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Burosumab versus conventional therapy in children with X-linked hypophosphataemia:

a randomised, active-controlled, open-label, Phase III trial

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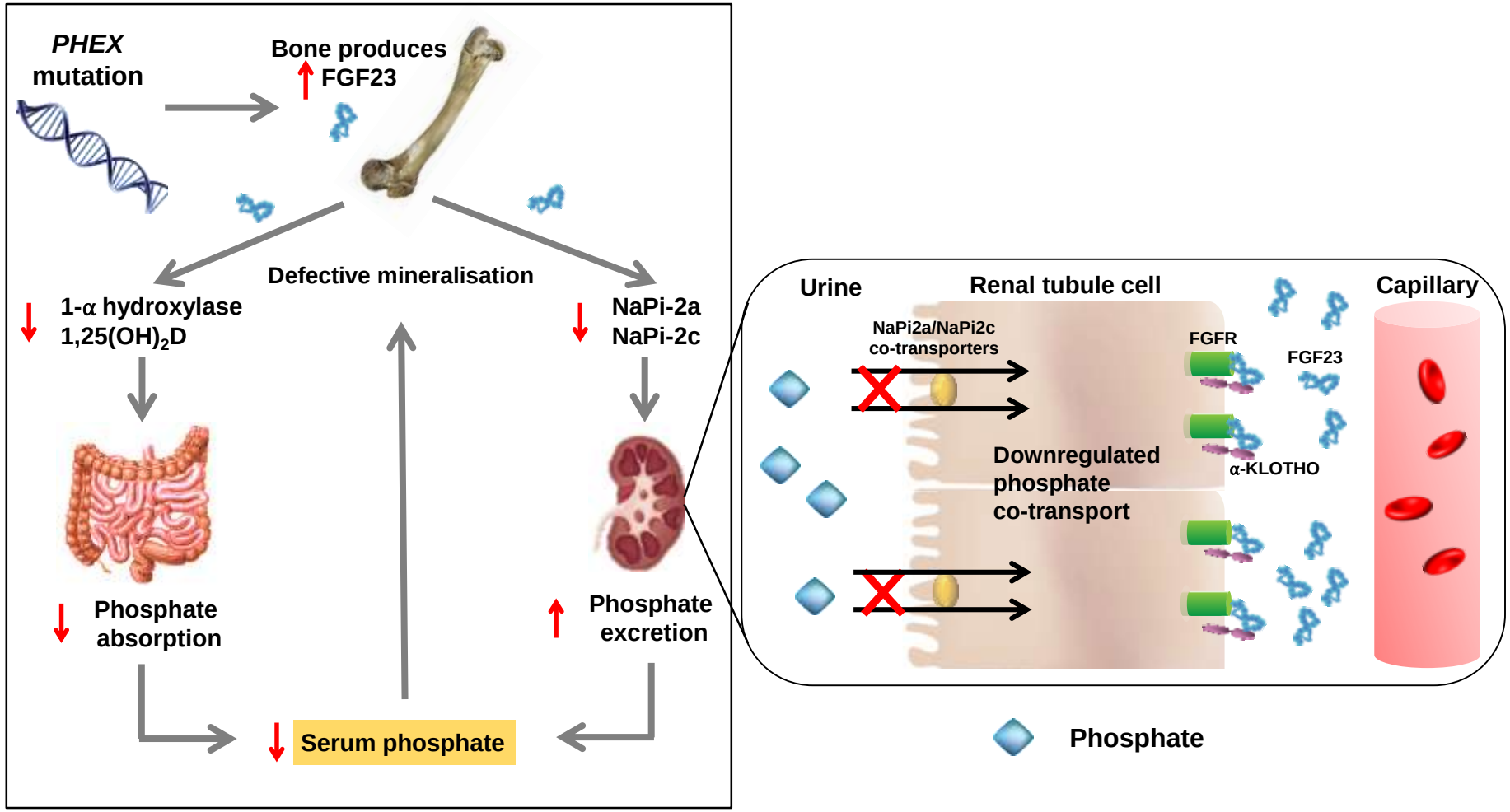
Introduction

Excess FGF23 in the pathophysiology of XLH



Burosumab, a fully human anti-FGF23 IgG_1 mAb

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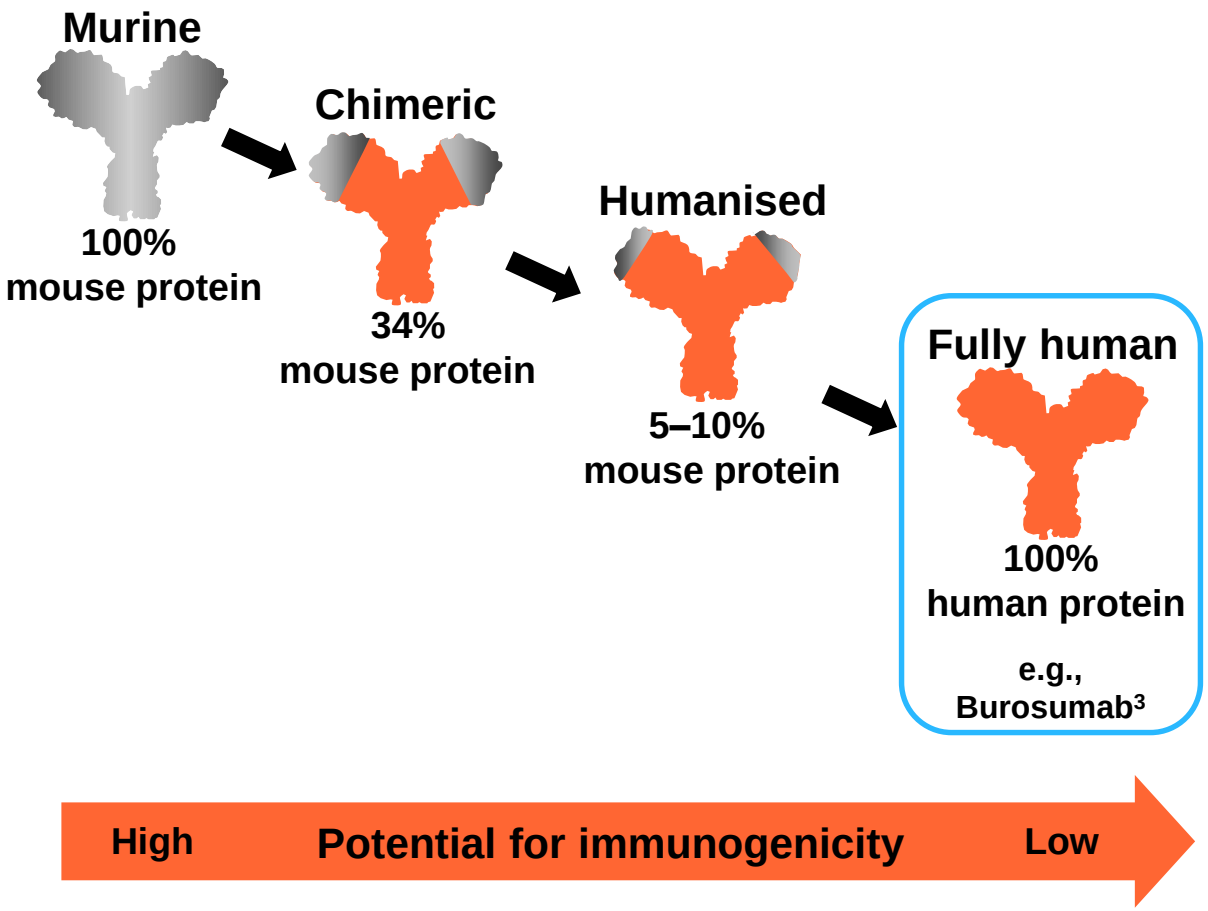
Evolution of antibody technologies



- Burosumab is a fully human anti-FGF23 IgG_1 mAb designed to bind and inhibit FGF23 activity
- Fully human mAbs usually exhibit low immunogenicity, and are currently the favoured type of mAb used for therapeutics

Radiographic Global Impression of Change (RGI-C) Score

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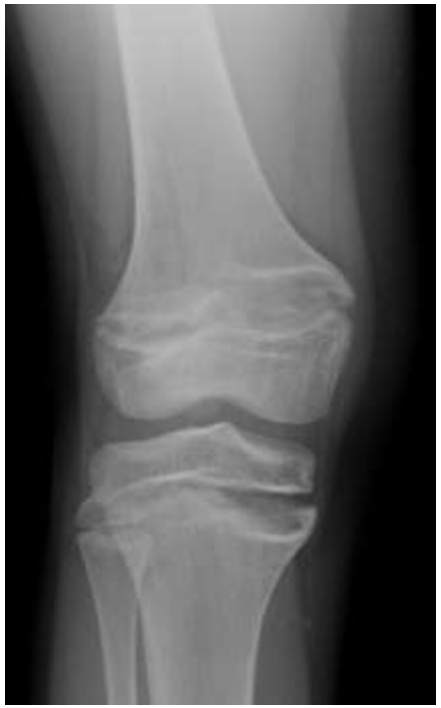
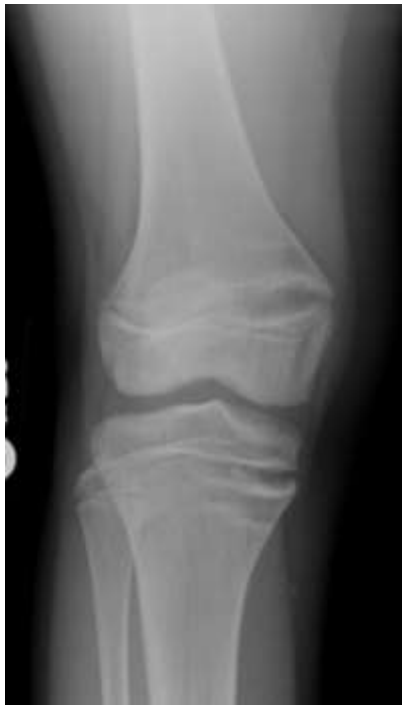
Baseline

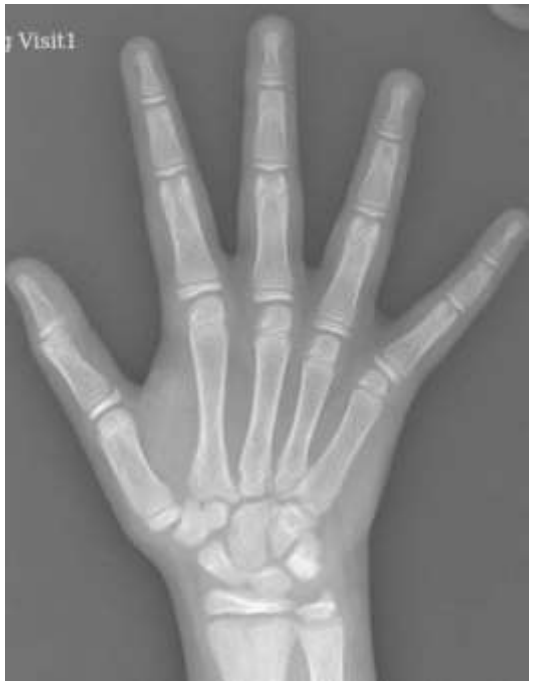


Week 40

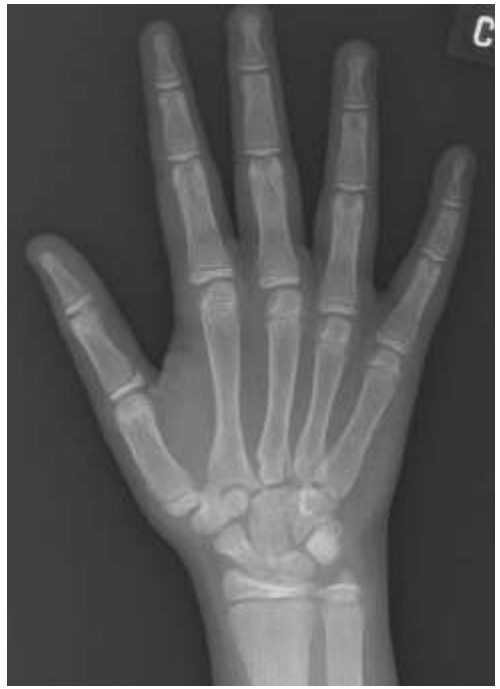


Knee RGI-C score at Week 40: +2.0

Screening



Week 40

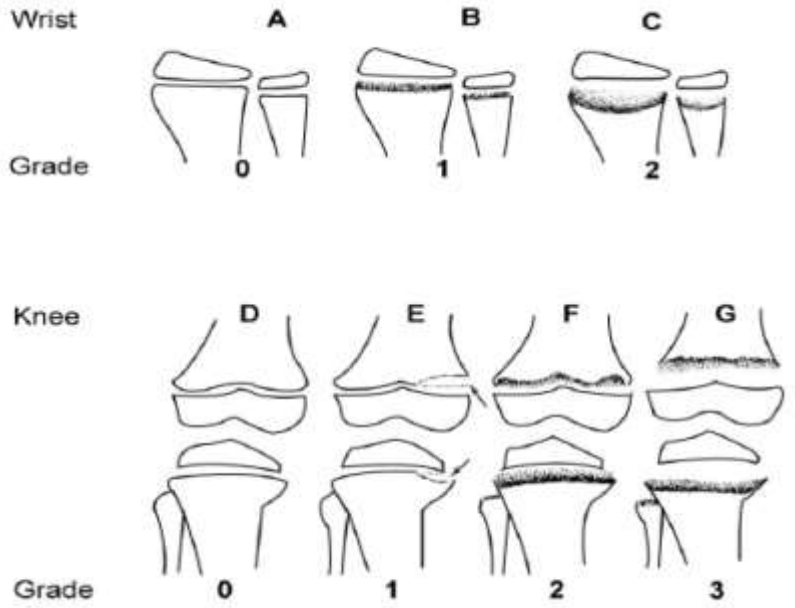


Wrist RGI-C score at Week 40: +2.67

How would you rate the change in XLH-related rickets in the KNEES? *Circle one*						
-3	**-2**	**-1**	**0**	**+1**	**+2**	**+3**
Severe worsening	Moderate worsening	Minimal worsening	No change	Minimal healing	Substantial healing	Complete or near complete healing

Thacher Rickets Severity Score (RSS)

- Developed by Dr Thacher originally to evaluate patients with nutritional rickets
- Total score of 0–10 points combining wrists (0–4) and knees (0–6)



Wrist – score radius and ulna separately
Grade
1: irregularity of margin, no concave cupping
2: Concavity

2 bones x 2 points = 4 points possible

Knee – score femur and tibia separately
Grade
1: partial lucency, smooth margin
2: partial lucency, smooth margin not visible
3: complete lucency
Multiplier
0.5: ≤1 condyle/plateau
1: 2 condyles or plateaus

2 bones x 1 point x 3 points= 6 points possible

0
No rickets

10
Most severe rickets

UX023-CL301
Phase III Randomized Clinical Trial

UX023-CL301 study design

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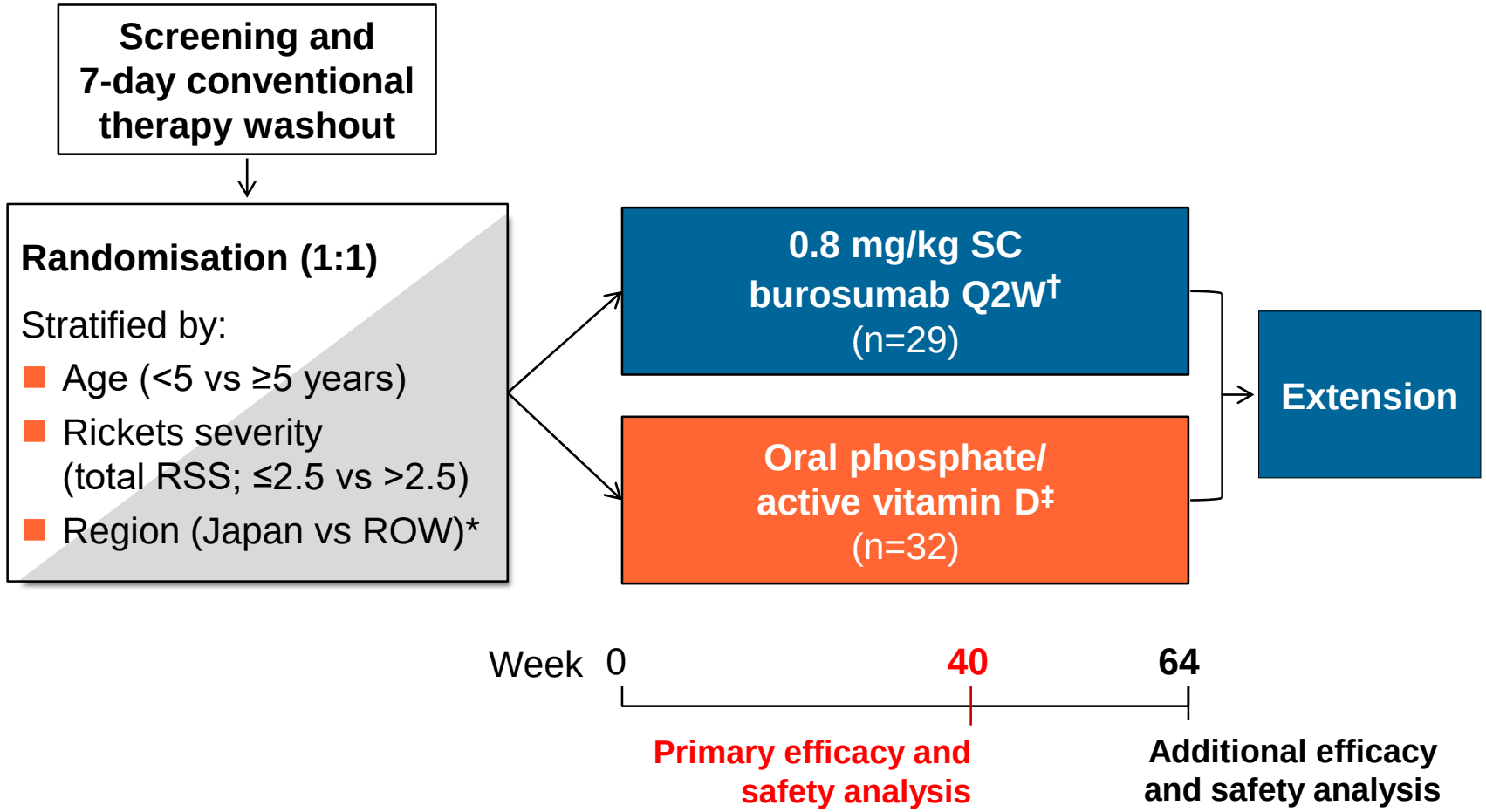
Study population (N=61)

- Children with XLH, 1–12 years old
- Total RSS ≥2.0
- Confirmed *PHEX* mutation (or variant of unknown significance) in the patient or a family member with appropriate X-linked inheritance
- Fasting serum phosphorus <0.97 mmol/L (3.0 mg/dL)
- Prior conventional therapy
  - ≥12 consecutive months for ages ≥3 years
  - ≥6 consecutive months for ages <3 years



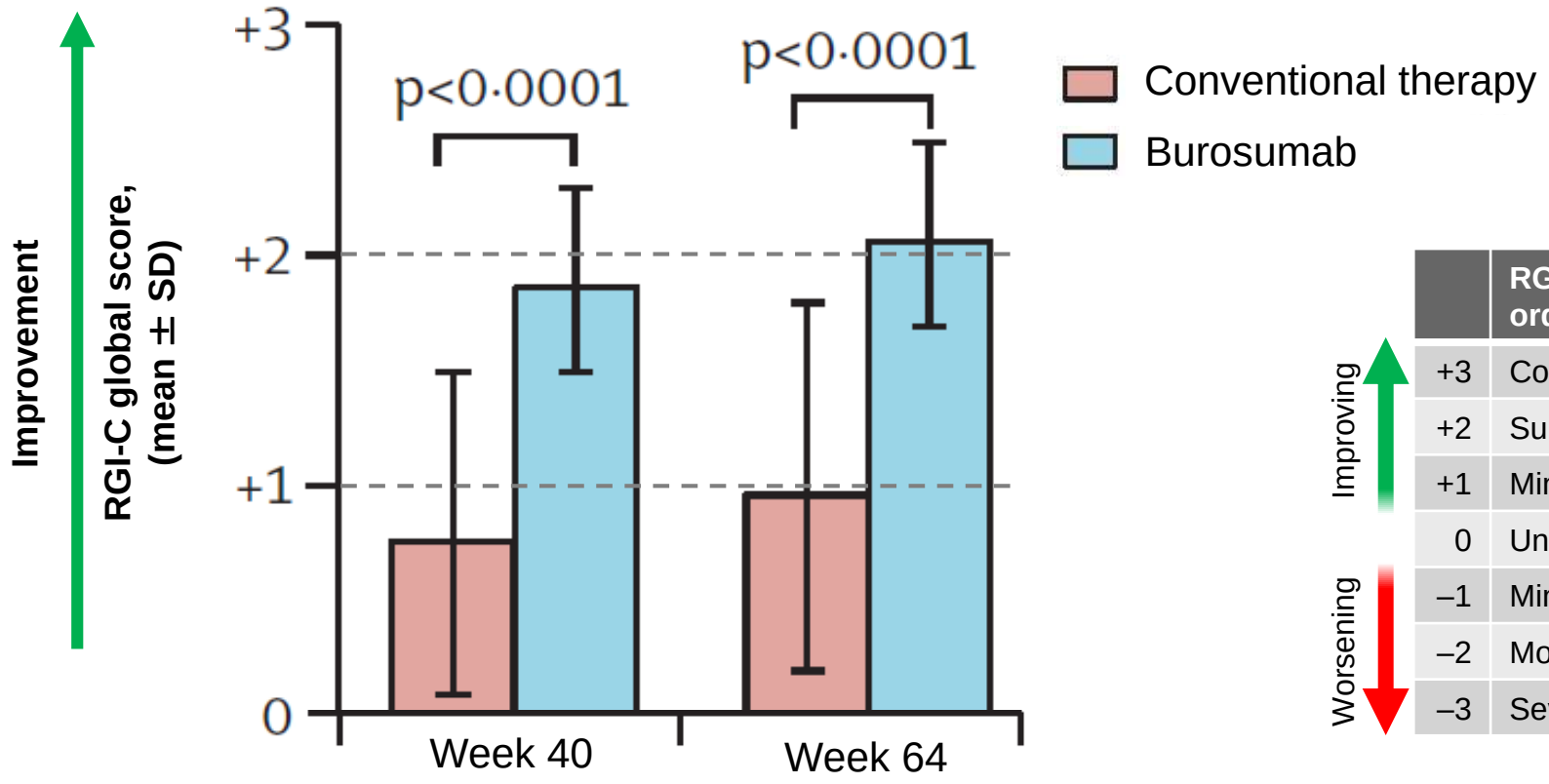
Demographics

Characteristic	Conventional therapy (n=32)	Burosumab (n=29)
Age, years (mean)	6.3 (3.2)	5.8 (3.4)
Height Z score, mean (SD)	-2.1 (0.9)	-2.3 (1.2)
Serum phosphorus, mmol/L, mean (SD)	0.74 (0.08)	0.78 (0.08)
Serum TmP/GFR, mmol/L, mean (SD)	0.65 (0.11)	0.71 (0.12)
Serum 1,25(OH)$_2$D, pmol/L, mean (SD)	96 (36)	110 (48)
Alkaline phosphatase, mean (SD), U/L / µkat/L	523.4 (154.4)/ 8.72 (2.57)	510.8 (124.9) / 8.51 (2.08)
Duration of prior conventional therapy, years, mean (SD)	4.3 (3.0)	3.3 (3.1)
Total RSS, mean (SD)	3.2 (1.1)	3.2 (1.0)

Efficacy results

RGI-C: global score (primary endpoint)

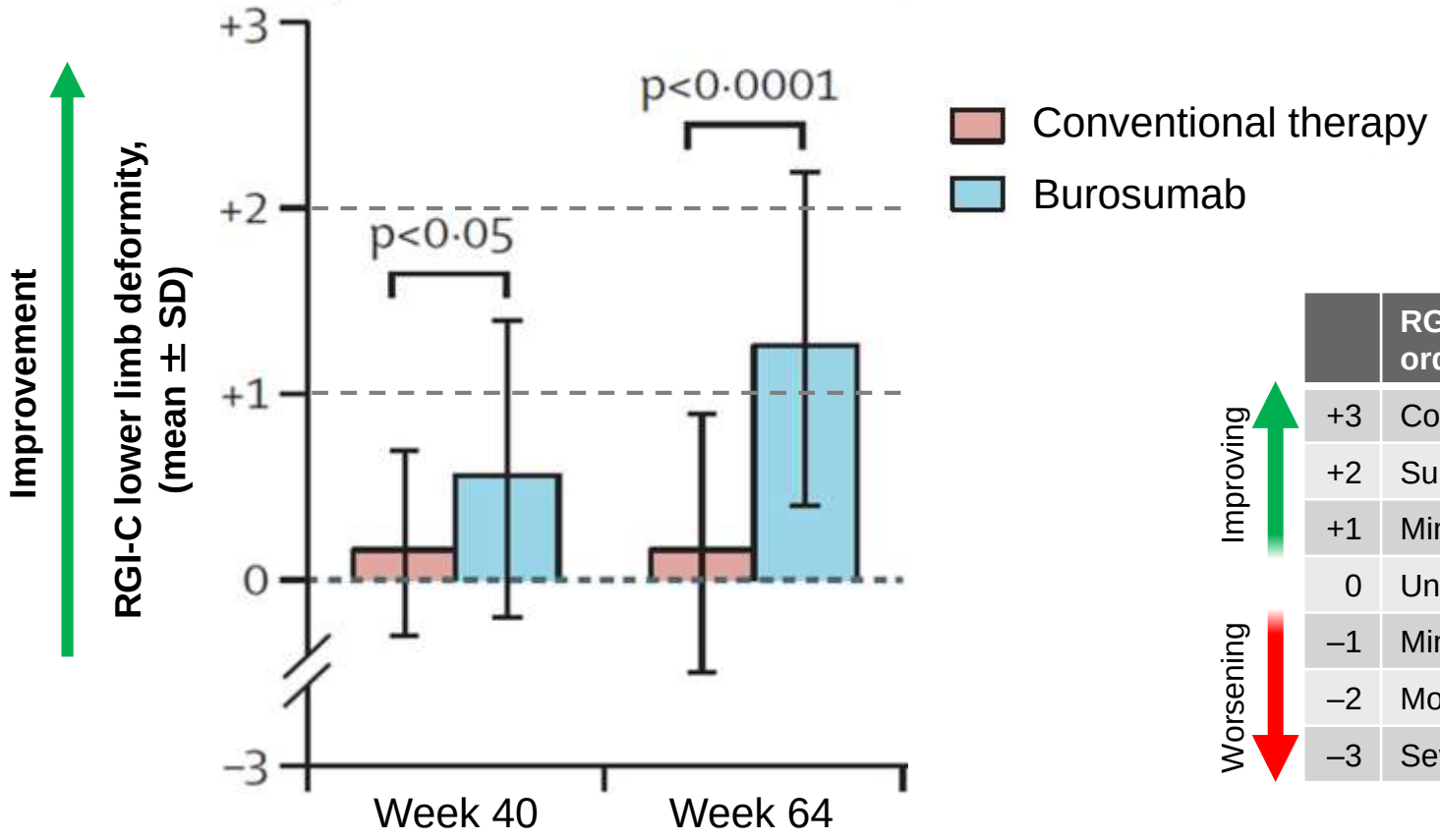
- Burosumab treatment demonstrated significantly greater improvements in RGI-C global score than conventional therapy at Week 40, which were maintained through to Week 64



	RGI-C 7-point ordinal scale
Improving	
+3	Complete healing
+2	Substantial healing
+1	Minimal healing
0	Unchanged
Worsening	
–1	Minimal worsening
–2	Moderate worsening
–3	Severe worsening

RGI-C: lower limb deformity

- Burosumab treatment was associated with a significantly greater improvement in lower limb deformities than conventional therapy at Weeks 40 and 64



	RGI-C 7-point ordinal scale
Improving	
+3	Complete healing
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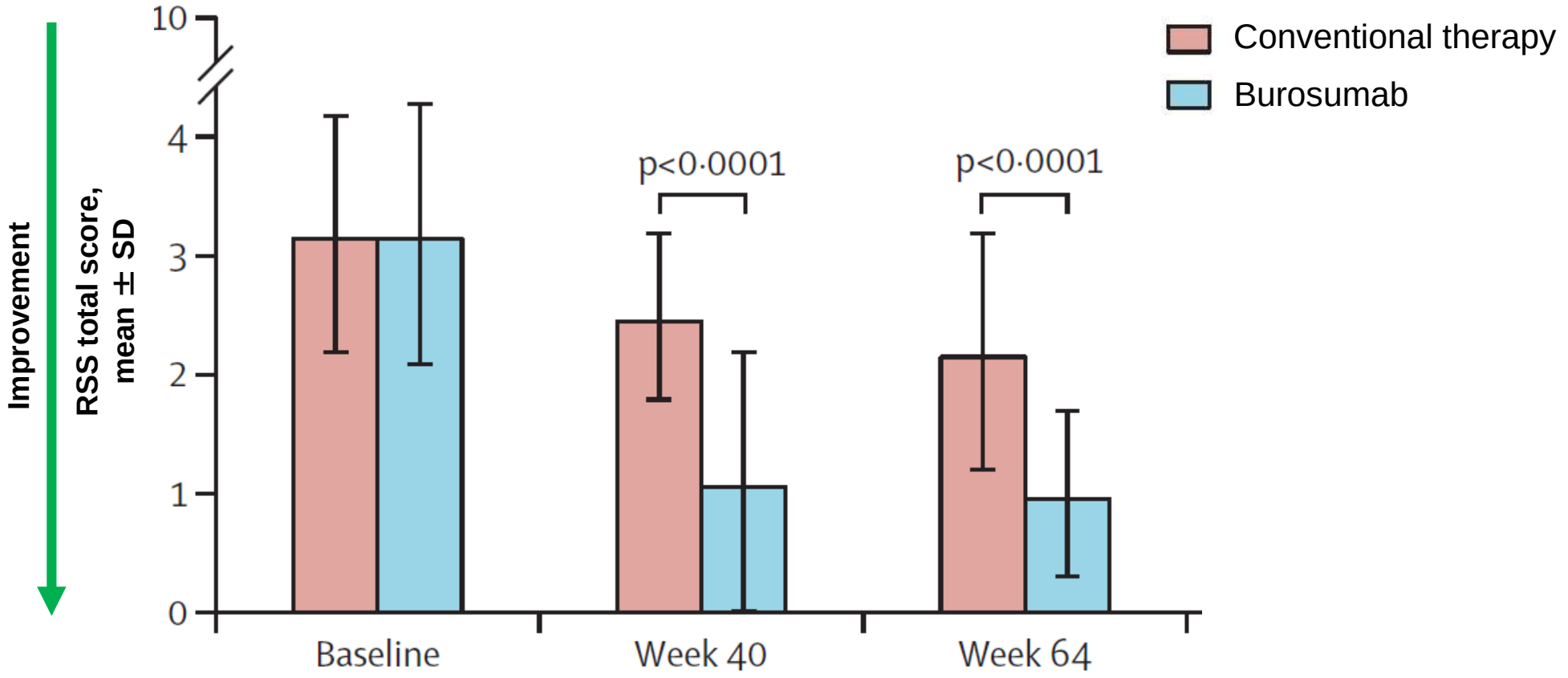
+1	Minimal healing
0	Unchanged
Worsening	
–1	Minimal worsening
–2	Moderate worsening
–3	Severe worsening

RSS: total score

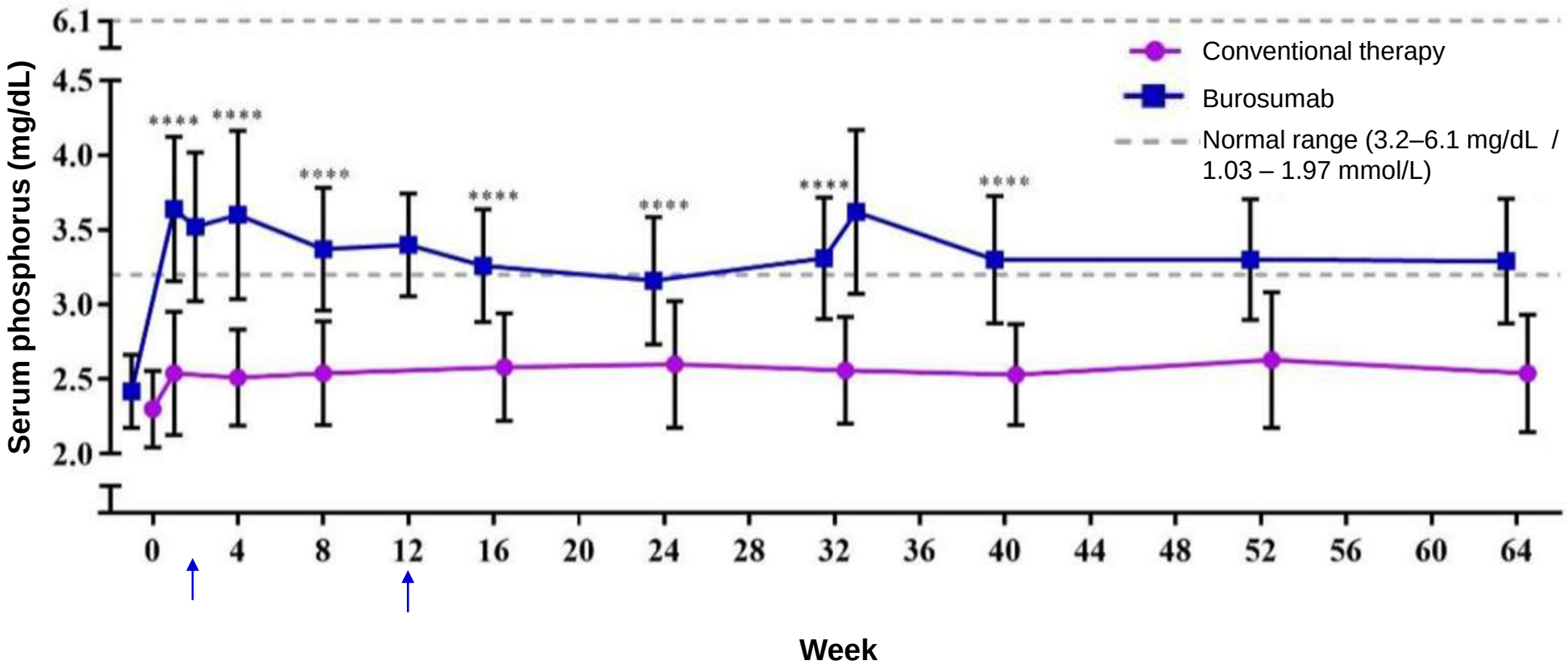
- Burosumab significantly decreased total RSS compared with conventional therapy at Weeks 40 and 64



Pharmacodynamics results

Fasting serum phosphorus

- Changes in serum phosphorus levels from baseline were significantly greater in the burosumab group than in the conventional therapy group throughout the study



TmP/GFR

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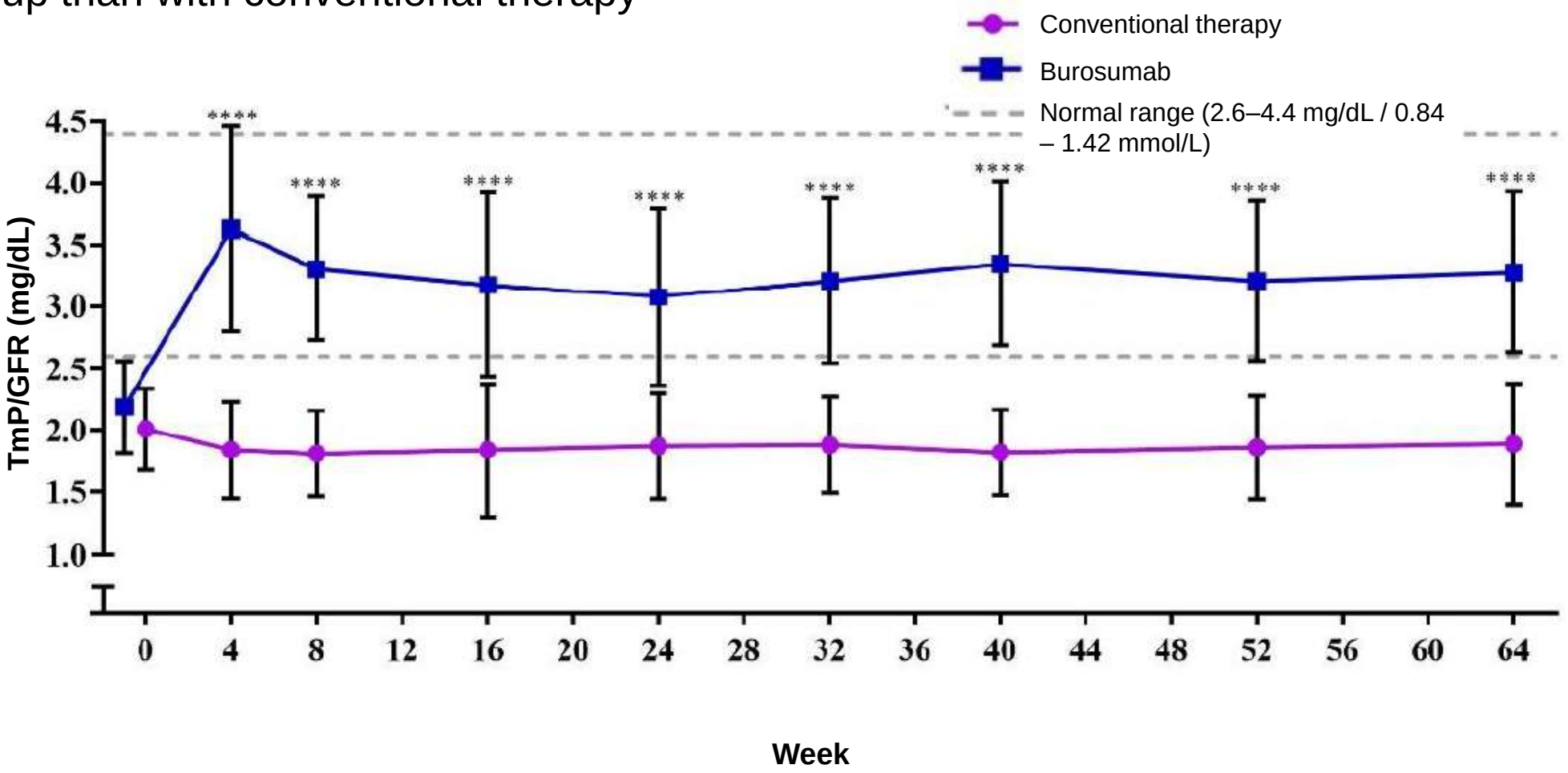
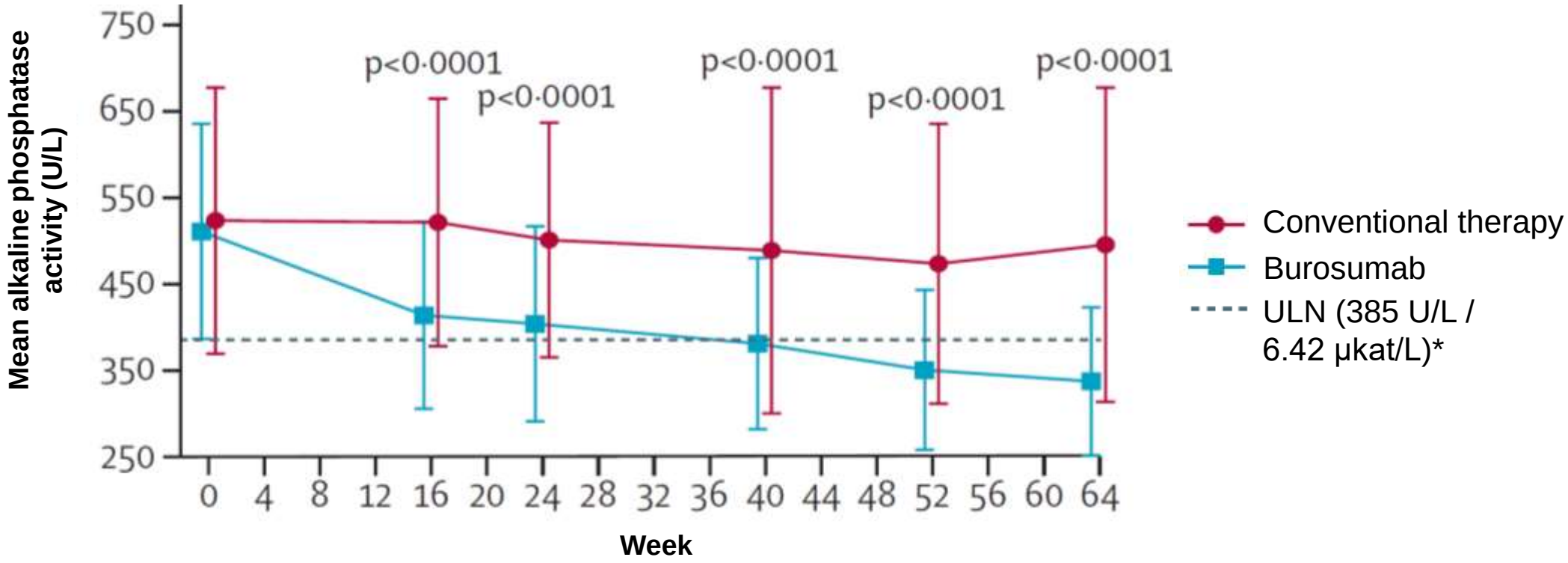
- Changes in TmP/GFR from baseline were statistically significantly greater in the burosumab group than with conventional therapy



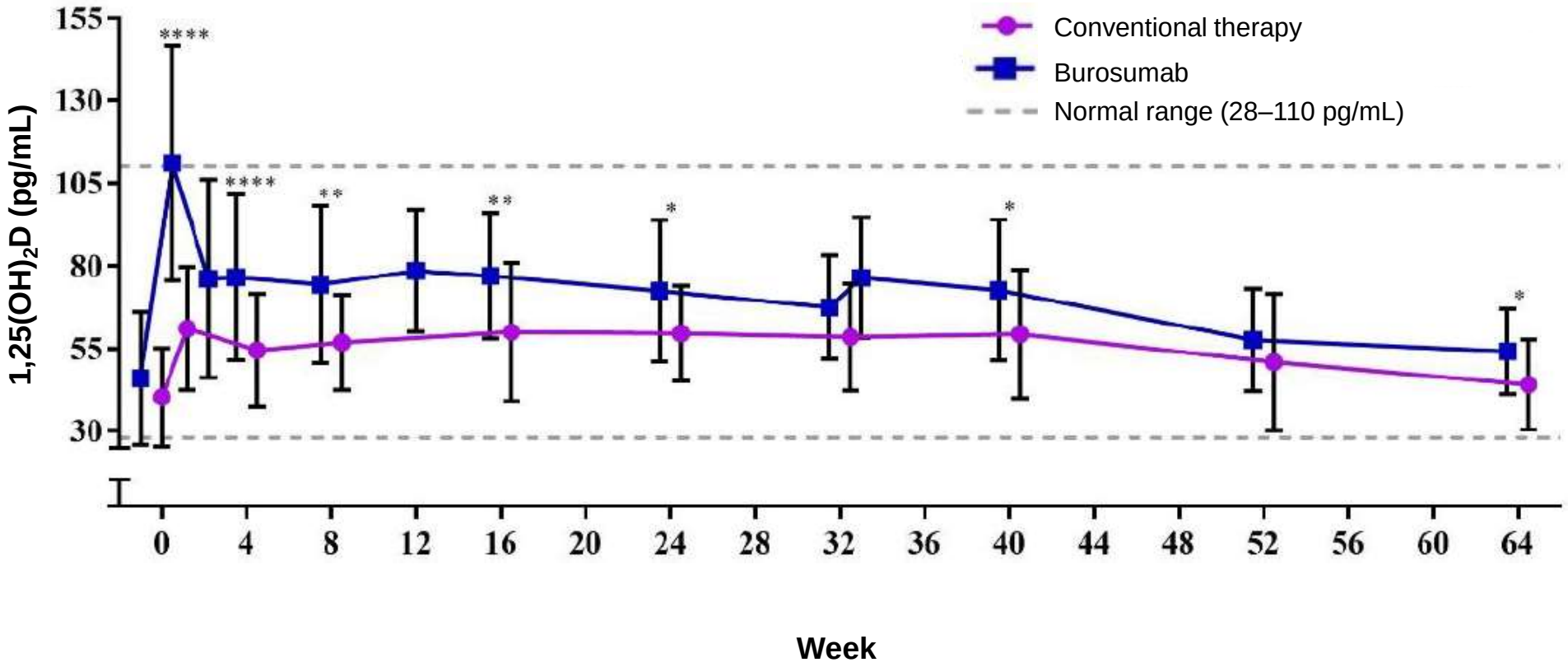
Alkaline phosphatase

- Burosumab treatment was associated with a significantly greater decrease in ALP levels than conventional therapy



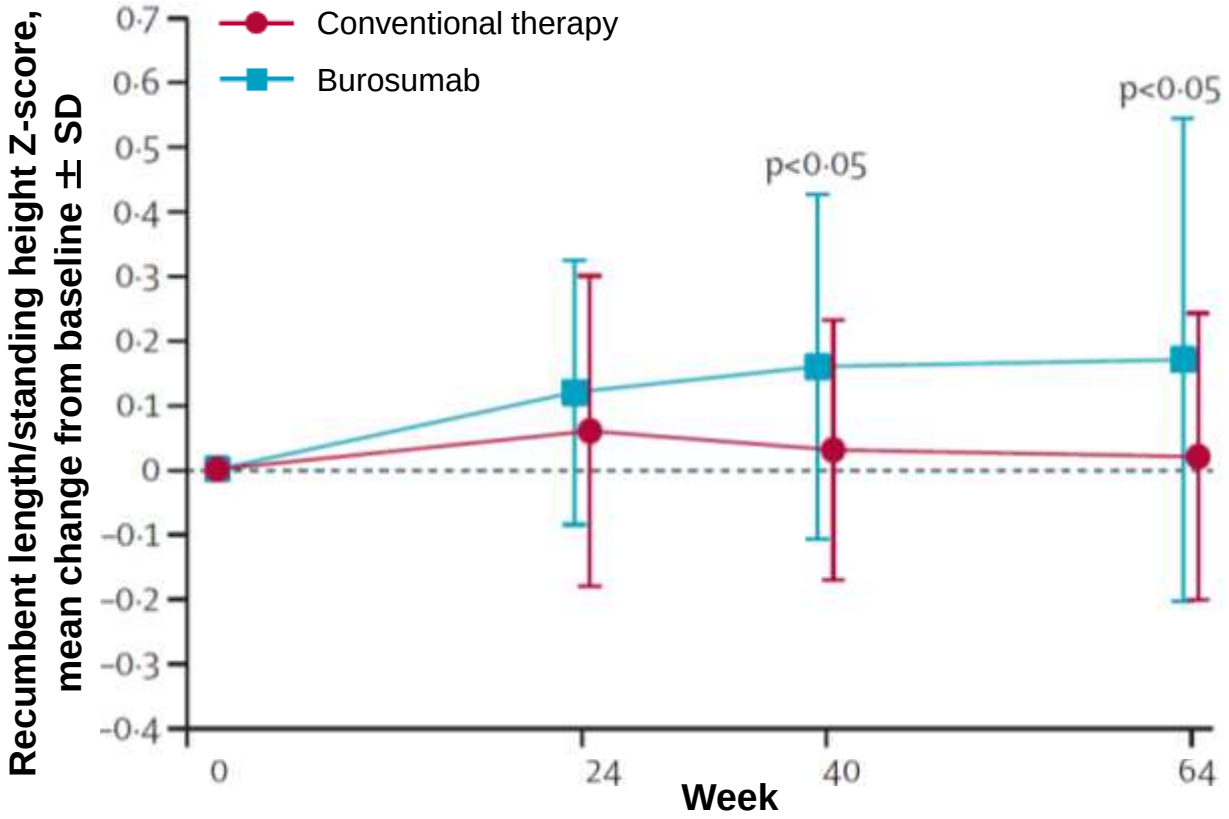
Serum $1,25(OH)_2D$

- Burosumab was associated with significantly greater increases in serum $1,25(OH)_2D$ than conventional therapy



Recumbent length/standing height Z-score

- Burosumab treatment was associated with a significantly greater increase in recumbent length/standing height Z-score at Week 64 versus conventional therapy



Safety results

Adverse event summary

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- The safety profile of burosumab was consistent with the previous profile of the Phase II studies

Assessment	Conventional therapy, n (%) [n=32]	Burosumab, n (%) [n=29]
TEAE	27 (84.4)	29 (100.0)
Serious TEAE	3 (9.4)	3 (10.3)
Related TEAE	7 (21.9)	17 (58.6)
Serious related TEAE	0 (0.0)	0 (0.0)
Grade 3 or 4 TEAE	3 (9.4)	4 (13.8)
TEAE leading to study discontinuation	0 (0.0)	0 (0.0)
TEAE leading to treatment discontinuation	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)
Predefined TEAEs of interest		
Injection site reactions	0 (0.0)	15 (51.7)
Hypersensitivity	6 (18.8)	11 (37.9)
Hyperphosphataemia	0 (0.0)	0 (0.0)
Ectopic mineralisation	0 (0.0)	0 (0.0)
Restless legs syndrome	0 (0.0)	0 (0.0)

Summary of results

- By countering the underlying pathophysiology of XLH, burosumab led to increased renal reabsorption of phosphate and normalization of serum phosphorus levels
- Burosumab treatment significantly improved rickets and lower limbs deformities in comparison to conventional treatment
- The safety profile of burosumab was consistent with the previous profile of the Phase II studies and was well tolerated.
- Conventional treatment under clinical trial setting (improved patient compliance) showed also some positive results in the treatment of rickets

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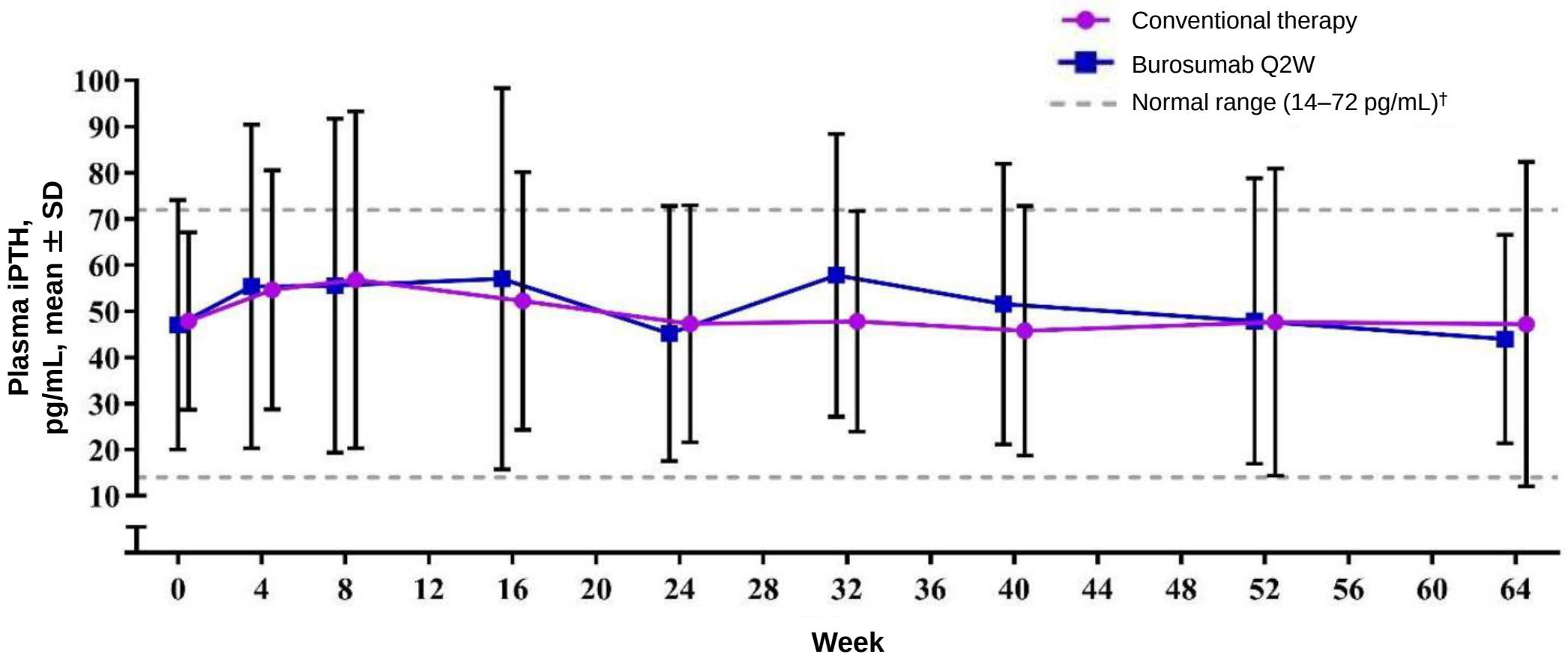
Thank you for you attention.

Intact parathyroid hormone over time

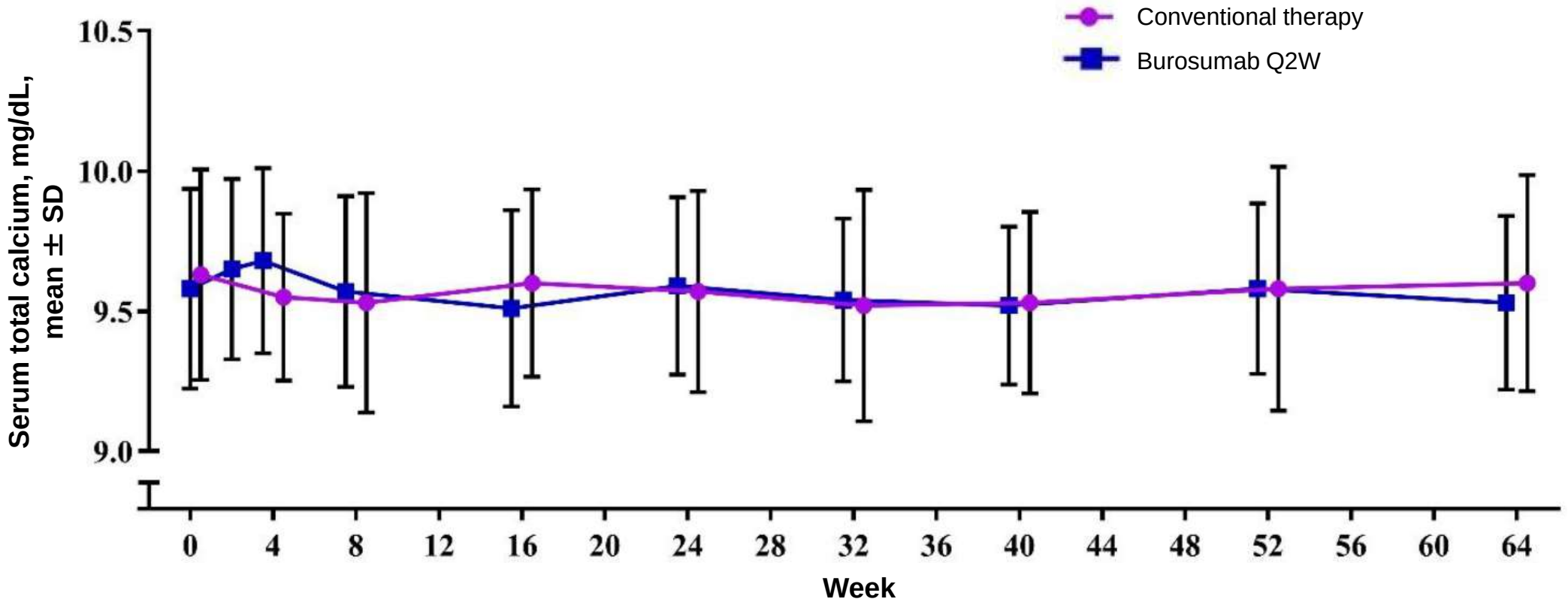
- There were minimal changes in plasma intact parathyroid hormone in both treatment groups throughout the study



†Normal (or target) ranges provided by Covance laboratories. Post-baseline values are offset from the actual treatment week to avoid overlapping error bars. iPTH, intact parathyroid hormone; SD, standard deviation.
Imel EA *et al. Lancet* 2019;DOI:10.1016/S0140-6736(19)30654-3 (supplementary material). Figure reprinted from Imel EA *et al.* Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet* 2019;DOI:10.1016/S0140-6736(19)30654-3 (supplementary material) with permission from Elsevier.

Serum calcium over time

- There were minimal changes in serum calcium in both treatment groups throughout the study



Post-baseline values are offset from the actual treatment week to avoid overlapping error bars
SD, standard deviation
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TEAEs ≥10% in either treatment group

Preferred term	Conventional therapy, n (%) [n=32]	Burosumab, n (%) [n=29]
Pyrexia	6 (18.8)	16 (55.2)
Cough	6 (18.8)	15 (51.7)
Arthralgia	10 (31.3)	13 (44.8)
Vomiting	8 (25.0)	12 (41.4)
Nasopharyngitis	14 (43.8)	11 (37.9)
Pain in extremity	10 (31.3)	11 (37.9)
Headache	6 (18.8)	10 (34.5)
Injection site erythema	0 (0.0)	9 (31.0)
Dental caries	2 (6.3)	9 (31.0)
Tooth abscess	3 (9.4)	8 (27.6)
Injection site reaction	0 (0.0)	7 (24.1)
Rhinorrhoea	2 (6.3)	7 (24.1)
Diarrhoea	2 (6.3)	7 (24.1)
Vitamin D decrease	1 (3.1)	6 (20.7)
Constipation	0 (0.0)	5 (17.2)
Nasal congestion	1 (3.1)	5 (17.2)
Oropharyngeal pain	1 (3.1)	5 (17.2)
Vitamin D deficiency	1 (3.1)	5 (17.2)
Contusion	0 (0.0)	4 (13.8)
Ear pain	1 (3.1)	4 (13.8)
Nausea	1 (3.1)	4 (13.8)
Asthma	1 (3.1)	4 (13.8)
Seasonal allergy	2 (6.3)	4 (13.8)
Influenza	6 (18.8)	4 (13.8)
Injection site pruritus	0 (0.0)	3 (10.3)
Injection site swelling	0 (0.0)	3 (10.3)
Fall	0 (0.0)	3 (10.3)
Injection site rash	0 (0.0)	3 (10.3)
Rash	2 (6.3)	3 (10.3)
Upper respiratory tract infection	3 (9.4)	3 (10.3)
Abdominal pain upper	3 (9.4)	3 (10.3)

TEAE, treatment-emergent adverse event

Imel EA *et al. Lancet* 2019;DOI:10.1016/S0140-6736(19)30654-3.

Serious adverse events listing

- The serious treatment-emergent adverse events in the conventional therapy group were hospitalisation or surgery for craniosynostosis, bilateral leg bowing (*genu varum*) deformities, and haematuria.
- The serious treatment-emergent adverse events in the burosumab group were craniosynostosis, a viral infection, and a migraine.