GETTING STARTED: STEPS FOR SUCCESSFUL ENROLLMENT IN ULTRACARE

Below are the most critical steps for ensuring complete and timely enrollment in UltraCare so your patient can benefit fully from the program's suite of support services.

1 SELECT PREFERRED PATIENT COMMUNICATION METHOD

Ask your patient and/or caregiver about how they will prefer to communicate with their UltraCare Guide and the best time to contact them

2 VERIFY THE PATIENT'S INSURANCE

- Provide a copy of the front and back of all of the patient's **medical** and **prescription** insurance cards
- Indicate if the patient does not have health insurance (medical and pharmacy)

3 OBTAIN PATIENT CONSENT[a]

- The patient signature is required to allow third parties to share protected health information with Ultragenyx and to facilitate:
  - Benefits investigation
  - Prior authorization
  - Specialty pharmacy provider prescription transfer
  - Home infusion agency
  - Additional services provided by UltraCare, including insurance coverage, financial assistance, and patient support programs

4 SELECT SITE OF CARE (SOC)

- Choose your preferred SOC for the administration of the medication:
  - Home injection
  - Office administration
  - Outpatient hospital setting

5 SPECIFY PRESCRIPTION

- Patient weight (kg) × recommended starting dose = total initial dose (rounded to nearest 10 mg)
  - Pediatric: Recommended starting dose is 0.8 mg/kg of body weight (round to nearest 10 mg and max dose is 90 mg) every 2 weeks
  - Adult: Recommended starting dose is 1 mg/kg of body weight (round to the nearest 10 mg and max dose is 90 mg) every 4 weeks
- Ensure the physician provides a wet signature and date, which are necessary to process the prescription

[a] If the patient wants to opt out of the patient consent section, inform the UltraCare team verbally on the phone or in writing to the address on the next page.

INDICATION

CRYSVITA® (burosumab-twza) is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Do not use CRYSVITA with oral phosphate and active vitamin D analogs.
- Do not initiate CRYSVITA if serum phosphorus is within or above the normal range for age.
- CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease.

WARNINGS AND PRECAUTIONS

Hypersensitivity

- Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment.

Hyperphosphatemia and Risk of Nephrocalcinosis

- For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels.

Injection Site Reactions

- Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment.

ADVERSE REACTIONS

Pediatric Patients

- The most common adverse reactions (more than 10%) in pediatric XLH patients are: headache, injection site reaction, vomiting, pyrexia, pain in extremity, vitamin D decreased, rash, toothache, myalgia, tooth abscess, and dizziness.

Adult Patients

- The most common adverse reactions (more than 5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, blood phosphorus increased.
- Spinal stenosis is prevalent in adults with XLH and spinal cord compression has been reported. It is unknown if CRYSVITA therapy exacerbates spinal stenosis or spinal cord compression.

USE IN SPECIFIC POPULATIONS

- There are no available data on CRYSVITA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Serum phosphorus levels should be monitored throughout pregnancy. Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-888-756-8657.
- There is no information regarding the presence of CRYSVITA in human milk, or the effects of CRYSVITA on milk production or the breastfed infant.

PATIENT COUNSELING INFORMATION

- Instruct patients to contact their physician if hypersensitivity reactions, injection site reactions, and restless leg syndrome induction or worsening of symptoms occur.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ultragenyx at 1-888-756-8657.

Please see accompanying full Prescribing Information for a complete discussion of the risks associated with CRYSVITA.

ultragenyx pharmaceutical

CRYSVITA®
burosumab-twza

UltraCare™

Toll-free Line: 888-756-8657 | **Fax:** 415-723-7474 | http://www.ultracaresupport.com
Email: UltraCare@ultragenyx.com | **Address:** 5000 Marina Boulevard, Brisbane, CA 94005

Patient Start Form

1 PATIENT INFORMATION: Be sure to choose your preferred contact method

First, Middle, Last Name _____
Gender ☐ Female ☐ Male
DOB (MM/DD/YYYY) _____ Last 4 Digits of Social Security # _____
Street Address _____
City _____ State _____ ZIP Code _____
Home Phone (____) _____ Work Phone (____) _____
Mobile Phone (____) _____ Best Time to Contact _____
Preferred Method of Contact ☐ Home ☐ Work ☐ Mobile ☐ Text ☐ Email
Preferred Language _____
Email _____
Caregiver Name (First and Last) _____
Relationship to Patient _____ Caregiver Phone (____) _____

2 INSURANCE INFORMATION: Be sure to provide copies of patient's MEDICAL and PRESCRIPTION cards

☐ Patient does not have health insurance ☐ Provide copies of all medical and prescription cards—front and back (primary and secondary, supplemental coverage) [No need to populate this section]

PRIMARY INSURANCE INFORMATION

Insurance Name_____ Insurance Phone (____) _____
Policyholder Name _____ Relationship to Patient _____
Group ID _____ Employer Name _____
Member ID _____

SECONDARY INSURANCE INFORMATION

Insurance Name_____ Insurance Phone (____) _____
Policyholder Name _____ Relationship to Patient _____
Group ID _____ Employer Name _____
Member ID _____

PRESCRIPTION CARD INFORMATION

Prescription Card Name_____ Prescription Phone (____) _____
Policyholder Name _____ Relationship to Patient _____
Member ID _____ BIN #_____
PCN # _____

3 PATIENT CONSENT TO SHARE PROTECTED HEALTH INFORMATION (PHI) AND SIGNATURE

I authorize each of my physicians and pharmacists (including any specialty pharmacies and other health care providers), and each of my health insurers, to disclose my PHI, including but not limited to medical records, information related to my medical condition and treatment, financial, lab values, insurance coverage information, my name, address, telephone number, and last 4 digits of Social Security number to Ultragenyx Pharmaceutical, Inc., and its agents, contractors, and assignees to use and disclose my PHI to enroll me in and contact me about UltraCare Patient Services, provide case management through telephone or electronic communications to assist with adherence to my medication regimen, and work with third parties to provide community resources and referrals. Third-party vendors, such as specialty pharmacies, may receive financial remuneration in exchange for data, product support services, reimbursement services, etc. This authorization expires one year from the date of execution, or one year after the date of my last prescription, whichever is later, unless a shorter period is required by state law. I understand I may refuse to sign this authorization and that my treatment, payment, enrollment, or eligibility for benefits, including my access to therapy, is not conditioned on my signing this authorization. I understand that revoking this authorization will not affect the ability to use and disclose PHI received prior to receipt of notification that I wish to discontinue my participation in the program. I understand I may revoke this authorization at any time verbally or by writing to the address listed at the top of this form. Once authorization has been revoked or expired, I understand my future PHI will not be disclosed. I understand that my PHI will not be used or disclosed for any other purposes, unless permitted by law, than for the purposes stated above. Information disclosed pursuant to this authorization or provided to a third-party may no longer be protected by federal privacy laws.

Patient Signature_____ **Date**_____

Parent/Guardian Signature (if patient is minor)_____ **Date**_____

4 PRESCRIBER INFORMATION: Be sure to choose your preferred site of care (SOC)

☐ Home Injection ☐ Office Administration ☐ Outpatient Hospital Setting
First and Last Name _____
Street Address _____
City _____ State _____ ZIP Code _____
Office Phone (_____) _____ Fax (_____) _____
Office Email _____
Office Contact Name/Title _____
Office Contact Phone (_____) _____
State License # _____ NPI # _____
☐ SOC is different from prescriber's location SOC Name_____
SOC Address _____

The prescriber is to comply with his/her state-specific prescription requirements such as e-prescribing, state-specific prescription form, fax language, etc. Non-compliance with state-specific requirements could result in outreach to the prescriber.

5 CRYSVITA PRESCRIPTION INFORMATION: Select ICD-10 code and type of prescription

Pediatric XLH: 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.
Adult XLH: Starting dose regimen is 1 mg/kg of body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every 4 weeks.
How Supplied: 10 mg/mL single-dose vial, 20 mg/mL single-dose vial, 30 mg/mL single-dose vial.
Subcutaneous injection only.

☐ E83.31 (familial hypophosphatemia) ☐ E83.39 (other disorders of phosphorus metabolism) ☐ Other _____

CRYSVITA Prescription	Weight Date Taken	Patient Weight (in kg)	Initial Dose Prescribed	Total Calculated Dose (Round to the nearest 10 mg and max dose is 90 mg)	Frequency	Days Supply (Limit: 28 days)	Refills
		x	☐ 0.8 mg/kg (Pediatric) ☐ 1 mg/kg (Adult)		☐ Every 2 weeks (Pediatric) ☐ Every 4 weeks (Adult)		

☐ Prescriber: Please check here to authorize ancillary supplies such as needles and syringes as needed to administer the therapy.
☐ RN visit to provide education related to therapy, disease state, and nurse administration of CRYSVITA to include dosing and titration as per prescriber order.

Prescriber Signature _____ Date _____
(No Stamps) Dispense as Written

Prescriber Signature _____ Date _____
(No Stamps) Substitution Permitted

Fast Start Prescription (For AllCarePlus Pharmacy Only)	Weight Date Taken	Patient Weight (in kg)	Initial Dose Prescribed	Total Calculated Dose (Round to the nearest 10 mg and max dose is 90 mg)	Frequency	Days Supply	
		x	☐ 0.8 mg/kg (Pediatric) ☐ 1 mg/kg (Adult)		☐ Every 2 weeks (Pediatric) ☐ Every 4 weeks (Adult)		

Prescriber Signature _____ Date _____
(No Stamps) Dispense as Written

Prescriber Signature _____ Date _____
(No Stamps) Substitution Permitted

Fast Start: For all naive to commercial therapy, patients and product must be sent to the HCP for administration at office, and cost will not be passed along to patient.

Concurrent Medications (Attached List) Special Instructions _____
Special Precautions (eg, Allergies) _____

I authorize Ultragenyx to act on my behalf for the limited purposes of transmitting this prescription to the appropriate pharmacy designated by the patient utilizing their benefit plan. The prescriber is to comply with his/her state-specific prescription requirements such as e-prescribing, state-specific prescription form, fax language, etc.

ultragenyx pharmaceutical

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CRYSVITA safely and effectively. See full prescribing information for CRYSVITA.

CRYSVITA® (burosumab-twza) injection, for subcutaneous use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
CRYSVITA is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
For subcutaneous use only (2)
- Pediatric XLH: Starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. (2.1)
  Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus. (2.1)
- Adult XLH: Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every four weeks. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL in a single-dose vial (3)

----------CONTRAINDICATIONS----------
- Do not use CRYSVITA with oral phosphate and active vitamin D analogs. (4)
- Do not initiate CRYSVITA if serum phosphorus is within or above the normal range for age. (4)
- CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity: Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment. (5.1)
- Hyperphosphatemia and Risk of Nephrocalcinosis: For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels. (5.2)
- Injection Site Reactions: Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment. (5.3, 6.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥25%) in pediatric XLH patients are: headache, injection site reaction, vomiting, pyrexia, pain in extremity, vitamin D decreased. (6.1)

Most common adverse reactions (≥5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, blood phosphorus increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ultragenyx at 1-888-756-8657 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CRYSVITA is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

2 DOSAGE AND ADMINISTRATION

CRYSVITA is administered by subcutaneous injection and should be administered by a healthcare provider.

Discontinue oral phosphate and active vitamin D analogs 1 week prior to initiation of treatment. Fasting serum phosphorus concentration should be below the reference range for age prior to initiation of treatment.

2.1 Pediatric Patients with X-linked Hypophosphatemia (1 to less than 18 years of age)

The recommended starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg.

After initiation of treatment with CRYSVITA, measure fasting serum phosphorus every 4 weeks for the first 3 months of treatment, and thereafter as appropriate. If serum phosphorus is above the lower limit of the reference range for age and below 5 mg/dL, continue treatment with the same dose. Follow dose adjustment schedule below to maintain serum phosphorus within the reference range for age.

Dose Adjustment

Reassess fasting serum phosphorus level 4 weeks after dose adjustment.

Do not adjust CRYSVITA more frequently than every 4 weeks.

Dose Increase: If serum phosphorus is below the reference range for age, the dose may be increased stepwise up to approximately 2 mg/kg, administered every two weeks (maximum dose of 90 mg) according to the dosing schedule shown in Table 1.

Table 1: Pediatric Dose Schedule for Stepwise Dose Increase

Body Weight (kg)	Starting Dose (mg)	First Dose Increase to (mg)	Second Dose Increase to (mg)
10 - 14	10	15	20
15 - 18	10	20	30
19 - 31	20	30	40
32 - 43	30	40	60
44 - 56	40	60	80
57 - 68	50	70	90
69 - 80	60	90	90
81 - 93	70	90	90
94 - 105	80	90	90
106 and greater	90	90	90

Dose Decrease: If serum phosphorus is above 5 mg/dL, withhold the next dose and reassess the serum phosphorus level in 4 weeks. The patient must have serum phosphorus below the reference range for age to reinitiate CRYSVITA. Once serum phosphorus is below the reference range for age, treatment may be restarted according to the dose schedule shown in Table 2. Reassess serum phosphorus level 4 weeks after dose adjustment. If the level remains below the reference range for age after the re-initiation dose, the dose can be adjusted according to Table 1.

Table 2: Pediatric Dose Schedule for Re-Initiation of Therapy

Previous Dose (mg)	Re-Initiation Dose (mg)
10	5
15	10
20	10
30	10
40	20
50	20
60	30
70	30
80	40
90	40

2.2 Adult Patients with X-linked Hypophosphatemia (18 years of age and older)

The recommended dose regimen in adults is 1 mg/kg body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every four weeks.

After initiation of treatment with CRYSVITA, assess fasting serum phosphorus on a monthly basis, measured 2 weeks post-dose, for the first 3 months of treatment, and thereafter as appropriate. If serum phosphorus is within the normal range, continue with the same dose.

Dose Decrease

Reassess fasting serum phosphorus level 2 weeks after dose adjustment.

Do not adjust CRYSVITA more frequently than every 4 weeks.

If serum phosphorus is above the normal range, withhold the next dose and reassess the serum phosphorus level after 4 weeks. The patient must have serum phosphorus below the normal range to be able to reinitiate CRYSVITA. Once serum phosphorus is below the normal range, treatment may be restarted at approximately half the initial starting dose up to a maximum dose of 40 mg every 4 weeks according to the dose schedule shown in Table 3. Reassess serum phosphorus 2 weeks after any change in dose.

Table 3: Adult Dose Schedule for Re-Initiation of Therapy

Previous Dose (mg)	Re-Initiation Dose (mg)
40	20
50	20
60	30
70	30
80 and greater	40

2.3 Missed Dose

If a patient misses a dose, resume CRYSVITA as soon as possible at the prescribed dose.

2.4 General Considerations for Subcutaneous Administration

Injection sites should be rotated with each injection administered at a different anatomic location (upper arms, upper thighs, buttocks, or any quadrant of abdomen) than the previous injection. Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.
The maximum volume of CRYSVITA per injection site is 1.5 mL. If more than 1.5 mL is required on a given dosing day, the total volume of CRYSVITA should be split and administered at two different injection sites. Monitor for signs of reactions.

Visually inspect CRYSVITA for particulate matter and discoloration prior to administration. CRYSVITA is a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution for subcutaneous injection. Do not use if the solution is discolored or cloudy or if the solution contains any particles or foreign particulate matter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL clear to slightly opalescent and colorless to pale brown-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

Do not use CRYSVITA with oral phosphate and active vitamin D analogs.

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients with CRYSVITA. Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment *[see Adverse Reactions (6.1)]*.

5.2 Hyperphosphatemia and Risk of Nephrocalcinosis

Increases in serum phosphorus to above the upper limit of normal may be associated with an increased risk of nephrocalcinosis. For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels *[see Dosage and Administration (2)]*.

5.3 Injection Site Reactions

Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Hyperphosphatemia and Risk of Nephrocalcinosis *[see Warnings and Precautions (5.2)]*
- Injection Site Reactions *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Pediatric Patients with XLH

The safety data described below reflect exposure to CRYSVITA in 65 pediatric XLH patients that included 52 exposed for at least 64 weeks (Study 1) and 13 exposed for at least 40 weeks (Study 2). Overall, pediatric XLH patients have been exposed to CRYSVITA for a mean duration of 108 weeks (min 40.9, max 150.0). CRYSVITA was studied in two pediatric open-label phase 2 studies (Study 1, ages 5 to 12 years, n = 52; Study 2, ages ≥ 1 to < 5 years, n = 13). Overall, the patient population was 1-12 years (mean age 7.4 years), 51% male, and 89% white/Caucasian and diagnosed with XLH. In Study 1, 26 of the patients received CRYSVITA 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 CRYSVITA every 4 weeks. In Study 2, patients received CRYSVITA at a mean dose of 0.89 mg/kg (range 0.8 – 1.2 mg/kg) every 2 weeks at Week 40. Adverse reactions reported in more than 10% of CRYSVITA-treated patients from Studies 1 and 2 are shown in Table 4.

Table 4: Adverse Reactions Reported in More Than 10% of Pediatric Patients Receiving CRYSVITA in Studies 1 and 2

Adverse Reaction	Study 1 (N=52) n (%)	Study 2 (N=13) n (%)	Overall (N=65) n (%)
Headache	38 (73)	1 (8)	39 (60)
Injection site reaction[1]	35 (67)	3 (23)	38 (59)
Vomiting	25 (48)	6 (46)	31 (48)
Pyrexia	23 (44)	8 (62)	31 (48)
Pain in extremity	24 (46)	3 (23)	27 (42)
Vitamin D decreased[2]	19 (37)	2 (15)	21 (32)
Rash[3]	14 (27)	1 (8)	15 (23)
Toothache	12 (23)	2 (15)	14 (22)
Myalgia	9 (17)	1 (8)	10 (15)
Tooth abscess	8 (15)	3 (23)	11 (17)
Dizziness[4]	8 (15)	0 (0)	8 (12)

n = number of patients with an event; N = total number of patients who received at least one dose of CRYSVITA

[1] Injection site reaction includes: injection site reaction, injection site erythema, injection site pruritus, injection site swelling, injection site pain, injection site rash, injection site bruising, injection site discoloration, injection site discomfort, injection site hematoma, injection site hemorrhage, injection site induration, injection site macule, and injection site urticaria

[2] Vitamin D decreased includes: vitamin D deficiency, blood 25-hydroxycholecalciferol decreased, and vitamin D decreased

[3] Rash includes: rash, rash pruritic, rash maculopapular, and rash pustular

[4] Dizziness includes: dizziness, and dizziness exertional

Hypersensitivity Reactions

In pediatric patients, the most frequent potential hypersensitivity events were rash (22%), injection site rash (6%), and urticaria (5%).

Hyperphosphatemia

In pediatric studies, there were no events of hyperphosphatemia reported.

Injection Site Reactions (ISR)

In pediatric studies, approximately 58% of the patients had a local reaction (e.g. injection site urticaria, erythema, rash, swelling, bruising, pain, pruritus, and hematoma) at the site of CRYSVITA 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.

Adverse Reactions in Adult Patients with XLH

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

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

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

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

Hypersensitivity Reactions

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

Hyperphosphatemia

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

Injection Site Reactions (ISR)

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

Restless Leg Syndrome (RLS)

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

Spinal Stenosis

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

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to burosumab-twza in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Pre-existing anti-drug antibodies (ADA) have been detected in up to 10% of patients in clinical studies. ADA was not detected in patients who were antibody negative at the start of treatment. However, the assay used to measure ADA is subject to interference by serum burosumab-twza, possibly resulting in an underestimation of the incidence of antibody formation. Due to the limitation of the assay conditions, the potential clinical impact of antibodies to burosumab-twza is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on CRYSVITA 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 64-fold higher, by AUC, than the human exposure at 1 mg/kg every 4 weeks and were accompanied in the non-XLH monkeys by maternal hyperphosphatemia and placental mineralization (*see Data*). Serum phosphorus levels should be monitored throughout pregnancy *[see Dosage and Administration (2.2)].* Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-888-756-8657.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

In a reproductive toxicity study in pregnant cynomolgus monkeys without XLH, burosumab-twza was administered intravenously once every two weeks from Day 20 of pregnancy to parturition or cesarean section on Day 133, which includes the period of organogenesis, at doses of 1-, 7- and 64-fold human exposure at the adult human dose of 1 mg/kg every 4 weeks. The treatment did not result in teratogenic effects in fetuses or offspring. An increase in late fetal loss, a shortened gestation period, and an increased incidence of preterm births were observed at 64-fold the human exposure at the adult human dose of 1 mg/kg every 4 weeks, concomitant with maternal hyperphosphatemia and placental mineralization. Burosumab-twza was detected in serum from fetuses indicating transport across the placenta. Hyperphosphatemia but no ectopic mineralization was present in fetuses and offspring of dams exposed to 64-fold human exposure at the 1 mg/kg dose every 4 weeks. Burosumab-twza did not affect pre- and postnatal growth including survivability of the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of burosumab-twza in human milk, or the effects of burosumab-twza on milk production or the breastfed infant. Maternal IgG is present in breast milk. However, the effects of local gastrointestinal exposure and limited systemic exposure to burosumab-twza in the breastfed infant are unknown. The lack of clinical data during lactation precludes a clear determination of the risk of CRYSVITA to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CRYSVITA and any potential adverse effects on the breastfed infant from CRYSVITA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of CRYSVITA have been established in pediatric patients 1 year and older. Efficacy in pediatric patients 1 year and older with XLH is based on open label studies of 52 pediatric

patients 5 to 12 years of age with XLH (Study 1), and in 13 pediatric patients 1 to 4 years of age with XLH (Study 2) evaluating serum phosphorus and radiographic findings. Efficacy in adolescents is supported by studies in pediatric patients less than 13 years of age. Dosing in this age group was derived using modeling and simulation of adult and pediatric PK and PD data.

Safety and efficacy for CRYSVITA in pediatric patients with XLH below the age of 1 have not been established *[see Adverse Reactions (6.1) and Clinical Studies (14)].*

8.5 Geriatric Use

Clinical studies of CRYSVITA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There have been no reports of overdose with CRYSVITA. CRYSVITA has been administered in pediatric clinical trials without dose limiting toxicity using doses up to 2 mg/kg body weight with a maximal dose of 90 mg, administered every two weeks. In adult clinical trials, no dose limiting toxicity has been observed using doses up to 1 mg/kg or a maximal total dose of 128 mg every 4 weeks. In non-XLH 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. Adverse effects on bone including reductions in bone mineral density, bone mineralization and bone strength were also observed at exposure greater than human exposure [*see Nonclinical Toxicology (13.2)*].

In case of overdose, it is recommended that serum phosphorus levels, serum calcium levels and renal function be measured immediately and monitored periodically until resolution to normal/baseline levels. In case of hyperphosphatemia, withhold CRYSVITA and initiate appropriate medical treatment.

11 DESCRIPTION

Burosumab-twza is a human immunoglobulin G subclass 1 (IgG1), anti-human fibroblast growth factor 23 (FGF23) antibody produced by recombinant DNA technology using Chinese hamster ovary cells. Burosumab-twza is composed of two heavy chain (γ1-chain) molecules and two light chain (κ-chain) molecules. Each heavy chain has an N-linked carbohydrate moiety at asparagine 297 (Asn297). The molecular weight of burosumab-twza determined by mass spectrometry is approximately 147,000.

CRYSVITA (burosumab-twza) injection for subcutaneous administration is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution in a single-dose vial.

Each 1 mL of solution contains 10 mg, 20 mg or 30 mg of burosumab-twza, L-histidine (1.55 mg), L-methionine (1.49 mg), polysorbate 80 (0.5 mg), D-sorbitol (45.91 mg) in Water for Injection, USP. Hydrochloric acid may be used to adjust to a pH of 6.25.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

X-linked hypophosphatemia is caused by excess fibroblast growth factor 23 (FGF23) which suppresses renal tubular phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D. Burosumab-twza binds to and inhibits the biological activity of FGF23 restoring renal phosphate reabsorption and increasing the serum concentration of 1,25 dihydroxy vitamin D.

12.2 Pharmacodynamics

Following SC administration in XLH patients, higher burosumab-twza concentrations were associated with greater increase of serum phosphorus levels. The increase in serum phosphorus was reversible and returned to baseline with elimination of systemic burosumab-twza.

Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) showed dose-dependent increases from baseline *[see Clinical Studies (14)].*

Elevation in serum total FGF23 was observed after initiation of burosumab-twza treatment, however, the clinical implication is unknown.

12.3 Pharmacokinetics

The following pharmacokinetic parameters were observed in patients with XLH administered the approved recommended starting dosage based on a 70 kg patient, unless otherwise specified.

Burosumab-twza exhibited linear pharmacokinetics following SC injections within the dose range of 0.1 to 1 mg/kg (0.08 to 0.8 times the maximum approved recommended dosage based on a 70 kg patient).

The steady-state trough mean (± SD) concentration of burosumab-twza was 5.8 (± 3.4) mcg/mL in adult patients.

Absorption

The burosumab-twza mean T_{max} values ranged from 8 to 11 days.

Distribution

The apparent volume of distribution of burosumab-twza is 8 L.

Elimination

The apparent clearance is 0.290 L/day. The half-life of burosumab-twza is approximately 19 days.

Metabolism

The exact pathway for burosumab-twza metabolism has not been characterized. Burosumab-twza is expected to be degraded into small peptides and amino acids via catabolic pathways.

Specific Populations

No clinical significant difference in burosumab-twza pharmacokinetics was observed based on age.

The effect of renal or hepatic impairment on the pharmacokinetics of burosumab-twza is unknown.

Pediatric Patients

The steady-state trough concentration was 15.8 (± 9.4) mcg/mL in patients aged 5-12 years, and 11.2 (± 4.6) mcg/mL in patients aged 1-4 years.

Body Weight

Clearance and volume of distribution of burosumab-twza increases with body weight.

Drug Interaction Studies

No drug interaction studies have been conducted with CRYSVITA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of burosumab-twza has not been evaluated in long term animal studies.

Studies have not been performed to evaluate the mutagenic potential of burosumab-twza.

No specific fertility studies have been performed in animals to evaluate the effects of burosumab-twza.

Toxicology studies with burosumab-twza of up to 40 weeks duration in non-XLH cynomolgus monkeys did not show significant adverse effects on female reproductive organs at doses up to 65-fold human exposure at the dose of 1 mg/kg every 4 weeks. In male monkeys, minimal mineralization of the rete testis or seminiferous tubules associated with hyperphosphatemia was observed at 11- to 37-fold human exposure, but semen analysis did not show any adverse effects.

13.2 Animal Toxicology and/or Pharmacology

In rabbits and cynomolgus monkeys, inhibition of FGF23 signaling by burosumab-twza increased serum phosphate and 1,25 dihydroxy vitamin D. Ectopic mineralization in multiple tissues and organs was observed at doses of burosumab-twza that resulted in supra-physiologic serum phosphate levels in the non-XLH animals. In a study in wild type (WT) and hypophosphatemic Hyp mice, a murine model of XLH, ectopic mineralization was markedly less in Hyp mice.

In adult cynomolgus monkeys, burosumab-twza increased bone turnover, mineral content and/or mineral density and cortical thickness at 37- to 65-fold human exposure at the dose of 1 mg/kg every 4 weeks. Adverse effects on bone including reductions in bone mineral density, bone mineralization and bone strength were observed in adult male monkeys at 37- to 47-fold human exposure at the dose of 1 mg/kg every 4 weeks.

In juvenile cynomolgus monkeys, burosumab-twza increased bone turnover, mineral content and/or mineral density and/or cortical thickness at 0.5- to 5-fold clinical pediatric exposure. Bone mineralization was decreased in a male monkey at 5-fold pediatric exposure but there was no effect on bone strength. Burosumab-twza did not affect bone development in juvenile monkeys at doses up to 5-fold pediatric exposure.

14 CLINICAL STUDIES

14.1 Pediatric X-linked Hypophosphatemia

CRYSVITA has been evaluated in 65 pediatric patients with XLH.

Study 1 (NCT 02163577) is a randomized, open-label study in 52 prepubescent XLH patients, 5 to 12 years old, which compared treatment with CRYSVITA administered every 2 weeks versus every 4 weeks. Following an initial 16-week dose titration phase, patients completed 48-weeks of treatment with CRYSVITA every 2 weeks. All 52 patients completed at least 64 weeks on study; no patient discontinued. Burosumab-twza dose was adjusted to target a fasting serum phosphorus concentration of 3.5 to 5.0 mg/dL based on the fasting phosphorus level the day of dosing. Twenty-six of 52 patients received CRYSVITA every two weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 mg/kg (range: 0.3, 1.5) at week 16, 0.98 mg/kg (range: 0.4, 2.0) at week 40 and 1.04 mg/kg (range: 0.4, 2.0) at week 60. The remaining 26 patients received CRYSVITA every four weeks. At study entry, the mean age of patients was 8.5 years and 46% were male. Ninety-six percent had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 7 (2.4) years. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment. Ninety-four percent of patients had radiographic evidence of rickets at baseline.

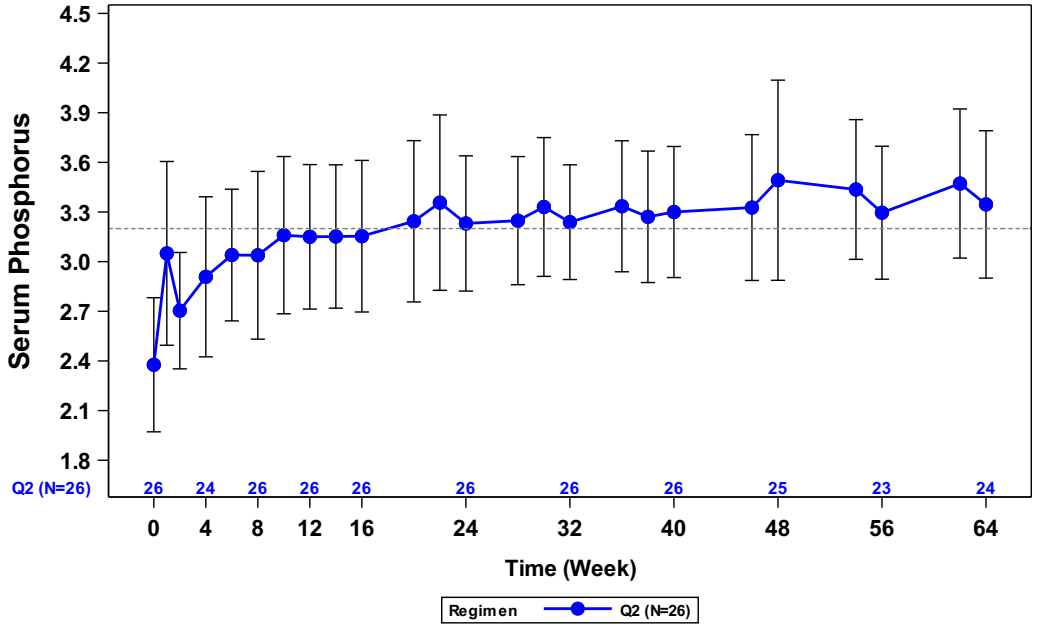
Study 2 (NCT 02750618) is a 64-week open-label study in 13 pediatric XLH patients, 1 to 4 years old. Patients received CRYSVITA at a dose of 0.8 mg/kg every two weeks with titration up to 1.2 mg/kg based on serum phosphorus measurements. All patients completed at least 40 weeks on study; no patients discontinued. At study entry, the mean age of patients was 2.9 years and 69% were male. All patients had radiographic evidence of rickets at baseline and had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 16.9 (13.9) months. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment.

Serum Phosphorus

In Study 1, CRYSVITA increased mean (SD) serum phosphorus levels from 2.4 (0.40) at baseline to 3.3 (0.40) and 3.4 (0.45) mg/dL at week 40 and week 64 in the patients who received CRYSVITA every 2 weeks (Figure 1). The ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) increased in these patients from mean (SD) of 2.2 (0.49) at baseline to 3.3 (0.60) and 3.4 (0.53) mg/dL at week 40 and week 64.

In Study 2, CRYSVITA increased mean (SD) serum phosphorus levels from 2.5 (0.28) mg/dL at baseline to 3.5 (0.49) mg/dL at week 40.

Figure 1: Serum Phosphorus Levels (mg/dL) Over Time in Children 5-12 Years Receiving CRYSVITA Every 2 Weeks in Study 1[a]



a) Serum Phosphorus Level (mg/dL) (Mean ±SD) - Q2W. The dotted line represents the lower limit of normal (3.2 mg/dL) for patients in Study 1.

Radiographic Evaluation of Rickets

Radiographs from 52 CRYSVITA-treated XLH patients in Study 1 and 13 patients in Study 2 were examined to assess XLH-related rickets using the 10-point Thacher Rickets Severity Score (RSS) and the 7-point Radiographic Global Impression of Change (RGI-C). The RSS score is assigned based on images of the wrist and knee from a single timepoint, with higher scores indicating greater rickets severity. The RGI-C score is assigned based on side-by-side comparisons of wrist and knee radiographs from two timepoints, with higher scores indicating greater improvement in radiographic evidence of rickets. A RGI-C score of +2.0 was defined as radiographic evidence of substantial healing.

In Study 1, baseline mean (SD) RSS total score was 1.9 (1.17) in patients receiving CRYSVITA every two weeks. After 40 weeks of treatment with CRYSVITA, mean total RSS decreased from 1.9 to 0.8 (see Table 6). After 40 weeks of treatment with CRYSVITA, the mean RGI-C Global score was +1.7 in patients receiving CRYSVITA every two weeks. Eighteen out of 26 patients achieved an RGI-C score of ≥ +2.0. These findings were maintained at week 64 as shown in Table 6.

In Study 2, baseline mean (SD) total RSS was 2.9 (1.37) in 13 patients. After 40 weeks of treatment with CRYSVITA, mean total RSS decreased from 2.9 to 1.2 and the mean (SE) RGI-C Global score was +2.3 (0.08). All 13 patients achieved a RGI-C global score ≥ +2.0. The mean (SE) lower limb deformity as assessed by RGI-C, using standing long leg radiographs, was +1.3 (0.14) (see Table 6).

Table 6: Rickets Response in Children 1-12 Years Receiving CRYSVITA Every 2 Weeks in Study 1 and Study 2

Endpoint Timepoint	**CRYSVITA Every 2 Weeks**	
	Study 1 (N=26)	**Study 2 (N=13)**
RSS Total Score		
Baseline Mean (SD)	1.9 (1.17)	2.9 (1.37)
LS Mean change from baseline in total score[a] (reduction indicates improvement) with 95% CI		
Week 40	-1.1 (-1.28, -0.85)	-1.7 (-2.03, -1.44)
Week 64	-1.0 (-1.2, -0.79)	
RGI-C Global Score		
LS Mean score[a] (positive indicates healing) with 95% CI		
Week 40	+1.7 (+1.48, +1.84)	+2.3 (+2.16, +2.51)
Week 64	+1. 6 (+1.34, +1.78)	

a) The estimates of LS means and 95% CI (confidence interval) are from the generalized estimation equation model accounting for baseline RSS, visits and regimen and its interaction for Study 1 and from ANCOVA model accounting for age and baseline RSS for Study 2.

Serum Alkaline Phosphatase Activity

For Study 1, mean (SD) serum total alkaline phosphatase activity was 462 (110) U/L at baseline and decreased to 354 (73) U/L at Week 64 (-23%, $p < 0.0001$) in the patients who received CRYSVITA every 2 weeks.

For Study 2, mean (SD) serum total alkaline phosphatase activity was 549 (194) U/L at baseline and decreased to 335 (88) U/L at Week 40 (mean change: -36%).

Growth

In Study 1, CRYSVITA treatment for 64 weeks increased standing mean (SD) height Z score from -1.72 (1.03) at baseline to -1.54 (1.13) in the patients who received CRYSVITA every two weeks (LS mean change of +0.19 (95% CI: 0.09 to 0.29).

14.2 Adult X-linked Hypophosphatemia

Study 3 (NCT 02526160) is a randomized, double-blind, placebo-controlled study in 134 adult XLH patients. The study comprises a 24-week placebo-controlled treatment phase. CRYSVITA was administered at a dose of 1 mg/kg every 4 weeks. At study entry, the mean age of patients was 40 years (range 19 to 66 years) and 35% were male. All patients had skeletal pain associated with XLH/osteomalacia at baseline. The baseline mean (SD) serum phosphorus concentration was below the lower limit of normal at 1.98 (0.31) mg/dL. Oral phosphate and active vitamin D analogs were not allowed during the study. One patient in the CRYSVITA group discontinued treatment.

Study 4 (NCT 02537431) is a 48-week, open-label, single-arm study in 14 adult XLH patients to assess the effects of CRYSVITA on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received 1 mg/kg CRYSVITA every four weeks. At study entry, the mean age of patients was 40 years (range 25 to 52 years) and 43% were male. Oral phosphate and active vitamin D analogs were not allowed during the study.

Serum Phosphorus

In Study 3 at baseline, mean (SD) serum phosphorus was 1.9 (0.32) and 2.0 (0.30) mg/dL in the placebo and CRYSVITA groups respectively. During the initial 24 weeks of treatment, mean (SD) serum phosphorus across the midpoints of dose intervals (2 weeks post dose) was 2.1 (0.30) and 3.2 (0.53) mg/dL in the placebo and CRYSVITA groups, and mean (SD) serum phosphorus across the ends of dose intervals was 2.0 (0.30) and 2.7 (0.45) mg/dL in the placebo and CRYSVITA groups.

A total of 94% of patients treated with CRYSVITA achieved a serum phosphorus level above the lower limit of normal (LLN) compared to 8% in the placebo group through week 24 (Table 7).

Table 7: Proportion of Adult Patients Achieving Mean Serum Phosphorus Levels Above the LLN at the Midpoint of the Dose Interval in Study 3

	Placebo (N = 66)	CRYSVITA (N = 68)
Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	5 (8%)	64 (94%)
95% CI	(3.3, 16.5)	(85.8, 97.7)
p-value[a]		< 0.0001

The 95% CIs are calculated using the Wilson score method.

[a] P-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving the primary endpoint and treatment group, adjusting for randomization stratifications.

At baseline, the mean (SD) ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) was 1.60 (0.37) and 1.68 (0.40) mg/dL in the placebo and CRYSVITA groups respectively. At week 22 (midpoint of a dose interval), mean (SD) TmP/GFR was 1.69 (0.37) and 2.73 (0.75) mg/dL in the placebo and CRYSVITA groups. At week 24 (end of a dose interval), mean (SD) TmP/GFR was 1.73 (0.42) and 2.21 (0.48) mg/dL in the placebo and CRYSVITA groups.

Radiographic Evaluation of Osteomalacia

In Study 3, a skeletal survey was conducted at baseline to identify osteomalacia-related fractures and pseudofractures. Osteomalacia-related fractures are defined as atraumatic lucencies extending across both bone cortices and pseudofractures are defined as atraumatic lucencies extending across one cortex. There were 52% of patients who had either active (unhealed) fractures (12%) or active pseudofractures (47%) at baseline. The active fractures and pseudofractures were predominantly located in the femurs, tibia/fibula, and metatarsals of the feet. Assessment of these active fracture/pseudofracture sites at week 24 demonstrated a higher rate of complete healing in the CRYSVITA group compared to placebo as shown in Table 8. During treatment through week 24, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving CRYSVITA, compared to 8 new abnormalities in 66 patients receiving placebo.

Table 8: Comparison of Fracture Healing with CRYSVITA vs Placebo in Study 3

	Active Fractures		Active Pseudofractures		Total Fractures	
	Placebo n (%)	CRYSVITA n (%)	Placebo n (%)	CRYSVITA n (%)	Placebo n (%)	CRYSVITA n (%)
No. of fractures at baseline	13	14	78	51	91	65
Healed at week 24	0 (0%)	7 (50%)	7 (9%)	21 (41%)	7 (8%)	28 (43%)

Bone Histomorphometry

In Study 4, after 48 weeks of treatment, healing of osteomalacia was observed in ten patients as demonstrated by decreases in Osteoid volume/Bone volume (OV/BV) from a mean (SD) score of 26% (12.4) at baseline to 11% (6.5), a change of -57%. Osteoid thickness (O.Th) declined in eleven patients from a mean (SD) of 17 (4.1) micrometers to 12 (3.1) micrometers, a change of -33%. Mineralization lag time (MLt) declined in 6 patients from a mean (SD) of 594 (675) days to 156 (77) days, a change of -74%.

16 HOW SUPPLIED/STORAGE AND HANDLING

CRYSVITA (burosumab-twza) injection for subcutaneous administration is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution. The product is available as one single-dose vial per carton in the following strengths:

10 mg/mL (NDC# 69794-102-01)

20 mg/mL (NDC# 69794-203-01)

30 mg/mL (NDC# 69794-304-01)

CRYSVITA vials must be stored in the original carton until the time of use under refrigerated conditions at 36°F to 46°F (2°C to 8°C). Keep CRYSVITA vial in the original carton to protect from light until time of use.

Do not freeze or shake CRYSVITA.

Do not use CRYSVITA beyond the expiration date stamped on the carton.

CRYSVITA vials are single-dose only. Discard any unused product.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise patients that CRYSVITA may cause hypersensitivity events such as rash, injection site rash and urticaria. Instruct the patients to contact their physician if such reactions occur [*see Adverse Reactions (6.1)*].

Injection Site Reactions

Inform patients that injection site reactions (e.g. erythema, rash, swelling, bruising, pain, pruritus, urticaria, and hematoma) have occurred at the site of CRYSVITA injection. Instruct the patients to contact their physician if such reactions occur [*see Adverse Reactions (6.1)*].

Restless Leg Syndrome

Advise patients that CRYSVITA can induce RLS or worsen the symptoms of existing RLS. Instruct the patients to contact their physician if such a reaction occurs [*see Adverse Reactions (6.1)*].

Pregnancy

Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-888-756-8657 *[see Use in Specific Populations (8.1)].*

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