Effects of KRN23, an Anti-FGF23 Antibody in Patients With Tumor-Induced Osteomalacia and Epidermal Nevus Syndrome: Results from an Ongoing Phase 2 Study

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Disclosures

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- Dr. Weber: PI on 2 clinical trials, travel fees and honoraria from Ultragenyx
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- Dr. Osei: previous employee of Ultragenyx
- Drs. Luca, Skrinar, and San Martin: employees of Ultragenyx
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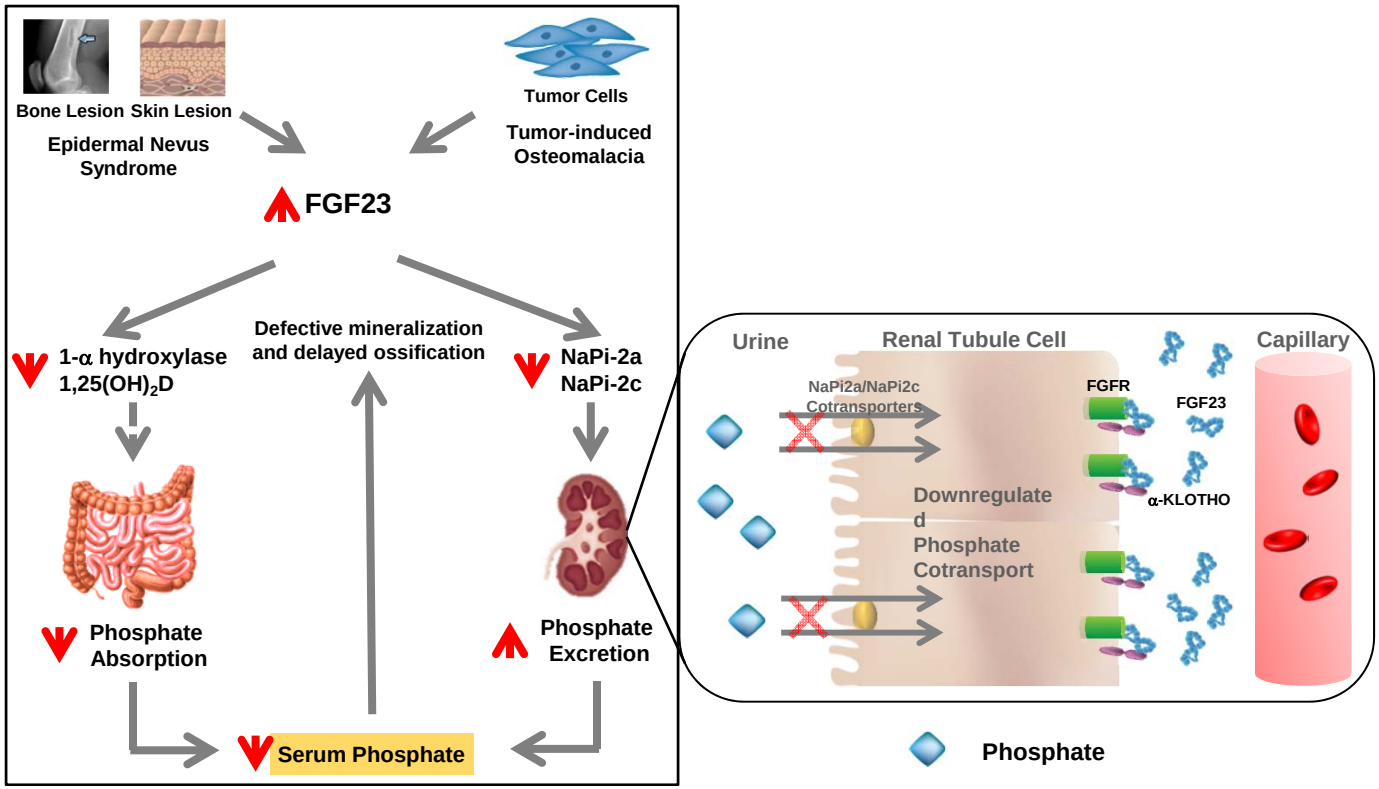
Background

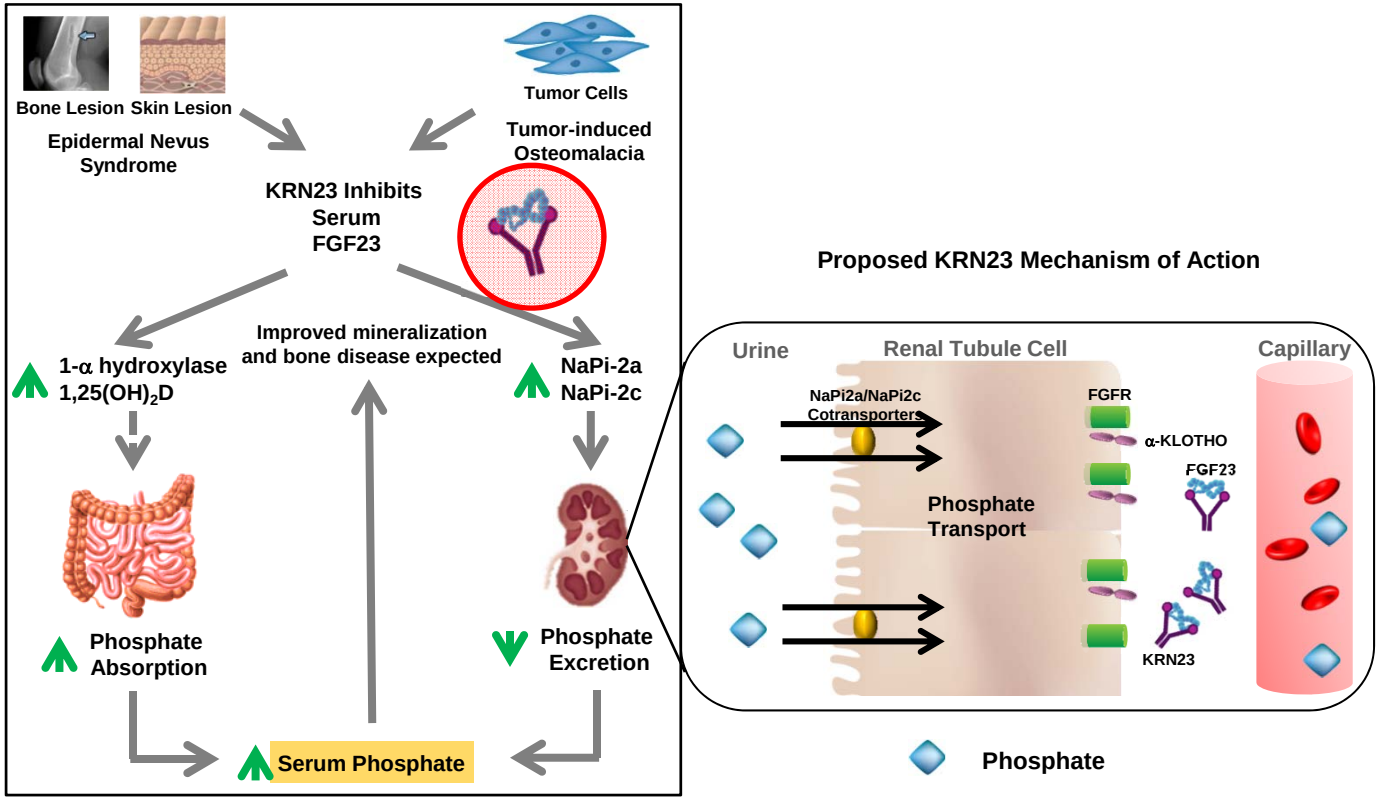
- Tumor-induced osteomalacia (TIO) and epidermal nevus syndrome (ENS) are rare diseases of excess Fibroblast Growth Factor 23 (FGF23) that are characterized by hypophosphatemia secondary to phosphaturia and impaired active vitamin D synthesis that results in bone pain, osteomalacia, fractures, and muscle weakness
- TIO is caused by small, slow growing, FGF23- secreting mesenchymal tumors and is cured when the tumor is completely resected.
  - Medical therapy with oral phosphate and calcitriol is indicated when the tumor can not be fully resected or located.
- ENS is characterized by skin lesions often associated with skeletal defects

Excess of FGF23 Impairs Renal Phosphate Reabsorption

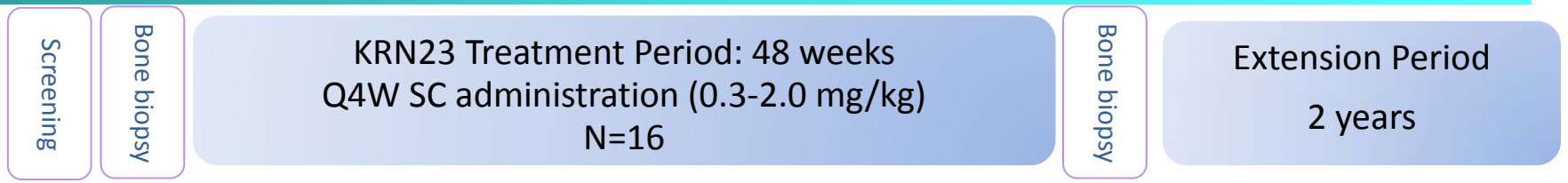


Adapted from Razzaque MS. Nat Rev Endocrinol 2009;5:611-9. Martin A, et al. Physiol Rev 2012;92:131-55.

KRN23, a Monoclonal Antibody, Is Designed to Bind and Inhibit FGF23



Study Design: Phase 2, Open-Label, Single-Arm, Dose-Finding Study



Co-primary endpoints

- Increase in serum phosphorus and improvement in osteomalacia as determined by bone biopsy

Additional efficacy measures

- Serum 1,25$(OH)_2$D, TmP/GFR, bone turnover markers
- Whole body bone scans, DXA
- Functional and mobility tests, patient reported outcomes

Key Inclusion Criteria

- Diagnosis of TIO with unidentified or unresectable tumor; or diagnosis of ENS
- Hypophosphatemia and low TmP/GFR (<2.5 mg/dL)
- FGF23 ≥2x ULN by Kainos assay (later amended to ≥ 100 pg/mL)

Current Data Summary

- N=8 subjects with Baseline and Week 24 data; N=1 subject with Week 48 bone biopsy

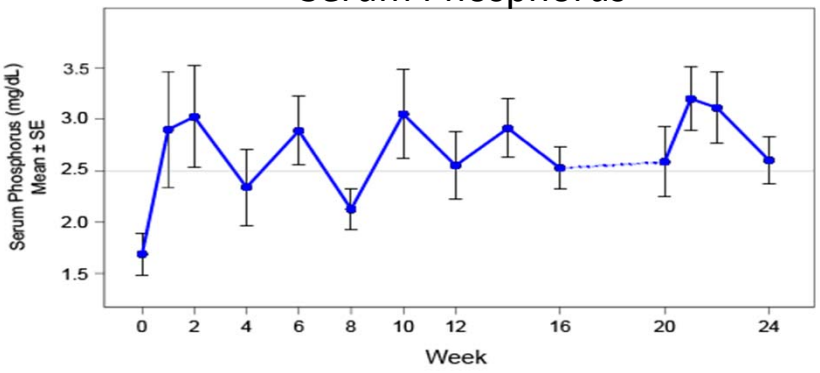
Baseline Characteristics

	KRN23 (N = 8)	Normal Range
Diagnosis **TIO** **ENS**	 7 (88%) 1 (12%)	
Male	5 (62%)	
Age, years	51.8 (18.0)	
Years since diagnosis	1 - 37	
Received prior treatment with phosphate and/or active vitamin D	8 (100%)	
Tumor located (TIO only*)	4 (57%)	
Serum phosphorus, mg/dL	1.69 (0.57)	2.5 - 4.5
TmP/GFR, mg/dL	1.39 (0.67)	2.5 - 4.5
Serum iPTH, pg/mL	84.6 (47, 198)	10 - 65
Serum FGF23, mg/dL	288.5 (94, 2569)	

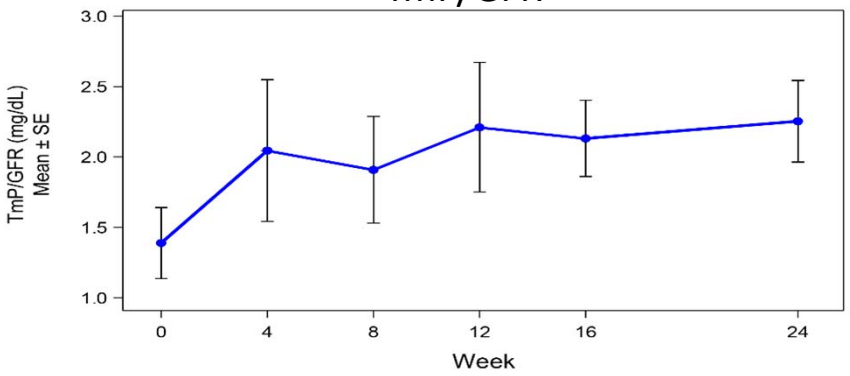
Values presented as mean (SD), median (min, max), range, or n (%) as indicated. SD, standard deviation
*N=7

Pharmacodynamics

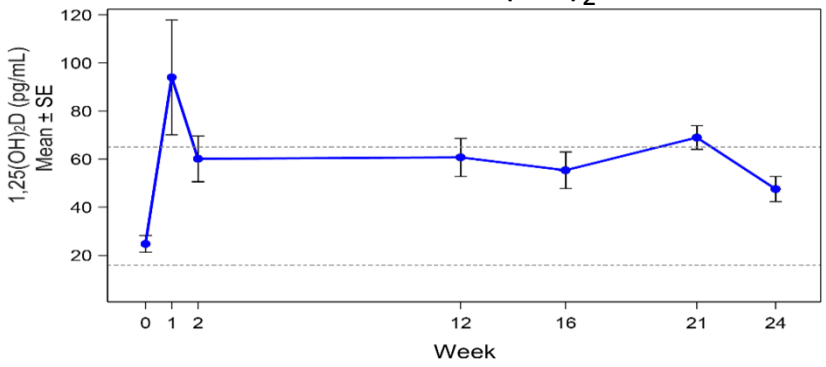
Serum Phosphorus



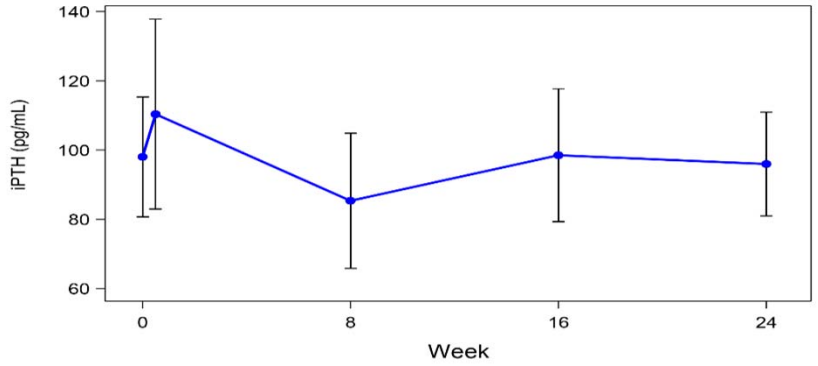
TmP/GFR



Serum $1,25(OH)_2D$

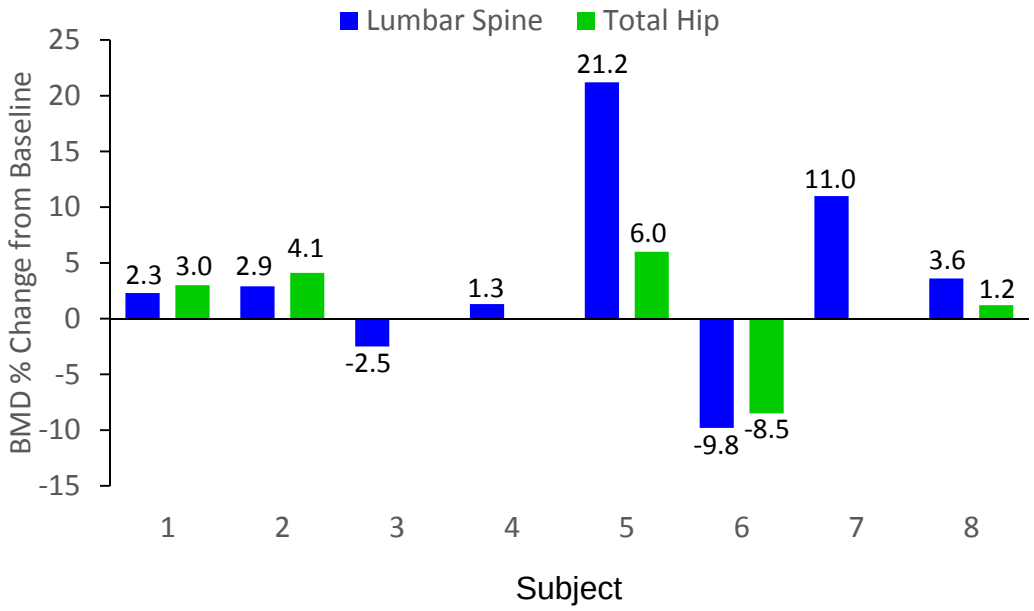


iPTH

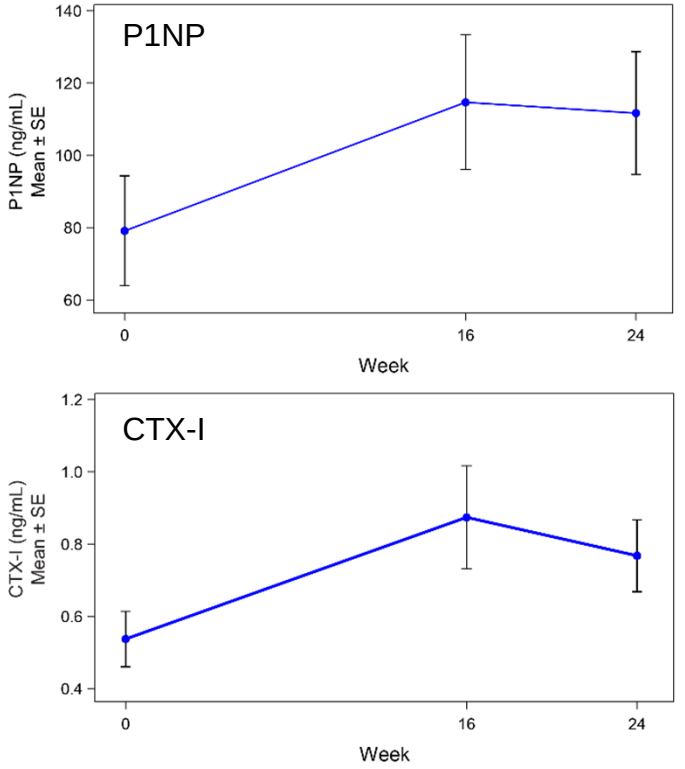


Bone Mineral Density and Bone Turnover Markers

BMD at Week 24 Increased in Most Subjects



Bone Turnover Markers Increased

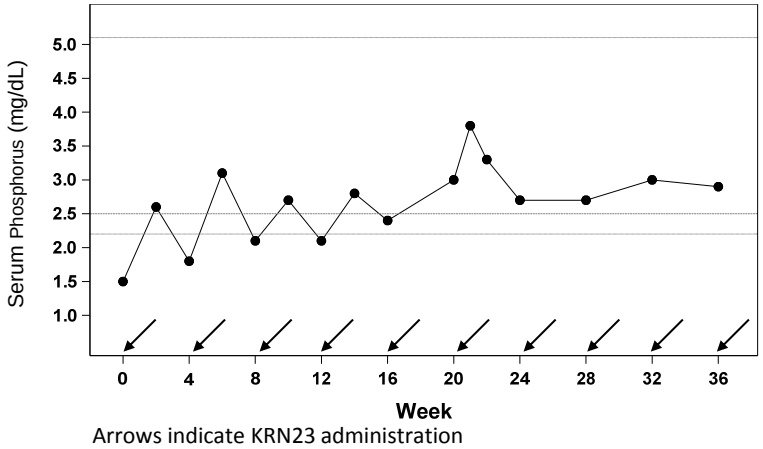


Adverse Events

Adverse event	Patient incidence (N = 8)
Any adverse events (AEs)	8 (100%)
AEs of interest	
Injection site reaction	0 (0%)
Restless leg syndrome	2 (25%)
Treatment-related AEs	3 (38%)
Vitamin D deficiency	1 (12.5%)
Rash	1 (12.5%)
Dysgeusia	1 (12.5%)
Serious AEs	1 (12.5%)

- SAE of neoplasm progression occurred in 1 non-responder subject: 68-year-old female with TIO Metastatic Spindle Sarcoma since 2002 and lower left limb amputation/multiple surgeries to remove metastatic lesions
  - No increase in serum phosphorus after dose escalation to 1.4 mg/kg Q4
  - Chemotherapy is planned
  - Due to lack of response and progression of underlying disease requiring more aggressive treatment, the PI and Sponsor agreed to discontinue the subject from the study

Case 1: 33-year-old male with TIO; 18 years since diagnosis

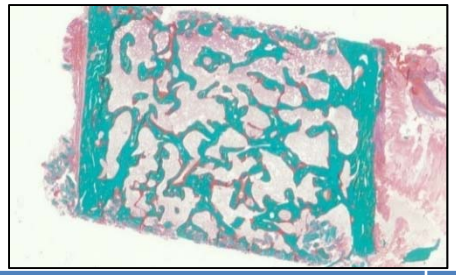


Arrows indicate KRN23 administration

At Week 24:

- Tc99 bone scan consistent with resolution of 4 rib/tibia fractures
- BMD (lumbar spine and total hip) increased by 2% and 3% respectively

Baseline



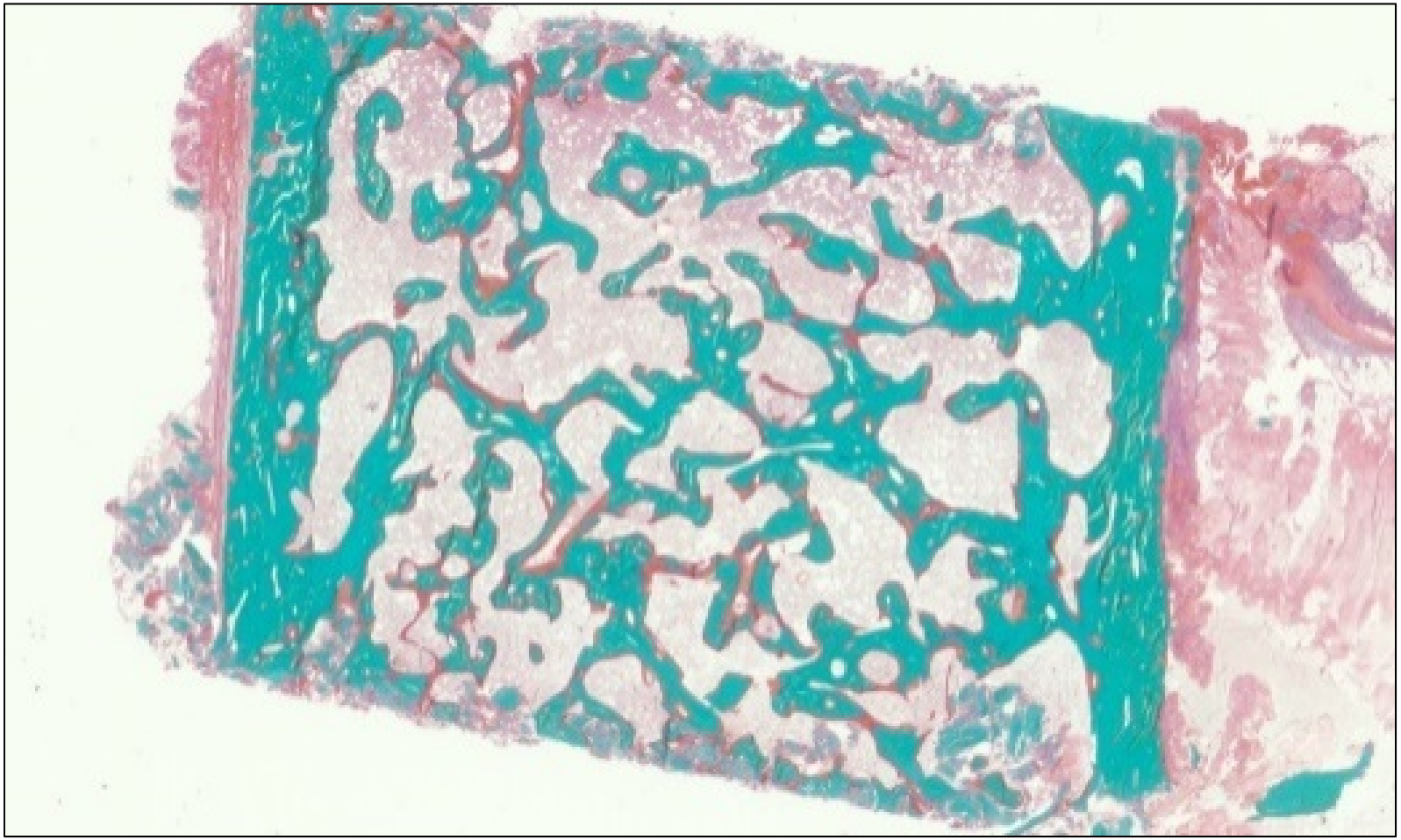
Week 48

Bone biopsy indices	Baseline	Week 48
Osteoid thickness (μm)	16.5	9.9
Osteoid/bone surface (%)	94	75
Osteoid/bone volume (%)	21	10.3
Mineralization lag time (days)	Unquantifiable	329.2
Mineralizing surface (%)	1.9	3.8
Conclusion	Severe osteomalacia	Mild osteomalacia

Summary and Conclusions

- In patients with TIO or ENS, KRN23 improved mean serum phosphorus, $1,25(OH)_2D$, and TmP/GFR over 24 weeks of treatment
- KRN23 improved bone mineralization as demonstrated by the first bone biopsy results
- The increases in BMD and bone turnover markers over 24 weeks provide additional clinical evidence of an improvement in skeletal health
- Treatment-related adverse events were mild in severity
- These data suggest KRN23 has the potential to reverse hypophosphatemia and provide clinical benefit to patients with TIO and ENS

Baseline



48 weeks