



For X-linked hypophosphataemia (XLH)

INTRODUCE A CHILD TO A WORLD OF CHOICE



This material is for Healthcare Professionals Only.

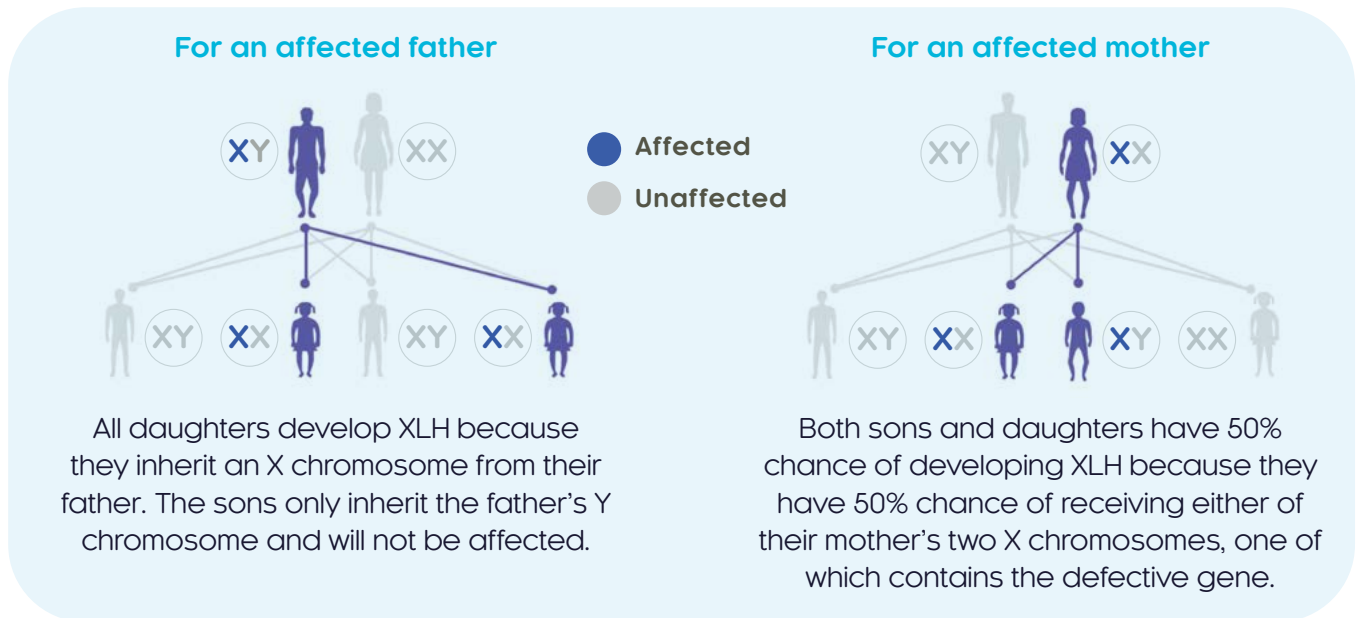
Kyowa KIRIN

XLH IS INHERITED IN AN X-LINKED DOMINANT MANNER^{1,2}



XLH is caused by inactivating mutations in PHEX, the gene responsible for phosphate regulation, leading to excess FGF23²

- Hereditary – inherited in X-linked dominant pattern²

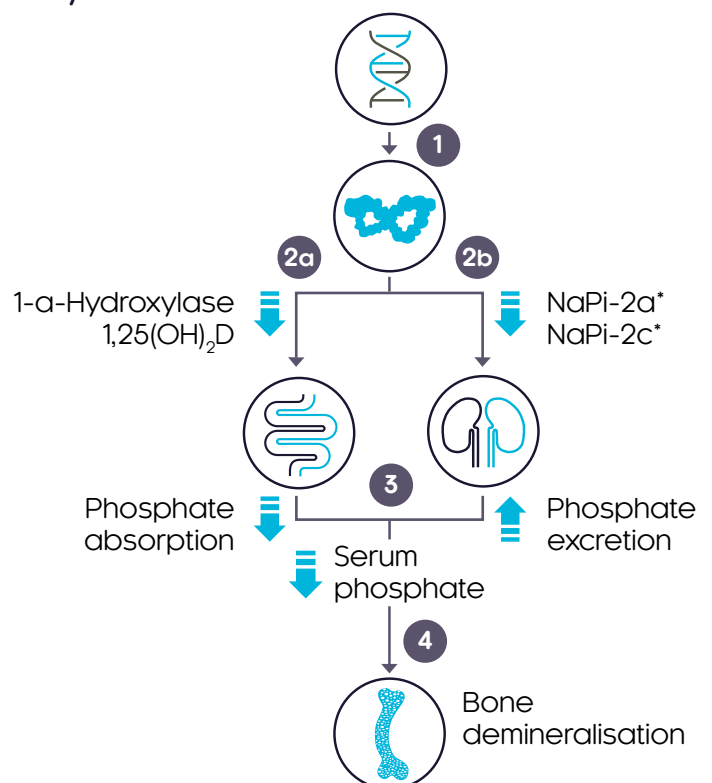


- Spontaneous genetic mutations – 20–30% of cases arise from spontaneous gene mutations^{3,4}
- Progressive condition – lifelong disease, symptoms can worsen with age⁵

Role of fibroblast growth factor 23 (FGF23) in XLH^{6,7}

In XLH, phosphate homeostasis is disrupted by the presence of excess FGF23 resulting in hypophosphataemia

- 1 PHEX mutation → ↑ FGF23
- 2a ↓ 1,25(OH)₂D → ↓ phosphate absorption in gut
- 2b ↓ Sodium phosphate co-transporters → ↓ phosphate reabsorption by kidney and therefore ↑ phosphate wasting in urine
- 3 ↓ Serum phosphate levels
- 4 Hypophosphataemia leads to osteomalacia and other musculoskeletal consequences in adults



*Sodium/phosphate co-transporter proteins

FGF23, fibroblast growth factor 23; NaPi, sodium-phosphate cotransporters; PHEX, phosphate-regulating endopeptidase homolog on the X chromosome; XLH, X-linked hypophosphataemia; 1,25(OH)₂D, 1,25 dihydroxy vitamin D.

Biochemical tests, radiological findings, family history and PHEX mutation tests can help to establish a diagnosis of XLH

Biochemical findings²

Laboratory tests	XLH
Main biochemical features	
1,25(OH) ₂ D	Normal [‡]
FGF23	Normal or ↑
Serum phosphate	↓
TmP/GFR	↓
Other biochemical features	
ALP	↑, ↑↑
25(OH)D	Normal
PTH	Normal or ↑ [§]
Serum calcium	Normal
Urinary phosphate	↑

↓, reduced; ↑, ↑↑, very elevated because normal phosphate concentrations vary with age.

‡Decreased relative to the serum phosphate concentration; §PTH might be moderately elevated.

Radiographic findings

Radiographs are indicated during the initial evaluation of XLH⁸

- Radiologic alterations are best visualised at the growth plate of rapidly growing bones⁹
- Radiographic findings include cupping, splaying, fraying, growth plate widening, and osteopenia¹⁰



Metaphyseal widening in knee in child with XLH



Metaphyseal widening in wrist in child with XLH

Images have been adapted from the original article "Whole exome sequencing confirms the clinical diagnosis of Marfan syndrome combined with X-linked hypophosphataemia" by Sheng X, et al. *J Transl Med.* 2015;13:179 (doi:10.1186/1880-6805-31-14).¹⁴ The original article is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

XLH can be a physically disabling condition, progressing into adulthood. A wide range of symptoms can be presented with disease.

Paediatric patients

- Rickets¹¹
- Delayed growth¹¹
- Craniosynostosis¹¹

Paediatric and adult patients

- Short stature^{12,13}
- Disproportionate growth¹⁴
- Lower extremity deformity¹¹
- Tooth abscesses¹¹
- Osteomalacia¹¹
- Bone pain¹¹
- Joint pain and stiffness^{11,12}
- Muscle pain^{12,13}
- Muscle weakness^{13,15}
- Chiari malformation¹¹
- Diminished quality of life including psychosocial impact^{12,13}

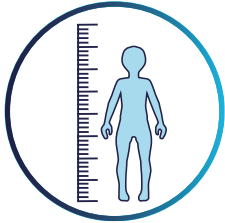
Adult patients

- Pseudofractures¹¹
- Osteoarthritis¹¹
- Hearing loss¹¹
- Extrasosseous calcifications including:¹¹**
 - Osteophytes
 - Enthesopathy
 - Spinal stenosis

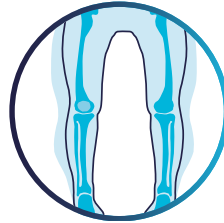
GOALS OF THERAPY IN CHILDREN²



Treatment seeks to improve the symptoms of rickets by correcting growth and minimizing both radiographic abnormalities and skeletal deformities



Improve growth



Strengthen legs



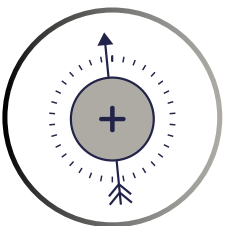
Reduce bone pain



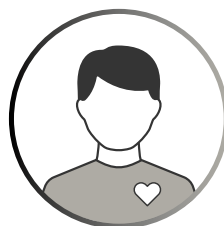
Improve dental health

25–40% of patients with well-controlled XLH show linear growth failure despite optimal treatment with conventional therapy¹¹

Conventional treatment with active vitamin D and oral phosphate salts has the following limitations:



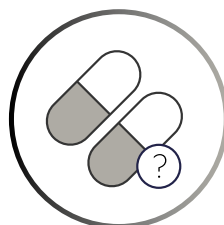
Sub-optimal efficacy^{2,11}



Patient adherence¹⁶



Long-term safety and tolerability²



Uncertainty over optimal dose ranges vary widely²



Causes transient increases in serum phosphate but does not correct renal phosphate wasting¹⁷

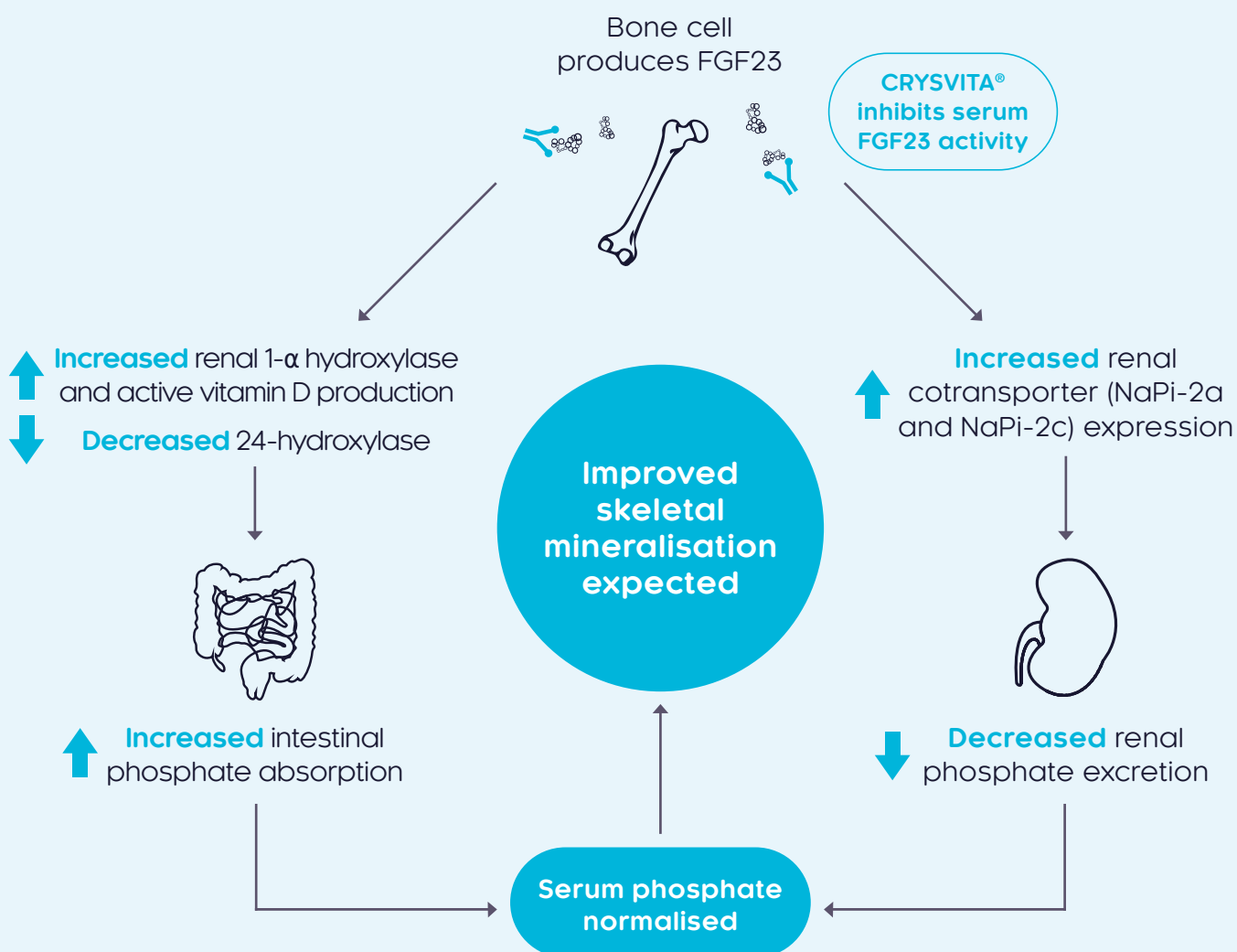
CRYSVITA® : A NEW FULLY HUMAN MONOCLONAL ANTIBODY FOR XLH TREATMENT



- CRYSVITA® is a recombinant fully human monoclonal antibody (IgG1) that binds to and inhibits the excess activity of FGF23¹⁸
- By inhibiting FGF23 activity, CRYSVITA® increases tubular reabsorption of phosphate from the kidney and increases serum concentration of 1,25(OH)₂D, so increasing serum phosphate levels¹⁸

CRYSVITA® is indicated for the treatment of X-linked hypophosphataemia (XLH) in adult and pediatric patients 1 year of age and older¹⁸

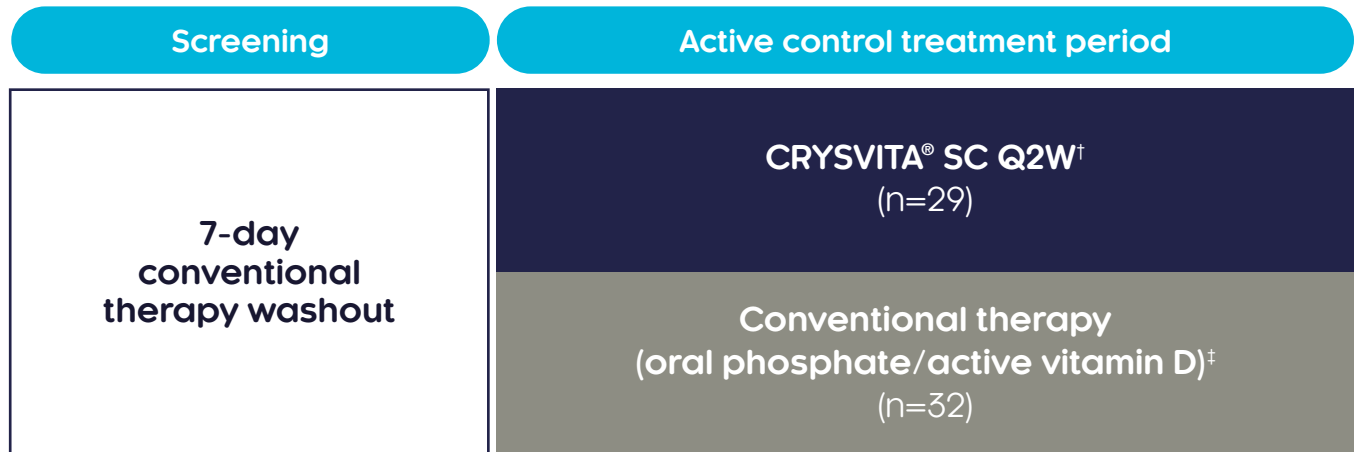
CRYSVITA® binds to and inhibits excess FGF23 activity, restoring phosphate homeostasis in XLH^{17,18}



THE EFFICACY AND SAFETY OF CRYSVITA® IN CHILDREN WITH XLH

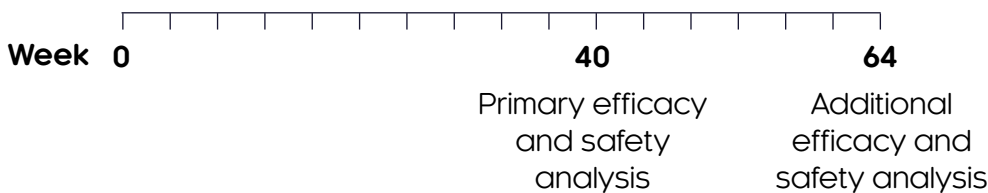


CRYSVITA® in paediatric patients: Phase III trial design in children with XLH, aged 1–12 years¹⁷



Primary outcome: change in RGI-C at week 40

Randomisation 1:1



Stratified by:

- Total RSS (≤ 2.5 vs > 2.5)
- Age (< 5 vs ≥ 5 years)
- Region (Japan vs ROW)

Study population

- Children aged 1-12 with XLH (n=61)

Inclusion criteria

- Confirmed PHEX mutation or variant of unknown significance in patient or a family member
- Total RSS ≥ 2.0
- Fasting serum phosphate < 0.97 mmol/L (3.0 mg/dL)
- Prior conventional therapy
 - ≥ 12 months for ages ≥ 3 years
 - ≥ 6 months for ages < 3 years

Exclusion criteria

- Tanner stage ≥ 4
- Height $> 50^{\text{th}}$ percentile for age
- Growth hormone use in previous 12 months
- Plasma PTH > 19 pmol/L (180 pg/mL)
- Hypo- or hypercalcaemia
- Grade 4 nephrocalcinosis
- Planned orthopaedic surgery

Primary outcome

- Change in RGI-C at week 40

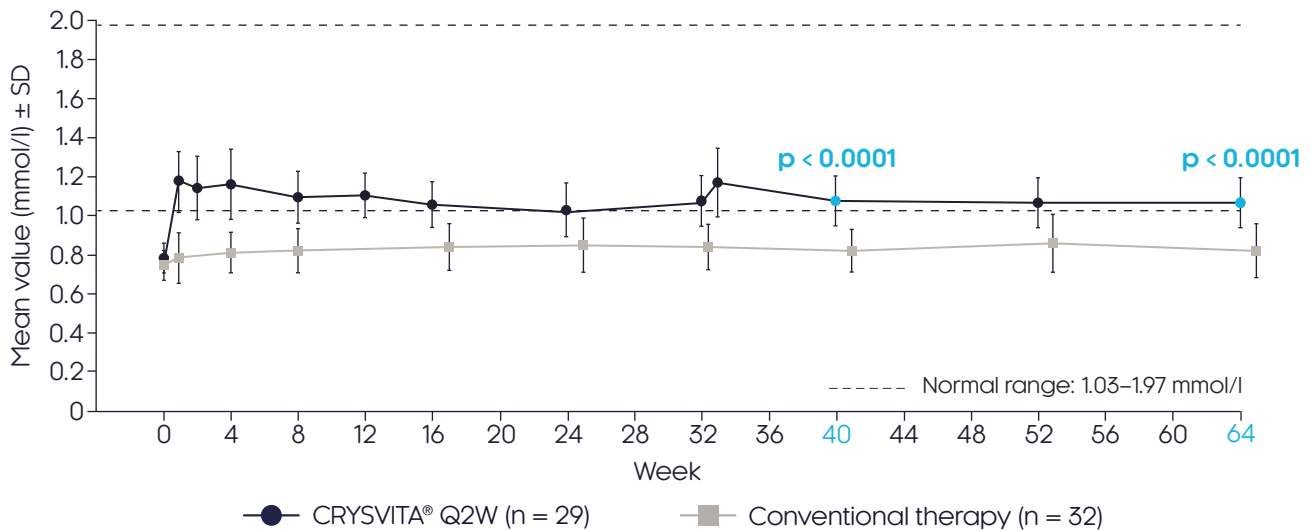
[†]**CRYSVITA® dosing:** Initiated at a dose of SC 0.8 mg/kg Q2W; increased to 1.2 mg/kg Q2W if two consecutive pre-dose, fasting, serum phosphate concentrations were below 1.03 mmol/L (3.2 mg/dL) and serum phosphate had increased by < 0.16 mmol/L (< 0.5 mg/dL) from baseline on a single measurement.

[‡]**Conventional therapy dosing:** The recommended oral phosphate dose in children is 20–60 mg/kg/day divided into three to five doses per day and alfacalcidol 40–60 ng/kg/day or calcitriol 20–30 ng/kg/day; depending on the formulation, the active vitamin D could be given one to three times a day.

PHEX, phosphate-regulating endopeptidase homolog on the X chromosome; **PTH**, parathyroid hormone; **Q2W**, every 2 weeks; **RGI-C**, Radiographic Global Impression of Change; **ROW**, rest of the world; **RSS**, Rickets Severity Score; **SC**, subcutaneous; **XLH**, X-linked hypophosphataemia.

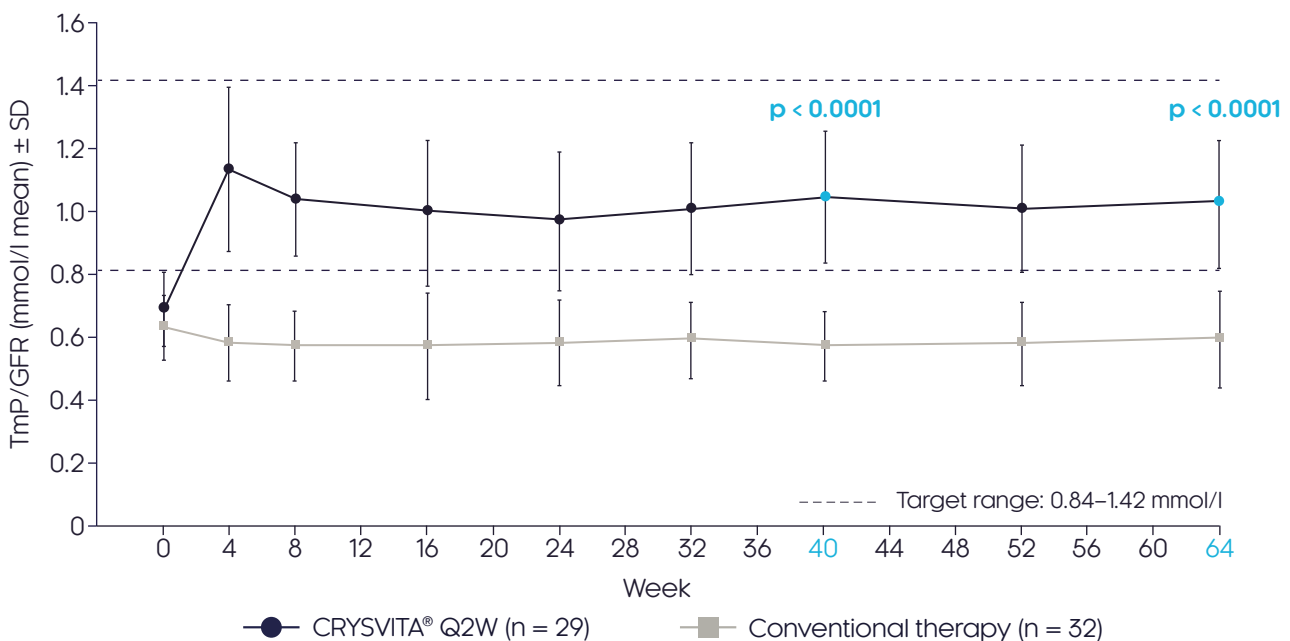
Increased serum phosphate levels

CRYSVITA® significantly improved mean serum phosphate levels compared with conventional therapy in the study population¹⁷



Increased renal phosphate resorption

CRYSVITA® significantly improved renal phosphate reabsorption compared with conventional therapy in the study population¹⁷

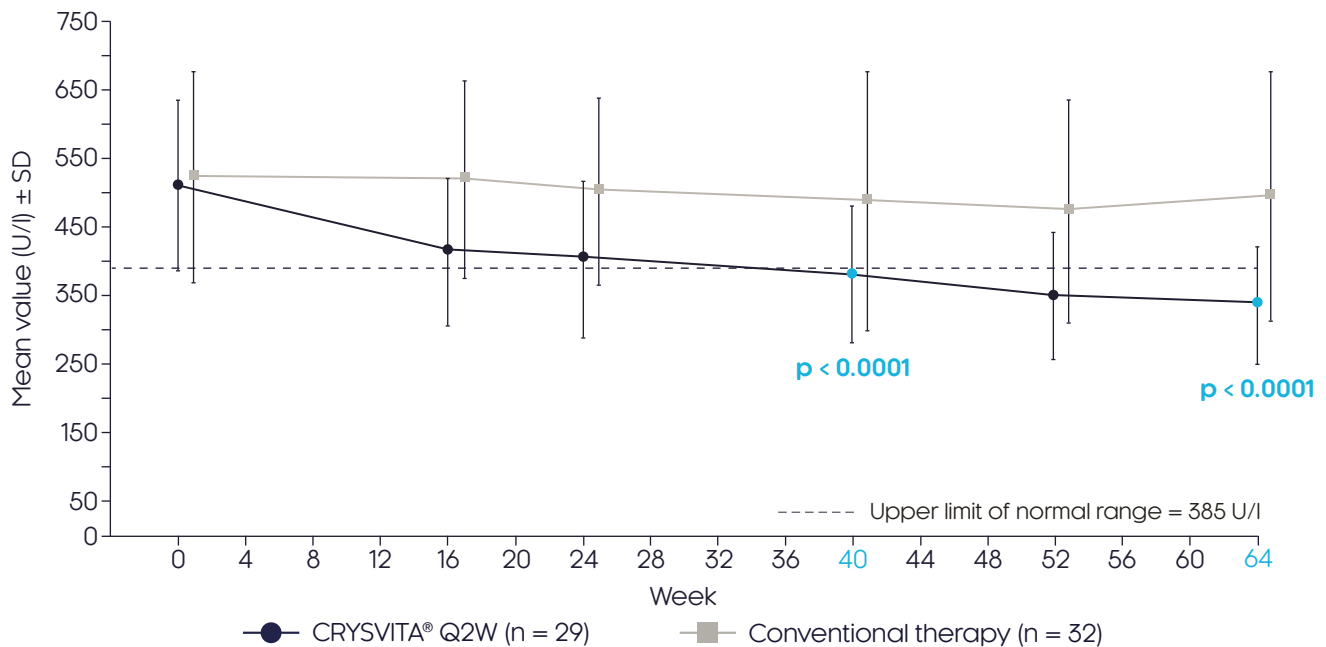


The graphs from this page are adapted from Imel EA et al. Lancet. 2019 Jun 15;393(10189):2416-2427. Eligible patients had radiographic evidence of rickets at baseline and were on long-term conventional therapy. Patients randomly assigned to receive CRYSVITA® 0.8 mg/kg Q2W or conventional therapy.

Q2W, every 2 weeks; SD, standard deviation; TmP/GFR, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate.

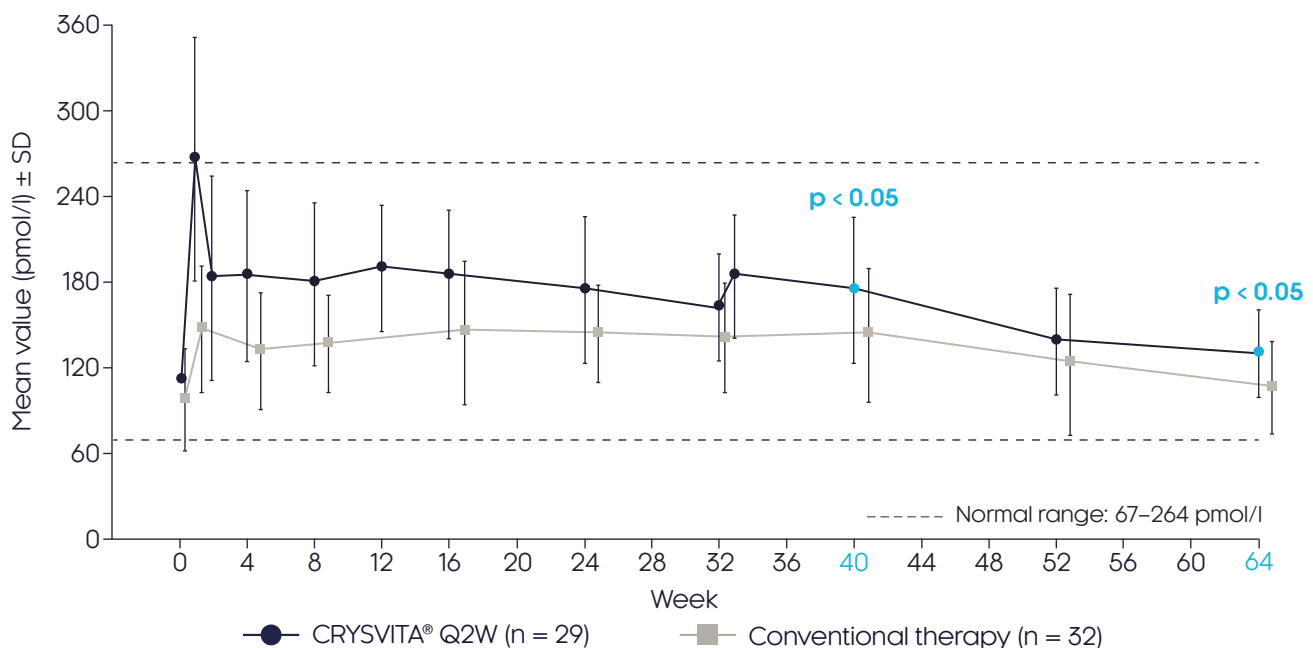
Decreased ALP levels

CRYSVITA® significantly decreased mean ALP levels compared with conventional therapy in the study population¹⁷



Increased 1,25(OH)₂D levels

CRYSVITA® significantly increased 1,25(OH)₂D levels compared with conventional therapy in the study population¹⁷



The graphs from this page are adapted from Imel EA et al. Lancet. 2019 Jun 15;393(10189):2416–2427. Post-baseline values are offset from the actual treatment week to avoid overlapping error bars. Eligible patients had radiographic evidence of rickets at baseline and were on long-term conventional therapy. Patients randomly assigned to receive CRYSVITA® 0.8 mg/kg Q2W or conventional therapy.

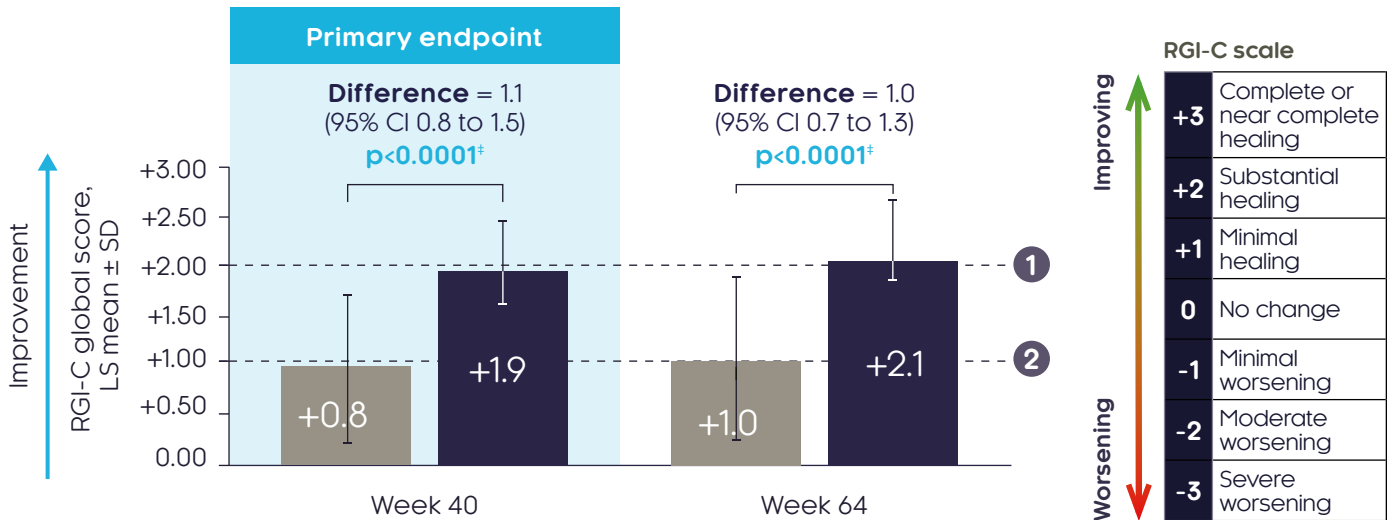
ALP, alkaline phosphatase; Q2W, every 2 weeks; SD, standard deviation; 1,25(OH)₂D, 1,25 dihydroxy vitamin D.

CRYSVITA® SIGNIFICANTLY IMPROVED HEALING OF RICKETS¹⁷



Improved RGI-C global score

CRYSVITA® demonstrated significant improvements in rickets as assessed by RGI-C global score compared with conventional therapy in the study population¹⁷

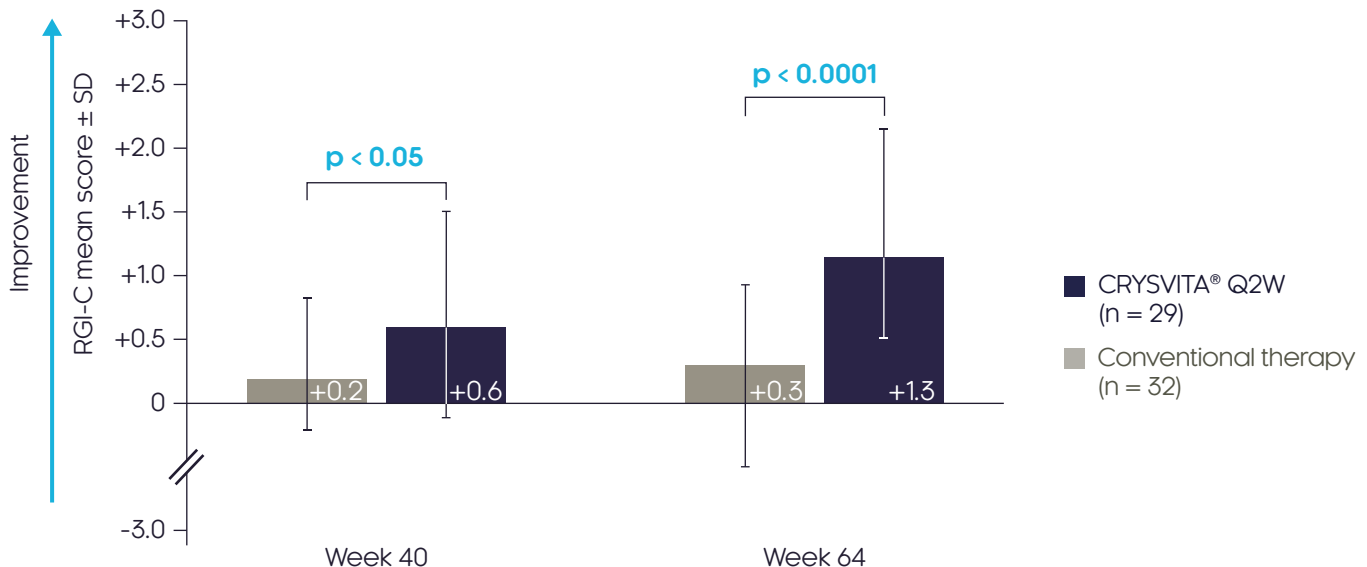


- ① Substantial healing ■ CRYSVITA® Q2W (n = 29)
- ② Minimal healing ■ Conventional therapy (oral phosphate and active vitamin D; n = 32)

[‡]Based on the comparison between treatment groups in the LS mean change, using the ANCOVA model at Week 40 and the GEE model for Week 64.

Improved lower limb deformity

CRYSVITA® continued to improve lower limb deformity compared with conventional therapy in the study population¹⁷



The graphs from this page are adapted from Imel EA et al. Lancet. 2019;393:2416–2427. Eligible patients had radiographic evidence of rickets at baseline and were on long-term conventional therapy. Patients randomly assigned to receive CRYSVITA® 0.8 mg/kg Q2W or conventional therapy.

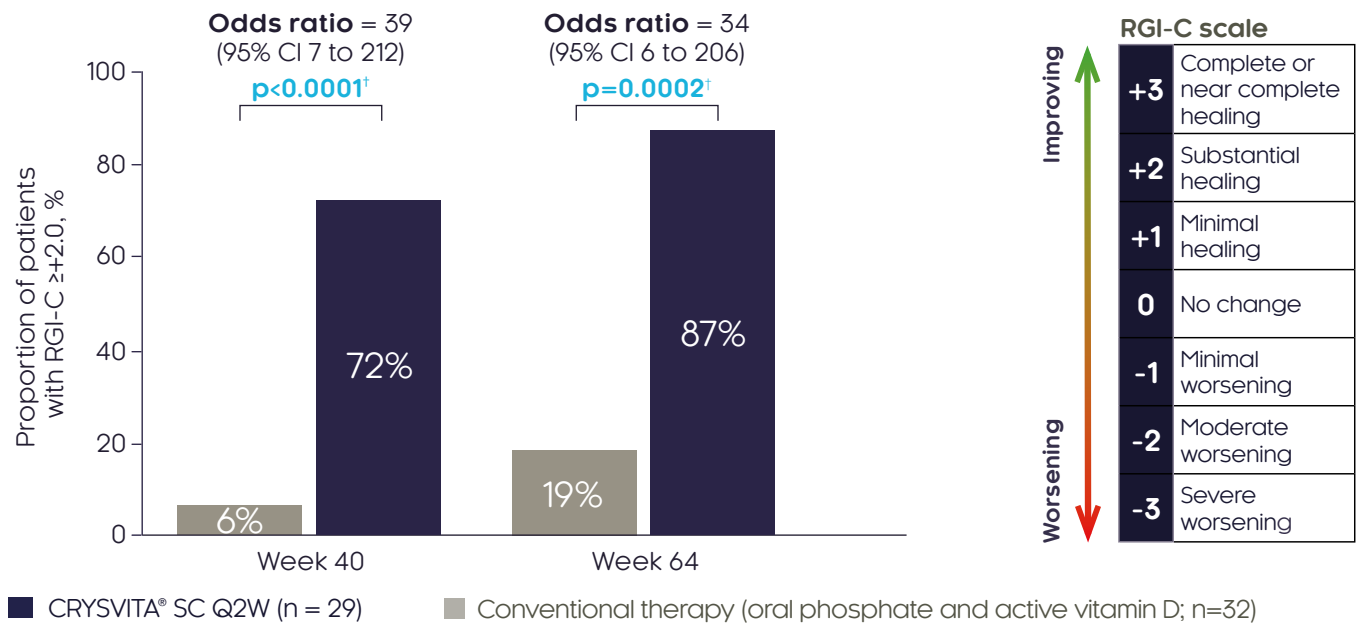
ANCOVA, analysis of covariance; **CI**, confidence interval; **GEE**, generalised estimating equation; **LS**, least squares; **Q2W**, every 2 weeks; **RGI-C**, Radiographic Global Impression of Change; **SC**, subcutaneous; **SD**, standard deviation; **XLH**, X-linked hypophosphataemia.

CRYSVITA® SIGNIFICANTLY IMPROVED HEALING OF RICKETS¹⁷



Higher percentage of patients achieving substantial healing of rickets

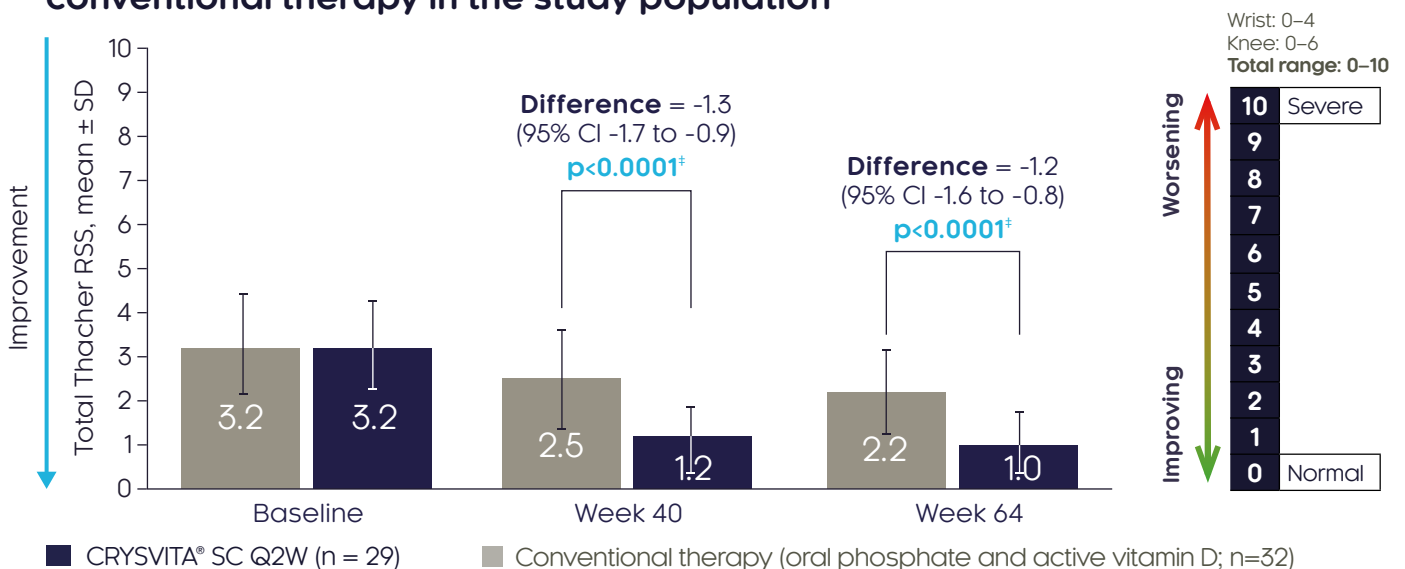
CRYSVITA® demonstrated substantial healing* (defined as an RGI-C score ≥ 2) of rickets in a significantly greater proportion of the study population (87%) than conventional therapy (17%) at week 64¹⁷



[†]Based on logistic regression model. *Substantial healing is defined as an RGI-C global score of at least +2.

Improved RSS

CRYSVITA® demonstrated significant improvements in RSS compared with conventional therapy in the study population¹⁷



[†]Based on the comparison between treatment groups in the LS mean change, using the ANCOVA model at Week 40 and the GEE model for Week 64.

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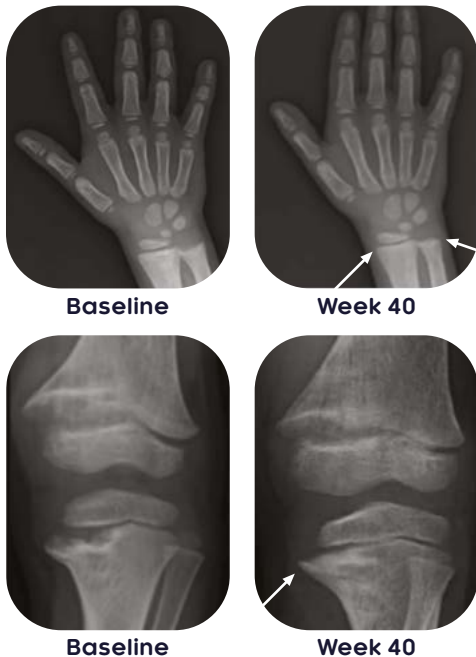
ANCOVA, analysis of covariance; **CI**, confidence interval; **GEE**, generalised estimating equation; **LS**, least squares; **Q2W**, every 2 weeks; **RGI-C**, Radiographic Global Impression of Change; **RSS**, Rickets Severity Score; **SC**, subcutaneous; **SD**, standard deviation; **XLH**, X-linked hypophosphataemia.

CRYSVITA® SIGNIFICANTLY IMPROVED HEALING OF RICKETS¹⁷



Radiographic evidence

Radiographs and rickets assessment scores in a 4-year-old girl with XLH treated with CRYSVITA®: Substantial healing (RGI-C) of rickets achieved at week 40^{†17}

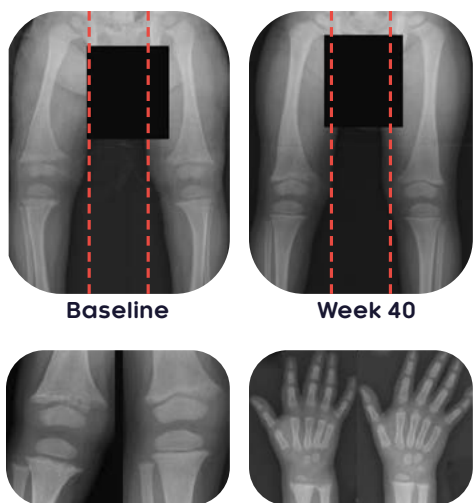


Adapted from Imel EA et al. Lancet. 2019;393:2416–27.

Score	Baseline	Week 40
Thacher RSS		
Wrist	2.0	0.5
Knee	1.5	1.0
Total	3.5	1.5
RGI-C score[†]		
Wrist	-	+2.3
Knee	-	+2.0
Global	-	+2.0

These RGI-C values demonstrate substantial healing of rickets

Radiographs and rickets assessment scores in 18-month-old boy with XLH treated with CRYSVITA®: Substantial healing (RGI-C \geq 2) of rickets achieved at week 40^{†19}



Adapted from Whyte MP et al. Lancet Diabetes Endocrinol. 2019 Mar;7(3):189–199

Rickets assessment in 18-month-old boy

Assessment	Baseline	Week 40
RSS		
Wrist	2.5	1.0
Knee	4.0	1.0
Total	6.5	2.0
RGI-C score[†]		
Wrist	-	+2.7
Knee	-	+2.3
Global	-	+2.3
Lower limb	-	+2.0

[†]Substantial healing is defined as an RGI-C score \geq +2.

[‡]Patient received conventional therapy for about 8 months before the 7-day wash-out period for the study.

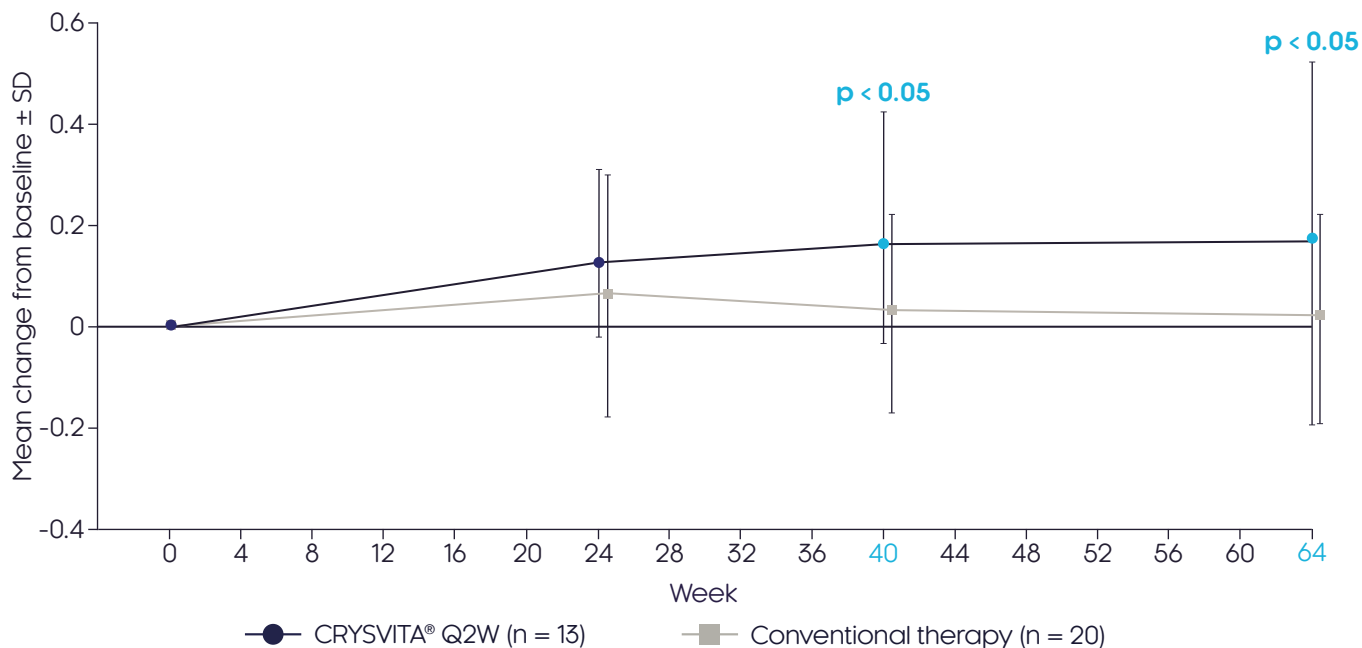
RGI-C, Radiographic Global Impression of Change; **RSS**, Rickets Severity Score; **XLH**, X-linked hypophosphataemia.

CRYSVITA® SIGNIFICANTLY IMPROVED GROWTH AND MOBILITY¹⁷



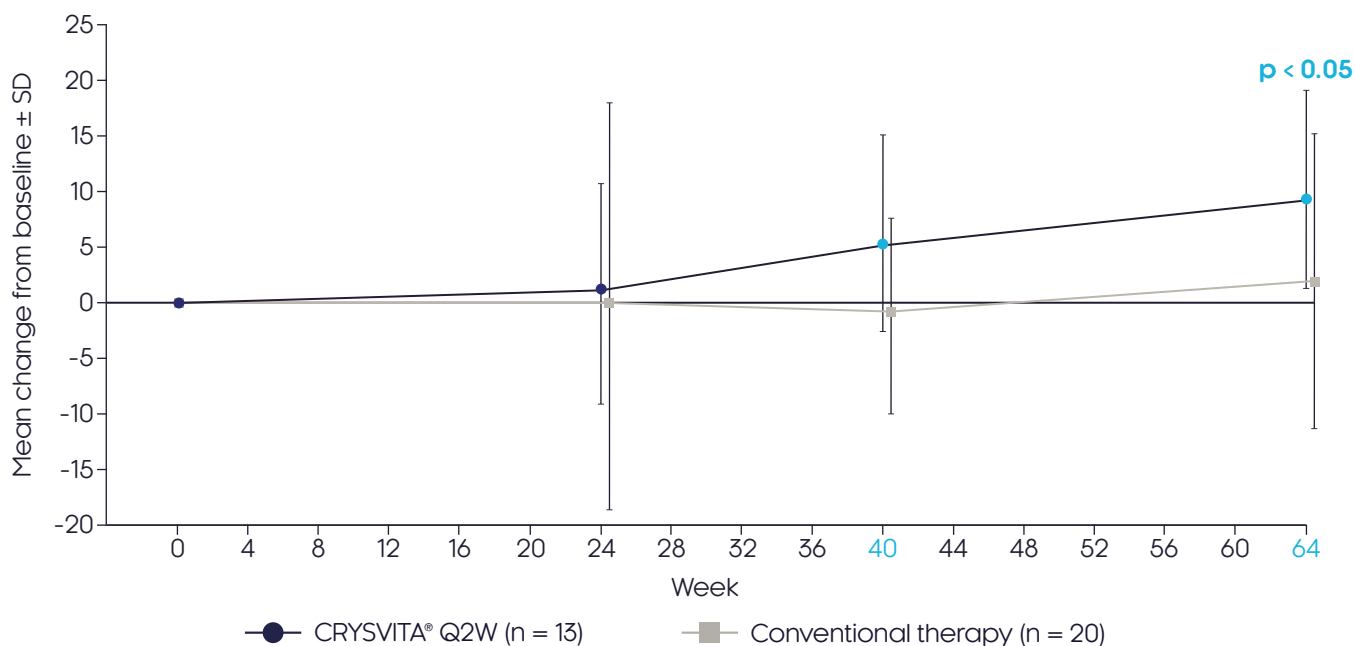
Increased in length/height Z score

CRYSVITA® showed significantly greater improvements in recumbent length/standing height Z score compared with conventional therapy in the study population¹⁷



Increased in the 6MWT

CRYSVITA® improved mobility compared with conventional therapy in the study population¹⁷



The graphs from this page are adapted from Imel EA et al. Lancet. 2019 Jun 15;393(10189):2416-2427. Post-baseline values are offset from the actual treatment week to avoid overlapping error bars. Eligible patients had radiographic evidence of rickets at baseline and were on long-term conventional therapy. Patients randomly assigned to receive CRYSVITA® 0.8mg/kg Q2W or conventional therapy.

Q2W, every 2 weeks; **SD**, standard deviation; **6MWT**, six-minute walking test.

CRYSVITA® SAFETY PROFILE OVER 64 WEEKS IN CHILDREN WITH XLH¹⁷



Adverse Reaction	Conventional Therapy (N=32) n (%)	CRYSVITA® (N=29) n (%)
Pyrexia	6 (19)	16 (55)
Injection site reaction	0 (0)	7 (24)
Cough	6 (19)	15 (52)
Vomiting	8 (25)	12 (41)
Pain in extremity	10 (31)	11 (38)
Headache	6 (19)	10 (35)
Tooth abscess	3 (9)	8 (28)
Dental caries	2 (6)	9 (31)
Diarrhea	2 (6)	7 (24)
Vitamin D decreased	1 (3)	6 (21)
Constipation	0 (0)	5 (17)
Rash	2 (6)	3 (10)
Nausea	1 (3)	4 (14)

Events were generally mild or moderate in severity¹⁷

No adverse drug reactions led to treatment discontinuation¹⁷

No events of hyperphosphataemia were reported¹⁷

These are the most common TEAEs with ≥10% incidence in either group. Please see publication for full safety profile.

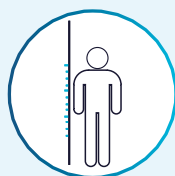
TEAE, treatment-emergent adverse event; **XLH**, X-linked hypophosphataemia.

CRYSVITA® OFFERED A THERAPEUTIC ADVANTAGE OVER CONTINUING CONVENTIONAL THERAPY IN CHILDREN WITH XLH¹⁷

Compared with continuing conventional therapy, switching to CRYSVITA®¹⁷:



Significantly improved rickets healing and reduced severity



Significantly improved growth and mobility outcomes



Significantly improved biochemical markers of phosphate regulation and bone health

Significantly greater clinical improvements were shown in rickets severity, growth, and biochemical parameters among children with XLH treated with CRYSVITA® compared with those continuing conventional therapy¹⁷

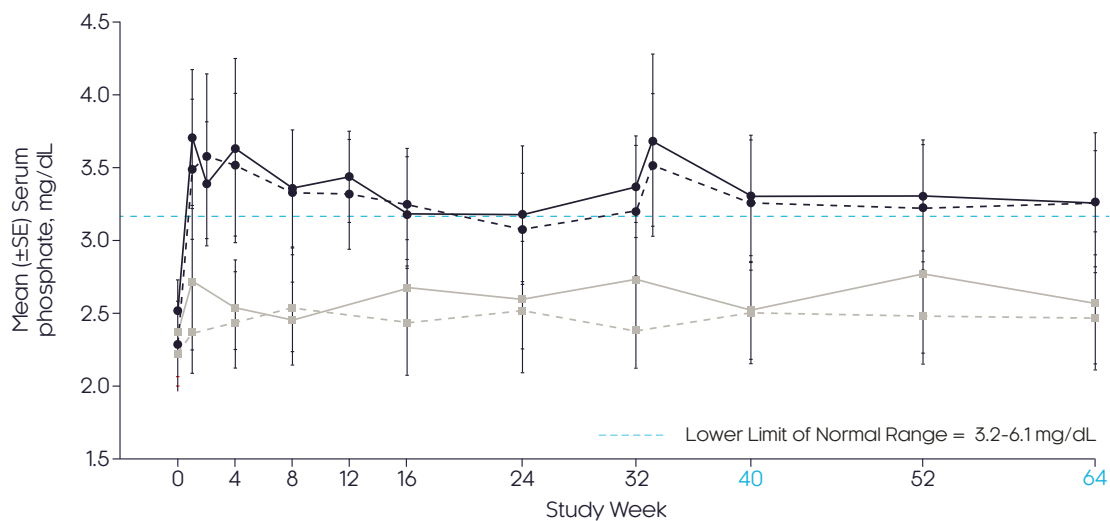
XLH, X-linked hypophosphataemia.

A post hoc analysis of the same study was conducted to evaluate the efficacy and safety of CRYSVITA[®] versus phosphate salts and active vitamin D (Conventional Therapy) in younger (<5 years) and older (5–12 years) children.²⁰

Biochemical changes in younger or older children receiving CRYSVITA[®] or Conventional Therapy.²⁰

Serum Phosphate

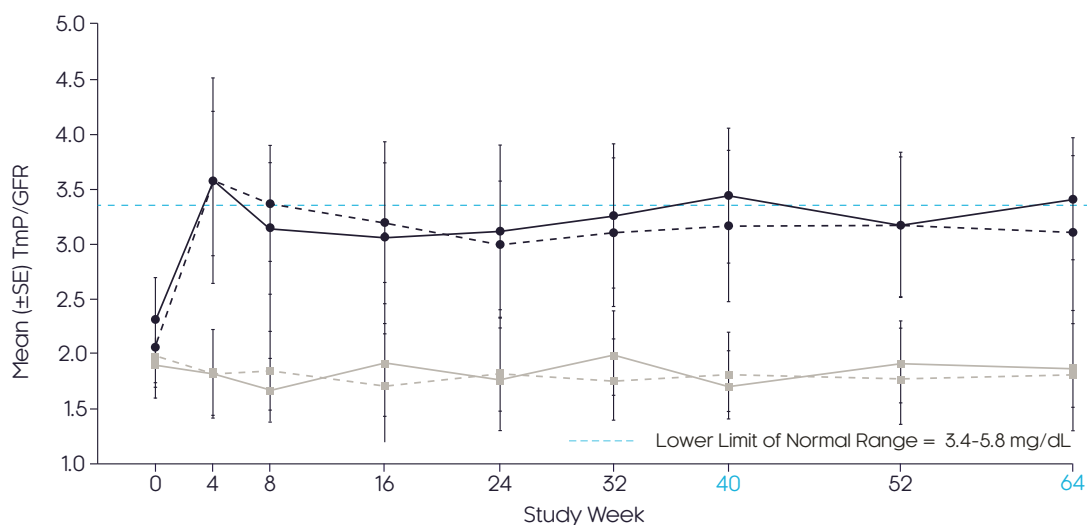
- Sustained increase in serum phosphate was observed in both age groups for those who received CRYSVITA[®]²⁰



- Conventional Therapy <5 years (n=12)
- Conventional Therapy ≥5 years (n=20)
- CRYSVITA[®] SC Q2W, <5 years (n=14)
- CRYSVITA[®] SC Q2W, ≥5 years (n=15)

Renal Phosphate Resorption

- Sustained increased was observed for TmP/GFR with CRYSVITA[®] for both age groups²⁰



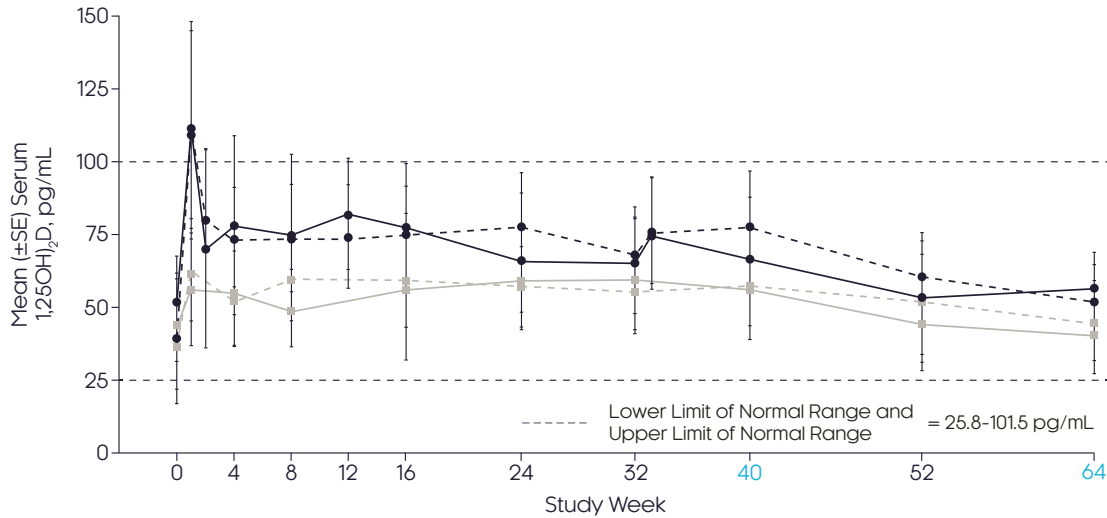
- Conventional Therapy <5 years (n=12)
- Conventional Therapy ≥5 years (n=20)
- CRYSVITA[®] SC Q2W, <5 years (n=14)
- CRYSVITA[®] SC Q2W, ≥5 years (n=15)

The graphs from this page are adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253. Patients randomly assigned to receive CRYSVITA[®] 0.8 mg/kg Q2W or Conventional Therapy.

Q2W, every 2 weeks; **SE**, standard error; **TmP/GFR**, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate.

Serum 1,25(OH)₂D

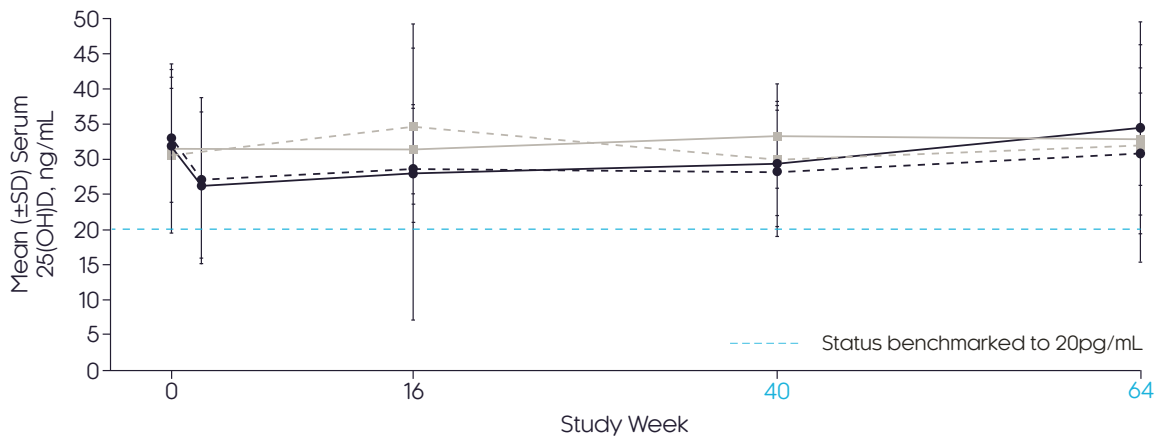
- Serum 1,25(OH)₂D was within normal range for both age groups with CRYSVITA[®] after the initial peak²⁰



- Conventional Therapy <5 years (n=12)
- Conventional Therapy ≥5 years (n=20)
- CRYSVITA[®] SC Q2W, <5 years (n=14)
- CRYSVITA[®] SC Q2W, ≥5 years (n=15)

Serum 25(OH)D

- Serum 25(OH)D decreased slightly after initial CRYSVITA[®] dose, before increasing steadily throughout the study for both age groups²⁰
- Serum 25(OH)D was relatively stable throughout for the Conventional Therapy groups²⁰



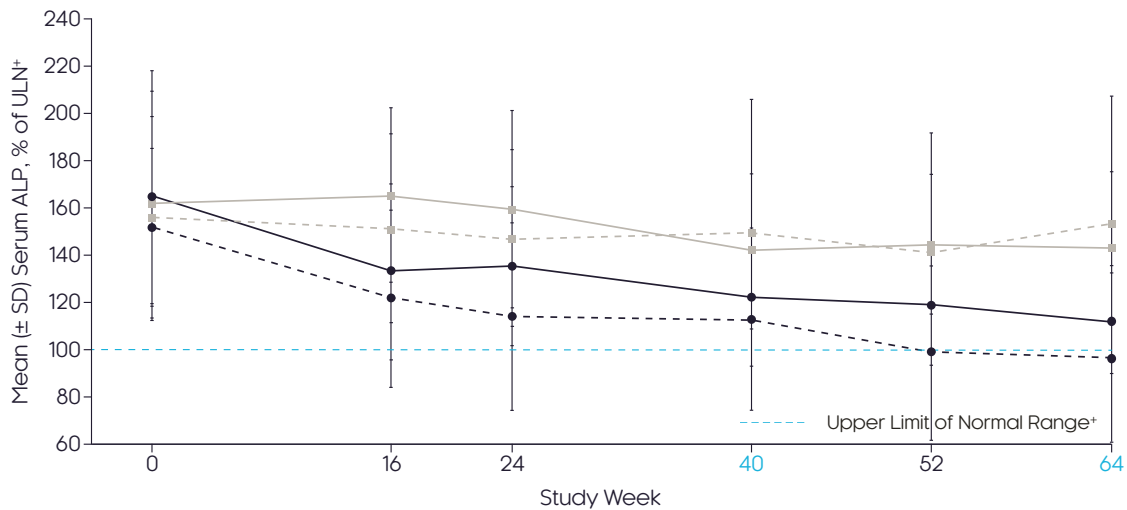
- Conventional Therapy <5 years (n=12)
- Conventional Therapy ≥5 years (n=20)
- CRYSVITA[®] SC Q2W, <5 years (n=14)
- CRYSVITA[®] SC Q2W, ≥5 years (n=15)

The graphs from this page are adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253. Patients randomly assigned to receive CRYSVITA[®] 0.8 mg/kg Q2W or Conventional Therapy.

1,25(OH)₂D, 1,25 dihydroxy vitamin D; **SE**, standard error; **pg/mL**, picograms per milliliter; **Q2W**, every 2 weeks; **SD**, standard deviation; **25(OH)D**, 25-hydroxyvitamin D; **ng/mL**, nanograms per milliliter.

Serum Alkaline Phosphatase

- In both age groups, serum alkaline phosphatase decreased greater with CRYSVITA[®] than with Conventional Therapy²⁰
- This decrease was greater in older children with CRYSVITA^{®20}

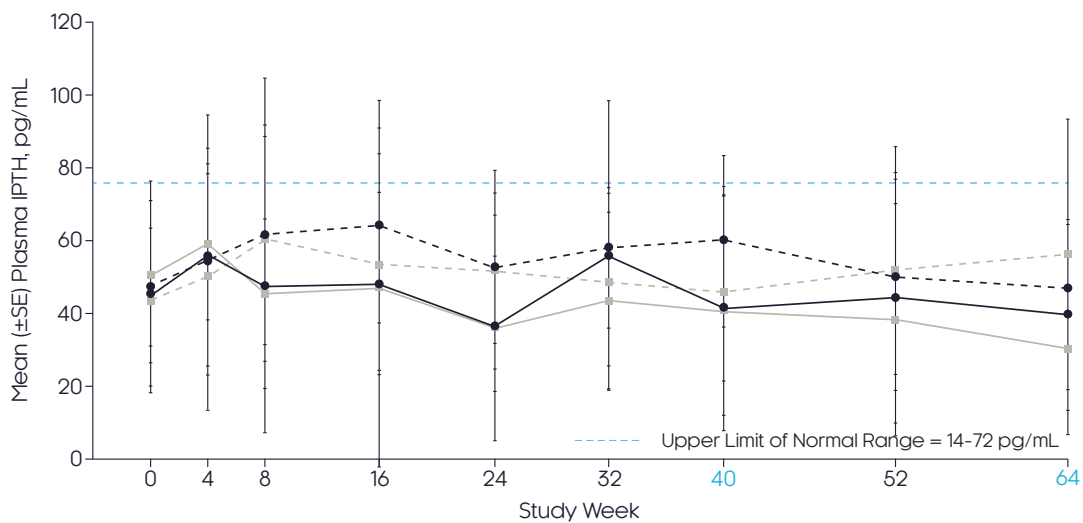


- Conventional Therapy <5 years (n=12)
- Conventional Therapy ≥5 years (n=20)
- CRYSVITA[®] SC Q2W, <5 years (n=14)
- CRYSVITA[®] SC Q2W, ≥5 years (n=15)

*Alkaline phosphatase is shown as the percentage of the ULN for age and sex, and the ULN is labeled as 100%, calculated from the following normal ranges: girls aged 1 to 4 years, 317 U/L; girls aged 4 to 7 years, 297 U/L; girls aged 7 to 10 years, 325 U/L; girls aged 10 to 15 years, 300 U/L; boys aged 1 to 4 years, 383 U/L; boys aged 4 to 7 years, 345 U/L; boys aged 7 to 10 years, 309 U/L; and boys aged 10 to 15 years, 385 U/L.

Intact Parathyroid Hormone

- Mean concentration of intact parathyroid hormone remained within normal range throughout the study for both age groups on CRYSVITA^{®20}



- Conventional Therapy <5 years (n=12)
- Conventional Therapy ≥5 years (n=20)
- CRYSVITA[®] SC Q2W, <5 years (n=14)
- CRYSVITA[®] SC Q2W, ≥5 years (n=15)

The graphs from this page are adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253. Patients randomly assigned to receive CRYSVITA[®] 0.8 mg/kg Q2W or Conventional Therapy.

ALP, alkaline phosphatase; SD, standard deviation; ULN, upper limit of normal; SE, standard error; IPTH, intact parathyroid hormone; pg/mL, picograms per milliliter; Q2W, every 2 weeks.

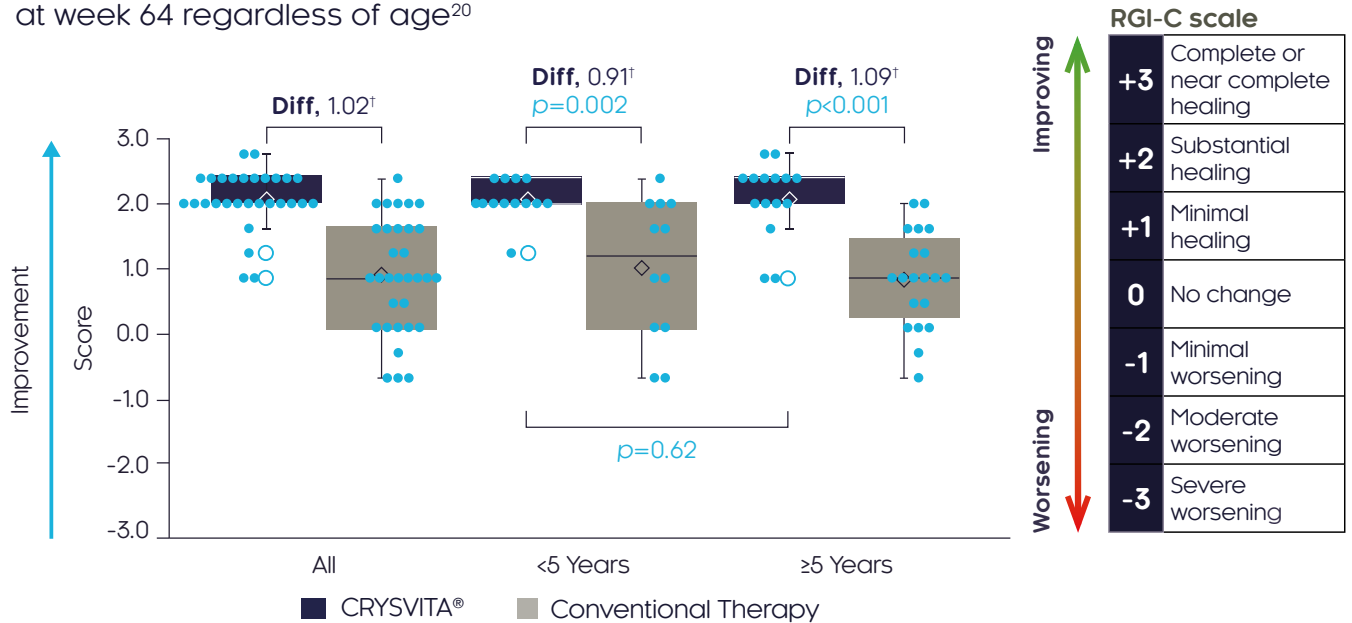
POST HOC ANALYSIS: RICKETS, LOWER LIMB DEFORMITY, AND GROWTH EVALUATIONS²⁰



Rickets, lower limb deformity, and growth evaluations in younger and older children receiving CRYSVITA® or Conventional Therapy.²⁰

RGI-C Rickets Total Score

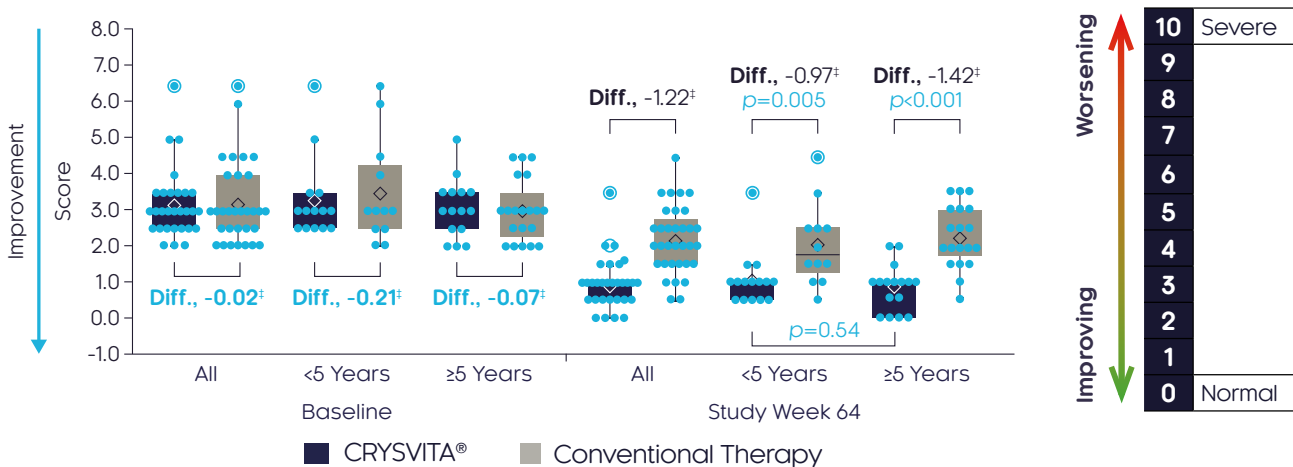
- RGI-C rickets total score was higher with CRYSVITA® compared with Conventional Therapy at week 64 regardless of age²⁰



[†]Based on the comparison between treatment groups in the LS mean change, using the ANCOVA model at Week 40 and the GEE model for Week 64. Diamonds indicate means, horizontal lines indicate medians with ranges, solid circles represent patients, and empty circles indicate outliers.

Total Rickets Severity Score

- Total rickets severity score was lower with CRYSVITA® compared with Conventional Therapy at week 64 regardless of age²⁰



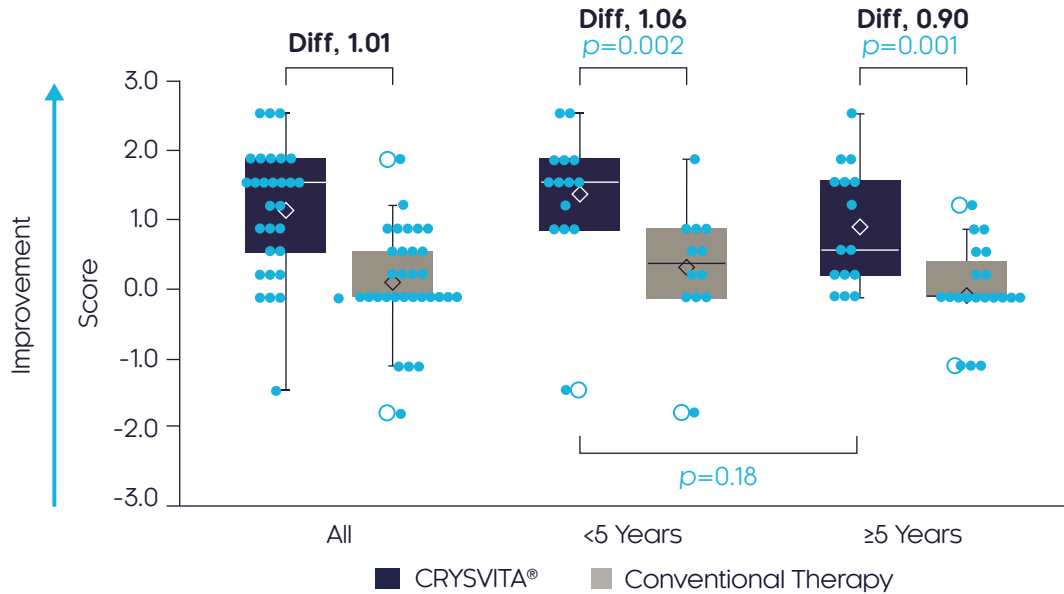
[†]Based on the comparison between treatment groups in the LS mean change, using the ANCOVA model at Week 40 and the GEE model for Week 64. Diamonds indicate means, horizontal lines indicate medians with ranges, solid circles represent patients, and empty circles indicate outliers.

POST HOC ANALYSIS: RICKETS, LOWER LIMB DEFORMITY, AND GROWTH EVALUATIONS²⁰



RGI-C Lower Limb Deformity Score

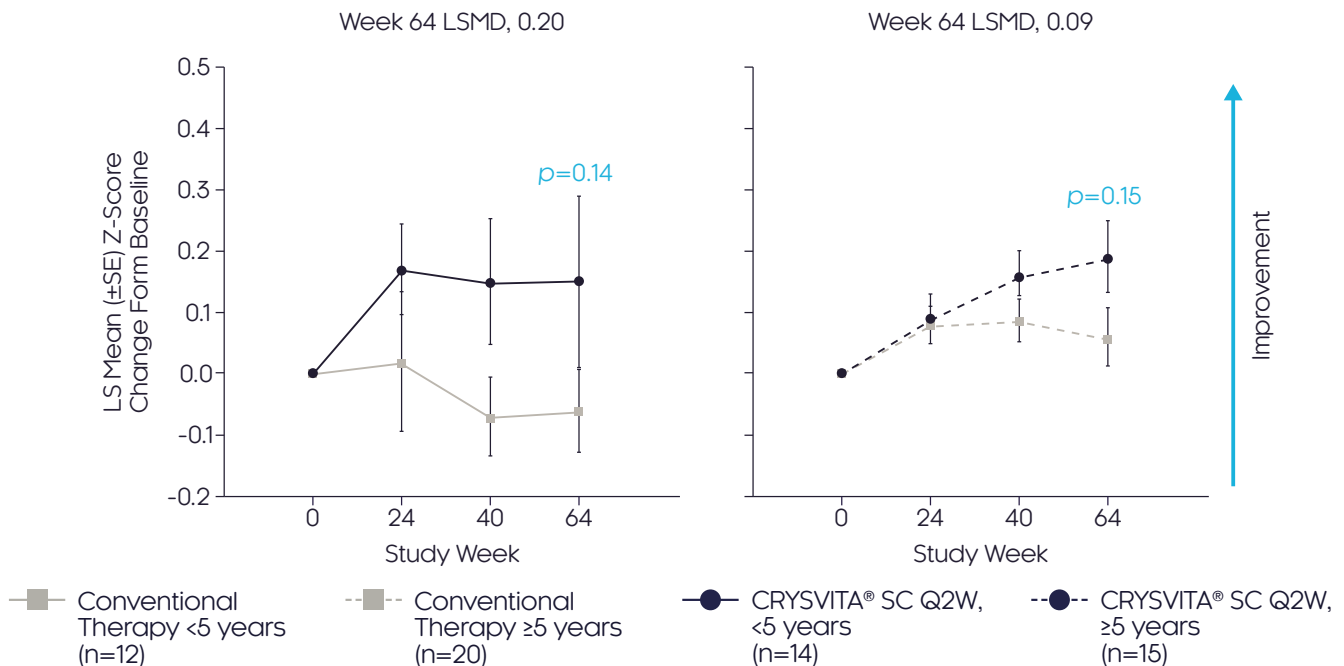
- RGI-C rickets total score was higher with CRYSVITA[®] compared with Conventional Therapy at week 64 regardless of age²⁰



Diamonds indicate means, horizontal lines indicate medians with ranges, solid circles represent patients, and empty circles indicate outliers.

Recumbent Length or Standing Height Z-Score

- In younger and older children, CRYSVITA[®] increased recumbent length or standing height Z-score from baseline to week 64; there was no significant difference between younger and older children (P=0.80)²⁰



The graphs from this page are adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253. Patients randomly assigned to receive CRYSVITA[®] 0.8 mg/kg Q2W or Conventional Therapy.

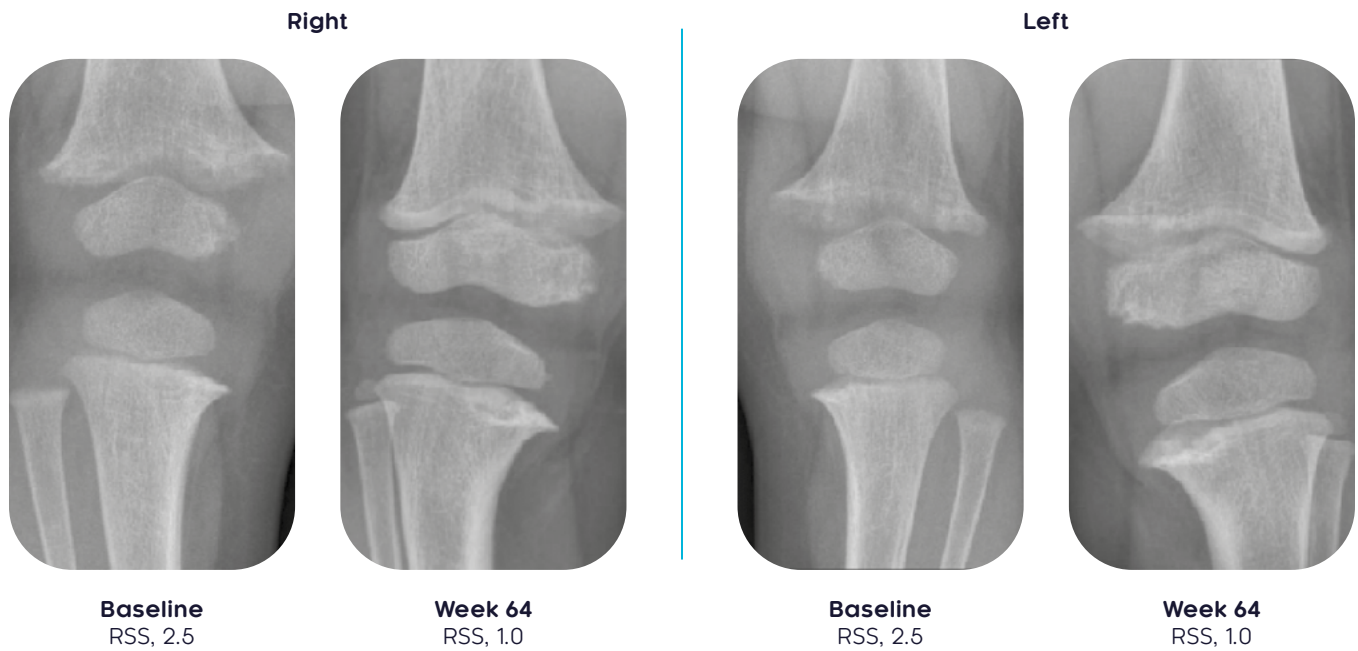
RGI-C, Radiographic Global Impression of Change; Diff, difference; LS, least squares; SE, standard error; Q2W, every 2 weeks; LSMD, least squares means difference

POST HOC ANALYSIS: RADIOGRAPHS OF RICKET IMPROVEMENT²⁰



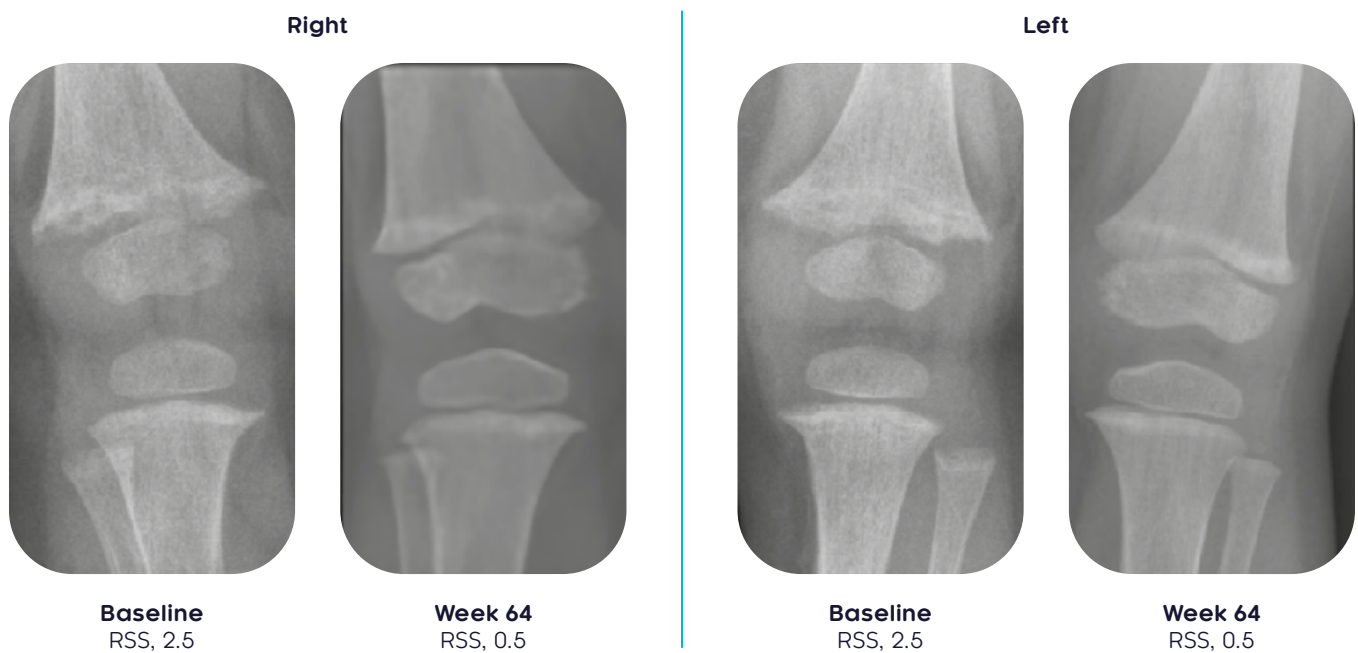
Knee radiographs showed greater ricket improvement with CRYSVITA[®] compared with Conventional Therapy. However, there was no observable difference in the magnitude of improvement between younger and older patients.²⁰

1.8-Year-Old Girl, Conventional Therapy



Adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253.

1.0-Year-Old Girl, CRYSVITA[®]



Adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253.

POST HOC ANALYSIS: RADIOGRAPHS OF RICKET IMPROVEMENT²⁰



11.9-Year-Old Boy, Conventional Therapy

Right

Left



Baseline
RSS, 2.0

Week 64
RSS, 1.5

Baseline
RSS, 2.0

Week 64
RSS, 1.5

Adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253.

12.5-Year-Old Boy, CRYSVITA[®]

Right

Left



Baseline
RSS, 2.0

Week 64
RSS, 0

Baseline
RSS, 2.0

Week 64
RSS, 0

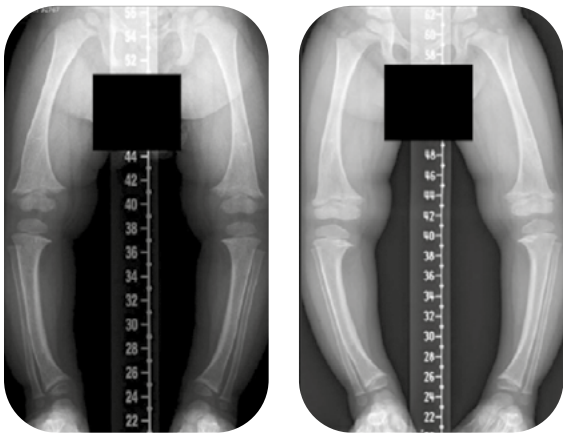
Adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253.

POST HOC ANALYSIS: IMPROVEMENT IN LOWER LIMB DEFORMITY²⁰



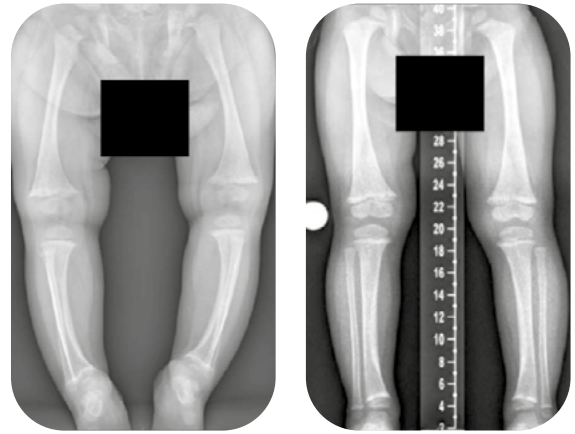
Similarly, radiographs of lower limb deformity in younger and older children showed greater improvements with CRYSVITA[®] than Conventional Therapy and there was no discernable difference in the magnitude of improvement with age.²⁰

1.8-Year-Old Girl, Conventional Therapy



Baseline to Week 64 RGI-C
Lower Limb Deformity, 0

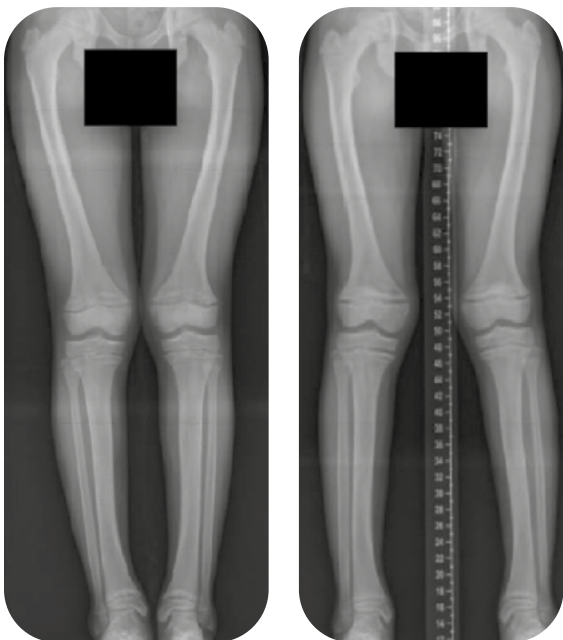
1.0-Year-Old Girl, CRYSVITA[®]



Baseline to Week 64 RGI-C
Lower Limb Deformity, +2.7

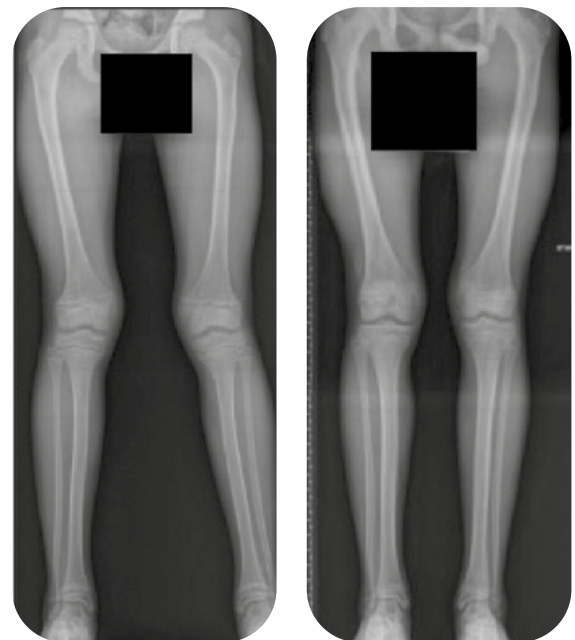
Adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253.

11.9-Year-Old Boy, Conventional Therapy



Baseline to Week 64 RGI-C
Lower Limb Deformity, 0

12.5-Year-Old Boy, CRYSVITA[®]



Baseline to Week 64 RGI-C
Lower Limb Deformity, +2.7

Adapted from Ward LM, et al. J Clin Endocrinol Metab 2022;107(8):e3241-e3253.

Overall, improvements in phosphate homeostasis, rickets, and lower limb deformities were consistently greater with CRYSVITA[®] than Conventional Therapy both in younger and older children with XLH. At a biochemical level, the improvements with CRYSVITA[®] were similar irrespective of age. Improvement with CRYSVITA[®] were also observable through radiographs of rickets healing and lower limb deformity, however, they did not show any difference with starting age.²⁰

XLH, X-linked hypophosphatemia

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CRYSVITA® Abbreviated Product Information

CRYSVITA® (burosumab). Based on Singapore Package Insert. Kyowa Kirin Asia Pacific Pte Ltd; 2021

INDICATIONS AND USAGE

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

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. For pediatric patients (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. For adult patients (18 years of age and older), the recommended 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.

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.

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. **Hyperphosphataemia 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.

ADVERSE REACTIONS

Adverse reactions (>10%) reported in paediatric patients during clinical trials were: injection site reactions, cough, headache, pyrexia, pain in extremity, vomiting, tooth abscess, vitamin D decreased, diarrhoea, rash, nausea, constipation, dental caries, dizziness and myalgia. Adverse reactions (>5%) reported in adult patients during clinical trials were: back pain, headache, tooth infection, restless legs syndrome, vitamin D decrease and dizziness, constipation and blood phosphorus increased.

Product is approved in selected markets and local approved prescribing information may differ. Please refer to local approval status and prescribing information.
This material is for Healthcare Professionals Only.

Kyowa KIRIN

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