WHEN MANAGING PATIENTS WITH XLH

Pr CRYSVITA®
burosumab injection
Solution for Subcutaneous Injection
10, 20, 30 mg/mL

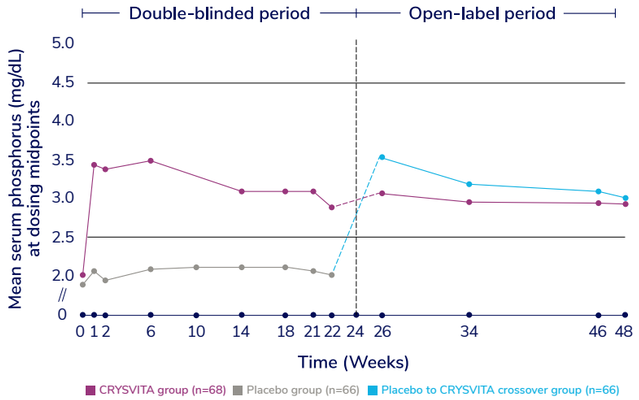
HELP THEM DISCOVER Pr CRYSVITA®

CRYSVITA (burosumab injection) is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

XLH=X-linked hypophosphatemia.

94% (95% CI: 85.8, 97.7) of patients receiving CRYSVITA achieved mean serum phosphorus concentrations above the LLN† through 24 weeks vs. 8% (95% CI: 3.3, 16.5) of patients receiving placebo; $p<0.0001$[1,2‡§]

Change in serum phosphorus at the midpoint of the dose interval through Week 48[1,3¶]



Adapted from Product Monograph and Portale AA, *et al.*, 2019.[1,3]

Mean serum phosphorus concentrations continued to remain **above the LLN†** through 48 weeks in the initial CRYSVITA treatment group and remained **at or above LLN†** in the placebo to CRYSVITA crossover group starting from **Week 26 through Week 48**.[1,3]

The placebo group was crossed over to CRYSVITA at Week 24.

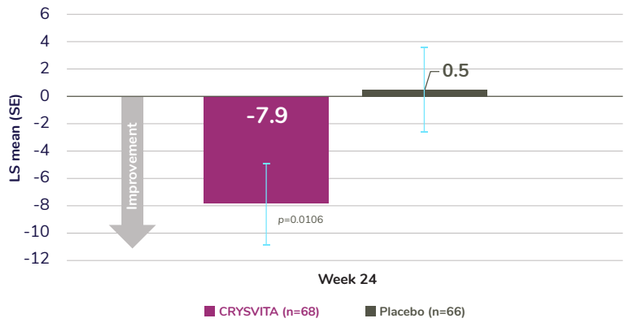
Note that 1 mg/dL is equivalent to 0.323 mmol/L.[4]

LLN=lower limit of normal.
† The normal range for serum phosphorus used was 2.5–4.5 mg/dL (LLN=2.5 mg/dL), with a dose-limiting toxicity threshold of >6.5 mg/dL.[1]
‡ *P* value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving the primary endpoint and treatment group, adjusting for randomization stratifications.[1]
§ Phase 3, randomized, double-blind, placebo-controlled study in 134 adults with XLH followed by an open-label extension study. Patients were randomized to receive either subcutaneous burosumab 1 mg/kg (CRYSVITA) every 4 weeks (n=68) or matching subcutaneous placebo every 4 weeks (n=66) followed by a 24-week open-label period in which patients randomized to placebo switched to CRYSVITA; all patients remained blinded to their original treatment assignment. Oral phosphate and active vitamin D analogues were not allowed during the study. The primary efficacy endpoint was the proportion of patients achieving mean serum phosphorus concentrations above 2.5 mg/dL (LLN) averaged across the midpoints of the dose interval between baseline and Week 24.[1,2]
¶ 1–2 weeks after a dose.[3]

DEMONSTRATED EFFICACY IN ADULT PATIENTS

CRYSVITA demonstrated significantly greater improvements in XLH-associated stiffness vs. placebo at Week 24 (secondary endpoint; as measured by the WOMAC Index)[1,2†]

WOMAC stiffness—LS mean change from baseline to Week 24[1]



Adapted from the Product Monograph.[1]

Mean WOMAC stiffness score (SD) declined from **64.7 (20.25) to 53.7 (20.76) in the CRYSVITA group** vs. **61.4 (20.77) to 60.4 (21.83) in the placebo group** from baseline to Week 24 (LS mean [SE]: CRYSVITA -7.9 [3.03] vs. placebo 0.5 [3.14], $p=0.0106$).[1]

The scores on each domain of the **Western Ontario and McMaster Universities Osteoarthritis Index** (WOMAC) are normalized and range from 0 to 100 with a **higher score indicating poorer functioning**.[1]

LS=least squares; SD=standard deviation; SE=standard error; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.
† Refer to study design information on page 2 (§).

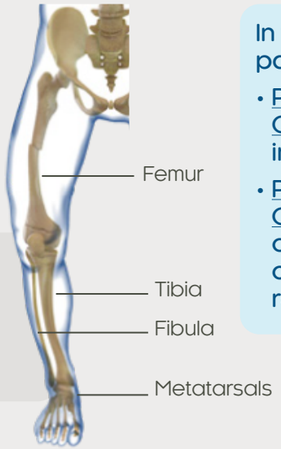
Comparison of fracture healing with CRYSVITA vs. placebo (exploratory endpoint)[1-3,5†]

	Active fractures		Active pseudofractures		Total fractures	
	CRYSVITA	Placebo	CRYSVITA	Placebo	CRYSVITA	Placebo
% of fractures healed at Week 24‡ (no. healed/ no. at baseline)	**50.0%** (7/14)	**0%** (0/13)	**41.2%** (21/51)	**9.0%** (7/78)	**43.1%** (28/65)	**7.7%** (7/91)

Adapted from the Product Monograph.[1]

Osteomalacia-related fractures are defined as atraumatic lucencies extending across both bone cortices, and pseudofractures are defined as atraumatic lucencies extending across one cortex.[1]

The active fractures/ pseudofractures were predominantly located in the femurs, tibia/fibula, and metatarsals of the feet.[1]



In the open-label period when all patients received CRYSVITA:[1]

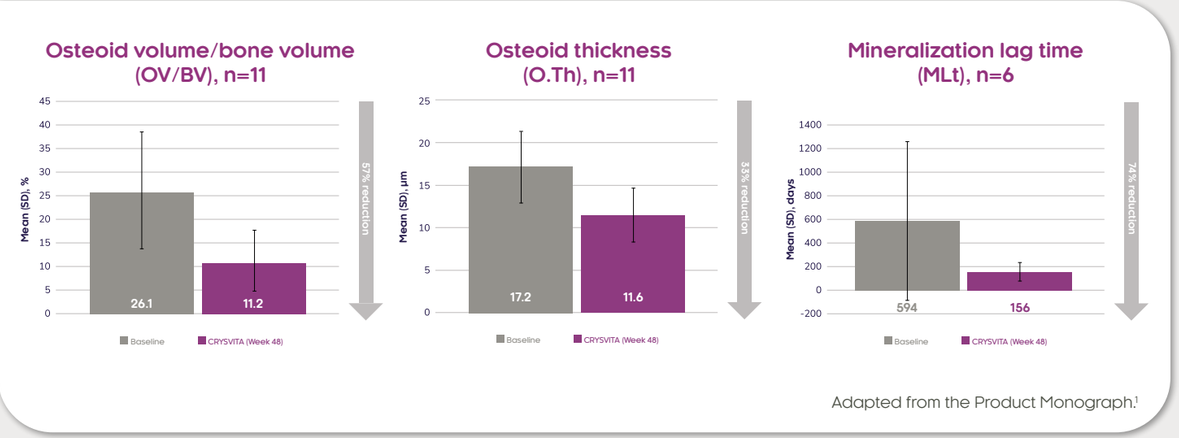
- Patients who continued receiving CRYSVITA: showed additional healing in all three categories.
- Patients who started receiving CRYSVITA: showed a higher rate of complete healing in all three categories compared to when they received the placebo.

†Refer to study design information on page 2 (§).
‡Percent based on baseline values.

DEMONSTRATED EFFICACY DATA IN ADULT PATIENTS

Assessment of the effects of CRYSVITA on the improvement of osteomalacia (as determined by histologic and histomorphometric evaluation of iliac crest biopsies in an open-label single-arm study)[1†]

After 48 weeks of treatment with CRYSVITA, histomorphometric improvement in osteomalacia was observed in ten patients as demonstrated by decreases in proxy measures.



Adapted from the Product Monograph.[1]

SD=standard deviation.
†Phase 3, open-label, single-arm study in 14 adults with XLH over 48 weeks. The study assessed the effects of CRYSVITA on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Oral phosphate and active vitamin D analogues were not allowed during the study. Of the 14 enrolled patients, 11 underwent paired bone biopsies. Mineralization lag time data are only presented for 6 patients, as imputation was required to calculate results for 5 patients due to profound mineralization defects.[1,6]

DEMONSTRATED SAFETY PROFILE IN ADULT PATIENTS

The safety profile of CRYSVITA was demonstrated in 175 adults with XLH exposed for a mean duration of 61 weeks[1]

Adverse events occurring in >5% of CRYSVITA-treated adult patients and in at least 2 patients more than with placebo from the 24-week placebo-controlled period of the Phase 3 study[1]

Adverse event	CRYSVITA (n=68) n (%)	Placebo (n=66) n (%)
Back pain	10 (15)	6 (9)
Headache†	9 (13)	6 (9)
Tooth infection‡	9 (13)	6 (9)
Restless legs syndrome	8 (12)	5 (8)
Vitamin D decreased§	8 (12)	3 (5)
Dizziness	7 (10)	4 (6)
Constipation	6 (9)	0 (0)
Muscle spasm	5 (7)	2 (3)
Blood phosphorus increased¶	4 (6)	0 (0)

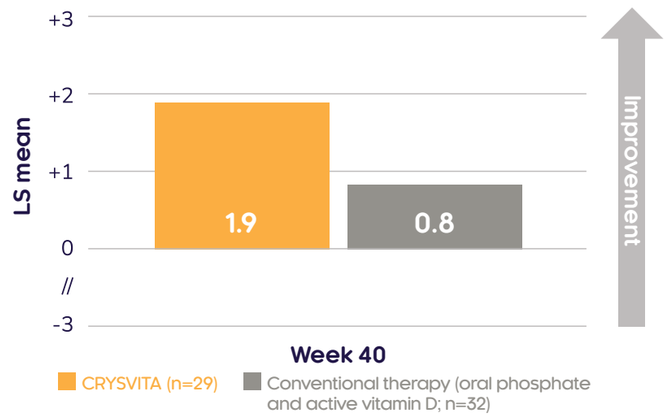
Adapted from the Product Monograph.[1]

†Headache includes: headache and head discomfort.
‡Tooth infection includes: tooth abscess and tooth infection.
§Vitamin D decreased includes: vitamin D deficiency, blood 25-hydroxycholecalciferol decreased, and vitamin D decreased.
¶Blood phosphorus increased includes: blood phosphorus increased and hyperphosphatemia.

DEMONSTRATED EFFICACY IN PEDIATRIC PATIENTS AGED 1 TO 12 YEARS

CRYSVITA achieved significantly greater improvement in XLH-related rickets severity vs. conventional therapy at Week 40 in an open-labelled study (Mean RGI-C global scores [95% CI]: 1.9 [1.70, 2.14] vs. 0.8 [0.56, 0.99]; p<0.0001)[1,7†‡§]

Mean RGI-C global scores in children 1–12 years old[1,7§]



Adapted from the Product Monograph and Imel EA *et al.*, 2019.[1,7]

At Week 64, the LS mean RGI-C Global score was +2.1 in the CRYSVITA group and +1.0 in the active control group (secondary endpoint).[7]

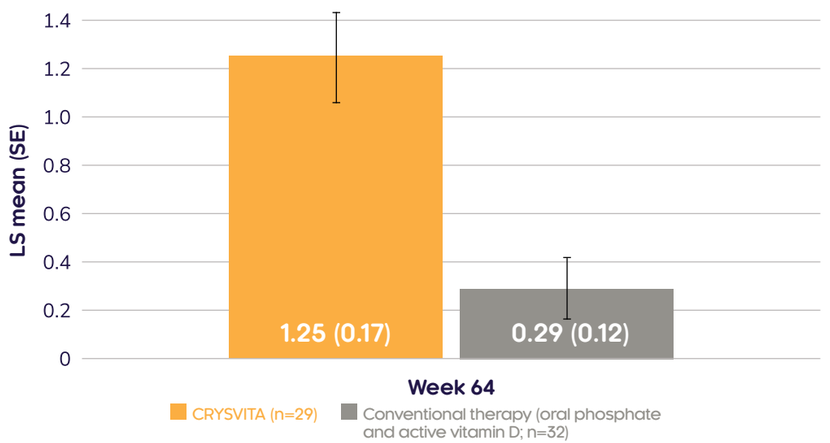
Substantial healing of rickets (defined as an RGI-C score of +2.0) was seen in 72% (21/29) of patients in the CRYSVITA group vs. 6% (2/32) in the conventional therapy group at Week 40; these findings were maintained at Week 64.[1,7]

ANCOVA=analysis of covariance; LS=least squares; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; SD=standard deviation; XLH=X-linked hypophosphatemia.
†Randomized, Phase 3, active-controlled, open-label study in 61 pediatric patients (aged 1 to 12) with XLH and radiographic evidence of rickets at baseline, who had RSS score of ≥2.0 and had received oral phosphate and active vitamin D analogues for a mean (SD) duration of 4 (3.1) years. Patients were randomized to receive either subcutaneous burosumab starting at 0.8 mg/kg (n=29) every 2 weeks (the CRYSVITA group) or oral phosphate (recommended dose 20–60 mg/kg/day) and active vitamin D analogues (recommended doses calcitriol 20–30 ng/kg/day or alfacalcidol 40–60 ng/kg/day) (n=32), as prescribed by investigators (the conventional therapy group). Oral phosphate and active vitamin D analogues were discontinued prior to study enrolment for a 7-day washout period and then reinitiated for patients in the conventional therapy group. All patients completed at least 64 weeks on study. The primary endpoint was change in rickets severity at Week 40, assessed by the RGI-C global score.[1,7]
‡Estimates of LS mean and 95% CI for Week 40 are from an ANCOVA model accounting for treatment group, baseline RSS and baseline age stratification factor. Subsequent *p* values are based on this comparison between treatment groups.[1,7]
§The RGI-C score is assigned based on side-by-side comparisons of wrist and knee radiographs from two time points, with higher scores indicating greater improvement in rickets.

Lower extremity skeletal abnormalities with CRYSVITA and conventional therapy at Week 64 (secondary endpoint)[1,7†]

Lower extremity skeletal abnormalities were assessed by RGI-C (adapted to assess leg bowing and knock knees) in standing long leg radiographs.[1,7]

LS mean RGI-C in standing long leg radiographs in children 1–12 years old[1,7]

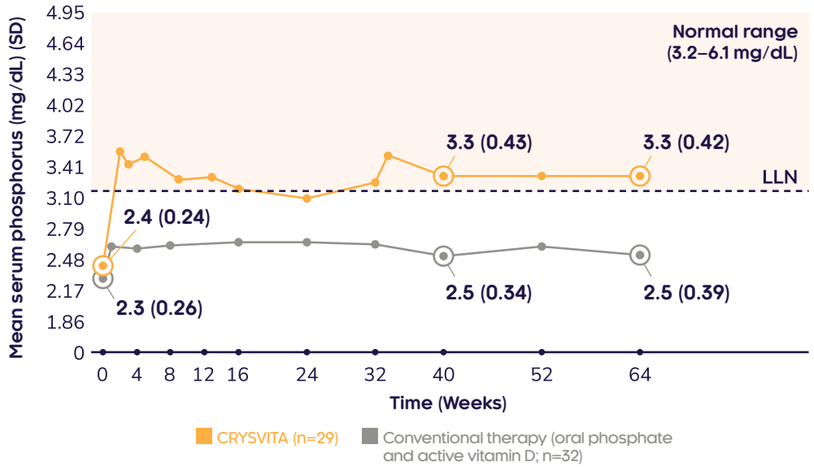


Adapted from the Product Monograph and Imel EA *et al.*, 2019.[1,7]

LS=least squares; RGI-C=Radiographic Global Impression of Change; SE=standard error.
†Refer to study design information on page 7 (†).

Demonstrated serum phosphorus results with CRYSVITA compared to conventional therapy at Week 40 and 64 (secondary endpoint)[1,7†]

Serum phosphorus in children 1–12 years old[1,7]



Adapted from the Product Monograph and Imel EA *et al.*, 2019.[1,7]

CRYSVITA treatment resulted in mean serum phosphorus levels that were **within the normal range for children** (3.2–6.1 mg/dL) at efficacy assessments at Week 40 and 64.[1]

Note that 1 mg/dL is equivalent to 0.323 mmol/L.[4]

LLN=lower limit of normal; SD=standard deviation.
†Refer to study design information on page 7 (†).

The safety profile of CRYSVITA was demonstrated in 94 children with XLH aged 1 to 12 years exposed for a mean duration of 98 weeks[1]

Adverse events reported in ≥10% of CRYSVITA-treated pediatric patients with higher frequency than the conventional therapy group in the Phase 3, active-controlled clinical trial[1]

Adverse event	CRYSVITA (n=29) n (%)	Conventional therapy (n=32) n (%)
Pyrexia	16 (55)	6 (19)
Injection site reaction†	15 (52)	0 (0)
Cough‡	15 (52)	6 (19)
Vomiting	12 (41)	8 (25)
Pain in extremity	11 (38)	10 (31)
Headache	10 (34)	6 (19)
Tooth abscess§	10 (34)	4 (13)
Dental caries	9 (31)	2 (6)
Diarrhea	7 (24)	2 (6)
Vitamin D decreased¶	7 (24)	1 (3)
Constipation	5 (17)	0 (0)
Rash††	4 (14)	2 (6)
Nausea	3 (10)	1 (3)

Adapted from the Product Monograph.[1]

No pediatric patients discontinued CRYSVITA due to adverse events.[1]

Rates of serious treatment-emergent adverse events were comparable in both groups. Serious treatment-emergent adverse events of craniosynostosis, viral infection, and migraine were reported by 3 patients (10%) in the CRYSVITA group.[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 hypersensitivity, injection site inflammation, injection site papule, injection site erosion, injection site discoloration, injection site discomfort, injection site hematoma, injection site hemorrhage, injection site induration, injection site macule, and injection site urticaria.
‡ Cough includes: cough and productive cough.
§ Tooth abscess includes: tooth abscess, tooth infection, toothache.
¶ Vitamin D decreased includes: vitamin D deficiency, blood 25-hydroxycholecalciferol decreased, and vitamin D decreased.
†† Rash includes: rash, rash pruritic, rash maculopapular, rash erythematous, rash generalized, and rash pustular.

Important safety information

Clinical use:

Treatment should be initiated and monitored by a health professional experienced in the management of patients with metabolic bone diseases.

- Safety and efficacy in geriatric patients (≥65 years) has not been established
- No clinical trial efficacy and safety experience with CRYSVITA in patients <1 year of age

Contraindications:

CRYSVITA is contraindicated:

- In use with oral phosphate and/or active vitamin D analogues (calcitriol or alfacalcidol)
- If serum phosphorus is within or above the normal range for age
- In patients with severe renal impairment or end-stage renal disease

Relevant warnings and precautions:

- Hyperphosphatemia and risk of ectopic mineralization, most commonly nephrocalcinosis
- Injection site reactions, especially in pediatric patients
- Vitamin D decrease
- Driving and operating machinery
- Hypersensitivity reactions such as rash, urticaria, and facial swelling
- Fertility
- Pregnant women
- Breastfeeding

For more information:

Please consult the CRYSVITA Product Monograph at https://www.kkna.kyowakirin.com/wp-content/uploads/Crysvita-PM-English.pdf for important information relating to contraindications, warnings and precautions, adverse reactions, drug interactions, dosing and administration, and conditions of clinical use. The Product Monograph is also available by calling us at 1-866-590-9508.

References: 1. CRYSVITA (burosumab injection) Product Monograph. Kyowa Kirin Inc. March 15, 2023. **2.** Insogna KL, *et al.* A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphataemia: Week 24 primary analysis. *J Bone Miner Res.* 2018;33:1381–1382. **3.** Portale AA, *et al.* Continued beneficial effects of burosumab in adults with X-linked hypophosphataemia: Results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calc Tiss Int.* 2019;105:271–284. **4.** ENDMEMO. Available from: http://www.endmemo.com/medical/unitconvert/Phosphorus.php. Consulted October 3, 2023. **5.** Ultragenyx Pharmaceutical Inc. UX023-CL303 Clinical Study Protocol Amendment 5. January 26, 2018. **6.** Insogna KL, *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. **7.** Imel EA, *et al.* Burosumab versus continuation of conventional therapy in children with X-linked hypophosphataemia: A randomised, active-controlled, open-label, phase 3 trial. *Lancet.* 2019;393(10189):2416–2427. **8.** Suppl to Imel EA, *et al.* Burosumab versus continuation of conventional therapy in children with X-linked hypophosphataemia: A randomised, active-controlled, open-label, phase 3 trial. *Lancet.* 2019;393(10189, Suppl):2416–2427.

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Solution for Subcutaneous Injection
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CRYSVITA: EFFICACY RESULTS IN BOTH PEDIATRIC AND ADULT PATIENTS WITH XLH

CRYSVITA IN CHILDREN:

Significantly greater improvement in the severity of XLH-related rickets were achieved with CRYSVITA vs. conventional therapy based on mean RGI-C global scores at Week 40.[1,7]

- 1.9 (95% CI: 1.70, 2.14) vs. 0.8 (95% CI: 0.56, 0.99); $p<0.0001$

72% of patients receiving CRYSVITA achieved substantial healing of rickets (RGI-C score of ≥+2.0) at Week 40 vs. 6% of patients receiving conventional therapy (secondary endpoint).[1,7,8]

The LS mean (SE) lower extremity skeletal abnormalities score (as assessed by RGI-C in standing long leg radiographs) was +1.25 (0.17) in patients treated with CRYSVITA and +0.29 (0.12) with placebo at Week 64.[1,7]

Mean serum phosphorus levels were within normal range (3.2–6.1 mg/dL) at Weeks 40 and 64 of CRYSVITA treatment (secondary endpoint).[1,7]

CRYSVITA IN ADULTS:

Significantly more patients on CRYSVITA vs. placebo achieved serum phosphorus concentrations above the LLN (2.5 mg/dL) averaged across the midpoints of the dose interval through 24 weeks.[1,2]

- 94% (95% CI: 85.8, 97.7) vs. 8% (95% CI: 3.3, 16.5); $p<0.0001$

Mean serum phosphorus concentrations remained at or above LLN (2.5–4.5 mg/dL) through 48 weeks of treatment for the initial CRYSVITA group (secondary endpoint).[1,3]

Significantly greater improvements in XLH-associated stiffness were demonstrated with CRYSVITA vs. placebo at Week 24 (secondary endpoint).[1,2]

- WOMAC stiffness score change (LS mean): -7.9 (CRYSVITA) vs. +0.5 (placebo); $p=0.0106$†

Assessment of active fracture/pseudofracture sites at Week 24 demonstrated a higher rate of complete healing in the CRYSVITA group compared to placebo at Week 24 (exploratory endpoint).[1-3]

In a single-arm study, treatment with CRYSVITA demonstrated histomorphometric improvement in osteomalacia at Week 48, as shown by decreases in proxy measures (osteoid volume/bone volume ratio, osteoid thickness, and mineralization lag time).[1]

LLN=lower limit of normal; LS=least squares; RGI-C=Radiographic Global Impression of Change; SE=standard error; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.
† A higher score indicates poorer functioning.

CRYSVITA® burosumab injection

Contact your Kyowa Kirin sales rep for more information about CRYSVITA

COMM-CA-CRY-0054 April 2025

KYOWA KIRIN

REVIEWED BY PAAB