Burosumab (KRN23): Effects on Phosphate and Vitamin D Dysregulation in Children < 5 Years Old with X-linked Hypophosphatemia (XLH)

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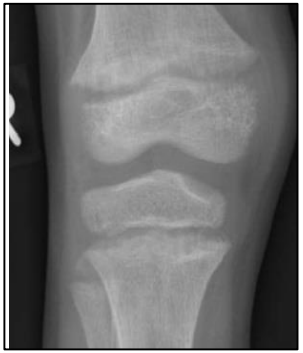
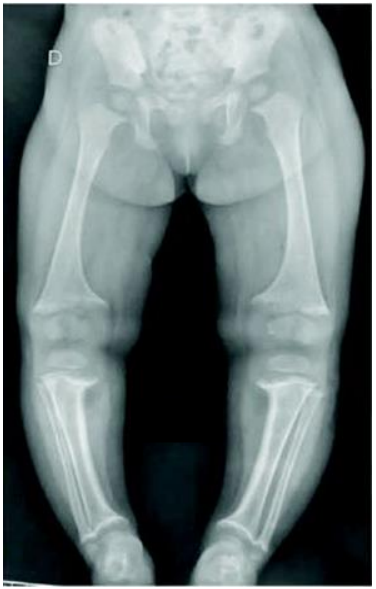
XLH Causes Rickets, Skeletal Deformity, and Impaired Growth in Children

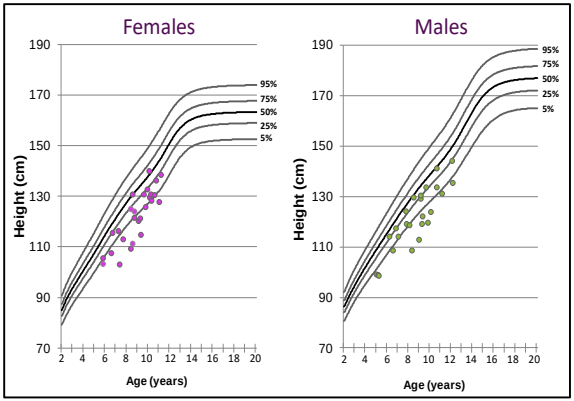
Rickets



Bowing of the Lower Limbs



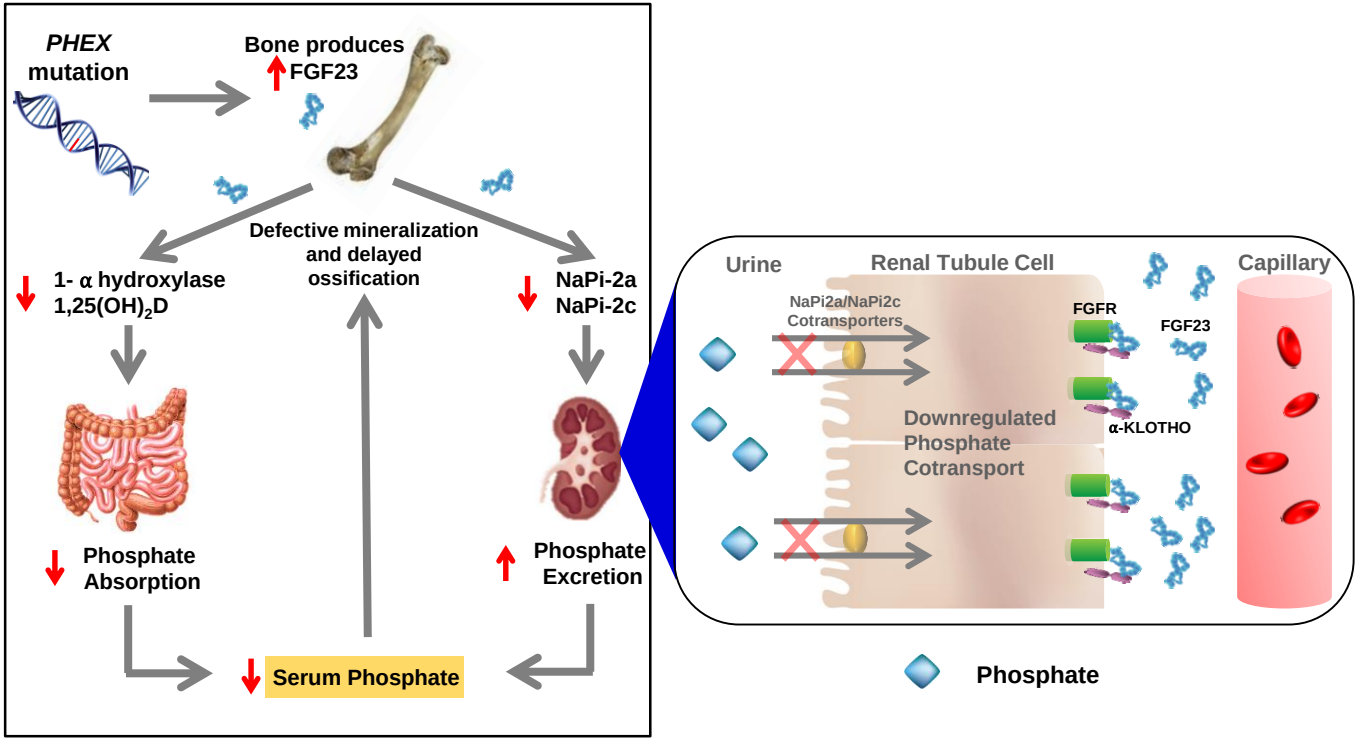
Growth Impairment



- Skeletal deformity and growth impairment begin in early childhood, and some studies suggest earlier initiation of treatment with phosphate and active vitamin D may lead to better height outcomes

XLH, X-linked hypophosphatemia

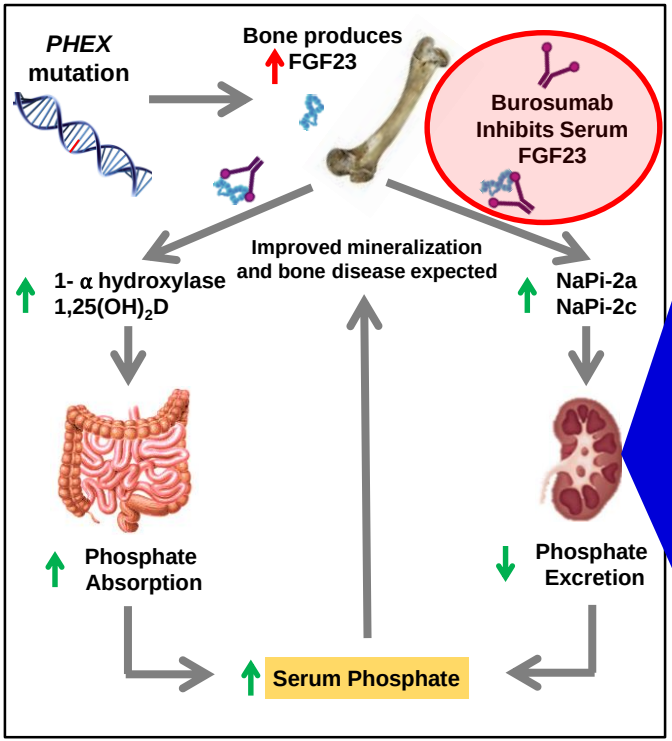
Excess FGF23 in XLH Pathophysiology



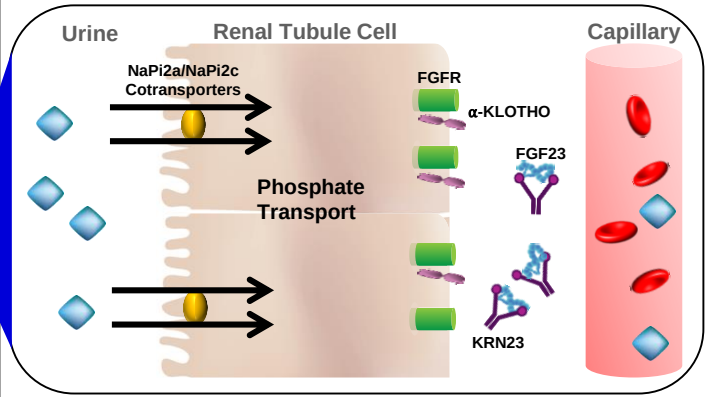
Razzaque MS. Nat Rev Endocrinol 2009;5:611-9. Martin A, et al. Physiol Rev 2012;92:131-55.

FGF23, Fibroblast growth factor 23; NAPi, sodium/phosphate cotransporter; PHEX, Phosphate Regulating Endopeptidase Homolog, X-Linked.

Burosumab (KRN23), a Monoclonal Antibody, Inhibits Serum FGF23



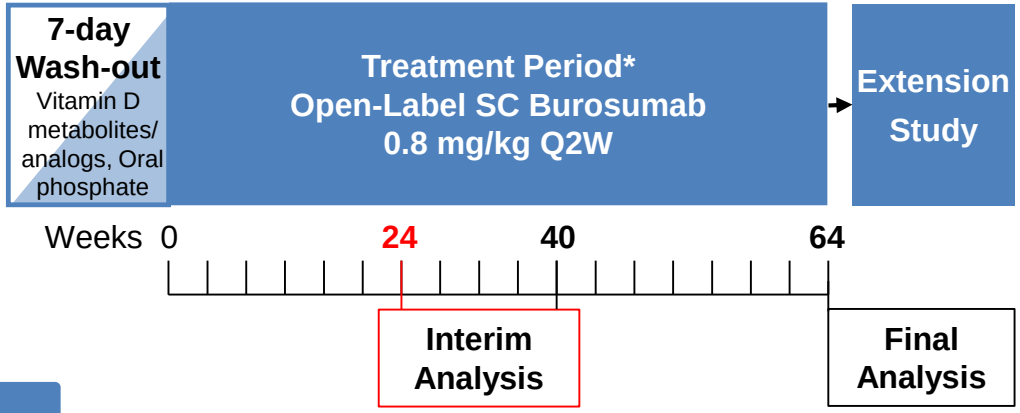
Proposed Mechanism of Action of Burosumab, an Investigational Product



Pediatric Phase 2 Study Design (Burosumab-CL205)

Population

- N = 13
- Children with XLH
- 1-4 years old
- A RSS at the knee of ≥ 1.5 required in ≥ 5 patients



Endpoints

- **Pharmacodynamics**: serum phosphorus (primary), serum 1,25$(OH)_2$D, serum alkaline phosphatase
- **Rickets and lower extremity skeletal abnormalities** (RSS and RGI-C *at week 40 and 64*)
- **Height** (cm, height-for-age z-scores, and percentiles)
- **Safety**

Week 20 biochemistry data and week 24 safety data for all 13 subjects

*Dose was increased to 1.2 mg/kg if serum phosphorus increased by < 0.16 mmol/L (0.5 mg/dL) from baseline or 2 consecutive measurements were below normal range. Only 2 patients had dose increases from 0.8 to 1.2 mg/kg at week 22.

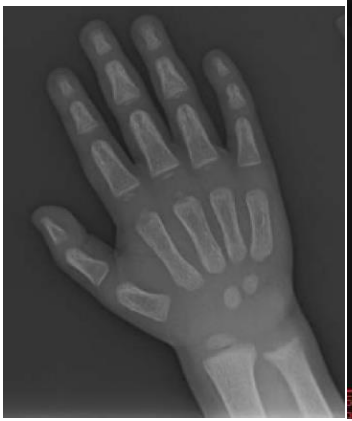
RGI-C, Radiographic Global Impression of Change; RSS, rickets severity score; SC, subcutaneous; TRP, tubular reabsorption of phosphate

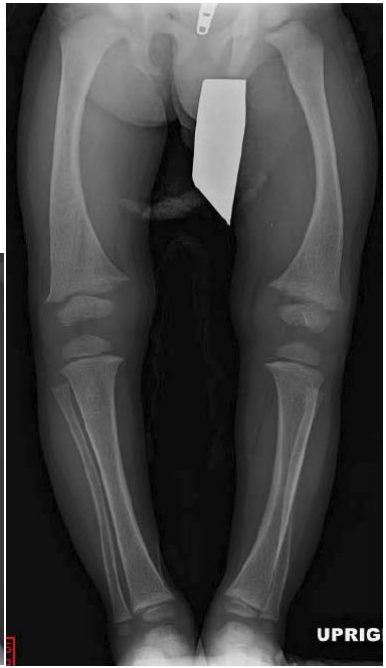
Burosumab-CL205 Baseline Characteristics

Characteristic	Burosumab Q2W (N = 13)
Age, yrs	2.94 (1.15)
Male	9 (69.2)
White	12 (92.3)
Weight, kg	12.92 (1.82)
Height Z score	-1.38 (1.19)
RSS total score Range	2.92 (1.37) (1.0-6.5)
Received prior oral P / active vitamin D	13 (100)
Duration of prior oral P / active vitamin D, mos	16.91 (13.90)
Values as mean (SD), median (min-max), or n (%) as indicated.	

Example: Baseline radiographs of 2-year-old male patient from this study

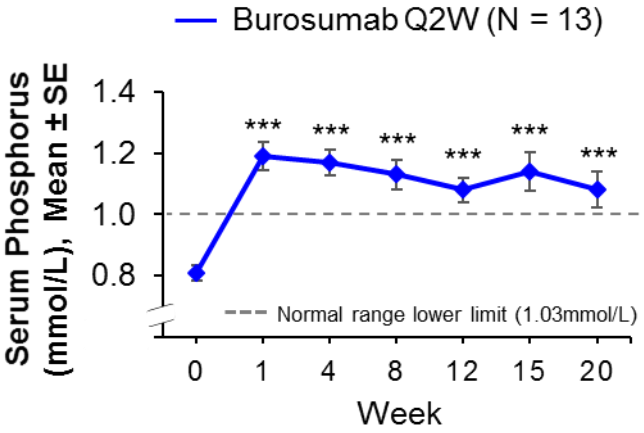
RSS	Score
Knee	1.5
Wrist	2.0
Global	3.5





P, phosphate; RSS, Thacher Rickets Severity Score.

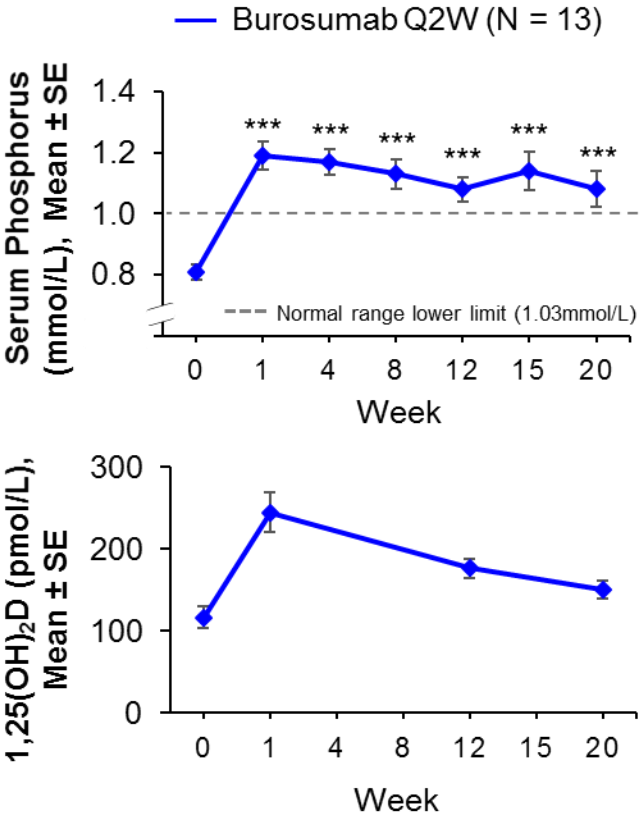
Improvement in Serum Phosphorus, 1,25(OH)$_2$D, and ALP



- **No hyperphosphatemia in any patient**
- For serum phosphorus and 1,25(OH)$_2$D, N = 10-13 based on available samples

*** P<0.0001 based on the Generalized Estimation Equation; Statistical comparisons only conducted for serum phosphorus.

Improvement in Serum Phosphorus, 1,25(OH)$_2$D, and ALP



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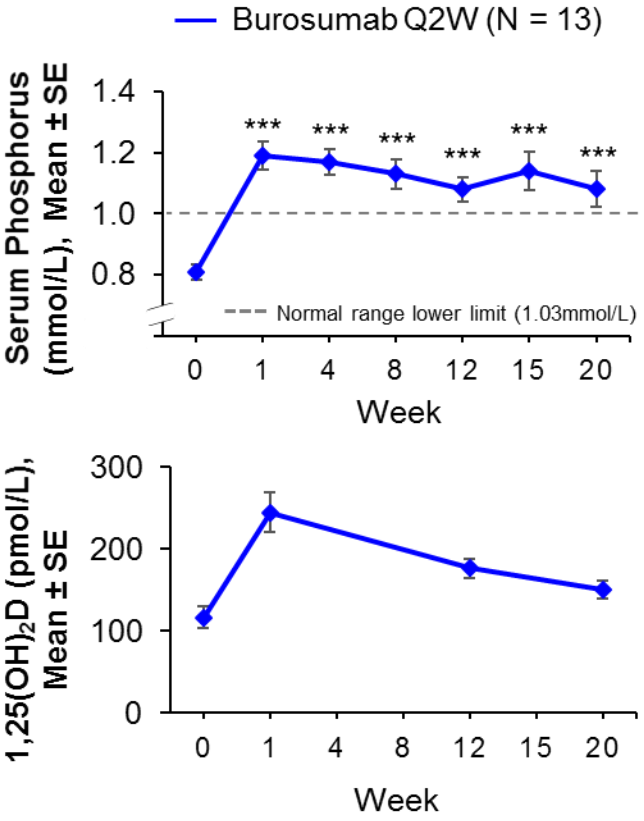

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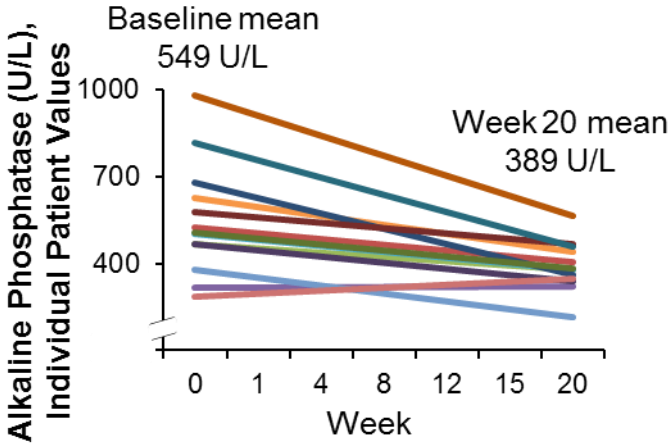

*Due to missing baseline value, the screening alkaline phosphatase value was used for the baseline value for 1 patient

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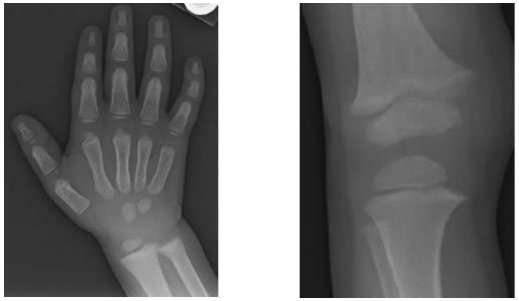
Summary of Safety Measures*

Incident (N = 13)	n (%)
Patients with any related treatment-emergent adverse events (AEs)	13 (100)
AEs of Interest	
Arthralgia	1 (7.7)
Blood parathyroid hormone increased	1 (7.7)
Bone pain	1 (7.7)
Contusion	1 (7.7)
Injection site erythema	1 (7.7)
Injection site pruritus	1 (7.7)
Injection site reaction	1 (7.7)
Nausea	1 (7.7)
Pain in extremity	1 (7.7)
Serious AEs	0 (0)
AEs leading to discontinuation	0 (0)
AEs leading to death	0 (0)

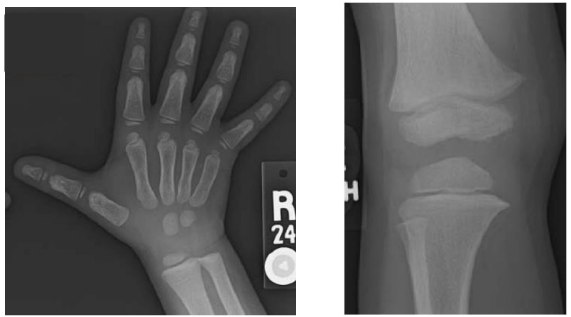
*Week 24 and including additional safety data through January 6, 2017

Week 40 Rickets Assessment Expected Late 2017

Example **baseline** radiographs in 3-year-old male patient from this study



Example **week 40** radiographs in same patient



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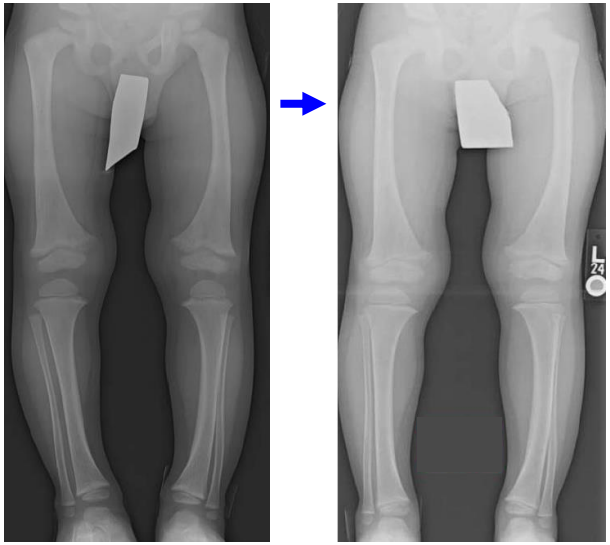


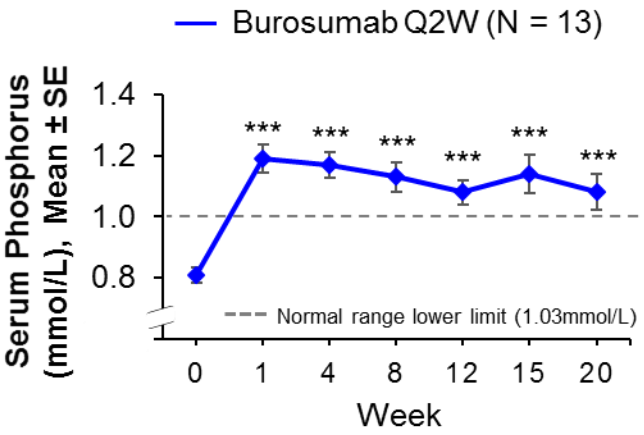
Summary and Conclusions

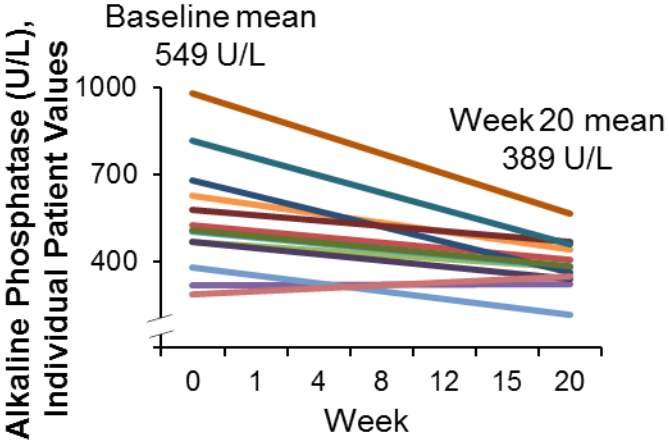
- In children 1-4 years old with XLH, treatment with burosumab for up to 24 weeks improved key pharmacodynamic parameters in XLH consistent with inhibiting FGF23:
  - Increased serum phosphorus
  - Increased serum $1,25(OH)_2D$
  - Decreased serum alkaline phosphatase
- Burosumab had a similar safety profile to previous pediatric trials; adverse events were predominately mild to moderate
  - There were no instances of hyperphosphatemia and no clinically meaningful changes observed in serum PTH, serum or urine calcium, hematology, or urine biochemical parameters
- Radiographic assessment of rickets will be conducted at week 40 and 64

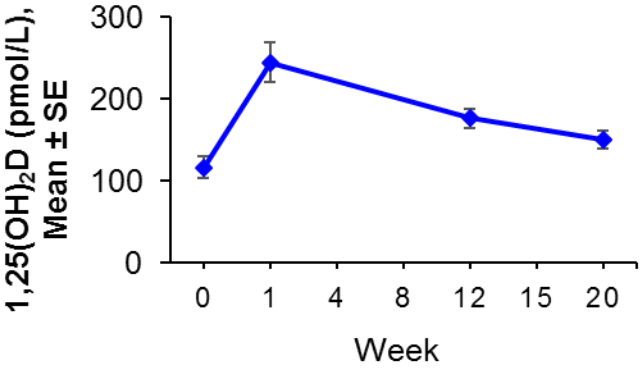
PTH, Parathyroid hormone.

Appendix

Improvement in Serum Phosphorus, 1,25(OH)$_2$D, and ALP







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