A Phase 3 Randomized, 24 Week, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults with X-Linked Hypophosphatemia (XLH)

Karl Insogna, MD
Yale School of Medicine, New Haven, CT, USA

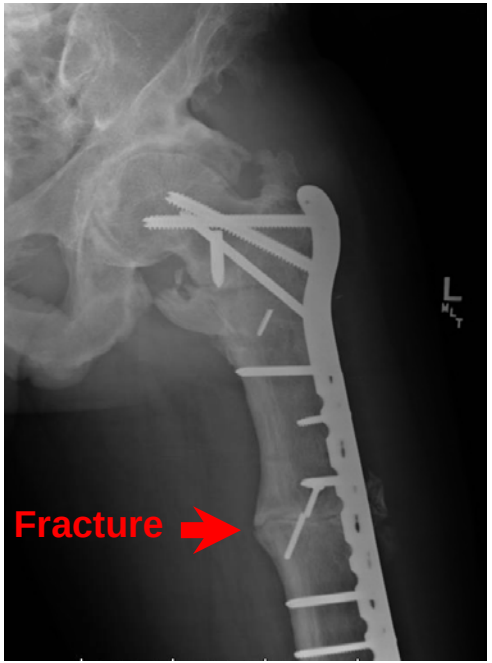
Karine Briot, MD, PhD; Erik Imel, MD; Peter Kamenický, MD, PhD; Mary Ruppe, MD;
Anthony Portale, MD; Thomas Weber, MD; Pisit Pitukcheewanont, MD;
Suzanne Jan de Beur, MD; Yasuo Imanishi, MD, PhD; Nobuaki Ito, MD;
Robin Lachmann, MD, PhD; Hiroyuki Tanaka, MD; Diana Luca, PhD;
Christina Theodore-Oklota, PhD; Matt Mealiffe, MD;
Javier San Martin, MD; Thomas O. Carpenter, MD

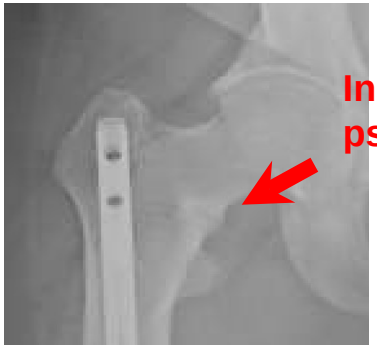
Disclosures

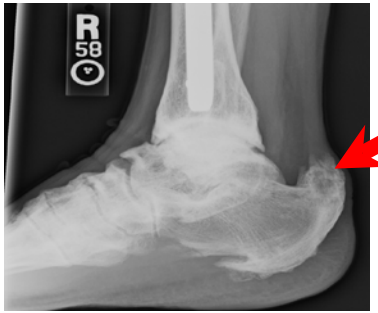
- Dr. Insogna: research support from Ultragenyx Pharmaceutical Inc.
- Dr. Briot: honoraria from Eli Lilly, Amgen, Kyowa Kirin, and research support from Ultragenyx, Pharmaceutical Inc.
- Drs. Imel, Ruppe, Portale, Weber and Carpenter: research support and honorarium from Ultragenyx Pharmaceutical Inc.
- Dr. Kamenický: honorarium from Ipsen and research support from Novartis and Ultragenyx Pharmaceutical Inc.
- Dr. Pitukcheewanont: honorarium from Alexion, Pfizer, Ipsen, Ferring, PTC Therapeutics, Ultragenyx Pharmaceutical Inc.; and research support from Alexion and Ultragenyx Pharmaceutical Inc.
- Drs. Imanishi, Ito, and Tanaka: research support from Kyowa Kirin International plc
- Dr. Jan de Beur: honorarium from Ultragenyx Pharmaceutical Inc. and Radius; and research support from Ultragenyx Pharmaceutical Inc., Mereo BioPharma Group Ltd, and Shire Plc
- Dr. Lachmann: honoraria and research support from Sanofi/Genzyme, Acetlion, Nutricia, and Ultragenyx Pharmaceutical Inc.
- Drs. Luca, Theodore-Oklota, Mealiffe, and San Martin: employees of Ultragenyx Pharmaceutical Inc.
- This study was sponsored and funded by Ultragenyx Pharmaceutical Inc. in partnership with Kyowa Kirin International plc
- Catherine Woods, PhD from Ultragenyx Pharmaceutical Inc. provided medical writing support

X-Linked Hypophosphatemia (XLH) in Adults

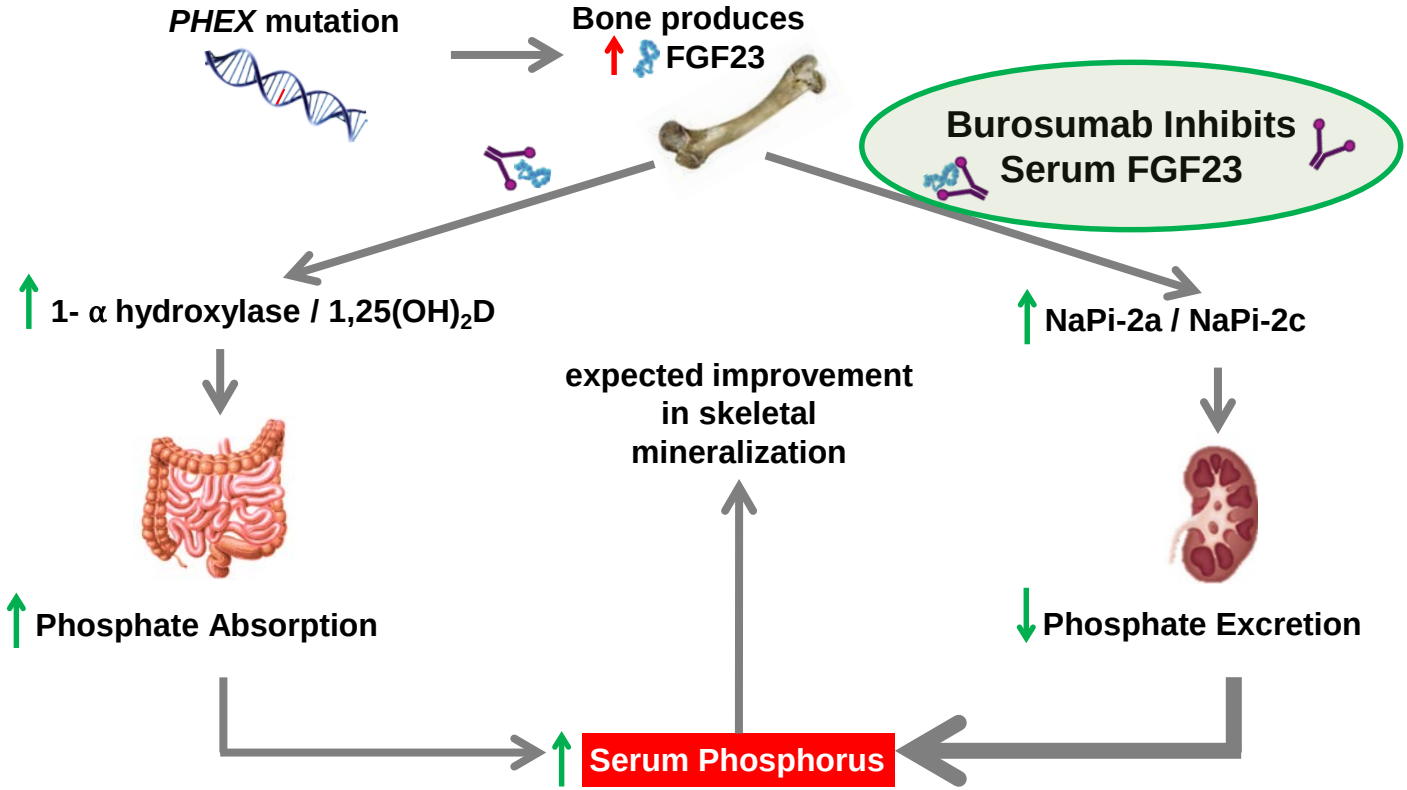
- Characterized by many skeletal complications due in large part to osteomalacia, that include fractures, pseudofractures and enthesopathy







Excess FGF23 in XLH Pathophysiology: Effect of Burosumab



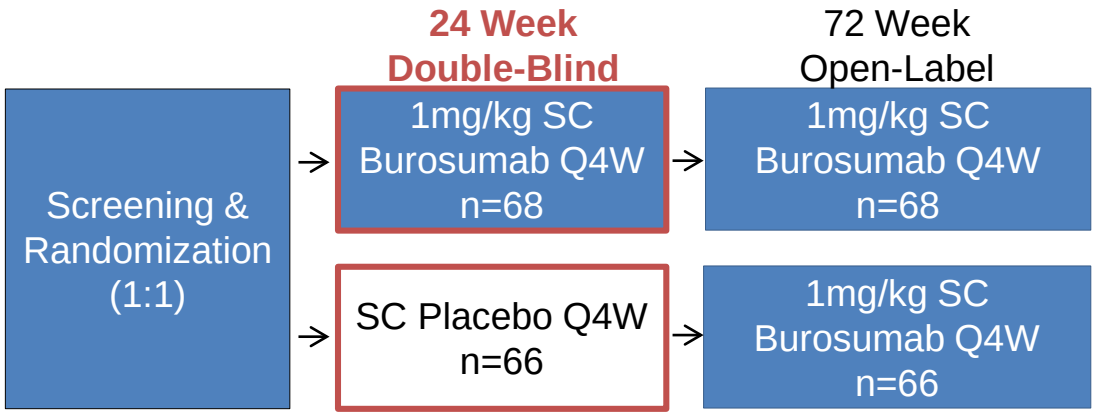
Razzaque MS. Nat Rev Endocrinol 2009;5:611-9. Martin A, et al. Physiol Rev 2012;92:131-55.

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

UX023-CL303 Study Design

Population

- Adults with XLH
- 18-65 years old
- N = 134
- Serum Pi < 2.5 mg/dL
- Measurable bone/joint pain (≥4 BPI-Q3 Worst Pain)



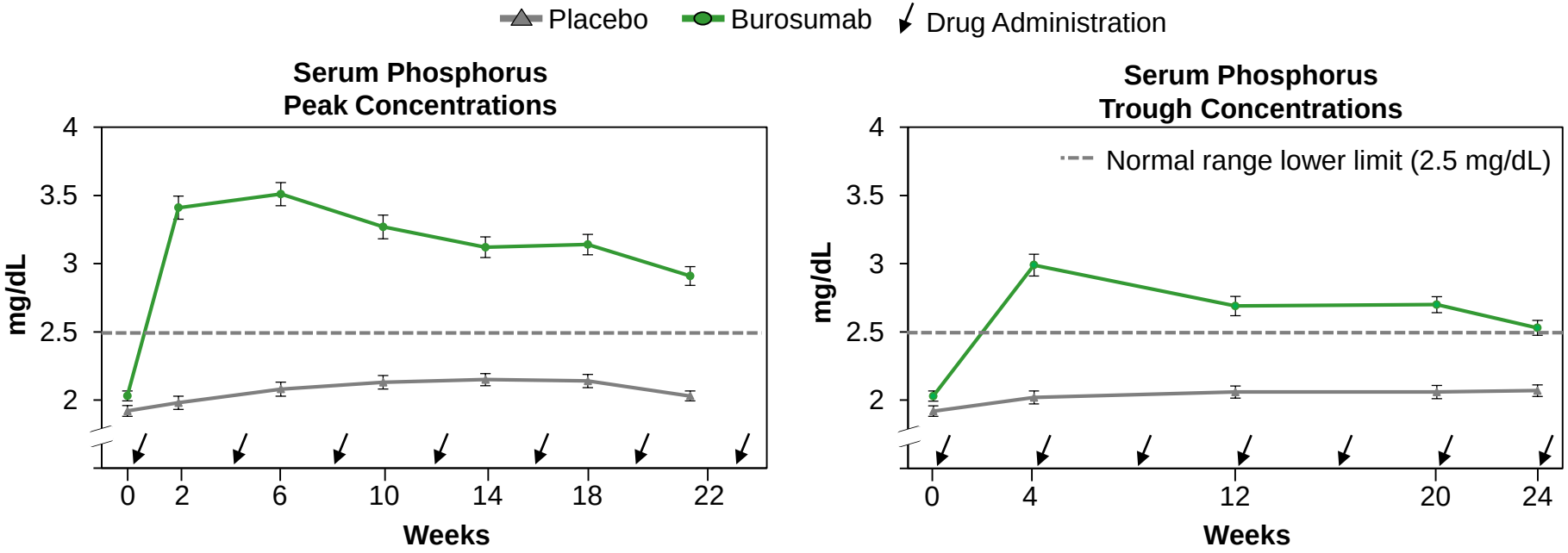
Key Endpoints

- **Primary**: The proportion of subjects achieving mean serum Pi above 2.5 mg/dL (LLN) across the mid-points of the dose interval between baseline and week 24
- **Key Secondary**: Change from baseline to week 24 in BPI Worst Pain, WOMAC Stiffness, and WOMAC Physical Function
- **Other Endpoints**: Change from baseline to week 24 in markers of bone formation (P1NP) and resorption (CTx); radiographic healing of fractures/active pseudofractures after 24 weeks of treatment; and safety

Baseline Characteristics

Patient Characteristic	Placebo Q4W (n = 66)	Burosumab Q4W (n = 68)	All Subjects (N = 134)
Age, y, mean (SD)	38.7 (12.8)	41.3 (11.6)	40.0 (12.2)
Female, n (%)	43 (65)	44 (65)	87 (65)
White, n (%)	53 (80)	55 (81)	108 (81)
Body Mass Index, kg/m^2, mean (SD)	30.6 (7.8)	30.0 (7.5)	30.3 (7.6)
Height, cm, mean (SD)	152.7 (11.8)	152.2 (9.5)	152.4 (10.7)
Serum Phosphorus, mg/dL, mean (SD)	1.92 (0.32)	2.03 (0.30)	1.98 (0.31)
Received prior phosphate, n (%)	63 (95)	62 (91)	125 (93)
Received prior vitamin D metabolites/analogs, n (%)	65 (98)	62 (91)	127 (95)

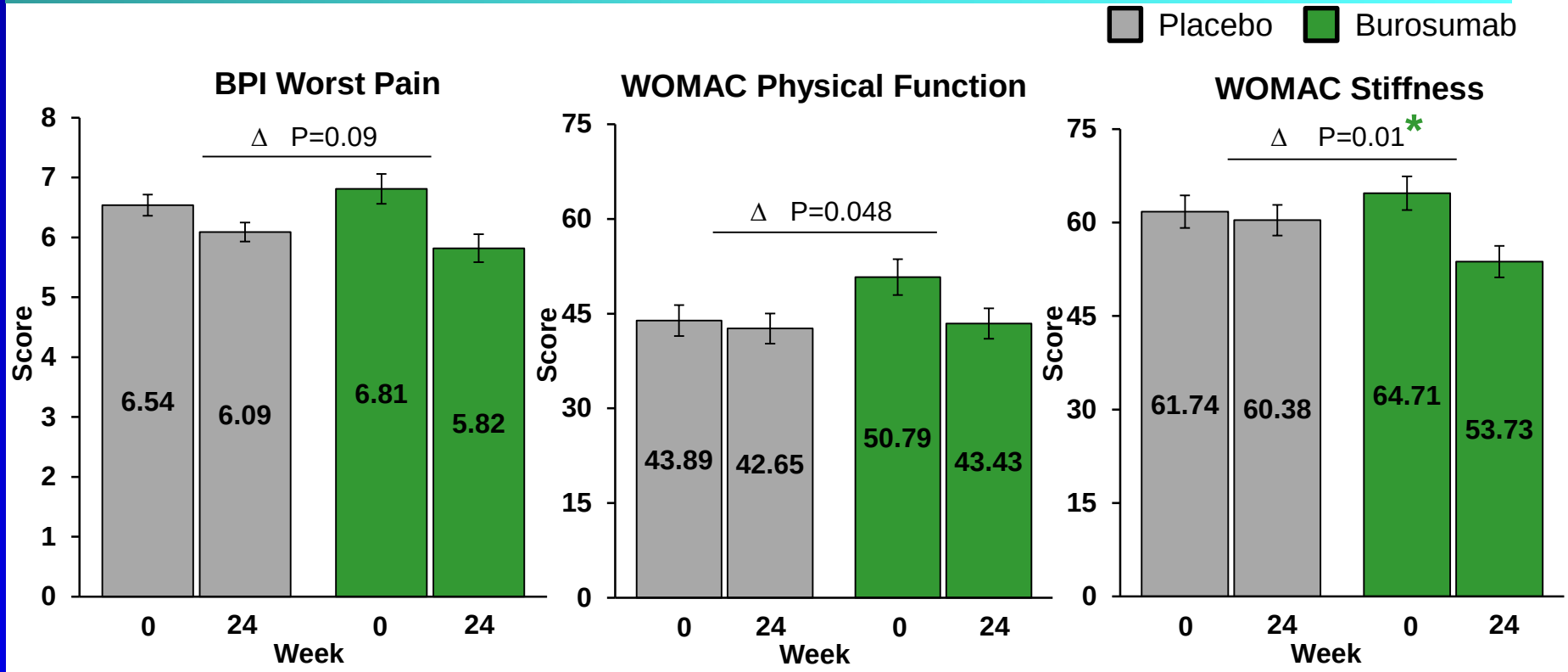
Burosumab Increased Serum Phosphorus Levels



- 94.1% of burosumab-treated subjects vs 7.6% of placebo-treated subjects achieved mean serum phosphorus > LLN at mid-point of the dose interval, averaged across dose cycles (P<0.0001)

Data expressed as mean ± SE

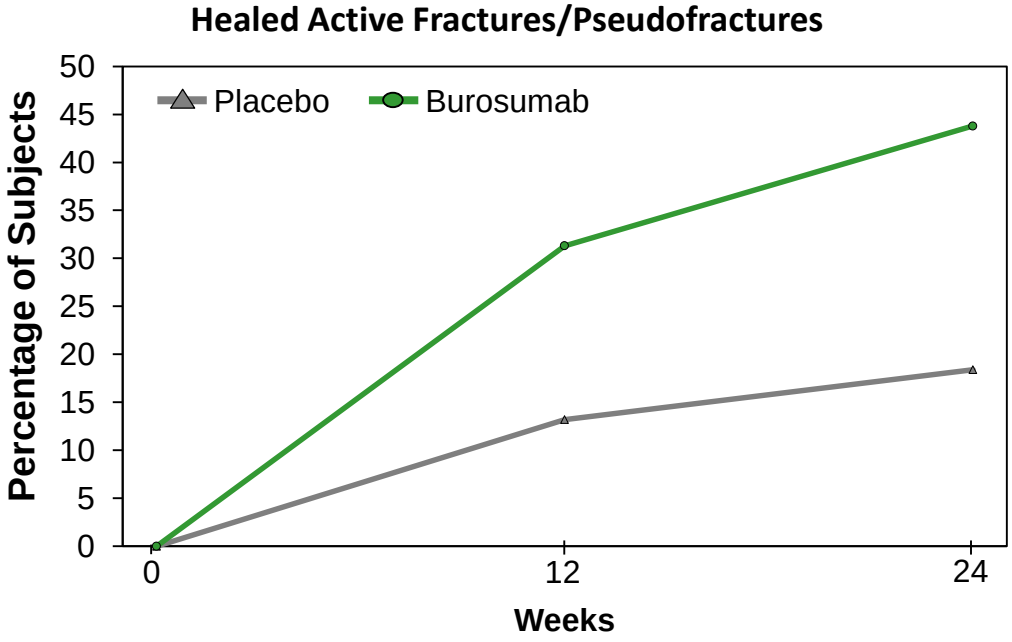
Burosumab was Associated with Improvements in Patient-Reported Stiffness at Week 24



*P-Values meet the significance level using Hochberg method (3rd test p ≤ 0.01)

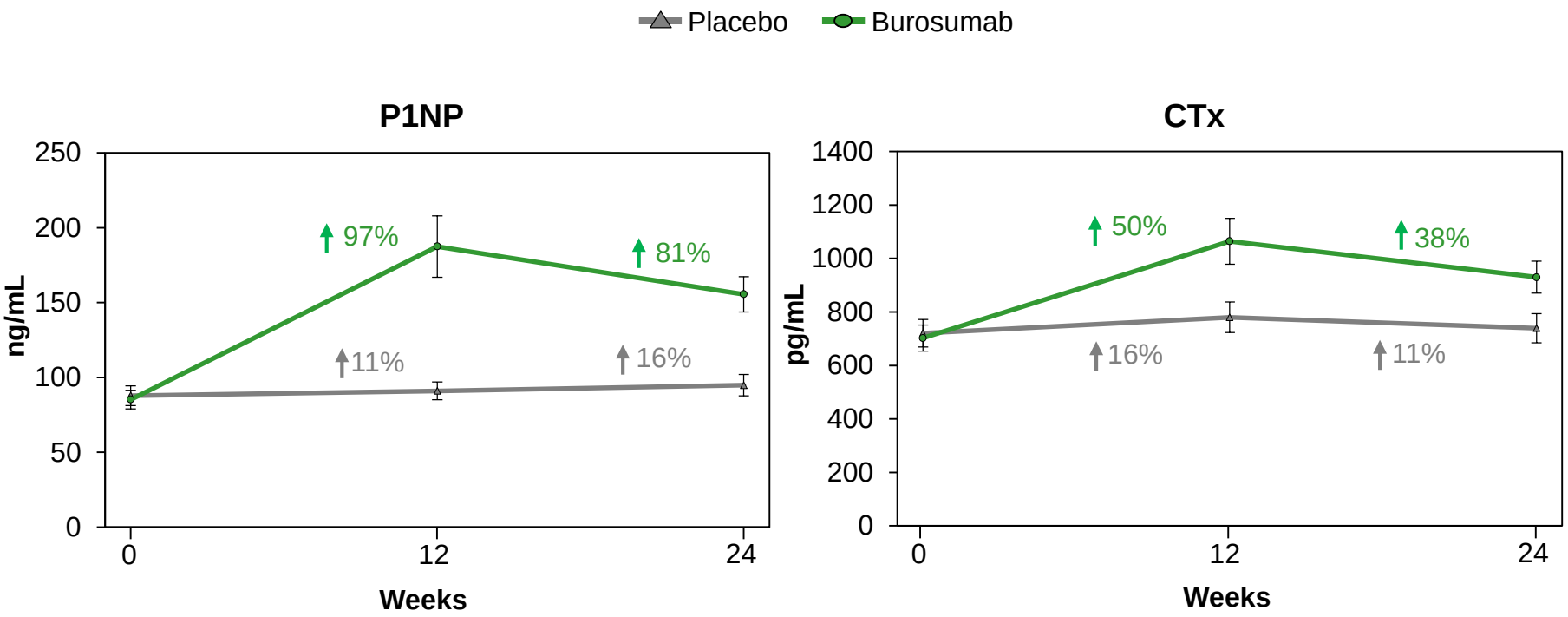
Mean ± SE.

Burosumab Treatment was Associated with Healing of Active Fractures/Pseudofractures (Fx/PFx)



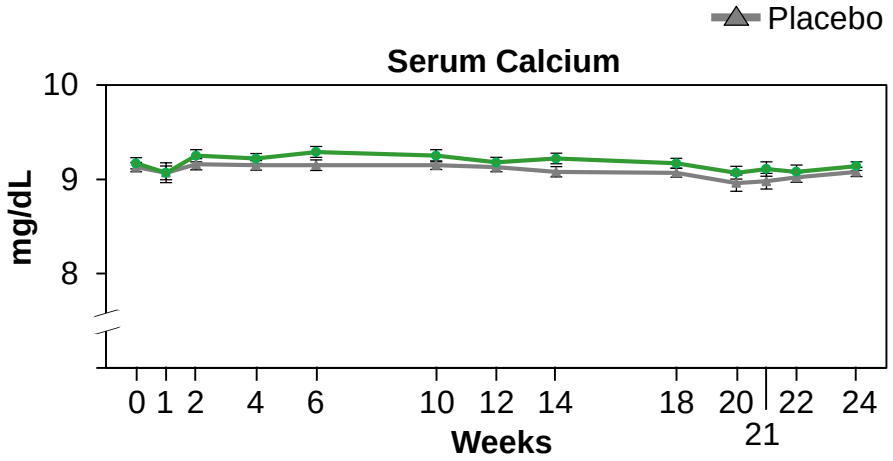
Active Fx/PFx	Placebo (n = 66)	Burosumab (n = 68)
Baseline		
Subjects with active Fx/PFx, n (%)	38 (57)	32 (47)
Active Fx/PFx, total number	91	65
Week 24		
Subjects with active Fx/PFx **healed**, n (%)	7 (18)	14 (44)
Active Fx/PFx **healed**, number (% baseline)	9 (10)	24 (37)
Odds Ratio (95% CI) for active Fx/PFx healing burosumab vs placebo	7.76 (2.56, 23.49) (p=0.0004)	

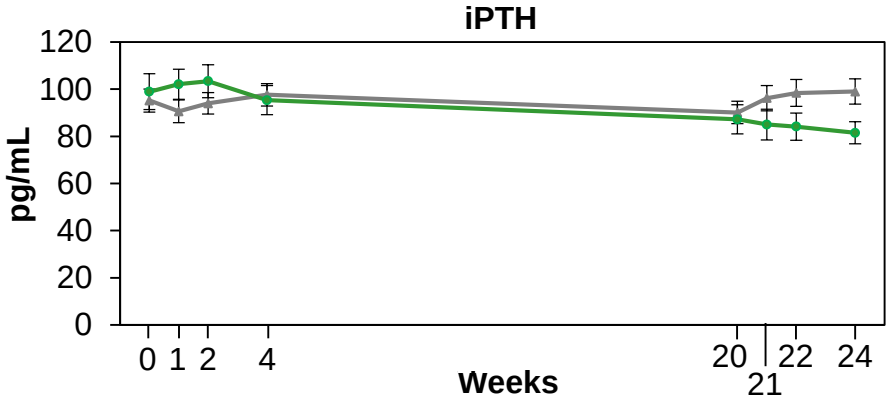
Treatment with Burosumab Increased Markers of Bone Formation and Reabsorption

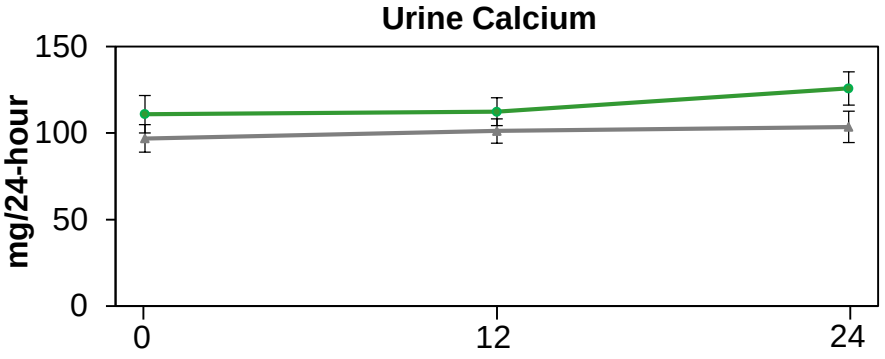


Data expressed as mean ± SE percentage change from baseline

No Clinically Meaningful Changes in Calcium and iPTH







Data expressed as mean ± SE

- 100 of the 131 evaluable subjects had no change in nephrocalcinosis score
- Nephrocalcinosis scores increased by 1 point:
  - 12 placebo-treated subjects
  - 11 burosumab-treated subjects
- No change greater than 1 point

Safety

Patient Incidence, n (%)	Placebo (n = 66)	Burosumab (n = 68)
Treatment-emergent adverse event (TEAE) Drug related TEAE	61 (92.4) 26 (39.4)	64 (94.1) 30 (44.1)
Serious TEAE Drug related Serious TEAE	2 (3.0) 0	2 (2.9) 0
Grade 3 or 4 TEAE	9 (13.6)	8 (11.8)
TEAE Leading to Study/Treatment Discontinuation	0	0
AEs of Interest Injection site reaction Immunogenicity Hyperphosphatemia Ectopic mineralization Restless leg syndrome	 8 (12.1) 4 (6.1) 0 0 5 (7.6)	 8 (11.8) 4 (5.9) 4 (5.9) 0 8 (11.8)

Summary

- In adults with XLH, burosumab reverses the underlying pathophysiology and by doing so:
  - Significantly increased serum phosphorus via improved renal phosphate reabsorption
  - Significantly reduced stiffness and was associated with positive effects on subjects' physical function and pain
  - Increased markers of bone remodeling and improved healing of fractures in adults with XLH
- The overall safety profile of burosumab was similar to placebo
- Burosumab represents an exciting new therapeutic opportunity for adults suffering with XLH

Thank You

We thank all clinical investigators, study site personnel, and the patients and their families