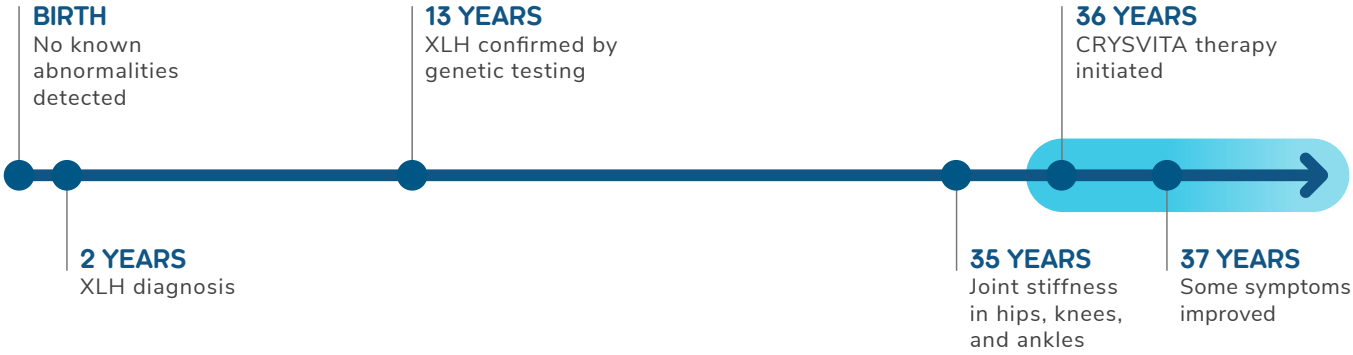
37-YEAR-OLD FEMALE WITH XLH*



Medical history

- **Age 2:** diagnosed with XLH
  - Initiated oral phosphate and calcitriol and was complaint
- **Age 13:** XLH diagnosis was confirmed by genetic testing

Family history

- Mother and maternal grandmother had XLH

XLH symptoms and associated complications in adulthood

- Chiari malformation requiring 2 corrective surgeries
- Chronic ankle pain and swelling in joints
- Gait abnormalities
- Sustained pelvic fracture during childbirth
- **Age 33:** discontinued oral phosphate and calcitriol

Indication

CRYSVITA® (burosumab-twza) is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

Important Safety Information

CONTRAINDICATIONS

CRYSVITA is contraindicated:

- In concomitant use with oral phosphate and/or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol) due to the risk of hyperphosphatemia.
- When serum phosphorus is within or above the normal range for age.
- In patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.

*This case is adapted from a real patient and is intended for illustrative purposes only, not as recommendations of care or management.
XLH=X-linked hypophosphatemia.

For important risk and use information, please see full Important Safety Information throughout and click to see full Prescribing Information for CRYSVITA.

Medical history (cont'd)

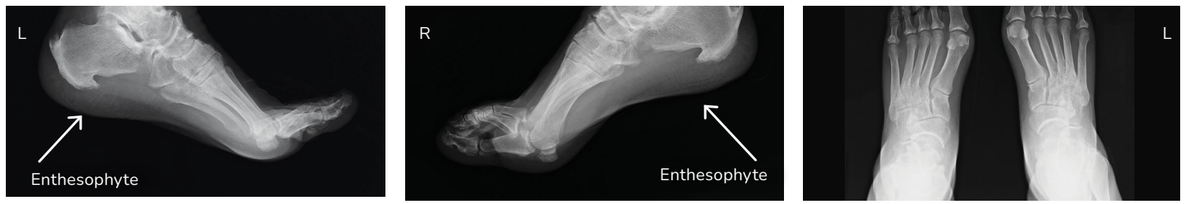
Evaluation prior to CRYSVITA®

- Age 35: presented to adult endocrinology with bowing of upper and lower extremities and joint stiffness in hips, knees, and ankles
- Physical exam
  - Height, 5'2"
  - Required the use of assistive walking device (cane) for long distances and handicap tags due to mobility challenges
  - Tinnitus in right ears
- Calcifications noted on prior renal ultrasound
- Laboratory findings (***Table**, page 3*)
- Physical therapy evaluation
  - Required assistance to rise from seated to standing position
  - Tight hip flexors; limited range of motion in hips
- X-rays
  - Prominent enthesophytes associated with the calcaneus bilaterally as well as ankle and midfoot arthritis; slight bowing seen bilaterally in lower legs (***X-ray 1**, below*)
  - Hypertrophic bone formation occurring at the hip articulation and trochanters; sclerosis at the sacroiliac joints; slight bilateral bowing of femurs (***X-ray 2**, below*)
  - Bowing deformity at each femur and degenerative changes of the knees including bilateral articular surface irregularities of the femoral condyles (***X-ray 3**, below*)
  - Bilateral bowing of femurs, tibias, and fibulas; bones diffusely demineralized and bilateral narrowing of joint space compartment also noted (***X-ray 4**, below*)

Diagnosis and initial treatment

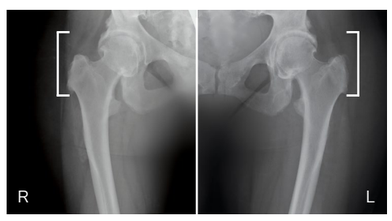
- XLH diagnosis reconfirmed
- Treatment: CRYSVITA

X-RAY 1: FEET (35 YEARS OLD)



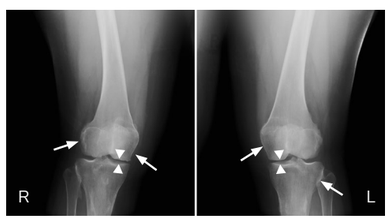
At 35 years old: prominent bilateral calcaneal enthesophytes; severe bilateral tibiotalar osteoarthritis; slight bilateral bowing in tibias and fibulas.

X-RAY 2: HIPS AND FEMURS (35 YEARS OLD)



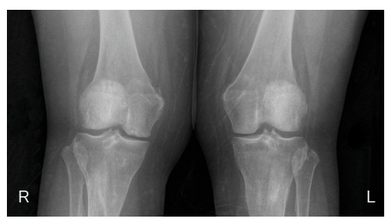
At 35 years old: hypertrophic bone formation at hip articulation and trochanters (brackets); sclerosis at the sacroiliac joints; slight bilateral bowing of femurs.

X-RAY 3: KNEES (35 YEARS OLD)



At 35 years old: degenerative changes of the knees including bilateral articular surface irregularities of the femoral condyles (arrows); diffusely demineralized bones with medial compartment joint space narrowing (arrow heads).

X-RAY 4: KNEES (35 YEARS OLD)



At 35 years old: bilateral bowing of femurs, tibias, and fibulas; diffused demineralization of bones; bilateral narrowing of joint space compartment.

CRYSVITA treatment

- Age 36: initiated CRYSVITA and reported progressive improvement in joint stiffness over time
- After 10 weeks: CRYSVITA dose reduced after a 30-pound intentional weight loss due to diet and increased physical activity
- Reported adverse events:
  - Myalgias and fatigue, left knee swelling and pain during the first 3 months
  - Adverse events managed with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid pain medication
  - No restless legs syndrome or injection site reactions were reported
- Laboratory findings: biochemical improvements after 35 weeks (***Table**, below*)

Laboratory test results[1-4]

Test (reference range† unit)	**Results** (age) Early evaluation (35 years)	CRYSVITA 35 weeks (37 years)
Serum phosphorus (2.5-4.5 mg/dL)	1.6	2.6
1,25(OH)$_2$D (18-72 pg/mL)	40.3	–
25(OH)D (20-50 ng/mL)	35	60.6
BSAP (2.9-14.5 µg/L)	25	19.1
PTH (14-72 pg/mL)	55	52
Creatinine (0.50-1.10 mg/dL)	0.74	0.70

†Indicates normal range, age, and gender matched. Note that normal range values may vary depending on reference dataset. Reference range values in this table were based on parameters in the clinical studies of CRYSVITA in adult patients with XLH, as well as values presented in Dahir et al.[2]
1,25(OH)$_2$D=1,25 dihydroxyvitamin D; 25(OH)D=25-hydroxyvitamin D (calcifediol); BSAP=bone-specific alkaline phosphatase, also known as BAP; PTH=parathyroid hormone.

Summary

1. Patient was diagnosed with XLH as a toddler and suffered from XLH-associated symptoms throughout adulthood, including fractures, joint stiffness, pain, and diminished physical function
2. At age 36, CRYSVITA was initiated and after nearly a year, patient demonstrated improvements in serum phosphorus levels and joint stiffness. Patient still experiences pain and diminished physical function
3. Adverse reactions reported during treatment included myalgia, fatigue, and left knee pain and swelling, which reduced within 3 months of treatment

Important Safety Information

WARNINGS AND PRECAUTIONS

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.

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Injection 10, 20, 30 mg/mL

CRYSVITA clinical studies results

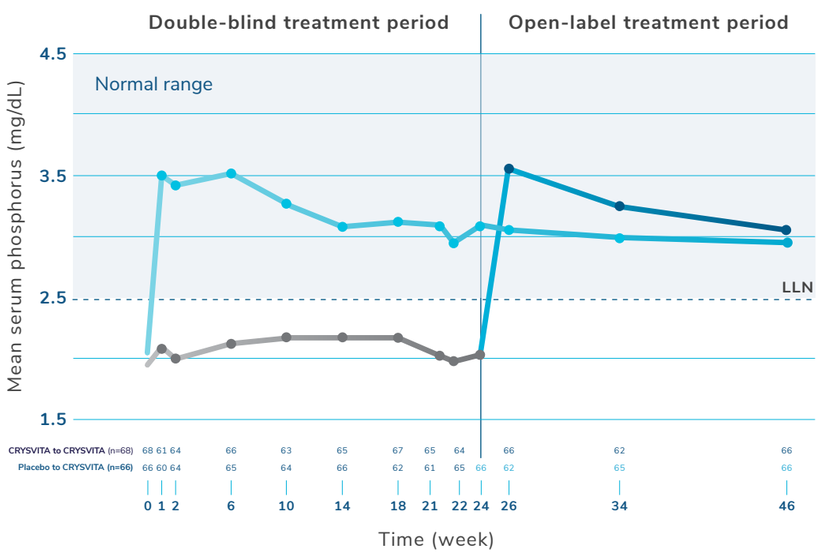
CRYSVITA was evaluated in 2 phase 3 clinical studies of 148 adults with XLH[5]

- Study 4: 24-week, randomized, double-blind, placebo-controlled, open-label, phase 3 study, followed by 24 weeks during which all patients received CRYSVITA (N=134, 19-66 years old)[5]
  - One patient in the CRYSVITA group discontinued treatment during the 24-week, placebo-controlled treatment period, and 7 patients discontinued CRYSVITA during the open-label treatment period
  - At baseline, 52% of patients had active fractures or pseudofractures, and all patients had skeletal pain associated with XLH/osteomalacia
- Study 5: 48-week, open-label, single-arm, phase 3 study (N=14, 25-52 years old)[5]
  - One patient discontinued at week 44[6]
- In both studies, oral phosphate and active vitamin D analogs were discontinued prior to enrollment[5]

CRYSVITA increased mean serum phosphorus levels within the normal range[5]

Study 4

Mean serum phosphorus levels in adults receiving CRYSVITA every 4 weeks or receiving placebo‡



A significantly higher proportion of patients, 94% (64/68), achieved normalized serum phosphorus between baseline and week 24 with CRYSVITA compared with 8% (5/66) with placebo (95% CI: CRYSVITA [85.8-97.7], placebo [3.3-16.5]; *P*<0.0001). Serum phosphorus was maintained with continued CRYSVITA treatment through week 48.[5]

‡Serum phosphorus level (mg/dL). The dotted line represents lower limit of normal (LLN, 2.5 mg/dL). Normal levels range from 2.5 to 4.5 mg/dL. Note that the normal levels vary by age and sex, and ranges may vary by testing laboratory. At baseline, mean (SD) serum phosphorus levels were 2.0 (0.30) and 1.9 (0.32) mg/dL for the CRYSVITA and placebo groups, respectively. During the initial 24-week double-blind, placebo-controlled period, mean serum phosphorus levels across midpoints of dose intervals (2 weeks post-dose) were 3.2 (0.53) and 2.1 (0.30) mg/dL for the CRYSVITA and placebo groups, respectively.[5]
SD=standard deviation.

CRYSVITA every 4 weeks demonstrated improvement in healing of osteomalacia[5]

Healing of osteomalacia was observed with CRYSVITA (Study 5, N=14) after 48 weeks of treatment[5]:

- Osteoid volume to bone volume decreased in 10 patients from a mean score of 26% at baseline to 11%, a mean change of -57%
- Osteoid thickness declined in 11 patients from a mean of 17 µm to 12 µm, a mean change of -33%
- Mineralization lag time declined in 6 patients from a mean of 594 days to 156 days, a mean change of -74%

CRYSVITA every 4 weeks helped heal osteomalacia-related fractures/pseudofractures, including in patients who switched from placebo[5]

CRYSVITA demonstrated a higher rate of fracture/pseudofracture healing compared with placebo[5]:

- Fracture/pseudofracture healing: 43% (28/65) in the CRYSVITA group vs 8% (7/91) in the placebo group from baseline to week 24 (Study 4, N=134)
- Active fracture healing: 50% (7/14) in the CRYSVITA group vs 0% (0/13) in the placebo group
- Active pseudofracture healing: 41% (21/51) in the CRYSVITA group vs 9% (7/78) in the placebo group
- Through week 24, 68 patients receiving CRYSVITA had a total of 6 new fractures or pseudofractures compared with 8 new abnormalities in 66 patients receiving placebo

During the open-label treatment period, patients who continued receiving CRYSVITA showed continued healing of fractures at week 48[5]:

- Active fractures: 57% (8/14) in the CRYSVITA group and 46% (6/13) in the placebo-to-CRYSVITA group
- Active pseudofractures: 65% (33/51) in the CRYSVITA group and 33% (26/78) in the placebo-to-CRYSVITA group

Osteomalacia-related fractures were defined as atraumatic lucencies extending across both bone cortices, and pseudofractures were defined as atraumatic lucencies extending across one cortex. These fractures were predominantly located in femurs, tibia/fibula, and metatarsals of the feet.[5]

CRYSVITA every 4 weeks impacted patient-reported joint stiffness[5]

CRYSVITA demonstrated a mean improvement in the joint stiffness severity score (-7.9), compared with placebo (+0.3), from baseline to week 24 (Study 4, N=134). No significant difference between CRYSVITA and placebo was demonstrated in patient-reported pain intensity or physical function score.

CRYSVITA adverse reactions in adult patients 20-63 years of age[5]

Adverse reactions (>5% and in at least 2 patients more than placebo) in adult patients were: back pain, headache, tooth infection, restless legs syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, and blood phosphorus increased.

Important Safety Information

WARNINGS AND PRECAUTIONS (cont'd)

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.

Hypercalcemia

- Increases in serum calcium have been reported in patients treated with CRYSVITA. Patients with risk factors such as pre-existing hyperparathyroidism, prolonged immobilization, dehydration, hypervitaminosis D, or renal impairment, are at higher risk of hypercalcemia. Monitor these patients for serum calcium and parathyroid hormone levels before and during CRYSVITA treatment for moderate to severe hypercalcemia. In patients with moderate to severe hypercalcemia, CRYSVITA should not be administered until hypercalcemia is adequately managed.

For important risk and use information, please see full Important Safety Information throughout and click to see full Prescribing Information for CRYSVITA.

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Important Safety Information

WARNINGS AND PRECAUTIONS (cont'd)

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.

ADVERSE REACTIONS

Pediatric Patients

- Adverse reactions reported in 10% or more of CRYSVITA-treated pediatric XLH patients across three studies are: pyrexia (55%, 44%, and 62%), injection site reaction (52%, 67%, and 23%), cough (52%), vomiting (41%, 48%, and 46%), pain in extremity (38%, 46%, and 23%), headache (34% and 73%), tooth abscess (34%, 15%, and 23%), dental caries (31%), diarrhea (24%), vitamin D decreased (24%, 37%, and 15%), toothache (23% and 15%), constipation (17%), myalgia (17%), rash (14% and 27%), dizziness (15%), and nausea (10%).

Adult Patients

- Adverse reactions reported in more than 5% of CRYSVITA-treated adult XLH patients and in at least 2 patients more than placebo in one study are: back pain (15%), headache (13%), tooth infection (13%), restless legs syndrome (12%), vitamin D decreased (12%), dizziness (10%), constipation (9%), muscle spasms (7%), and blood phosphorus increased (6%).
- 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 Kyowa Kirin, Inc. Adverse Event reporting line at 1-844-768-3544.
- There is no information regarding the presence of CRYSVITA in human milk or the effects of CRYSVITA on milk production or the breastfed infant. 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.

PATIENT COUNSELING INFORMATION

- Advise patients not to use any oral phosphate and/or active vitamin D analog products.
- Instruct patients to contact their physician if hypersensitivity reactions, injection site reactions, and restless legs 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 Kyowa Kirin, Inc. at 1-844-768-3544.

For important risk and use information, please click to see the full Prescribing Information for CRYSVITA.

References:

1. Portale AA, Carpenter TO, Brandi ML, et al. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int.* 2019;105(3):271-284. doi:10.1007/s00223-019-00568-3 **2.** Dahir K, Zanchetta MB, Stanciu I, et al. Diagnosis and management of tumor-induced osteomalacia: perspectives from clinical experience. *J Endocr Soc.* 2021;5(9):bvab099. doi:10.1210/jendso/bvab099 **3.** Imel EA, Zhang X, Ruppe MD, et al. Prolonged correction of serum phosphorus in adults with X-linked hypophosphatemia using monthly doses of KRN23. *J Clin Endocrinol Metab.* 2015;100(7):2565-2573. doi:10.1210/jc.2015-1551 **4.** Data on file. 304 EOS CSR. Ultragenyx Pharmaceutical Inc.; 2019. **5.** CRYSVITA (burosumab-twza). US Prescribing Information. Kyowa Kirin, Inc.; August 2025. **6.** Insogna KL, Rauch F, Kamenický P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. *J Bone Miner Res.* 2019;34(12):2183-2191. doi:10.1002/jbmr.3843

KYOWA KIRIN

CRYSVITA® burosumab-twza injection 10, 20, 30 mg/mL

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