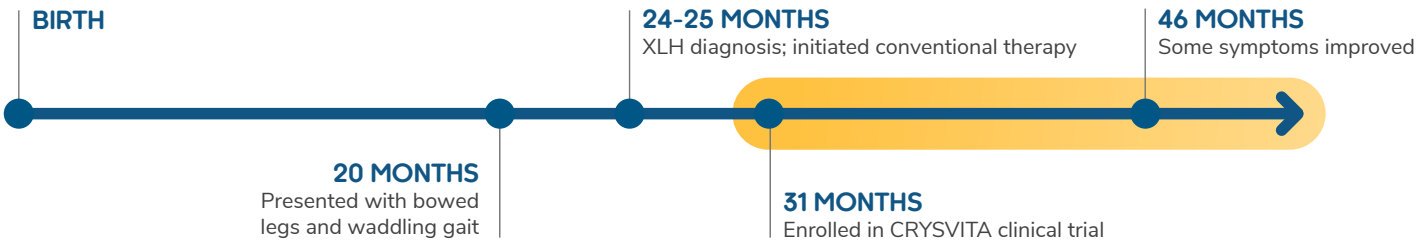
4-YEAR-OLD MALE WITH SPONTANEOUS XLH*



Medical history

- 20-month-old male presented with bowed legs
  - Bowing present since birth, worsened once patient started walking
- Other physical exam findings: waddling gait, cannot run well
- Suspected diagnosis: congenital bilateral knee bowing
- Exam at 24 months: worsened bowing of legs and waddling gait noted
- X-ray findings: bilateral bowing of femur and tibia; cupping of distal femur, proximal and distal tibia and fibula
- Suspected diagnosis: rickets

Evaluation at academic center

- Physical exam at 24.5 months: severe knee bowing, intercondylar distance of 5 cm, short stature, height in 1st percentile *(**Growth chart**, **page 2**)*
- X-rays: metaphyseal flaring at wrists and ankles
- Laboratory findings *(**Table**, **page 3**)*
- Suspected diagnosis: hypophosphatemic rickets
- Upon genetic evaluation at 25 months, pathologic *PHEX* variant identified; mother negative

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.

Diagnosis and initial treatment

- Spontaneous XLH
- Treatment: oral calcitriol and phosphate

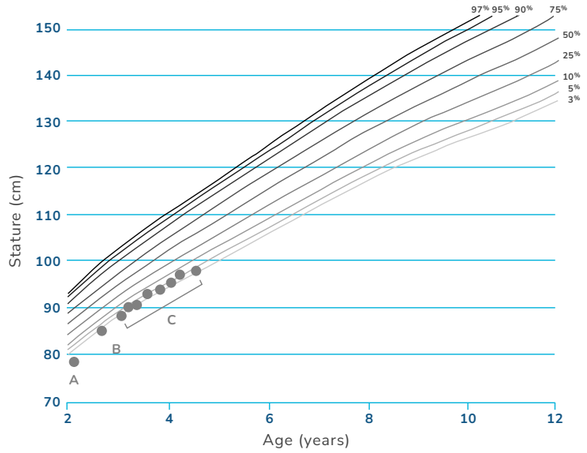
Diagnosis progression

Evaluation at academic center

- Physical exam at **29 months**: femoral bowing; obvious genu varus—knees 4.5 cm apart, ankles touching; bilateral tibial bowing
  - Height 5th percentile *(**Growth chart**, B)*
- X-rays: metaphyseal widening at wrists, mild cupping of distal radius and ulna
  - Knees: marked bowing, cupping and fraying of growth plates *(**X-rays**, below)*
- Laboratory findings *(**Table**, page 3)*
- Enrolled in CRYSVITA clinical trial at **31 months**

GROWTH CHART

Stature for age percentiles, boys aged 2-12 years[1†]



Patient growth evolution.
A: At 24.5 months, the patient's height was in the 1st percentile.
B: At enrollment, the patient's height was in the 5th percentile.
C: While on CRYSVITA, the patient's height was in the 10th percentile.

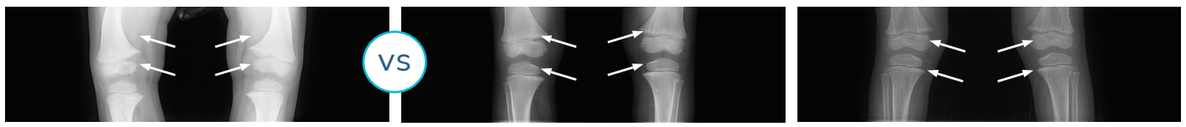
†The reference percentiles on the graph are combined from the 2 clinical growth charts for boys 2-20 years of age provided by the Centers for Disease Control and Prevention.

X-rays: evolution of rickets and lower limb deformity

PRIOR TO CRYSVITA
(29 months old)

CRYSVITA 40 WEEKS
(40 months old)

CRYSVITA 64 WEEKS
(46 months old)



Cupping and fraying of growth plates, marked bowing.

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(29 months old)

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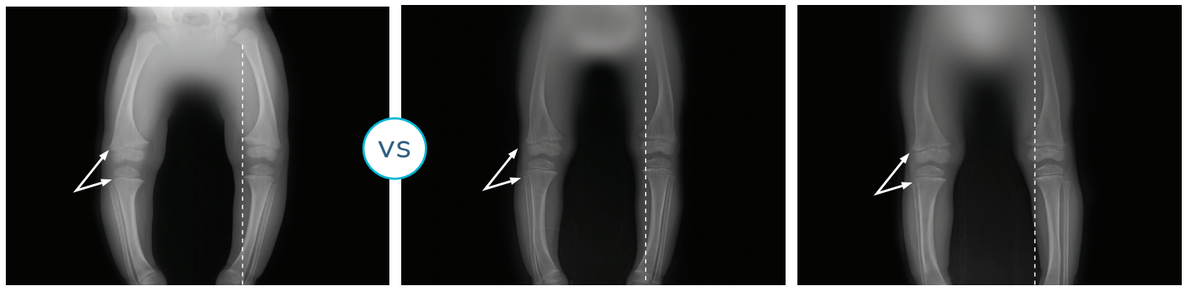


Resolved cupping and fraying of metaphysis of radius and ulna; improved fraying of femoral metaphysis; decreased widening of femoral growth plate.

CRYSVITA® treatment

- Physical exam at **46 months**: femoral bowing; bilateral tibial bowing
  - Genu varum resolved; knees straight
  - Height 10th percentile *(**Growth chart**, C)*
- X-rays: resolved cupping and fraying of metaphysis of radius and ulna; improved fraying of femoral metaphysis; decreased widening of femoral growth plate *(**X-rays**, page 2)*
- Laboratory findings: tests improved *(**Table**, below)*

Laboratory test results[2-4]

Test (reference range‡ unit)	Early evaluation (24.5 months)	Prior to CRYSVITA (31 months)	**Results** (age) CRYSVITA 40 weeks (40 months)	CRYSVITA 64 weeks (46 months)
Serum phosphorus (3.2-6.1 mg/dL)	2.9	2.9	3.7	4
TmP/GFR§ (>1 year: 2.6-4.4 mg/dL)	n/a	2.8	3.7	4
25(OH)D (20-50 ng/dL)	26	24	36	26
ALP (ULRR for 1-15 y: 297-385 U/L)	636	459	283	299
Serum calcium (0-2 y: 9.0-11.0 mg/dL) (2-18 y: 8.4-10.3 mg/dL)	9.4	9.5	9.6	9.6
PTH (14-72 pg/mL)	56	20	36	23

‡Indicates normal range, age, and gender matched. Reference range values in this table were based on parameters in a phase 3 study of CRYSVITA in pediatric patients, as well as values presented in Dahir et al.[3] 25(OH)D=25-hydroxyvitamin D (calcifediol); ALP=alkaline phosphatase; PTH=parathyroid hormone; TmP/GFR=ratio of tubular maximum reabsorption of phosphorus to glomerular filtration rate; ULRR=upper limit of reference range.
§Target range.

Summary

1. Physical patient presented with symptoms at 20 months and underwent several specialty evaluations before XLH diagnosis at 25 months
2. Conventional therapy initiated; XLH symptoms continued to progress
3. Patient enrolled in CRYSVITA clinical trial at 31 months
4. After 64 weeks on CRYSVITA, patient demonstrated improvements in laboratory findings and lower limb deformity

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.

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

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

CRYSVITA® clinical studies results

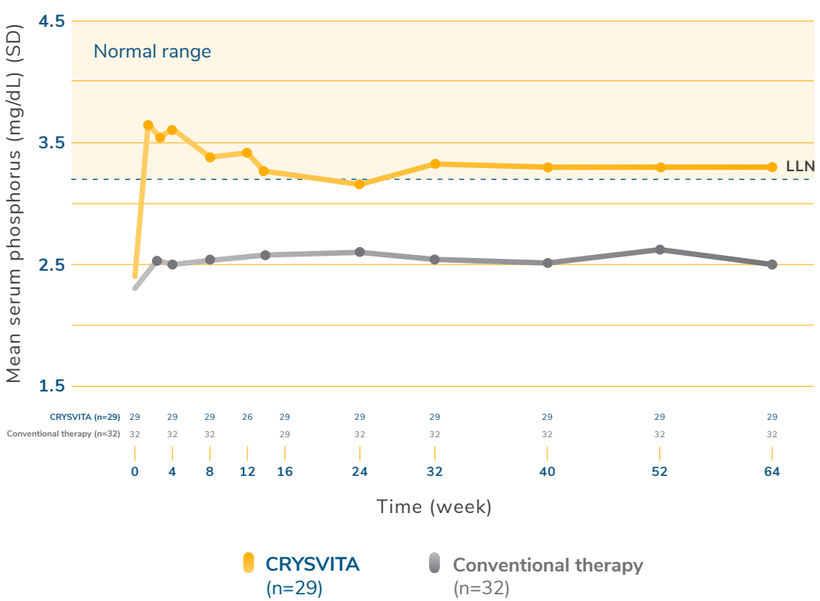
CRYSVITA was evaluated in phase 3 and phase 2 clinical studies of 126 children with XLH[5]

- Phase 3 study (Study 1): 64 weeks, randomized, open-label, active-control (conventional therapy: oral phosphate and active vitamin D), N=61, ages 1-12 years
- Phase 2 studies (Study 2): 64 weeks, randomized, open-label, N=52, ages 5-12 years; and (Study 3) 64 weeks, open-label, N=13, ages 1-4 years
- No patients discontinued
- Oral phosphate and active vitamin D analogs were discontinued prior to enrollment and reinitiated as appropriate
- In Studies 1 and 3, all patients had radiographic evidence of rickets at baseline
- In Study 2, 94% of patients had radiographic evidence of rickets at baseline

CRYSVITA led to increased and sustained mean serum phosphorus levels[5]

Mean serum phosphorus levels in children receiving CRYSVITA every 4 weeks or receiving placebo[‖]

Study 1



Study 1: CRYSVITA increased mean (SD) serum phosphorus levels from 2.4 (0.24) mg/dL at baseline to 3.3 (0.43) mg/dL at week 40 and to 3.3 (0.42) mg/dL at week 64. In the active control group, mean (SD) serum phosphorus concentrations increased from 2.3 (0.26) mg/dL at baseline to 2.5 (0.34) mg/dL at week 40 and to 2.5 (0.39) mg/dL at week 64.[5]

Studies 2 and 3: CRYSVITA every 2 weeks 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.[5]

Normal levels range from 3.2 to 6.1 mg/mL.[2] Note that normal levels vary by age and sex, and ranges may vary by testing laboratory.[6]
‖Serum phosphorus level (mg/dL) (mean ±SD). The dotted line represents the lower limit of normal (LLN, 3.2 mg/dL).[5]
Conventional therapy=oral phosphate and active vitamin D; SD=standard deviation.

CRYSVITA every 2 weeks reduced total alkaline phosphatase (ALP) activity[5]

In 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 Study 2 (n=26) at week 64 and Study 3 (N=13) at week 40, respectively.

CRYSVITA every 2 weeks led to rickets healing[5]

Rickets was assessed by Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C). Mean RSS scores declined from[5]:

- 3.2 with CRYSVITA and 3.2 with conventional therapy in the phase 3 study (Study 1, N=61) at baseline to 1.1 and 2.5 at week 40, respectively. Findings were maintained at week 64
- 1.9 at baseline to 0.8 at week 40 in a phase 2 study (Study 2, n=26). Findings were maintained at week 64
- 2.9 at baseline to 1.2 at week 40 in a phase 2 study (Study 3, N=13)

CRYSVITA helped more patients achieve substantial healing of rickets, as measured by RGI-C[5]:

- 72% (21/29) of patients treated with CRYSVITA vs 6% (2/32) treated with conventional therapy in the phase 3 study (Study 1, N=61) 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 a phase 2 study (Study 2, n=26) and 100% (13/13) of patients in a phase 2 study (Study 3, N=13) achieved substantial healing of rickets after 40 weeks of treatment

CRYSVITA every 2 weeks improved growth[5]

In the phase 3 study (Study 1, N=61), CRYSVITA increased standing height z-score from -2.32 at baseline to -2.11 at week 64 vs conventional therapy from -2.05 at baseline to -2.03 at week 64. In 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 1-12 years of age[5]

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

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.

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.

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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burosumab-twza
Injection 10, 20, 30 mg/mL

Important Safety Information

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%).
- 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 (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 full Prescribing Information for CRYSVITA.

References:

1. Centers for Disease Control and Prevention. Clinical growth charts. Children 2 to 20 years. Published May 30, 2000. Accessed May 21, 2019. https://www.cdc.gov/growthcharts/clinical_charts.htm **2.** Data on file. 301 CSR. Ultragenyx Pharmaceutical Inc.; 2018. **3.** 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 **4.** Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet.* 2019;393(10189)(suppl):2416-2427. **5.** CRYSVITA (burosumab-twza). US Prescribing Information. Kyowa Kirin, Inc.; March 2023. **6.** Koek WNH, Campos-Obando N, van der Eerden BCJ, et al. Age-dependent sex differences in calcium and phosphate homeostasis. *Endocr Connect.* 2021;10(3):273-282. doi:10.1530/EC-20-0509

KYOWA KIRIN

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

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