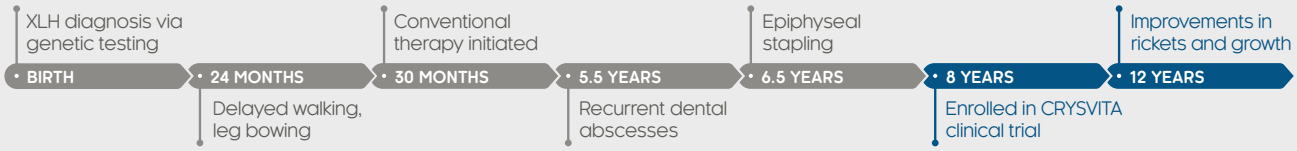
CASE STUDY*

# 12-YEAR-OLD FEMALE WITH XLH




## MEDICAL HISTORY

### Early evaluation

- Positive family history of X-linked hypophosphatemia (XLH); mother and older brother have XLH
- Early symptoms included leg bowing and delayed walking

## DIAGNOSIS AND INITIAL TREATMENT

- XLH confirmed by genetic testing shortly after birth
- Conventional therapy with oral calcitriol and phosphate initiated at 30 months

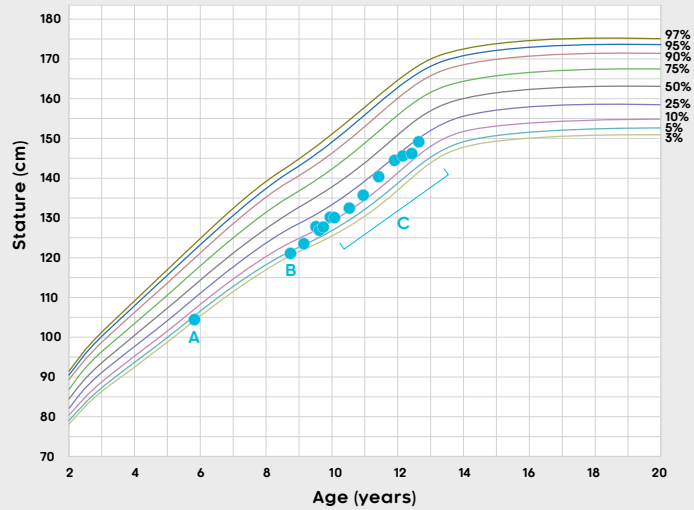
## DISEASE PROGRESSION

### XLH symptoms and associated complications

- Age 5.5: history of recurrent dental abscesses, hip pain, and abnormal gait; conventional therapy continued
  - Physical exam: genu valgum (knock-knees), more pronounced on the right leg than left leg; height: 104.7 cm, between 3rd and 5th percentile **(Growth chart, A)**
- Age 6.5: underwent epiphyseal stapling of the proximal femur bilaterally and right proximal tibia to correct deformities
- Age 8.8: transitioned from conventional therapy to CRYSVITA
  - Physical exam: height between 3rd and 5th percentile **(Growth chart, B)**; no genu valgum; mild torsion of left tibia; renal ultrasound shows no evidence of nephrocalcinosis
  - Laboratory findings **(Table, page 2)**
  - Enrolled in CRYSVITA clinical trial

**GROWTH CHART**

**STATURE FOR AGE PERCENTILES, GIRLS AGED 2-20 YEARS[1,†]**




Patient growth evolution prior to and after CRYSVITA.

**A:** Prior to 6 years, the patient's height was at the 3rd to 5th percentile.

**B:** At enrollment in the CRYSVITA clinical trial, the patient's height was at the 3rd to 5th percentile.

**C:** During CRYSVITA treatment, the patient's height increased to the 10th to 25th percentile.

†The reference percentiles on the graph are combined from the two clinical growth charts for girls 2-20 years of age in Sets 1 and 2 of the clinical charts provided by the Centers for Disease Control and Prevention.

## 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.

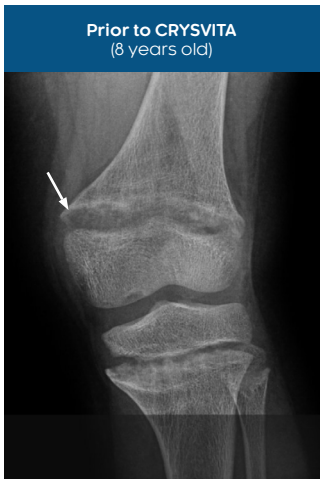
**Please see Important Safety Information on pages 3 and 4 and accompanying full Prescribing Information.**

*The information for this case study was provided courtesy of Dr. Anthony Portale, Division of Pediatric Nephrology, UCSF Benioff Children's Hospital, San Francisco. This case study represents a real patient and is intended to be illustrative, not a recommendation for treatment or management. Not all patients will respond the same to CRYSVITA treatment. Results may vary. This case study does not claim to represent typical results.

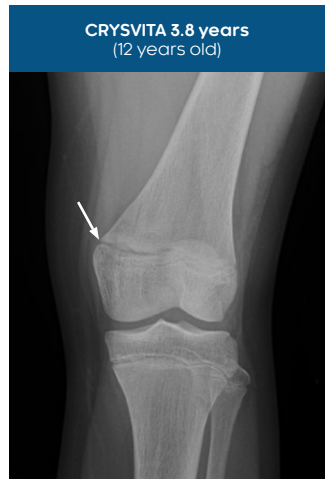
## CRYSVITA treatment, 3.8 years

- Physical exam at age 12: height at the 10th to 25th percentile **(Growth chart, C, page 1)**
- Laboratory findings: **tests improved (Table, below)**
- Radiology: **rickets improved**; mild residual widening and irregularity of physis of distal femur are observed **(X-rays, below)**; renal ultrasound shows no evidence of nephrocalcinosis

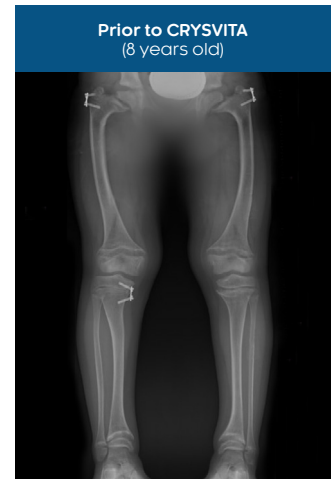
## X-RAYS: EVOLUTION OF RICKETS AND LOWER LIMB DEFORMITY



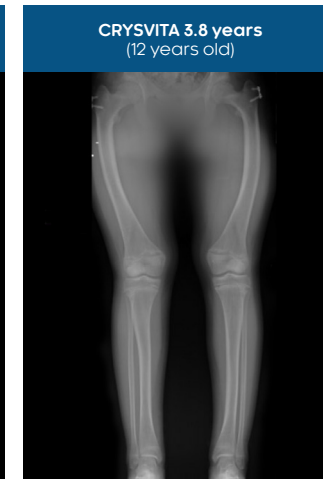

Active rickets at knee.




Mild widening of physis of distal femur.




Femoral bowing, coxa vara.




Persistent femoral bowing.

## LABORATORY TEST RESULTS

| Test (reference range[a] unit) | Results (age) | | | | |
|---|---|---|---|---|---|
| | Early evaluation (8.8 years) | Prior to CRYSVITA (8.9 years) | CRYSVITA 40 weeks (9.6 years) | CRYSVITA 2 years (11 years) | CRYSVITA 3.8 years (12 years) |
| **Serum phosphorus** (3.2-6.1 mg/dL) | 2.4 | 1.9 | 3.4 | 3.6 | 3.2 |
| **TmP/GFR** (4.0-5.2 mg/dL) | n/a | 1.7 | 3.1 | 3.2 | 3.0 |
| **25(OH)D** (20-50 ng/mL) | n/a | 38 | n/a | 29 | 24 |
| **ALP** (156-369 U/L) | 492 | 490 | 538 | 404 | 300 |
| **Serum calcium** (8.8-10.3 mg/dL) | 9.5 | 9.7 | n/a | 9.7 | 9.4 |
| **PTH** (18-80 pg/mL) | 16 | 38 | 45 | 38 | 70 |

25(OH)D, 25-hydroxy vitamin D (calcifediol); ALP, alkaline phosphatase; PTH, parathyroid hormone; TmP/GFR, ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate; ULN, upper limit of normal.

[a]Indicates normal range, age, and sex matched. Note that normal range values may vary depending on reference dataset. The range in this table was provided by the treating physician.

## SUMMARY

- Patient was diagnosed with XLH shortly after birth based on positive family history and genetic testing
- Conventional therapy was initiated at 30 months; XLH symptoms continued to progress
- Patient enrolled in CRYSVITA clinical trial at 8.8 years of age
- After approximately 4 years of treatment with CRYSVITA, patient demonstrated improvements in rickets severity, laboratory findings, and linear growth

**Per Dr. Portale - edit required:**

**In the legend to the table showing laboratory results, the abbreviation 25(OH)D is shown as 25-hydroxy vitamin D. There should be no space between "hydroxy" and "vitamin D". The correct form is 25-hydroxyvitamin D.**

# CRYSVITA CLINICAL TRIALS RESULTS

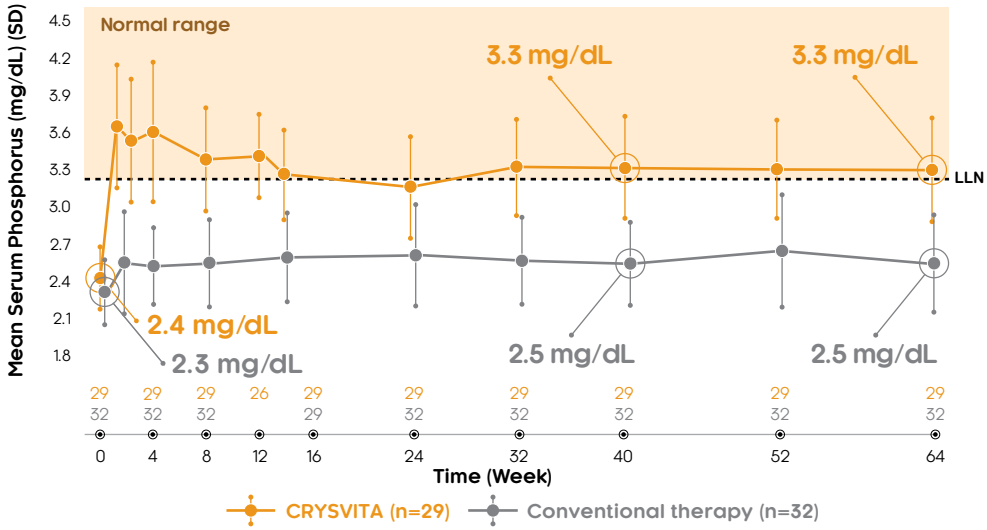
## CRYSVITA WAS EVALUATED IN PHASE 3 AND PHASE 2 CLINICAL STUDIES OF 126 CHILDREN WITH XLH

- Phase 3 study (Study 1): 64 weeks, randomized, open-label, active-control (conventional therapy: oral phosphate and active vitamin D), N=61, ages 1 to 12 years
- Phase 2 studies (Studies 2 and 3): 64 weeks, randomized, open-label, N=52, ages 5 to 12 years; and 40 weeks, open-label, N=13, ages 1 to 4 years
- No patients discontinued
- Oral phosphate and active vitamin D analogs were discontinued prior to enrollment and reinitiated as appropriate
- Baseline: all but 3 patients enrolled had radiographic evidence of rickets and all but 3 patients received conventional therapy

## CRYSVITA LED TO INCREASED AND SUSTAINED SERUM PHOSPHORUS LEVELS WITHIN THE NORMAL RANGE

**MEAN SERUM PHOSPHORUS LEVELS IN CHILDREN RECEIVING CRYSVITA EVERY 2 WEEKS OR RECEIVING CONVENTIONAL THERAPY[2,3,*]**

**Phase 3 (Study 1)**
**(N=61, ages 1 to 12 years)**




**Phase 2 studies:**
CRYSVITA increased mean serum phosphorus levels from 2.4 mg/dL and 2.5 mg/dL at baseline to 3.3 mg/dL and 3.5 mg/dL at Week 40 in the Phase 2 studies (Study 2, n=26 and Study 3, N=13, respectively). Findings were maintained at Week 64 in Study 2.

Conventional therapy, oral phosphate and active vitamin D; SD, standard deviation.
*Serum phosphorus level (mg/dL) (mean ±SD). The dotted line represents the lower limit of normal (LLN, 3.2 mg/dL).
Normal levels range from 3.2 to 6.1 mg/mL. Note that normal levels vary by age and sex, and ranges may vary by testing laboratory.[3]

## CRYSVITA EVERY 2 WEEKS REDUCED TOTAL ALKALINE PHOSPHATASE (ALP) ACTIVITY

In the Phase 3 study (Study 1, n=29), CRYSVITA led to a **33% mean reduction** in ALP activity from baseline to Week 64 vs 5% with conventional therapy. There were **23% and 36% mean reductions** in the Phase 2 study (Study 2, n=26) at Week 64 and the Phase 2 study (Study 3, N=13) at Week 40, respectively.

# IMPORTANT SAFETY INFORMATION

## CONTRAINDICATIONS

- With oral phosphate and/or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol).
- When serum phosphorus is within or above the normal range for age.
- 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.

**Please see Important Safety Information on pages 3 and 4 and accompanying full Prescribing Information.**

# CRYSVITA CLINICAL TRIALS RESULTS (continued)

### CRYSVITA EVERY 2 WEEKS LED TO RICKETS HEALING

Rickets was assessed by Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C). Mean RSS scores declined from:

- 3.2 with CRYSVITA and 3.2 with conventional therapy in the Phase 3 study (Study 1, n=29) at baseline to 1.1 and 2.5 at Week 40, respectively, a **2.9 times greater reduction** with CRYSVITA. Findings were maintained at Week 64
- 1.9 at baseline to 0.8 at Week 40 in the Phase 2 study (Study 2, n=26), a **58% reduction**. Findings were maintained at Week 64
- 2.9 at baseline to 1.2 at Week 40 in the Phase 2 study (Study 3, N=13), a **59% reduction**

CRYSVITA was superior to conventional therapy, as measured by RGI-C.

- **72% (21/29)** of patients treated with CRYSVITA vs **6% (2/32)** treated with conventional therapy in the Phase 3 study (Study 1, n=29) achieved substantial healing of rickets (RGI-C score of +2.0) at Week 40. Findings were maintained at Week 64
- **69% (18/26)** of patients in the Phase 2 study (Study 2, n=26) and **100% (13/13)** of patients in the Phase 2 study (Study 3, N=13) achieved substantial healing of rickets

### CRYSVITA EVERY 2 WEEKS IMPROVED GROWTH

In the Phase 3 study (Study 1, n=29), CRYSVITA increased standing height z-score from -2.32 at baseline to -2.11 at Week 64 vs conventional therapy, -2.05 at baseline to -2.03 at Week 64. In the Phase 2 study (Study 2, n=26), the z-score increased from -1.72 at baseline to -1.54 at Week 64.

### CRYSVITA ADVERSE REACTIONS IN PEDIATRIC PATIENTS 1 TO 12 YEARS OF AGE

The most common adverse reactions (in 10% or more of CRYSVITA-treated pediatric XLH patients across all studies) were: pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, dental caries, diarrhea, vitamin D decreased, toothache, constipation, myalgia, rash, dizziness, and nausea.

# IMPORTANT SAFETY INFORMATION (continued)

### ADVERSE REACTIONS

#### Pediatric Patients

- Adverse reactions reported in 10% or more of CRYSVITA-treated pediatric XLH patients across all studies are: pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, dental caries, diarrhea, vitamin D decreased, toothache, constipation, myalgia, rash, dizziness, and nausea.
- Postmarketing experience reported in CRYSVITA-treated pediatric XLH patients: blood phosphorus increased.

#### 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, headache, tooth infection, restless legs syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, and 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 Kyowa Kirin, Inc. 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

- 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 **1-888-756-8657**.

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


### REFERENCES:

**1.** Clinical growth charts. Centers for Disease Control and Prevention website. Last reviewed June 16, 2017. Accessed September 24, 2020. https://www.cdc.gov/growthcharts/clinical_charts.htm **2.** CRYSVITA (burosumab-twza) US Prescribing Information; June 2020. **3.** Data on file. Ultragenyx Pharmaceutical Inc.

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