Burosumab: Νέα εποχή στη Θεραπεία της XLH & TIO

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Disclosures

- Received speaker and/or advisory board fees from Amgen, Lilly, Vianex, ITF Hellas, Takeda, UCB, Genesis.

RICKETS RESISTANT TO VITAMIN D THERAPY

FULLER ALBRIGHT, M.D.

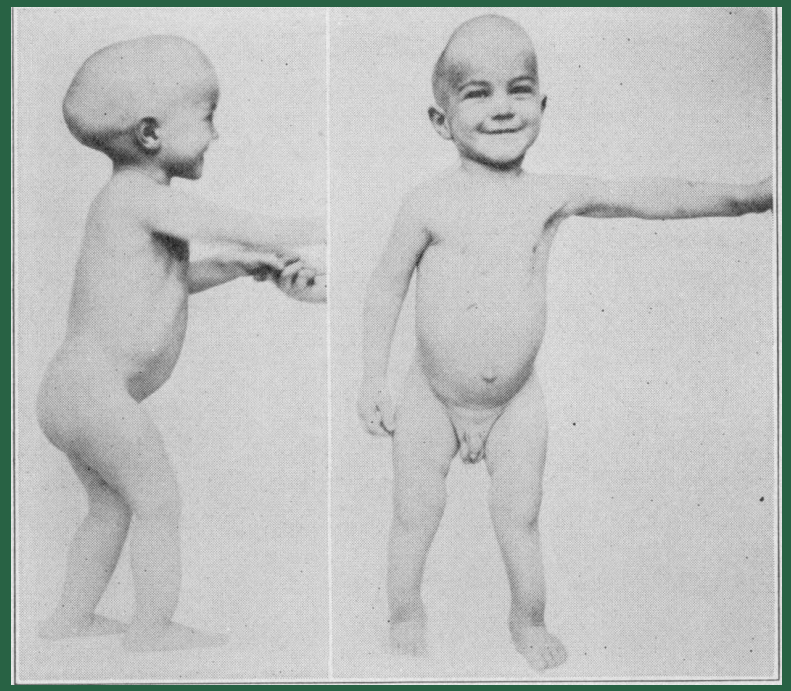
ALLAN M. BUTLER, M.D.

AND

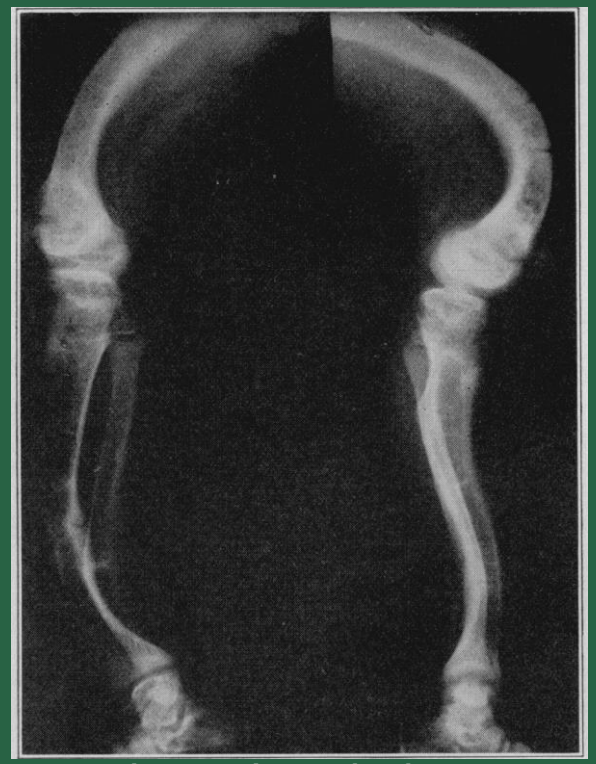
ESTHER BLOOMBERG, B.S.

BOSTON

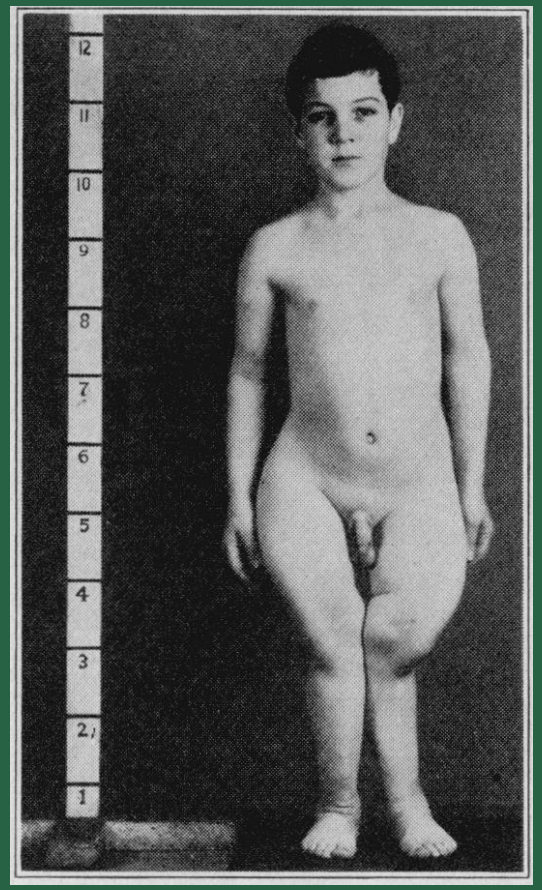
Albright F, Butler AM, Bloomberg E (1937).
Am J Dis Child 54(3):529–547



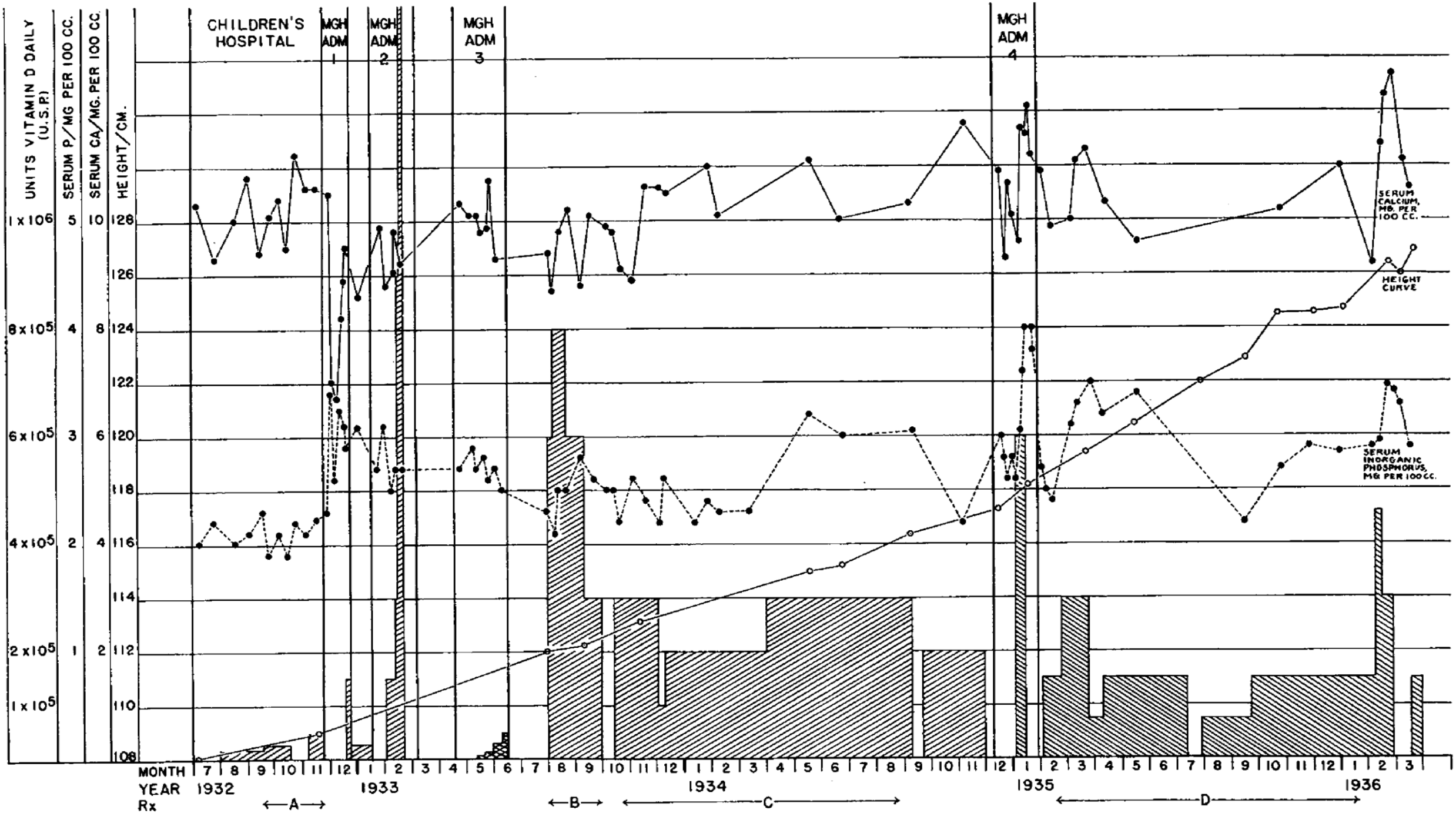
Photograph of the patient taken in January 1925, at the age of 4JA years, showing the deformities and the unusual shape of the head.



Roentgenogram taken in April 1931, when the patient was 10^4 years old, showing active rickets, deformities and multiple fractures.



Photograph of the patient taken in April 1935, when he was 14^4 years old.


UNITS VITAMIN D DAILY (U.S.P.)
SERUM P/MG PER 100 CC.
SERUM CA/MG. PER 100 CC.
HEIGHT/CM.
CHILDREN'S HOSPITAL
MGH ADM 1
MGH ADM 2
MGH ADM 3
MGH ADM 4
1 x 10^6
8 x 10^5
6 x 10^5
4 x 10^5
2 x 10^5
1 x 10^5
5
4
3
2
1
10
8
6
4
2
128
126
124
122
120
118
116
114
112
110
108
SERUM CALCIUM, MG. PER 100 CC.
HEIGHT CURVE
SERUM INORGANIC PHOSPHORUS, MG PER 100 CC.
MONTH 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3
YEAR 1932 1933 1934 1935 1936
Rx ←A→ ←B→ ←C→ ←D→

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 4, Number 4, 1989
Mary Ann Liebert, Inc., Publishers

FGF23 dependent Hypophosphatemia

Parabiosis Suggests a Humoral Factor Is Involved in *X*-Linked Hypophosphatemia in Mice

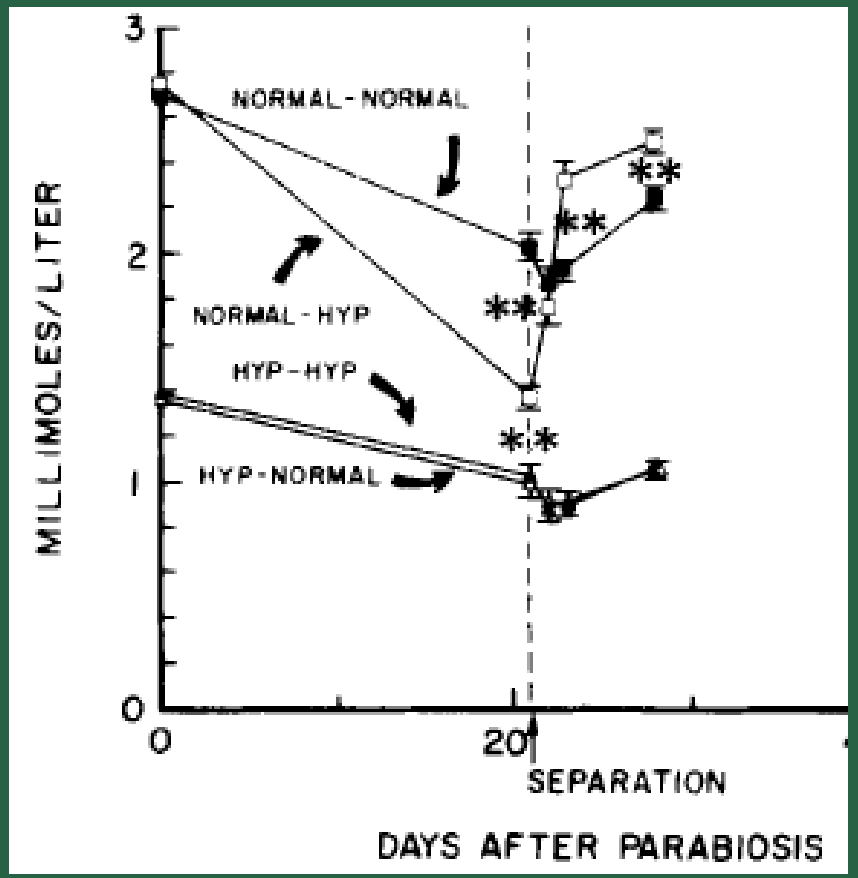
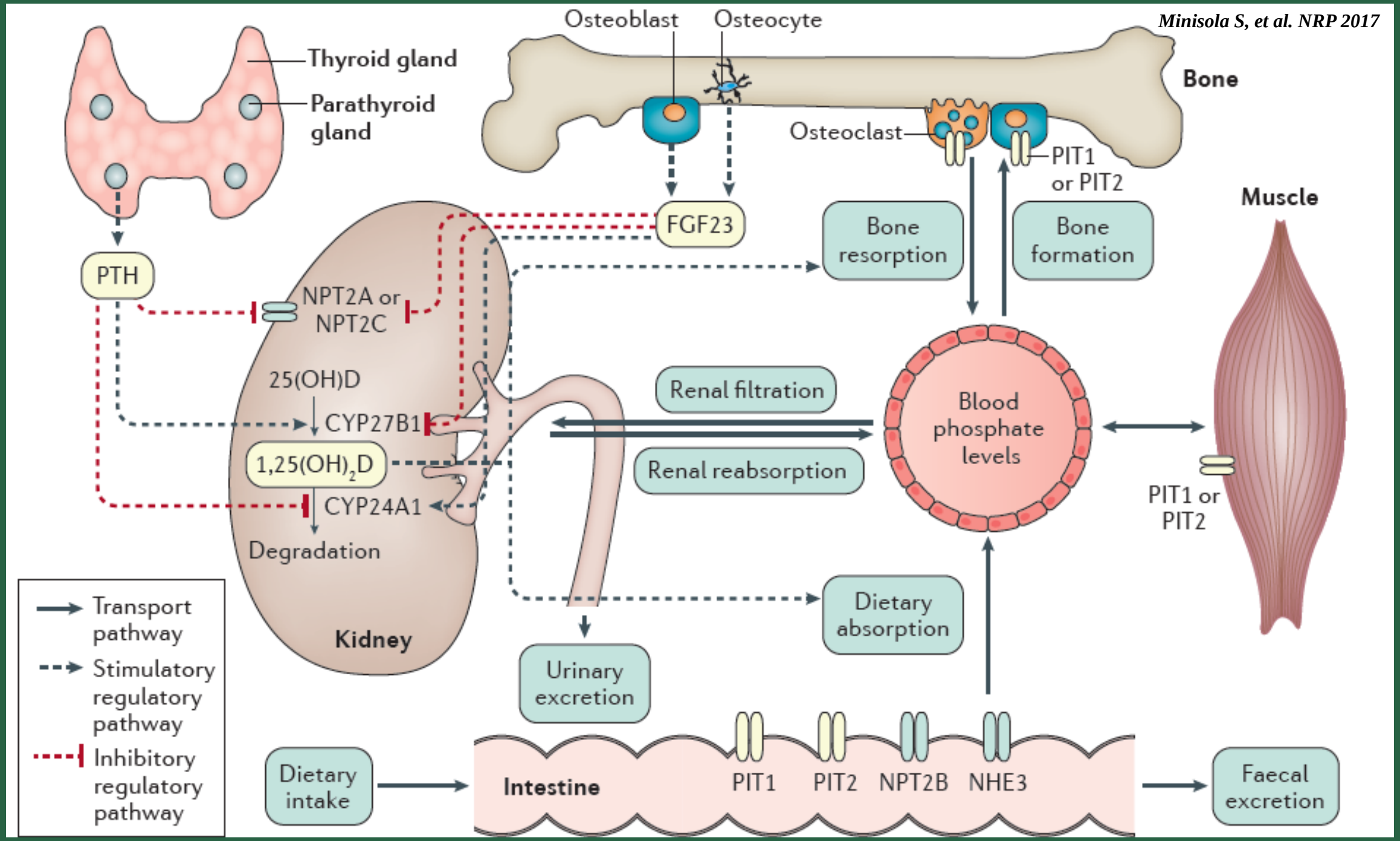
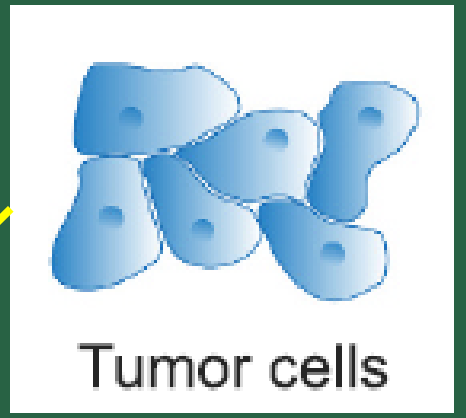


TABLE 1. EFFECT OF PARABIOSIS ON PLASMA MINERALS AND SKELETAL GROWTH IN NORMAL AND *Hyp* MICE 3 WEEKS AFTER SURGERY[a]

	Normal to normal	*Normal to* Hyp		Hyp *to* Hyp
		Normal	Hyp	
Presurgery data				
Plasma				
Phosphate	2.88 ± 0.04 (30)	2.84 ± 0.05 (17)	1.44 ± 0.05 (17)[c]	1.43 ± 0.03 (30)[b]
Physical data				
Body weight	12.1 ± 0.4 (30)	12.1 ± 0.5 (17)	11.3 ± 0.4 (17)	11.2 ± 0.3 (30)
Body length	72.1 ± 0.8 (30)	71.9 ± 1.1 (17)	69.0 ± 0.8 (17)[c]	69.5 ± 0.6 (30)[b]
Tail length	64.0 ± 0.7 (30)	64.6 ± 0.8 (17)	56.3 ± 0.6 (17)[c]	56.6 ± 0.4 (30)[b]
3 Weeks after parabiosis				
Plasma				
Phosphate	2.33 ± 0.05 (28)	1.66 ± 0.06 (15)[b]	1.54 ± 0.06 (15)[d]	1.35 ± 0.04 (25)[b]
Calcium	2.10 ± 0.02 (28)	2.02 ± 0.03 (16)[b]	2.01 ± 0.03 (15)	1.99 ± 0.02 (25)[b]
$1,25\text{-}(OH)_2\text{-}D$	78 ± 32 (6)	35 ± 20 (3)	37 ± 22 (3)	69 ± 23 (6)


Minisola S, et al. NRP 2017
Osteoblast
Osteocyte
Bone
Osteoclast
PIT1
or PIT2
Thyroid gland
Parathyroid
gland
PTH
FGF23
Bone
resorption
Bone
formation
Muscle
NPT2A or
NPT2C
25(OH)D
CYP27B1
1,25(OH)2D
CYP24A1
Degradation
Renal filtration
Renal reabsorption
Blood
phosphate
levels
PIT1 or
PIT2
Kidney
Dietary
absorption
Urinary
excretion
Transport
pathway
Stimulatory
regulatory
pathway
Inhibitory
regulatory
pathway
Dietary
intake
Intestine
PIT1
PIT2
NPT2B
NHE3
Faecal
excretion

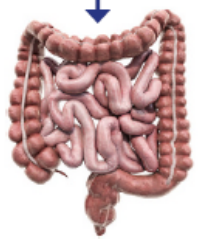
PHEX
Xp22.11.



FGF23 ↑↑↑

Potential additional direct/indirect effects

1α-hydroxylase ↓
24-hydroxylase ↑
1,25(OH)$_2$D ↓



Phosphate absorption ↓

MUSCULOSKELETAL DISORDERS

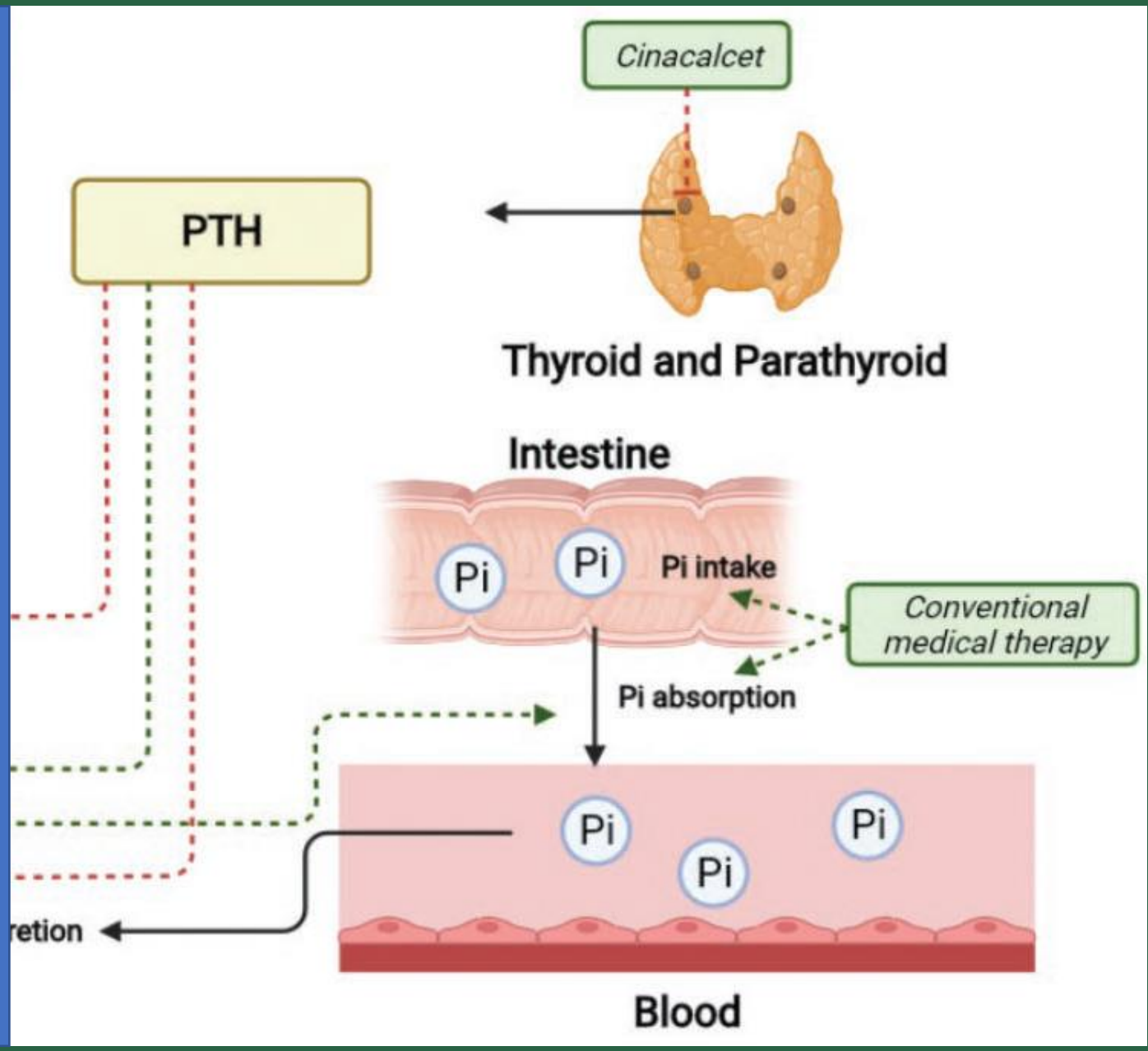
Defective mineralization
Osteomalacia
Bone pain
Fractures
Muscle weakness

NaPi-IIa ↓
NaPi-IIc ↓

Phosphate reabsorption ↓
Phosphate excretion ↑

Serum phosphate ↓↓↓

Mechanism of actions for the existing and potential novel therapies.



BONE RESPONSE TO PHOSPHATE SALTS, ERGOCALCIFEROL, AND CALCITRIOL IN HYPOPHOSPHATEMIC VITAMIN D-RESISTANT RICKETS

FRANCIS H. GLORIEUX, M.D., PH.D., PIERRE J. MARIE, D.SC., JOHN M. PETTIFOR, M.B., B.CH., AND EDGARD E. DELVIN PH.D.

Abstract We treated 11 children with vitamin D-resistant rickets with a phosphate mixture either alone (1.2 to 3.6 g per day) or combined with ergocalciferol (vitamin D_2, 25 to 50×10^3 IU per day) or with calcitriol (1,25-dihydroxyvitamin D_3, 0.25 to 1 μg per day). Serum calcitriol concentrations were normal in all patients. Calcitriol therapy raised circulating levels of the hormone to values above normal and increased intestinal phosphate absorption. In some patients this regimen decreased the need for phosphate supplements. None of the treatment regimens corrected the renal phosphate leak. Radiologic studies and bone histomorphometric analyses showed that phosphate (alone or with ergocalciferol) induced the mineralization of the growth plate but not of the endosteal bone surface. Combined calcitriol and phosphate therapy for a total of 2850 patient-days greatly improved the mineralization of trabecular bone. Short-term episodes of hypercalcemia were easily controlled by changes in calcitriol dosage. The data indicate that the combined calcitriol and phosphate regimen is useful in the treatment of vitamin D-resistant rickets. (N Engl J Med. 1980; 303: 1023-31.)

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peutic trials in VDRR. We found that long-term administration of phosphate alone or combined with ergocalciferol induced mineralization of the epiphyseal plate but not of the endosteal bone surface. The

From the Genetics Unit, Montreal Shriners Hospital; the departments of Surgery and Pediatrics, McGill University; and le Département de Pédiatrie, Université de Montréal, Montréal (address reprint requests to Dr. Glorieux at the Genetics Unit, Shriners Hospital, 1529 Cedar Ave., Montreal, Quebec, Canada H3G 1A6).

Supported by the Shriners of North America, the Queen Elizabeth II Research Fund (Children's Diseases), and le Conseil de la Recherche en Santé du Québec.

Parts of this work have been presented at the Third Workshop on Phosphate and Other Minerals (Madrid, Spain, 1977), the Annual Meeting of the Canadian Orthopaedic Research Society (Vancouver, B.C., Canada, 1978), and the Fourth Vitamin D Workshop (Berlin, West Germany, 1979).

secondary to phosphate had developed. When she entered the study at age 11, there was a "brown tumor" in the mandible. When she was given calcitriol and Pi treatment, radiologic studies showed that the tumor regressed, but serum iPTH and calcium levels remained elevated. A subtotal parathyroidectomy was performed at the time of the second bone biopsy. VDRR had been diagnosed in Patient 4 in infancy, and she was overtreated with ergocalciferol by her mother, who also had VDRR. The child had several episodes of intoxication. All therapy was withheld for 10 weeks before the first biopsy. She was then placed on the calcitriol and Pi regimen. Bone biopsy was repeated two and 17 months later.

Patient 5 had been given Pi (2.5 g per day) for 15 months before the first biopsy. Three months after calcitriol was added to the treatment, bone biopsy was repeated. Patient 7 had been treated for four years with ergocalciferol and Pi. The former drug was discontinued six weeks before the first biopsy. The second biopsy was performed after five months of treatment with calcitriol and Pi.

Patients 9 and 10 were siblings. Both had been treated with Pi

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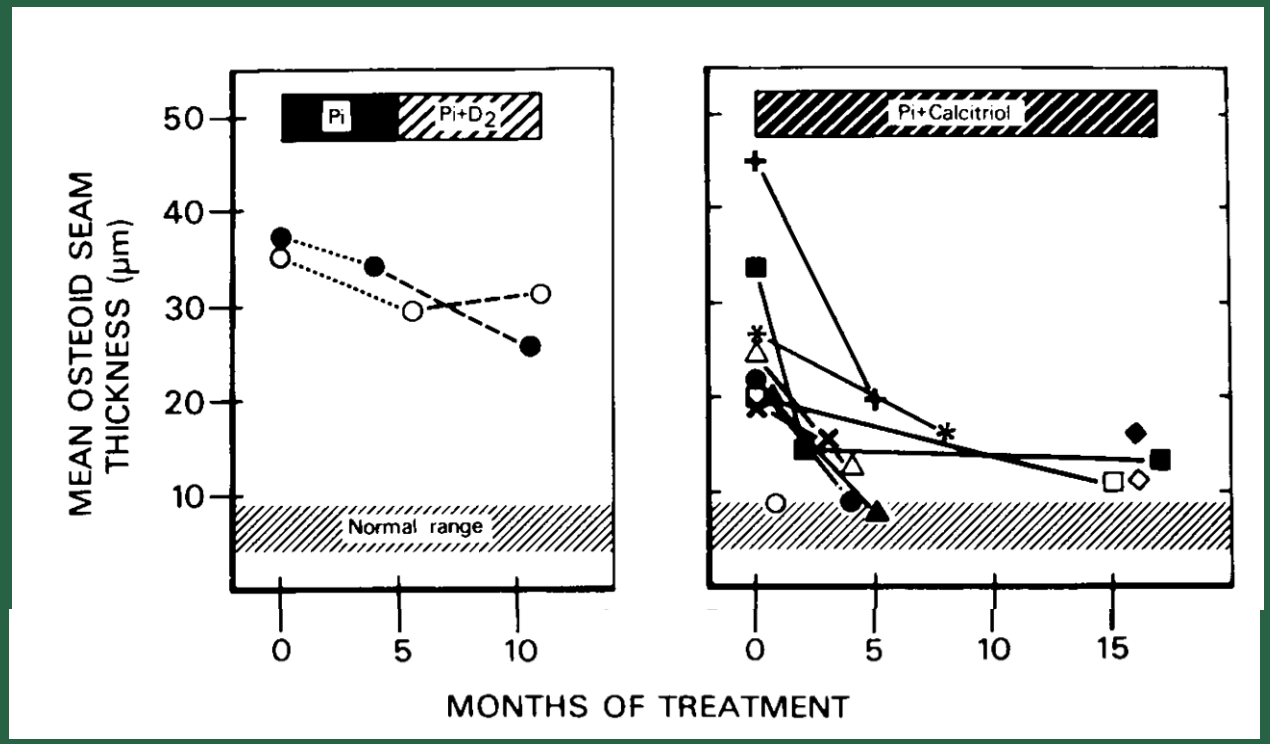
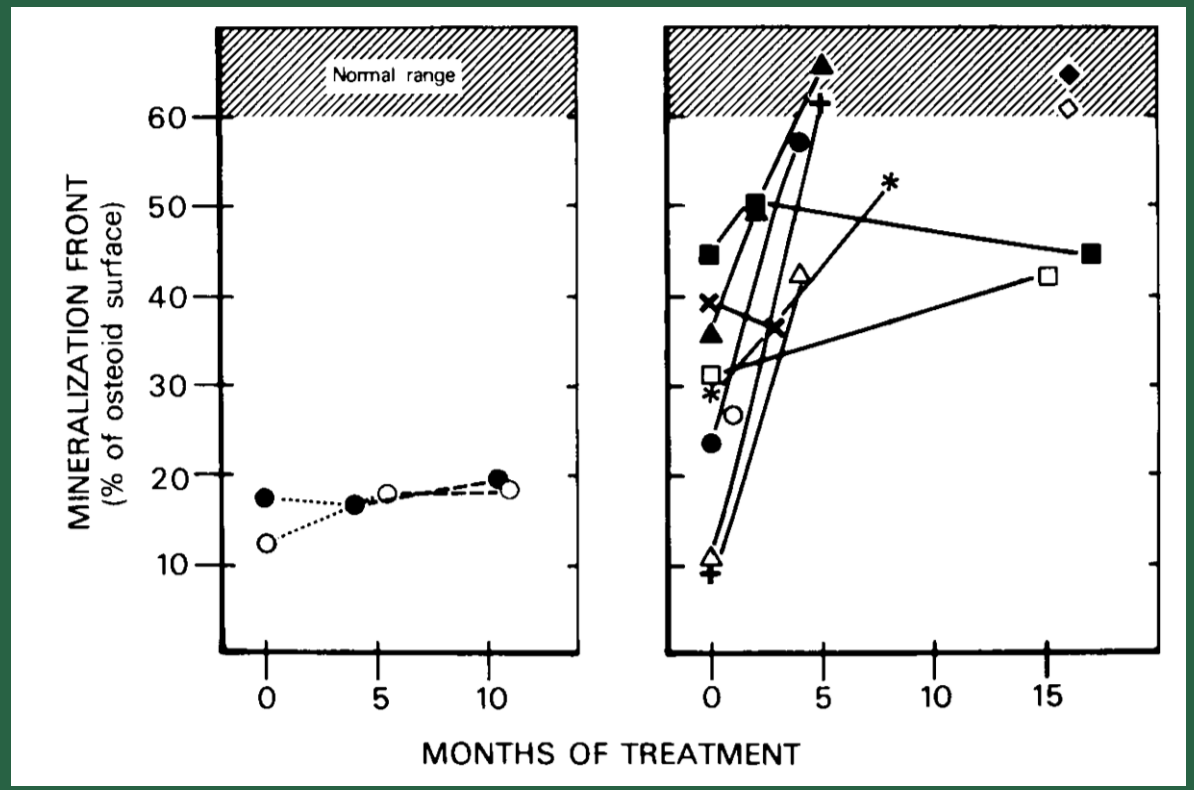




Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia

Nature Reviews Endocrinology 2022

Conventional treatment in children: recommendations.

- Vitamin D analogues and phosphate supplements can be offered to all children with XLH, as soon as the diagnosis is established.
- Starting doses of elemental phosphate range from 20 to 60 mg/kg body weight per day (0.7–2.0 mmol/kg)[2] in four to six divided doses, according to the severity of the disease.
- Calcitriol should be given at a starting dose of 20–30 ng/kg body weight per day, in one or two doses, or alfacalcidol once daily at an initial dose of 30–50 ng/kg per day.

Conventional treatment in adults: recommendations.

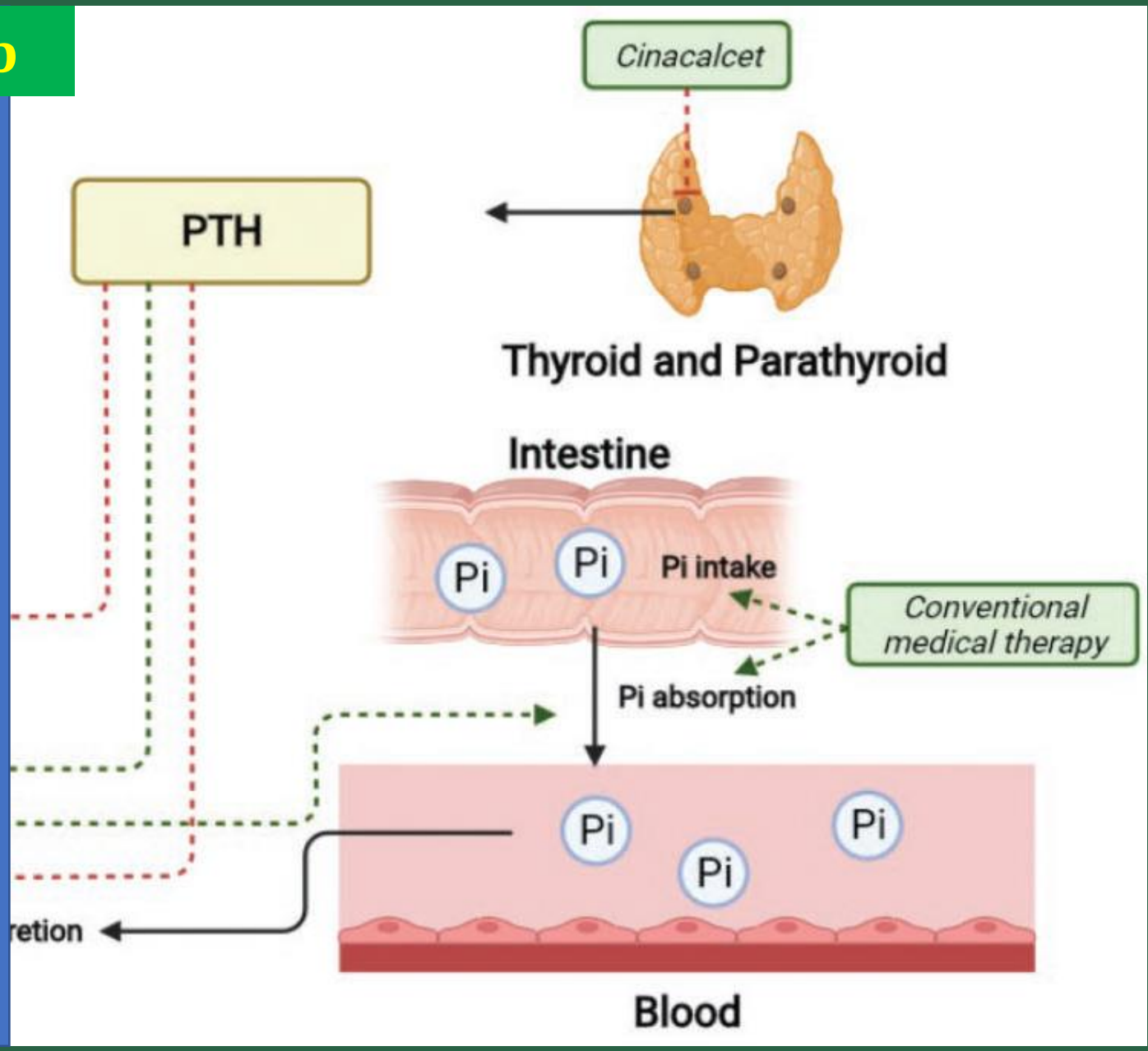
- Treatment in adults should include: vitamin D analogues (alfacalcidol 0–1.5 µg per day, once per day, or calcitriol 0–1.0 µg per day, in one or two doses) alone or with phosphate supplements (ideally smaller doses (than in children), which are evenly distributed across the day, 0–2,000 mg per day).
- Management of bone pain might be required in adults with XLH owing to osteomalacia, fractures or pseudofractures.
- In adults with XLH, clinicians should evaluate the need for orthopaedic surgery or the presence of dental complications.
- We suggest considering treatment with vitamin D analogues and phosphate supplements during pregnancy and breastfeeding. No data, to our knowledge, are available regarding the effect of therapy in postmenopausal women. Consistent evidence is still missing for treating enthesopathies.
- We do not recommend treatment of asymptomatic adult patients, unless they develop pseudofractures, even without symptoms.

Unmet need in XLH -TIO

- Η συμβατική θεραπεία δεν είναι αιτιολογική, δεν διορθώνει τη φωσφορουρία και αυξάνει τα επίπεδα του FGF23
- Δύσκολη η συμμόρφωση, ιδίως στη χορήγηση φωσφορικών αλάτων
- Ανεπιθύμητες ενέργειες κύρια από το ΓΕΣ
- Πλημμελής αποκατάσταση των διαταραχών
  - Χαμηλό Ανάστημα
  - Οστικές παραμορφώσεις (60-70% μηριαίο/κνήμη- 50-90% ορθοπαιδικές επεμβάσεις)
  - Οδοντικές ανωμαλίες
  - Νεφρασβέστωση (30-70%)
  - Υπερπαραθυρεοειδισμός άμεσα σχετιζόμενος με τη χορήγηση φωσφορικών αλάτων (25% SHPT-10% THPT)
  - Μυϊκή αδυναμία- διάχυτα οστικά άλγη
  - Κατάγματα (44%)
  - Σπονδυλική στένωση (21%)
  - Ενθεσοπάθεια-οστεοαρθρίτιδα (80%)
  - Διαταραχές ακοής
  - Υπέρταση (νεφροπάθεια, υπερπαραθυρεοειδισμός, ΧΝΝ)
- Μείωση επιβίωσης

Mechanism of actions for the existing and potential novel therapies.

Burosumab



Burosumab

- Burosumab (previously called KRN23) is a recombinant human IgG1 monoclonal antibody targeted to FGF23 that was developed for the treatment of XLH
- February 2018, the European Medicines Agency (EMA) granted a conditional marketing authorization in the European Union for burosumab for the treatment of XLH with radiographic evidence of bone disease in children ≥1 year of age and in adolescents with a growing skeleton. In 2020 approved for adults.
- In April 2018, burosumab received FDA approval for clinical use for the treatment of XLH in adult and pediatric patients of 1 year of age and older.
- Approval for TIO
  - FDA: 18/6/2020
  - EMA:19/8/2022

Burosumab- Indications

Nature Reviews Endocrinology 2022

Burosumab treatment in children: recommendations.

- Consider burosumab treatment as first-line therapy in children with XLH aged 1 year or older (6 months in some countries, such as the USA), and in adolescents with radiographic evidence of severe bone disease.
- In children with mild disease, a trial of conventional therapy is suggested rather than considering burosumab as a first-line therapy.
- Once started, treatment with burosumab should be continued until the closure of the growth plate. A multidisciplinary evaluation should be conducted with the adult team to consider the follow-up of burosumab through adulthood.

Burosumab treatment in adults: recommendations.

- Burosumab could be suggested as a second-line therapy in adults with XLH with overt osteomalacia, with pseudofractures that are not responding to conventional treatment or in patients intolerant to conventional treatment.

Children: The starting dose of burosumab is 0.8 mg/kg/2 weeks sbc (maximum dose 2 mg/kg per 14 days or 90 mg per 14 days).
Adults: 1 mg/kg/4 wks (max 90 mg)
All doses should be rounded to the nearest 10 mg

ORIGINAL ARTICLE

Burosumab Therapy in Children with X-Linked Hypophosphatemia

Thomas O. Carpenter, M.D., Michael P. Whyte, M.D., Erik A. Imel, M.D., Annemieke M. Boot, M.D., Ph.D., Wolfgang Högler, M.D., Agnès Linglart, M.D., Ph.D., Raja Padidela, M.D., William van't Hoff, M.D., Meng Mao, Ph.D., Chao-Yin Chen, Ph.D., Alison Skrinar, Ph.D., Emil Kakkis, M.D., Ph.D., Javier San Martin, M.D., and Anthony A. Portale, M.D.

N Engl J Med 2018;378:1987-98.

Phase 2, open label, 64 wk

Children: 5 and 12 years

Parallel 1:1 (Q2W) vs. (Q4W) dosing

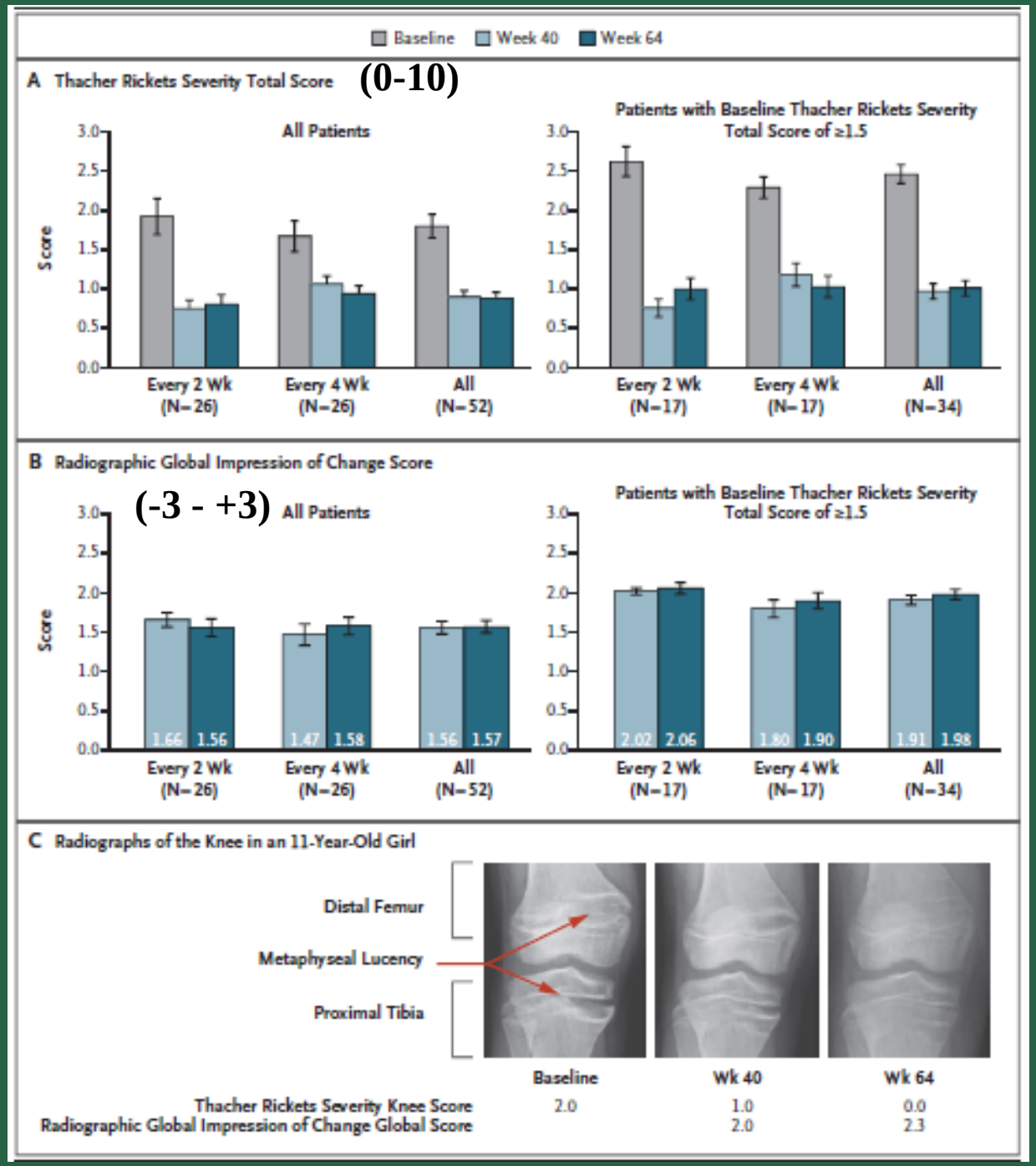
- 0.2 - 0.3 mg/kg/2 weeks
- 0.4 - 0.6 mg/kg/4 weeks

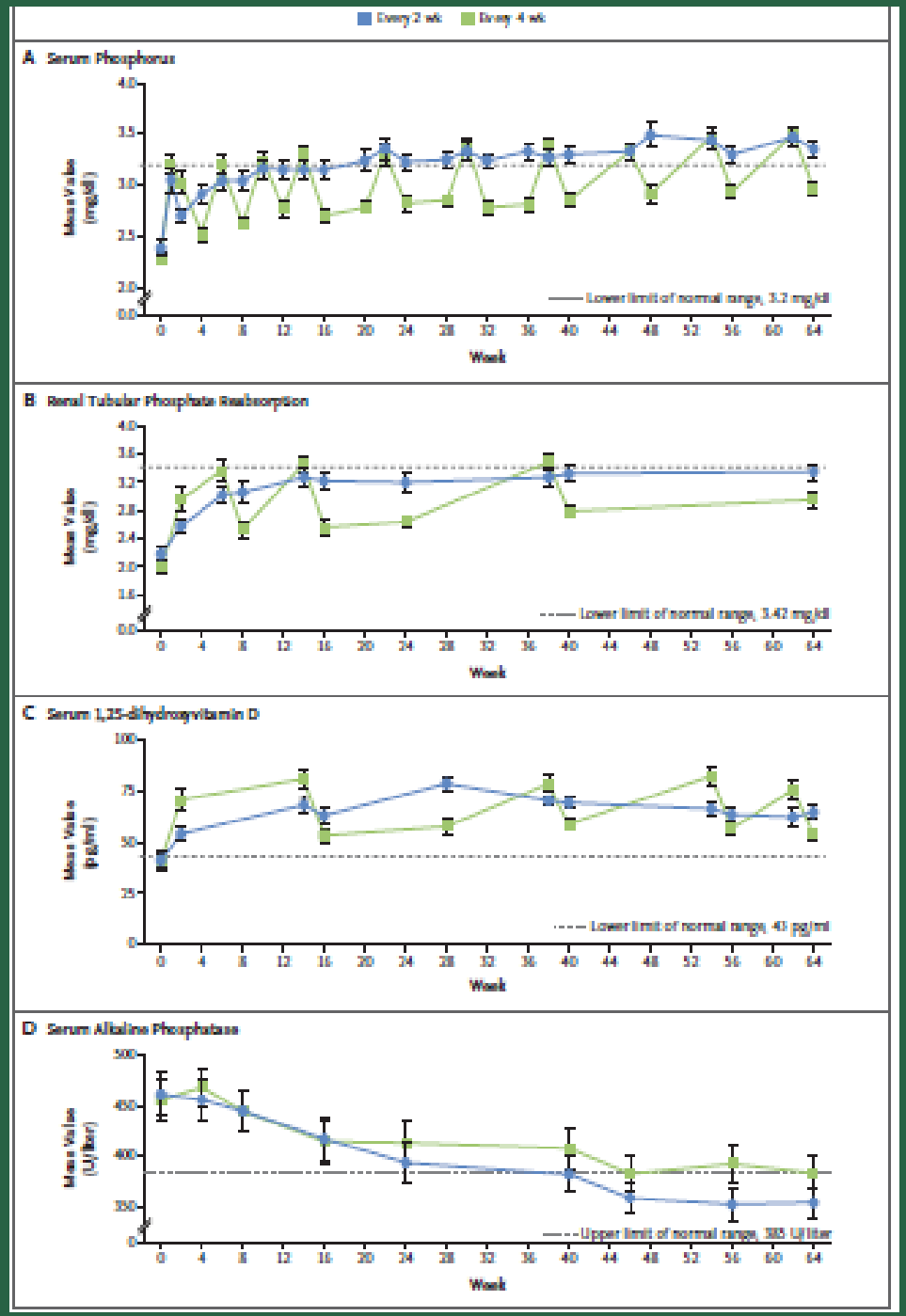
Primary Endpoint:

1. Change from baseline to wk 40 & wk 64 in the **Thacher rickets severity total score**

2. **Radiographic Global Impression of Change (RGI)** was used to evaluate rachitic changes from baseline to wk 40 & wk 64

Characteristic	Burosumab Every 2 Weeks (N=26)	Burosumab Every 4 Weeks (N=26)	All Patients (N=52)
Age — yr			
Mean	8.7±1.7	8.3±2.0	8.5±1.9
Range	5–12	5–12	5–12
Male sex — no. (%)	12 (46)	12 (46)	24 (46)
White race — no. (%)†	23 (88)	23 (88)	46 (88)
Weight — kg	31.9±7.9	29.1±10.7	30.5±9.4
Standing height			
z Score	−1.7±1.0	−2.1±1.0	−1.9±1.00
Percentile for age and sex	11.1±13.8	6.2±8.2	8.7±11.5
Geographic region — no. (%)			
United States	17 (65)	19 (73)	36 (69)
Europe	9 (35)	7 (27)	16 (31)
Previous conventional therapy for X-linked hypophosphatemia — no. (%)	24 (92)	26 (100)	50 (96)
Duration of conventional therapy — yr	7.0±2.1	6.7±2.6	6.9±2.4
Age when conventional therapy was initiated — yr	2.2±1.5	1.9±1.2	2.1±1.3
Renal tubular phosphate reabsorption — mg/dl†§	2.2±0.5	2.0 ±0.3	2.1±0.4
Serum phosphorus — mg/dl§	2.4±0.4	2.3±0.3	2.3±0.4
Serum 1,25-dihydroxyvitamin D — pg/ml§	41.3±22.0	41.4±15.3	41.3±18.7
Serum alkaline phosphatase — U/liter§	462±110	456±101	459±105
Thacher rickets severity total score¶			
Mean	1.9±1.2	1.7±1.0	1.8±1.1
Range	0–4.5	0–3.0	0–4.5
Positive for pathogenic *PHEX* mutation — no. (%)‖	23 (88)	22 (85)	45 (87)
Nephrocalcinosis grade — no. (%)**			
0	17 (65)	17 (65)	34 (65)
1	6 (23)	5 (19)	11 (21)
2	3 (12)	4 (15)	7 (13)


Baseline
Week 40
Week 64
A Thacher Rickets Severity Total Score (0-10)
All Patients
Patients with Baseline Thacher Rickets Severity Total Score of ≥1.5
Score
Every 2 Wk (N=26)
Every 4 Wk (N=26)
All (N=52)
Every 2 Wk (N=17)
Every 4 Wk (N=17)
All (N=34)
B Radiographic Global Impression of Change Score
(-3 - +3)
All Patients
Patients with Baseline Thacher Rickets Severity Total Score of ≥1.5
1.66 1.56
1.47 1.58
1.56 1.57
2.02 2.06
1.80 1.90
1.91 1.98
C Radiographs of the Knee in an 11-Year-Old Girl
Distal Femur
Metaphyseal Lucency
Proximal Tibia
Baseline
Wk 40
Wk 64
Thacher Rickets Severity Knee Score 2.0 1.0 0.0
Radiographic Global Impression of Change Global Score 2.0 2.3


Every 2 wk
Every 4 wk
A Serum Phosphorus
Mean Value (mg/dl)
Lower limit of normal range, 3.2 mg/dl
Week
B Renal Tubular Phosphate Reabsorption
Mean Value (mg/dl)
Lower limit of normal range, 3.42 mg/dl
Week
C Serum 1,25-dihydroxyvitamin D
Mean Value (pg/ml)
Lower limit of normal range, 41 pg/ml
Week
D Serum Alkaline Phosphatase
Mean Value (U/liter)
Upper limit of normal range, 385 U/liter
Week

Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial

Erik A Imel, Francis H Glorieux, Michael P Whyte, Craig F Munns, Leanne M Ward, Ola Nilsson, Jill H Simmons, Raja Padidela, Noriyuki Namba, Hae Il Cheong, Pisit Pitukcheewanont, Etienne Sochett, Wolfgang Högler, Koji Muroya, Hiroyuki Tanaka, Gary S Gottesman, Andrew Biggin, Farzana Perwad, Meng Mao, Chao-Yin Chen, Alison Skrinar, Javier San Martin, Anthony A Portale

Lancet 2019; 393: 2416–27

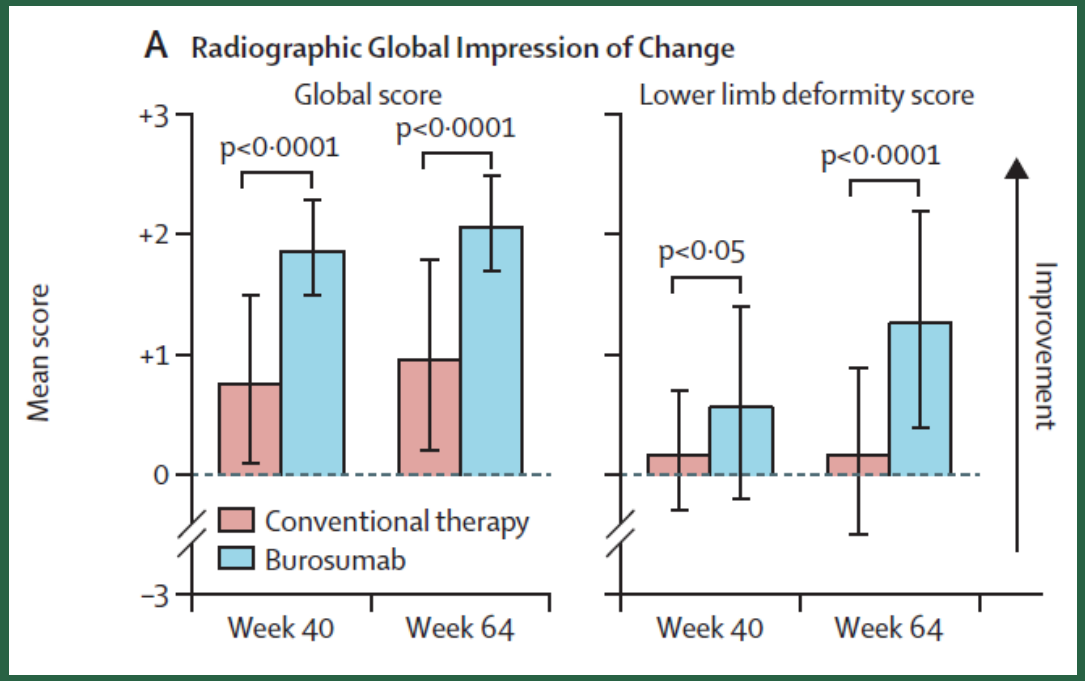
Summary

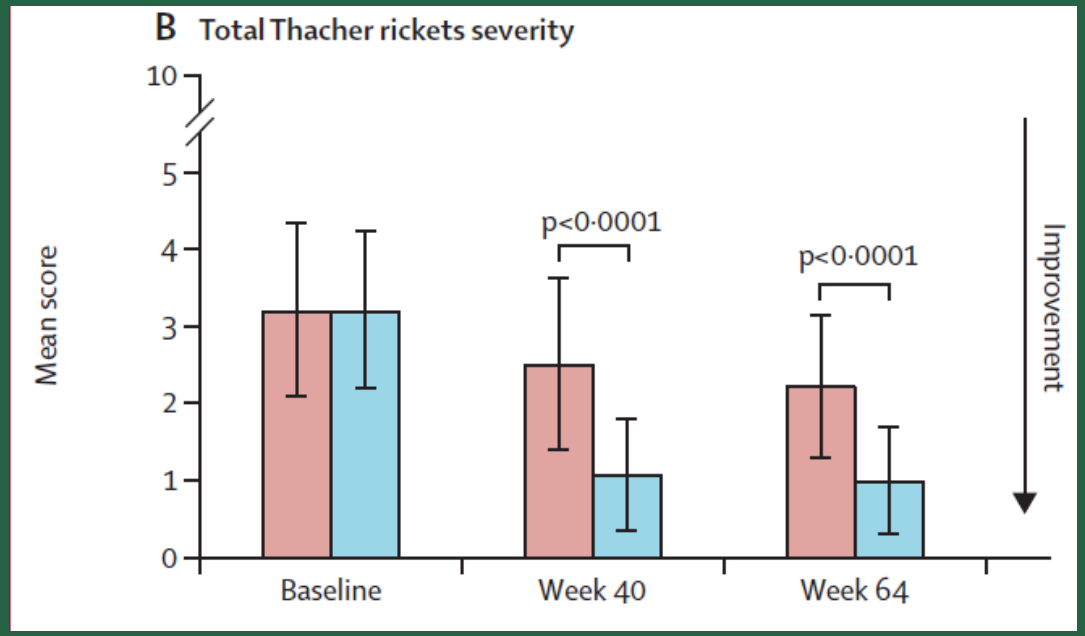
Background X-linked hypophosphataemia in children is characterised by elevated serum concentrations of fibroblast

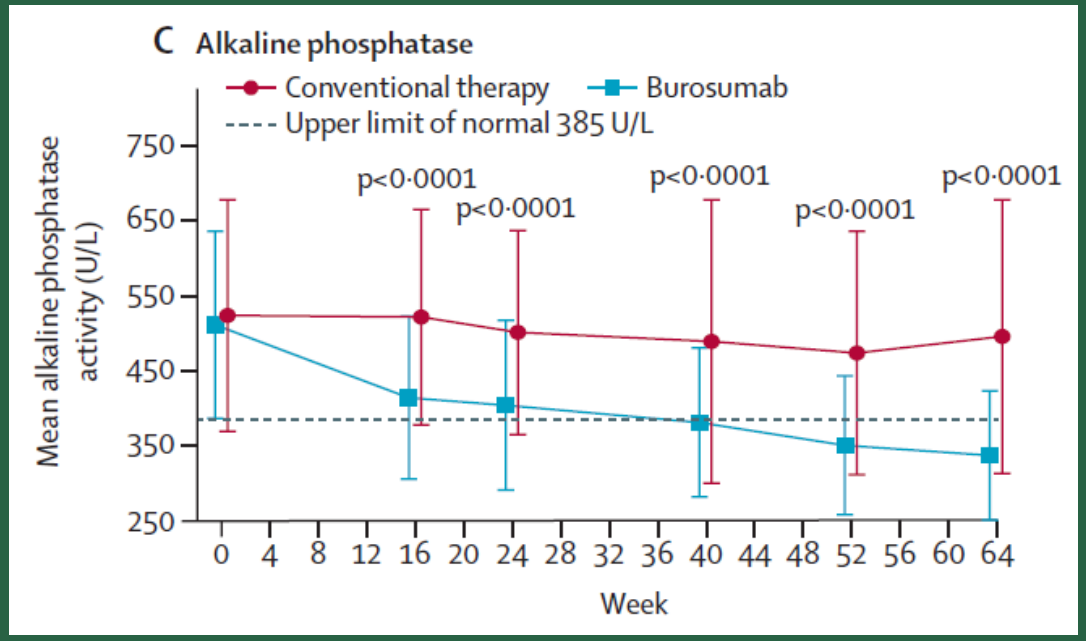
1 mg/dl= 0,323 mmol/L

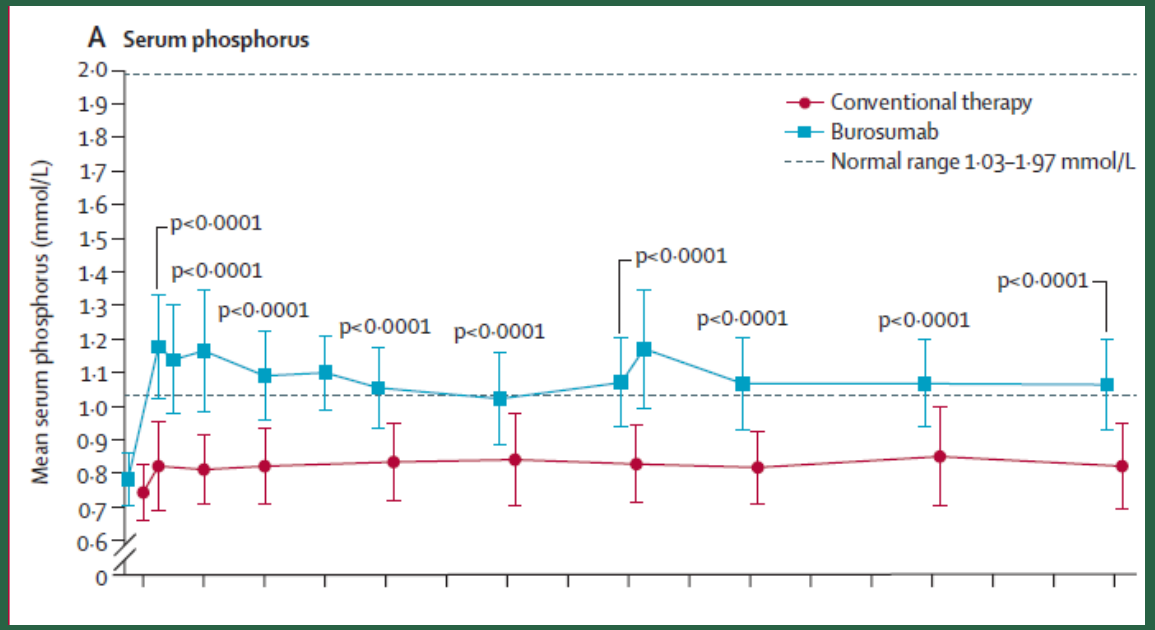
aged 1–12 years.

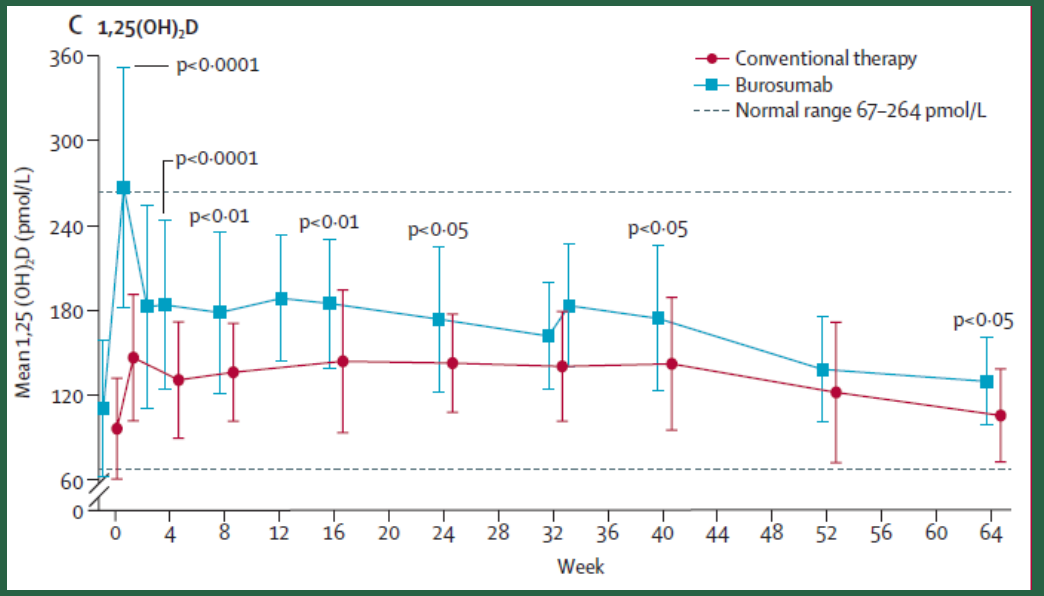
	Conventional therapy (n=32)	Burosumab (n=29)
Mean age (years)	6·3 (3·2)	5·8 (3·4)
Patients younger than 5 years	12 (38%)	14 (48%)
Girls	18 (56%)	16 (55%)
Boys	14 (44%)	13 (45%)
Ethnic origin		
White	25 (78·1%)	25 (86·2%)
Asian	6 (18·8%)	2 (6·9%)
Other	1 (3·1%)	2 (6·9%)
Geographical region		
Japan	3 (9%)	2 (7%)
USA	15 (47%)	16 (55%)
Canada	7 (22%)	2 (7%)
Europe	3 (9%)	2 (7%)
South Korea	2 (6%)	0
Australia	2 (6%)	7 (24%)
Height Z score		
Mean	−2·1 (0·9)	−2·3 (1·2)
Median	−2·1 (−2·51 to −1·44)	−2·3 (−3·05 to −1·45)
Mean serum phosphorus concentration (mmol/L)	0·74 (0·08)	0·78 (0·08)
Mean TMP/GFR ratio (mmol/L)	0·65 (0·11)	0·71 (0·12)
Mean serum $1,25(OH)_2D$ concentration (pmol/L)	96 (36)	110 (48)
Mean serum 25(OH)D concentration (nmol/L)	79·38 (25·14)	80·63 (26·15)
Mean alkaline phosphatase concentration (U/L)	523·4 (154·4)	510·8 (124·9)
Years of duration of previous conventional therapy		
Mean	4·3 (3·0)	3·3 (3·1)
Median	3·5 (1·88–6·33)	2·2 (1·56–3·47)
Total Thacher rickets severity score		
Mean	3·2 (1·1)	3·2 (1·0)
Median	3·0 (2·50–4·00)	3·0 (2·50–3·50)
Patients with a total Thacher rickets severity score higher than 2·5	20 (63%)	19 (66%)

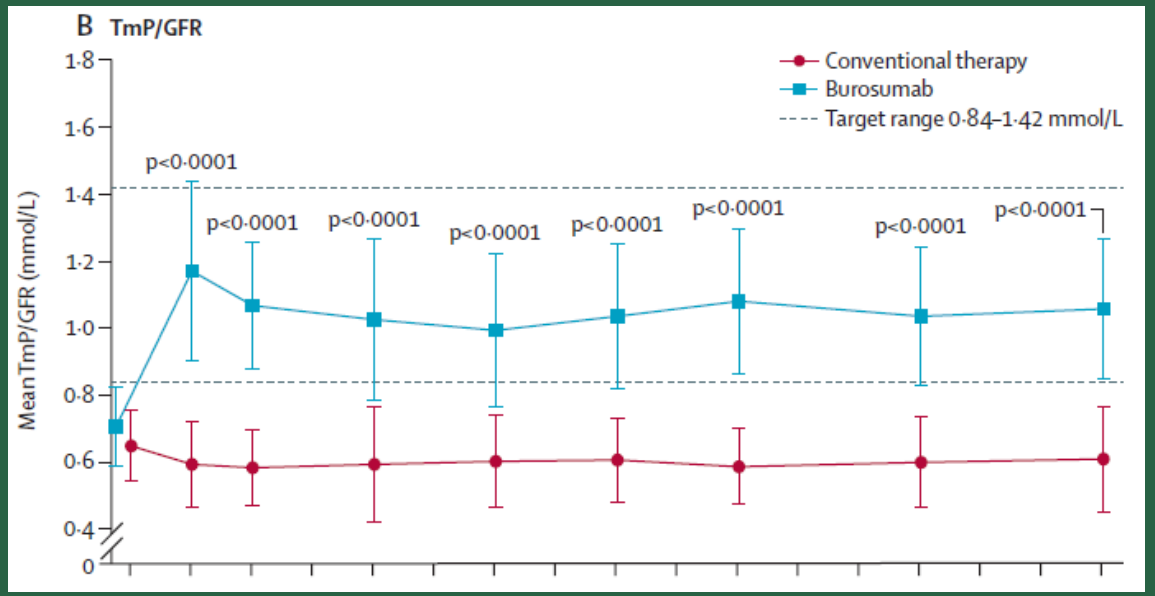

A Radiographic Global Impression of Change
Global score
Lower limb deformity score
Mean score
+3
+2
+1
0
−3
p<0·0001
p<0·0001
p<0·05
p<0·0001
Improvement
Conventional therapy
Burosumab
Week 40
Week 64
Week 40
Week 64

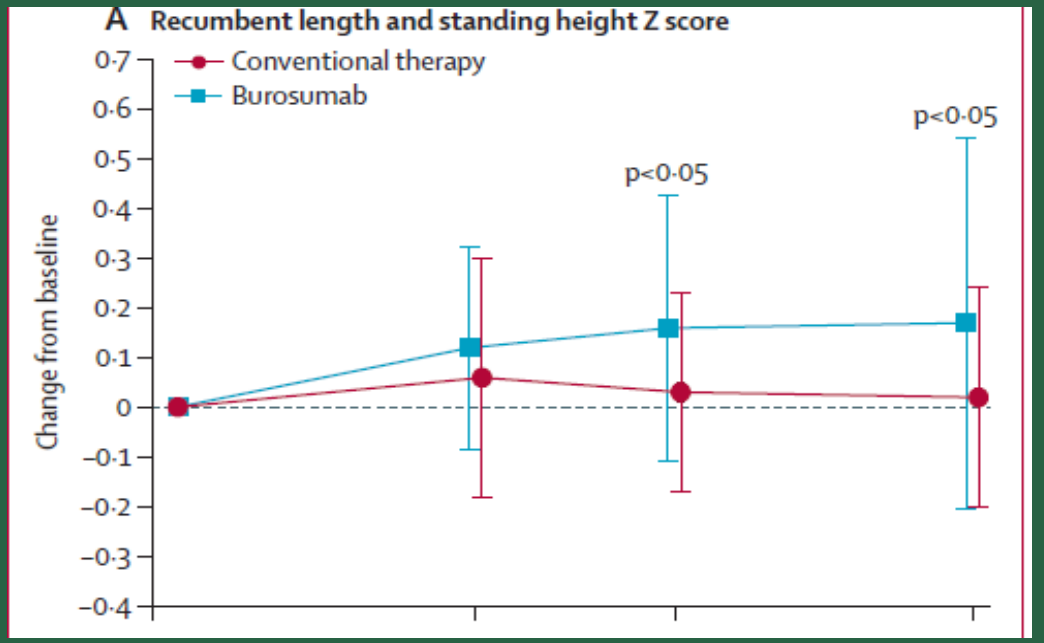

B Total Thacher rickets severity
Mean score
10
5
4
3
2
1
0
p<0·0001
p<0·0001
Improvement
Baseline
Week 40
Week 64


C Alkaline phosphatase
Conventional therapy
Burosumab
Upper limit of normal 385 U/L
Mean alkaline phosphatase activity (U/L)
750
650
550
450
350
250
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64
Week


A Serum phosphorus
Mean serum phosphorus (mmol/L)
Conventional therapy
Burosumab
Normal range 1·03–1·97 mmol/L
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001


C 1,25(OH)2D
Mean 1,25 (OH)2D (pmol/L)
Conventional therapy
Burosumab
Normal range 67–264 pmol/L
p<0·0001
p<0·0001
p<0·01
p<0·01
p<0·05
p<0·05
p<0·05
Week

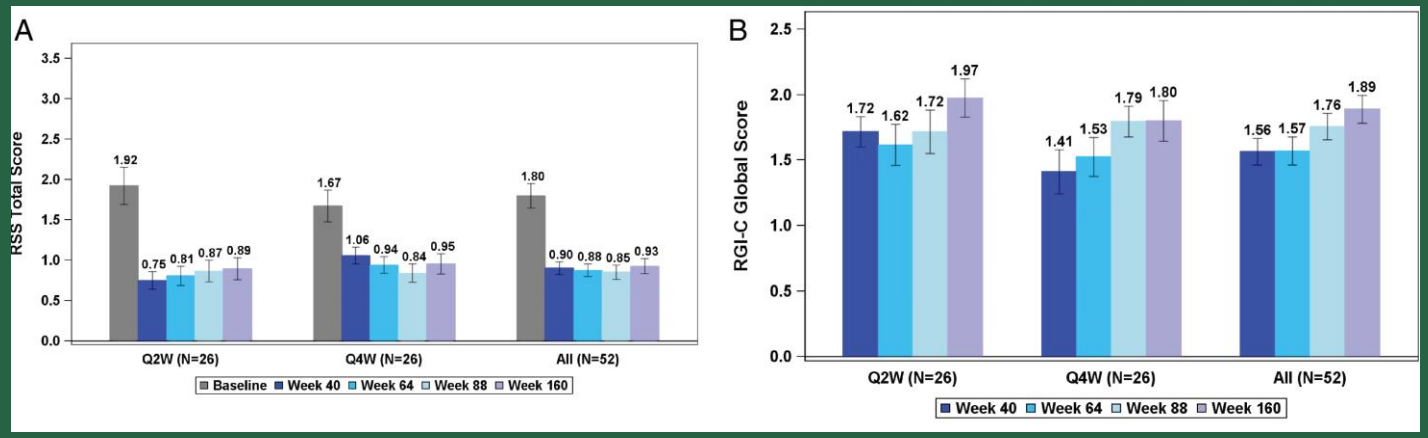

B TmP/GFR
Mean TmP/GFR (mmol/L)
Conventional therapy
Burosumab
Target range 0·84–1·42 mmol/L
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001
p<0·0001

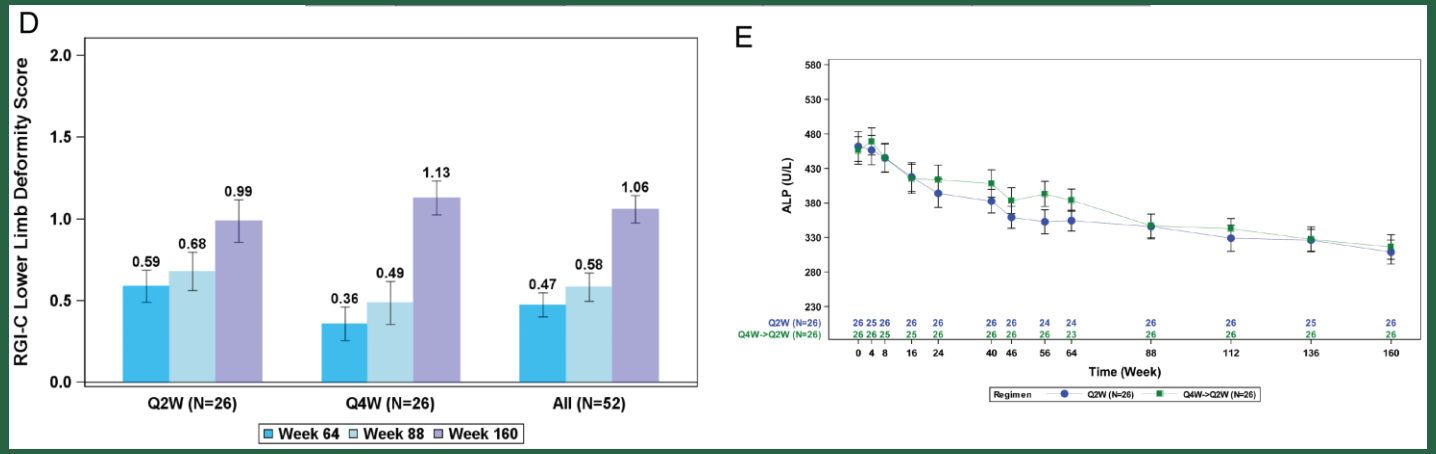

A Recumbent length and standing height Z score
Change from baseline
Conventional therapy
Burosumab
p<0·05
p<0·05

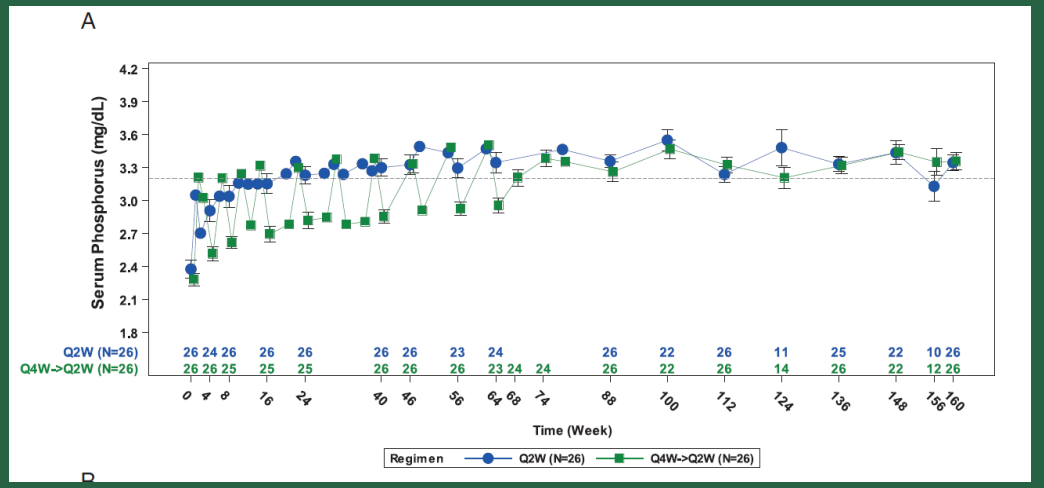
Sustained Efficacy and Safety of Burosumab, a Monoclonal Antibody to FGF23, in Children With X-Linked Hypophosphatemia

Agnès Linglart,[1,2] Erik A. Imel,[3] Michael P. Whyte,[4,5] Anthony A. Portale,[6] Wolfgang Högler,[7,8] Annemieke M. Boot,[9] Raja Padidela,[10] William van't Hoff,[11] Gary S. Gottesman,[12] Angel Chen,[13] Alison Skrinar,[13] Mary Scott Roberts,[13] and Thomas O. Carpenter[14]

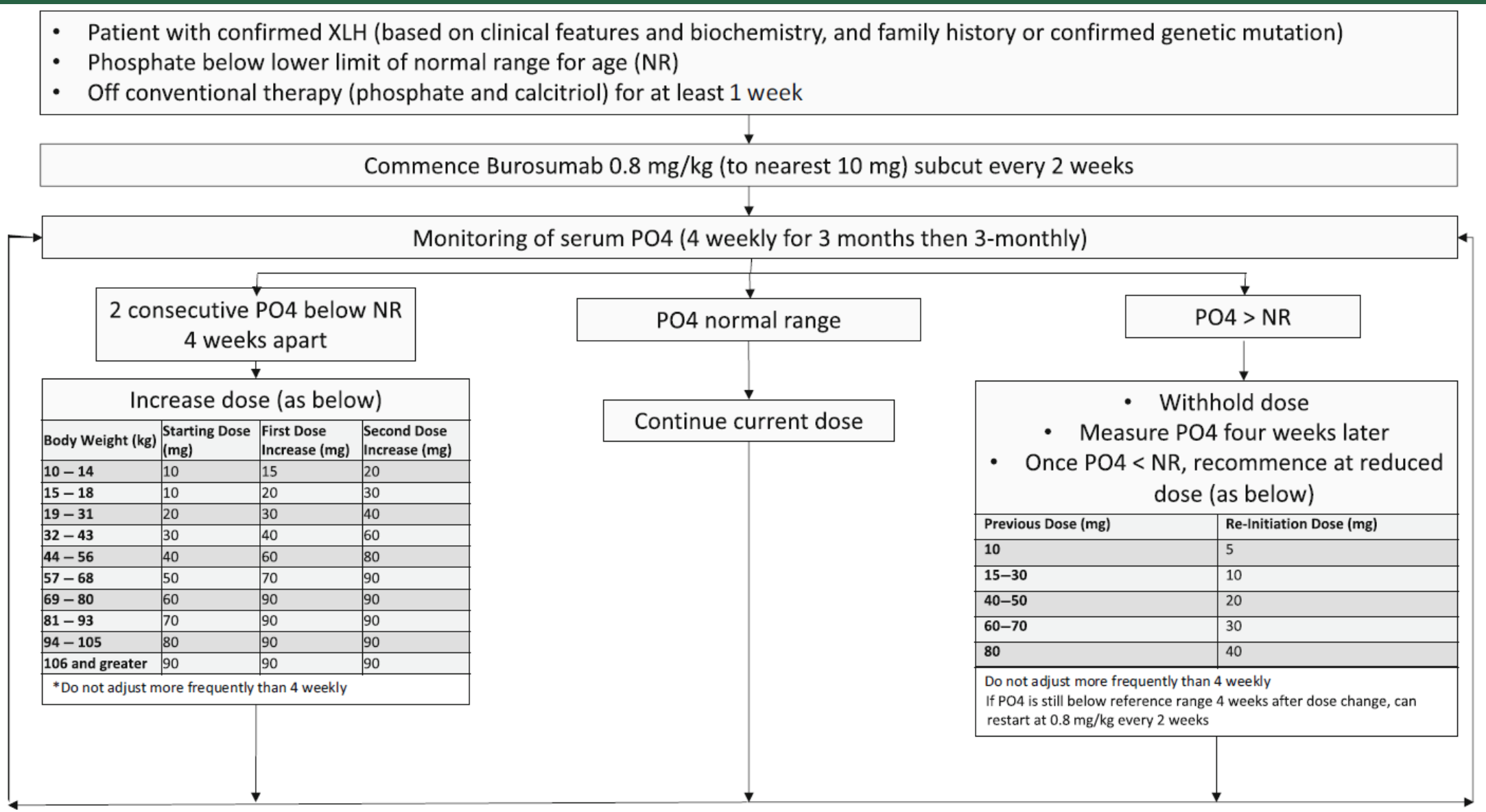
JCEM 2022





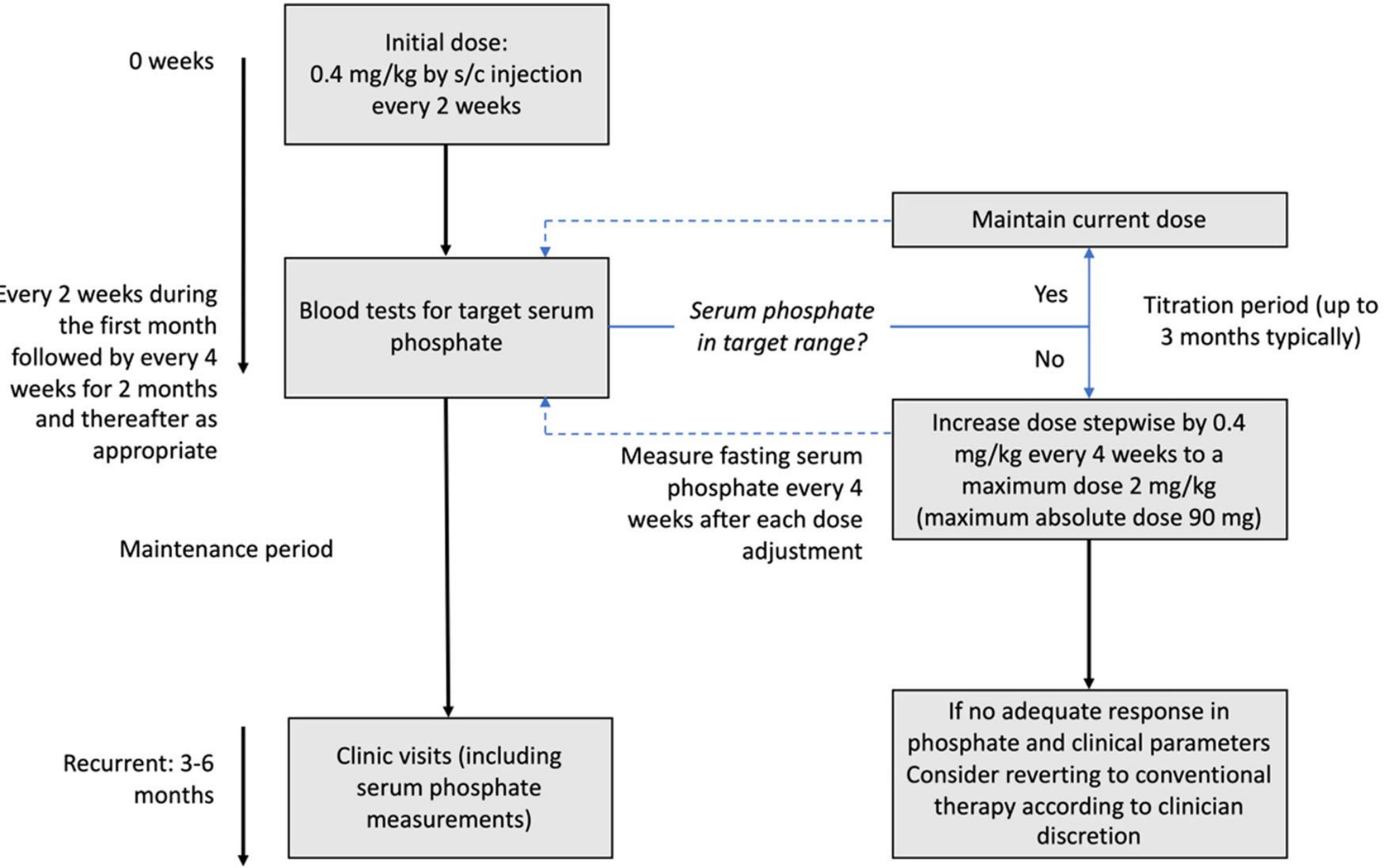


3 yrs


• Patient with confirmed XLH (based on clinical features and biochemistry, and family history or confirmed genetic mutation)
• Phosphate below lower limit of normal range for age (NR)
• Off conventional therapy (phosphate and calcitriol) for at least 1 week
Commence Burosumab 0.8 mg/kg (to nearest 10 mg) subcut every 2 weeks
Monitoring of serum PO4 (4 weekly for 3 months then 3-monthly)
2 consecutive PO4 below NR 4 weeks apart
PO4 normal range
PO4 > NR
Increase dose (as below)
Body Weight (kg) | Starting Dose (mg) | First Dose Increase (mg) | Second Dose Increase (mg)
10 – 14 | 10 | 15 | 20
15 – 18 | 10 | 20 | 30
19 – 31 | 20 | 30 | 40
32 – 43 | 30 | 40 | 60
44 – 56 | 40 | 60 | 80
57 – 68 | 50 | 70 | 90
69 – 80 | 60 | 90 | 90
81 – 93 | 70 | 90 | 90
94 – 105 | 80 | 90 | 90
106 and greater | 90 | 90 | 90
*Do not adjust more frequently than 4 weekly
Continue current dose
• Withhold dose
• Measure PO4 four weeks later
• Once PO4 < NR, recommence at reduced dose (as below)
Previous Dose (mg) | Re-Initiation Dose (mg)
10 | 5
15–30 | 10
40–50 | 20
60–70 | 30
80 | 40
Do not adjust more frequently than 4 weekly
If PO4 is still below reference range 4 weeks after dose change, can restart at 0.8 mg/kg every 2 weeks

Endocrine Connections
(2020) 9, 1051–1056

Burosumab dosing and monitoring of serum phosphate algorithm



Increasing the burosumab dose should be considered after two consequent measurements of phosphate levels being below the lower end of the normal reference range (4 weeks). The increase of the dose will also depend on the clinician's discretion (checking patient's weight).
Dose to be adjusted according to the SPC

If fasting serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate reassessed within 4 weeks

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis

Journal of Bone and Mineral Research, Vol. 33, No. 8, August 2018, pp 1383–1393

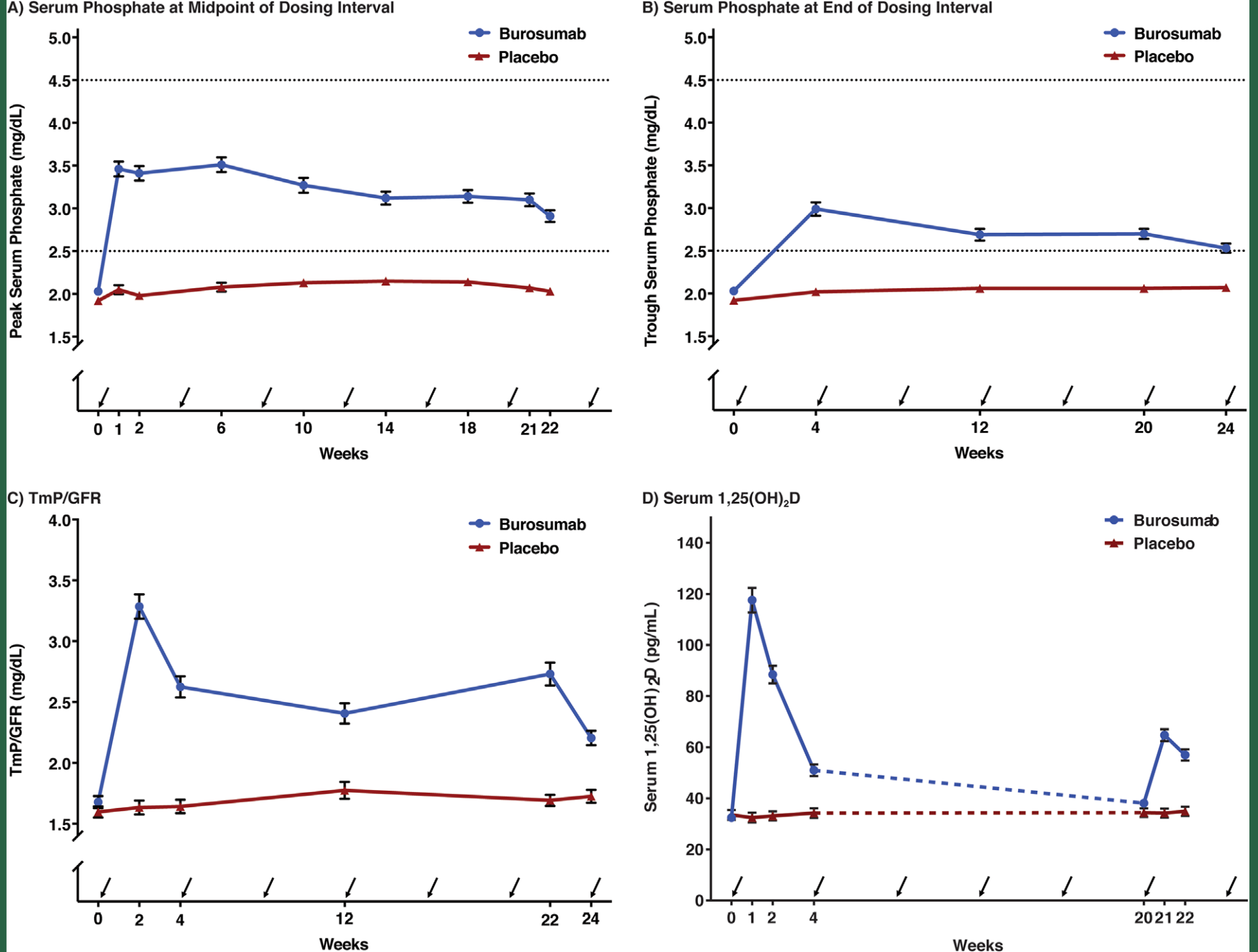
Table 1. Baseline Demographics and Characteristics

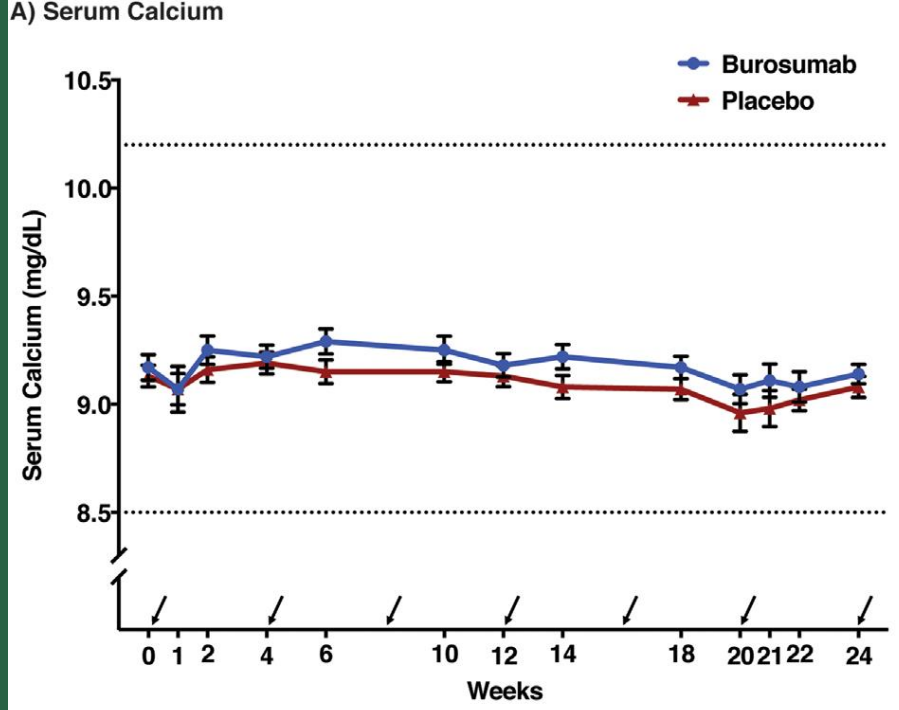
	Placebo ($n = 66$)	Burosumab ($n = 68$)	Total ($n = 134$)
Age (years)			
Mean ± SD	38.7 ± 12.8	41.3 ± 11.6	40.0 ± 12.2
Range	18.5–65.5	20.0–63.4	18.5–65.5
Female, *n* (%)	43 (65.2)	44 (64.7)	87 (64.9)
Race, *n* (%)			
White	53 (80.3)	55 (80.9)	108 (80.6)
Asian	9 (13.6)	12 (17.6)	21 (15.7)
Black	3 (4.5)	0	3 (2.2)
Other	1 (1.5)	1 (1.5)	2 (1.5)
Geographic region, *n* (%)			
North America/Europe	58 (87.9)	58 (85.3)	116 (86.6)
Japan	5 (7.6)	6 (8.8)	11 (8.2)
South Korea	3 (4.5)	4 (5.9)	7 (5.2)
Height,[a] mean ± SD			
Centimeters	153 ± 11.8	152 ± 9.5	152 ± 10.7
Z-score[b]	−2.3 ± 1.3	−2.3 ± 1.2	−2.3 ± 1.3
Percentile	7.2 ± 12.1	6.4 ± 12.9	6.8 ± 12.5
Body mass index[a] (kg/m^2), mean ± SD	30.6 ± 7.8	30.0 ± 7.5	30.3 ± 7.6
PHEX mutation, *n* (%)			
Pathogenic	50 (75.8)	45 (66.2)	95 (70.9)
Likely pathogenic	7 (10.6)	8 (11.8)	15 (11.2)
Variant of uncertain significance	8 (12.1)	9 (13.2)	17 (12.7)
No mutation	1 (1.5)	6 (8.8)	7 (5.2)

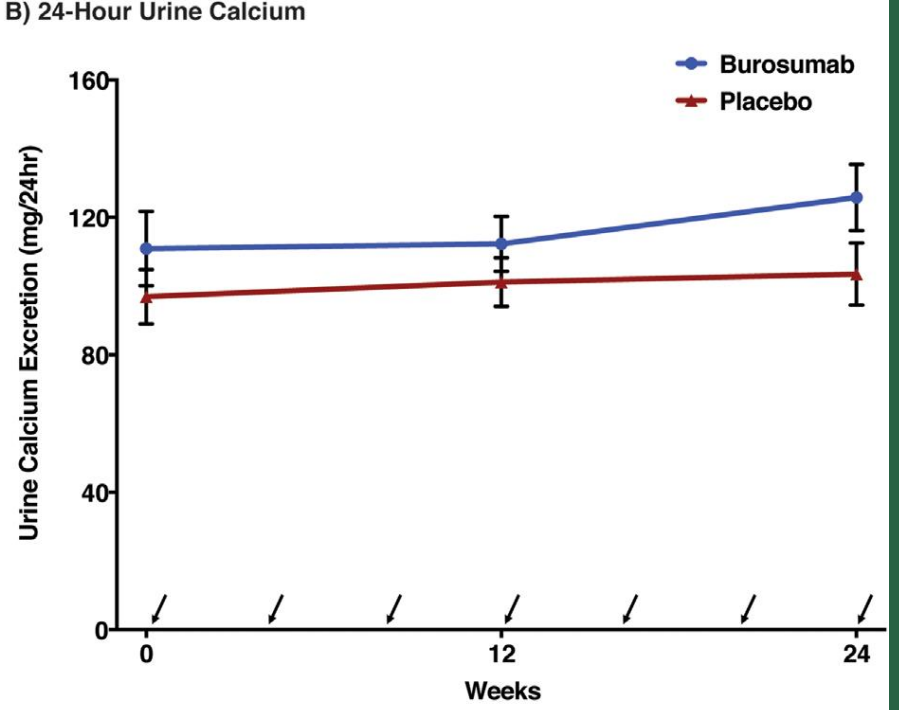
Table 1. Baseline Demographics and Characteristics

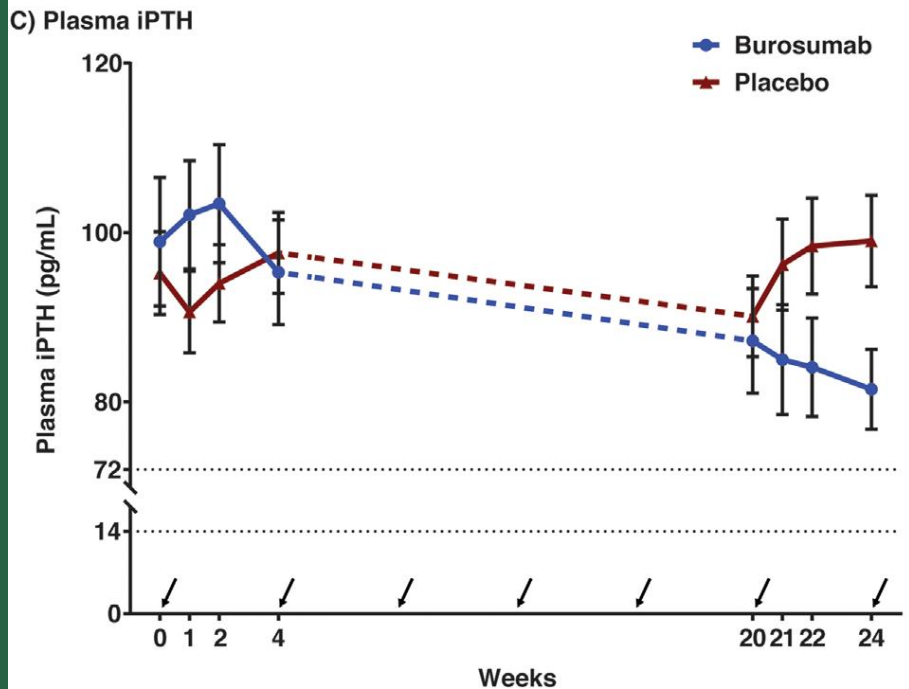
	Placebo ($n = 66$)	Burosumab ($n = 68$)	Total ($n = 134$)
Serum phosphate (mg/dL),[c] mean ± SD	1.9 ± 0.32	2.0 ± 0.30	2.0 ± 0.31
TmP/GFR (mg/dL),[c] mean ± SD	1.6 ± 0.37	1.7 ± 0.40	1.6 ± 0.39
Serum 1,25$(OH)_2$D (pg/mL),[c] mean ± SD	33.5 ± 15.6	32.4 ± 13.0	33.0 ± 14.3
Serum calcium (mg/dL),[c] mean ± SD	9.1 ± 0.41	9.2 ± 0.49	9.2 ± 0.45
Serum iPTH (pg/mL),[c] mean ± SD	95.2 ± 38.8	98.9 ± 60.8	97.0 ± 50.9
Conventional therapy ever, *n* (%)			
Phosphate + vitamin D metabolites or analogs	62 (93.9)	59 (86.8)	121 (90.3)
Phosphate alone	1 (1.5)	3 (4.4)	4 (3.0)
Vitamin D metabolites or analogs alone	3 (4.5)	3 (4.4)	6 (4.5)
Conventional therapy before age 18 years, *n* (%)			
Phosphate + vitamin D metabolites or analogs	48 (72.7)	45 (66.2)	93 (69.4)
Phosphate alone	2 (3.0)	5 (7.4)	7 (5.2)
Vitamin D metabolites or analogs alone	4 (6.1)	5 (7.4)	9 (6.7)
Conventional therapy duration (years), mean ± SD			
Phosphate[d]	16.2 ± 10.2	16.8 ± 10.7	16.5 ± 10.4
Vitamin D metabolites or analogs[e]	17.5 ± 11.9	19.0 ± 10.0	18.2 ± 11.0
BPI worst pain >6.0, *n* (%)	43 (65.2)	53 (77.9)	96 (71.6)
Any pain medication at baseline, *n* (%)	44 (66.7)	47 (69.1)	91 (67.9)
Any opioid at baseline, *n* (%)	13 (19.7)	17 (25.0)	30 (22.4)
Enthesopathy on X-ray, *n* (%)	65 (98.5)	68 (100.0)	133 (99.3)
Nephrocalcinosis score >0,[f] *n* (%)	39 (59.1)	34 (50.0)	73 (54.5)
Medical history, *n* (%)			
Orthopedic surgery	47 (71.2)	45 (66.2)	92 (68.7)
Osteoarthritis	38 (57.6)	47 (69.1)	85 (63.4)

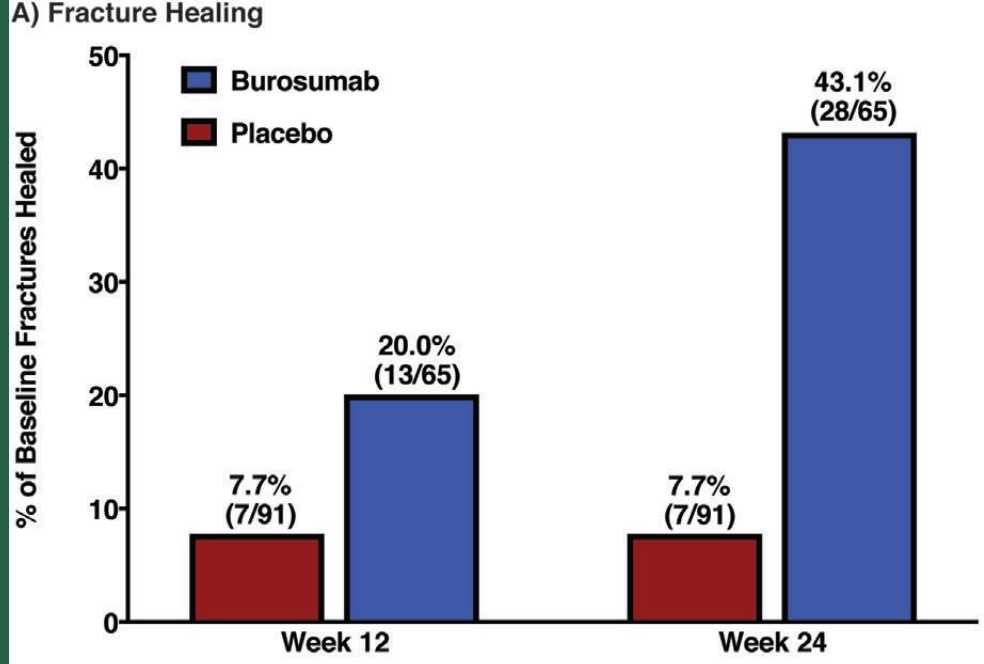
burosumab 1.0 mg/kg or matching placebo administered Q4W.

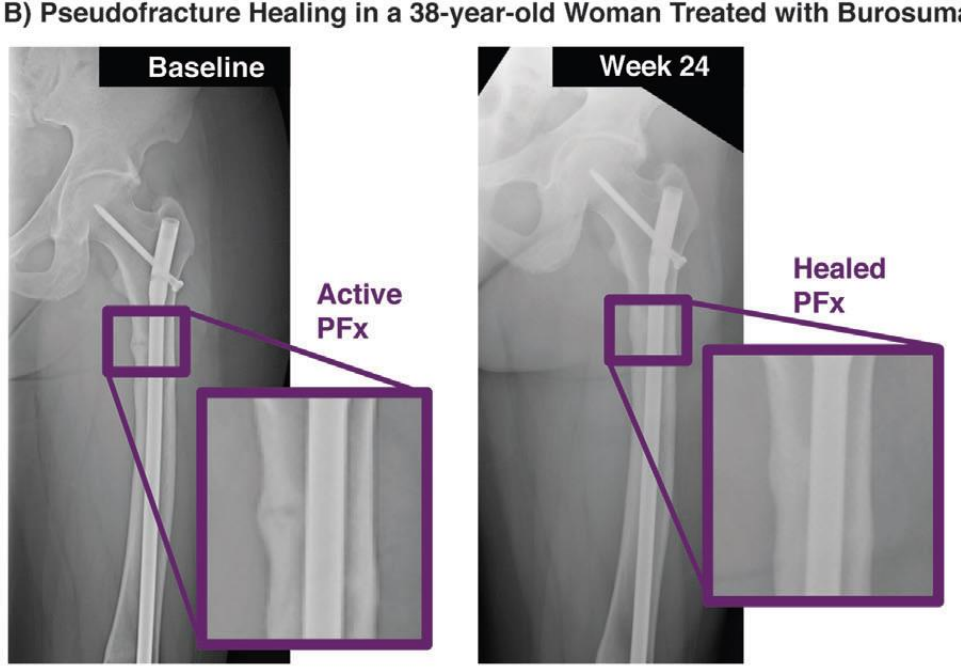

A) Serum Phosphate at Midpoint of Dosing Interval
Burosumab
Placebo
Peak Serum Phosphate (mg/dL)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0 1 2 6 10 14 18 21 22
Weeks
B) Serum Phosphate at End of Dosing Interval
Burosumab
Placebo
Trough Serum Phosphate (mg/dL)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0 4 12 20 24
Weeks
C) TmP/GFR
Burosumab
Placebo
TmP/GFR (mg/dL)
4.0
3.5
3.0
2.5
2.0
1.5
0 2 4 12 22 24
Weeks
D) Serum 1,25(OH)2D
Burosumab
Placebo
Serum 1,25(OH)2D (pg/mL)
140
120
100
80
60
40
20
0
0 1 2 4 20 21 22
Weeks


A) Serum Calcium
Burosumab
Placebo
Serum Calcium (mg/dL)
10.5
10.0
9.5
9.0
8.5
0 1 2 4 6 10 12 14 18 20 21 22 24
Weeks

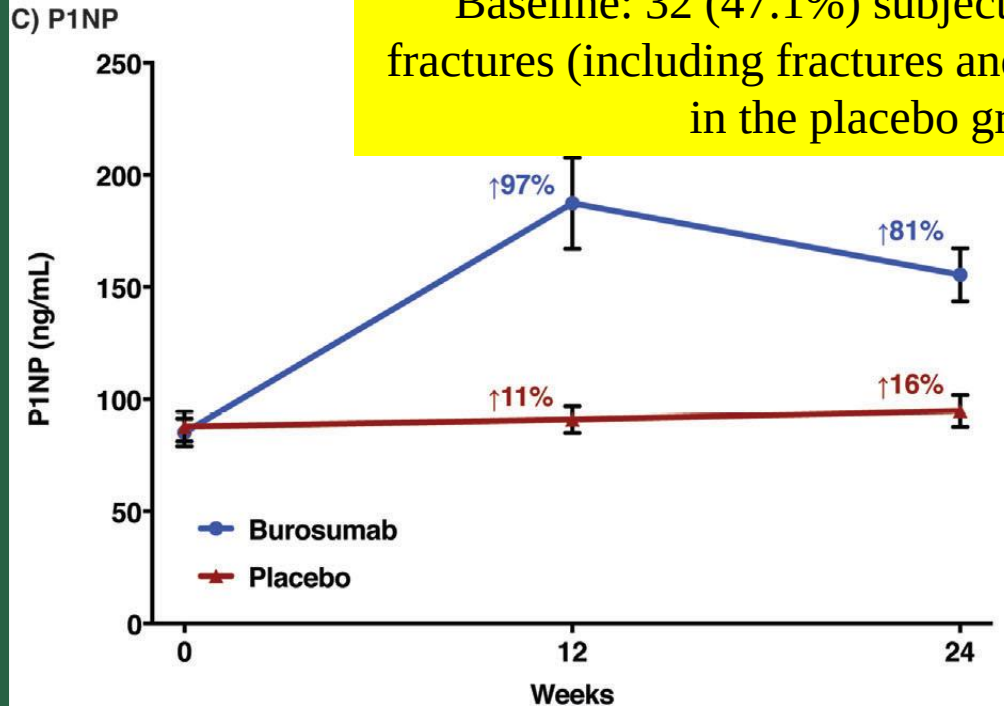

B) 24-Hour Urine Calcium
Burosumab
Placebo
Urine Calcium Excretion (mg/24hr)
160
120
80
40
0
0 12 24
Weeks

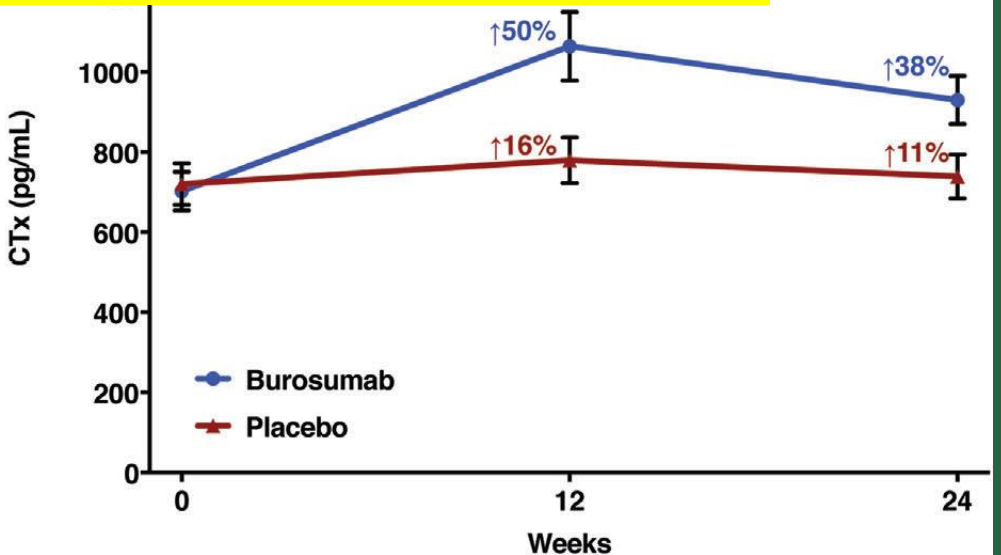

C) Plasma iPTH
Burosumab
Placebo
Plasma iPTH (pg/mL)
120
100
80
72
14
0
0 1 2 4 20 21 22 24
Weeks



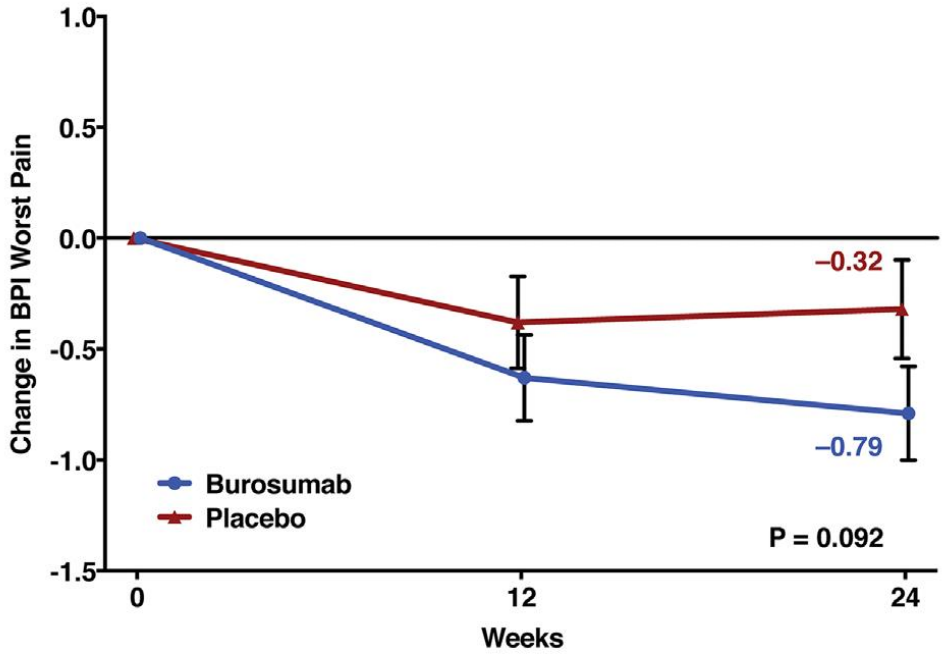


Baseline: 32 (47.1%) subjects in the burosumab group had 65 active fractures (including fractures and pseudofractures) and 38 (57.6%) subjects in the placebo group had 91 active fractures

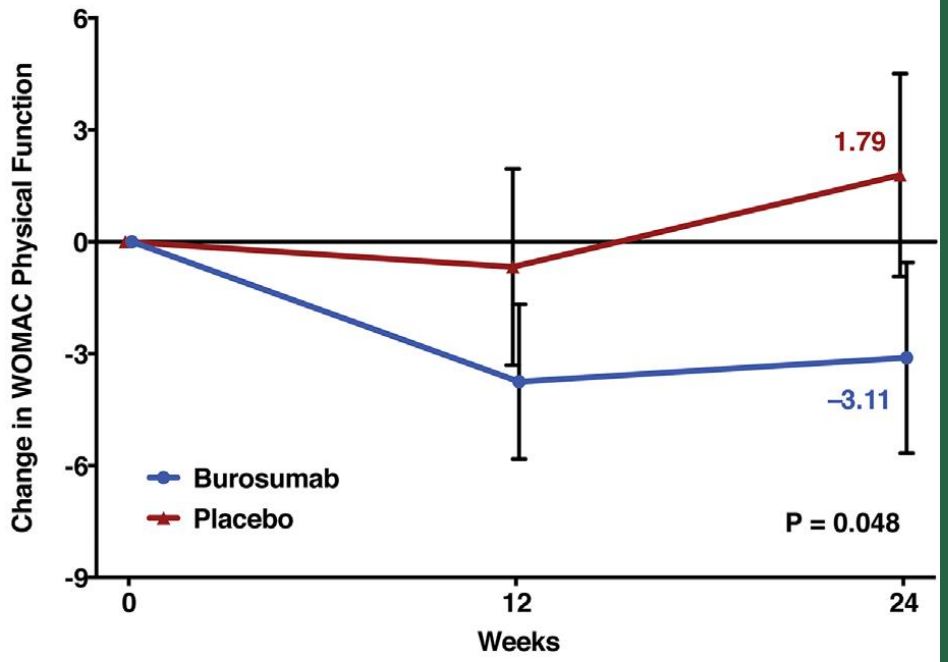




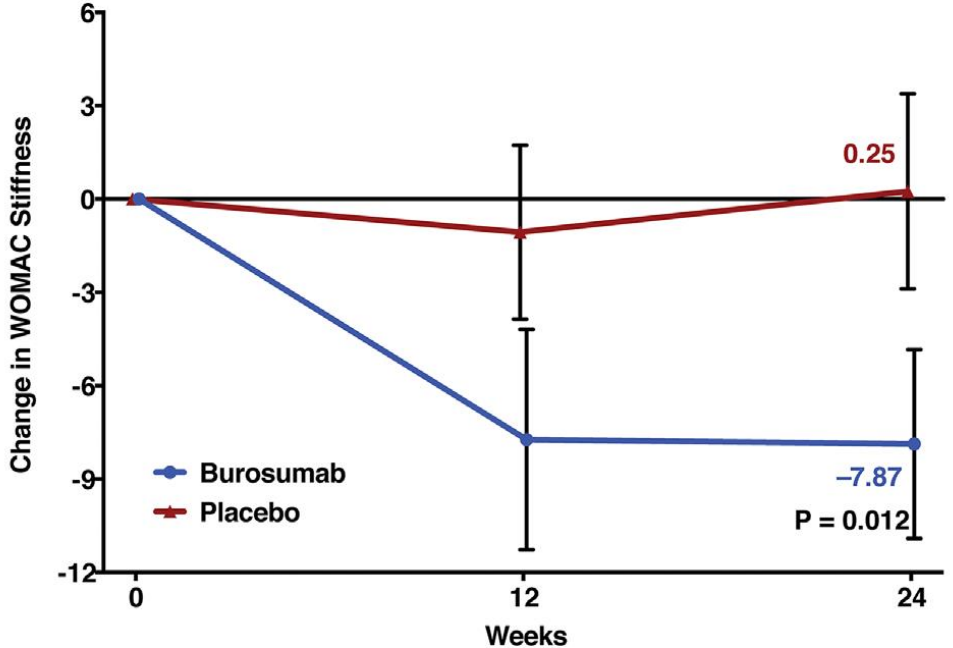
A) BPI Worst Pain



B) WOMAC Physical Function



C) WOMAC Stiffness



The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

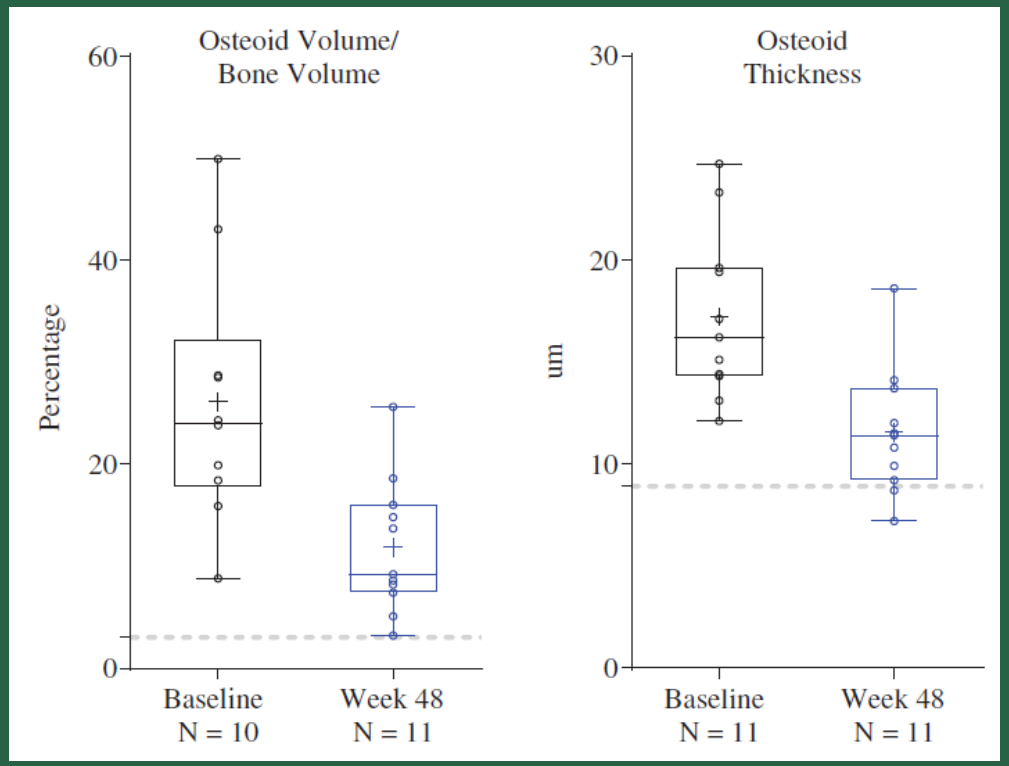
CLINICAL TRIAL

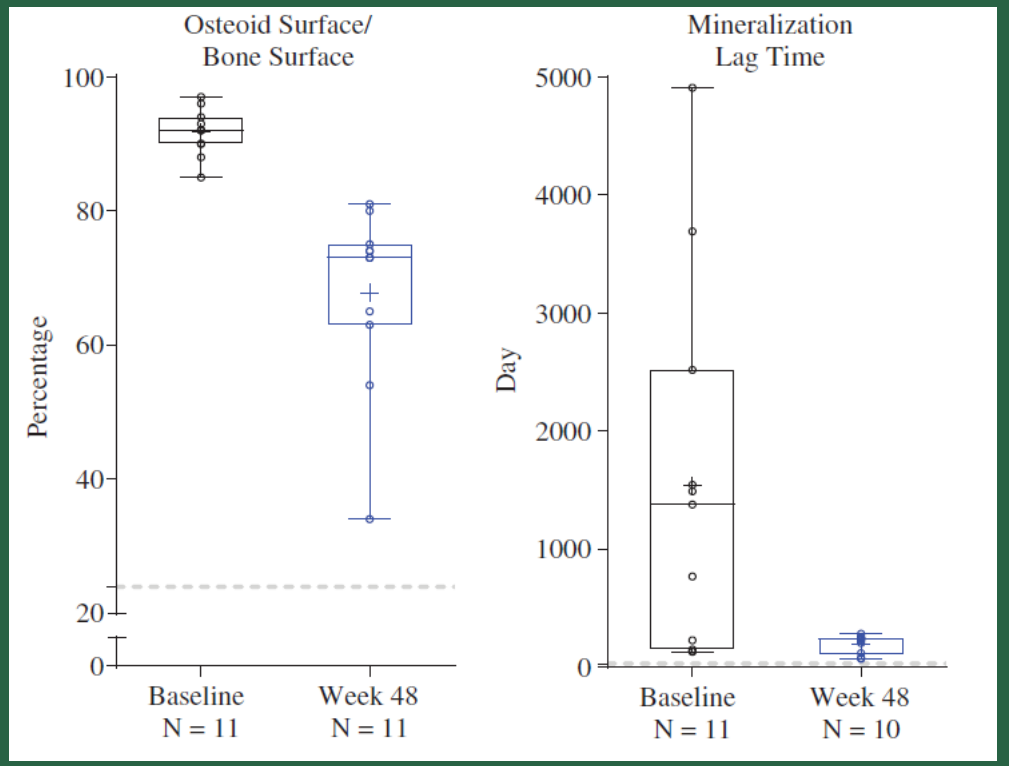
JBMR®

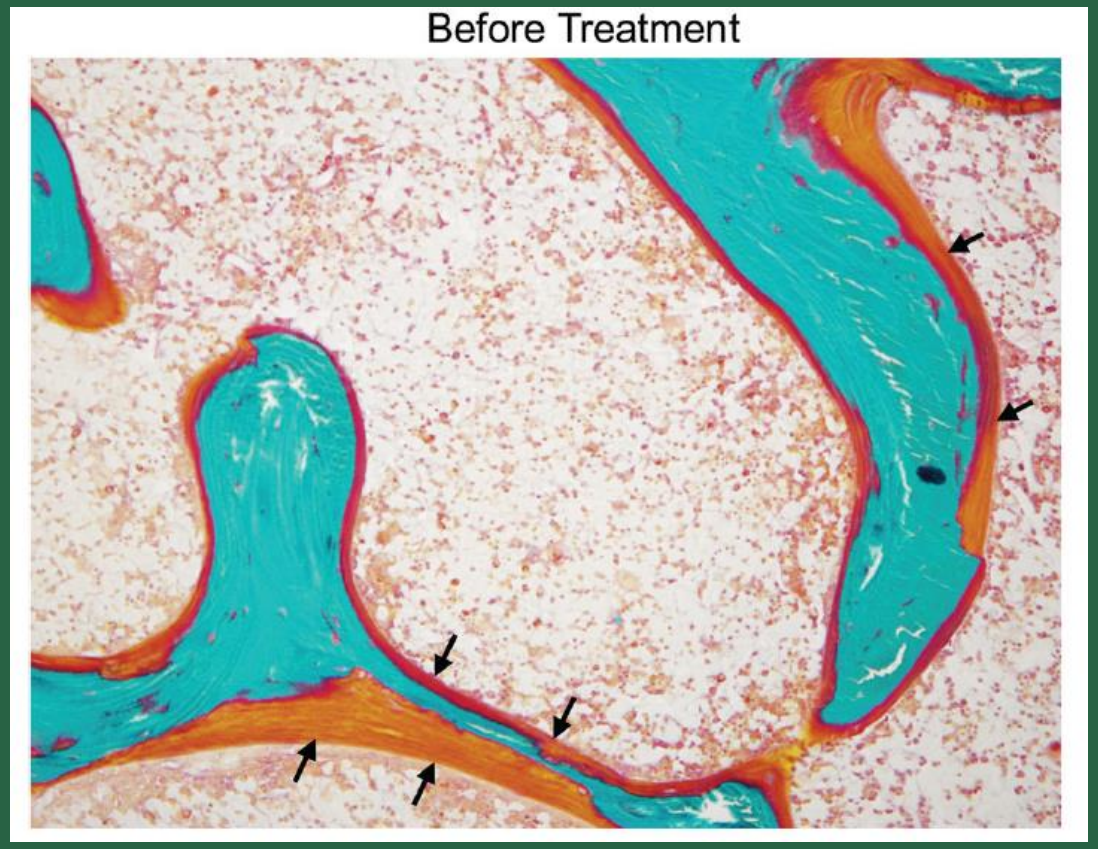
Burosumab Improved Histomorphometric Measures of Osteomalacia in Adults with X-Linked Hypophosphatemia: A Phase 3, Single-Arm, International Trial

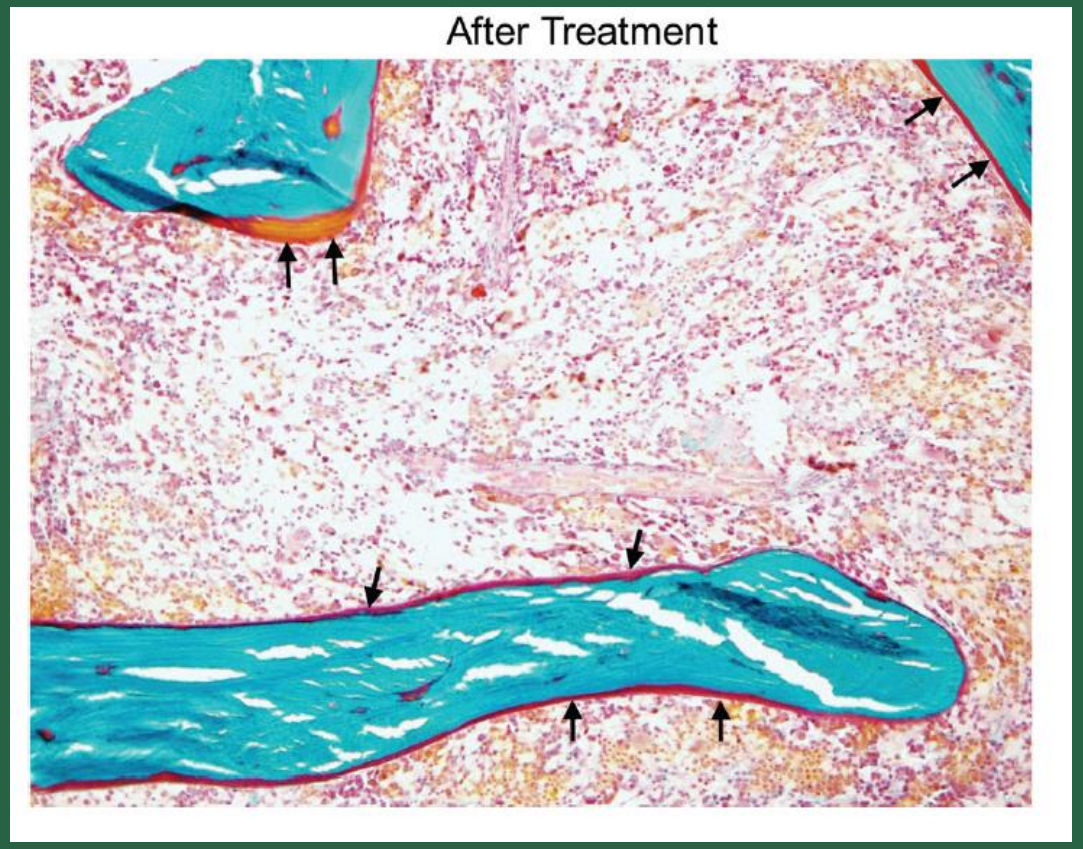
Karl L Insogna,[1] Frank Rauch,[2] Peter Kamenický,[3] Nobuaki Ito,[4] Takuo Kubota,[5] Akie Nakamura,[6] Lin Zhang,[7] Matt Mealiffe,[7] Javier San Martin,[7] and Anthony A Portale[8]

Journal of Bone and Mineral Research, Vol. 34, No. 12, December 2019, pp 2183–2191.









Mineralized bone is shown in green, unmineralized osteoid is shown in orange or red

The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, 155–165
https://doi.org/10.1210/clinem/dgac518
Advance access publication 8 September 2022
Clinical Research Article

Long-term Burosumab Administration Is Safe and Effective in Adults With X-linked Hypophosphatemia

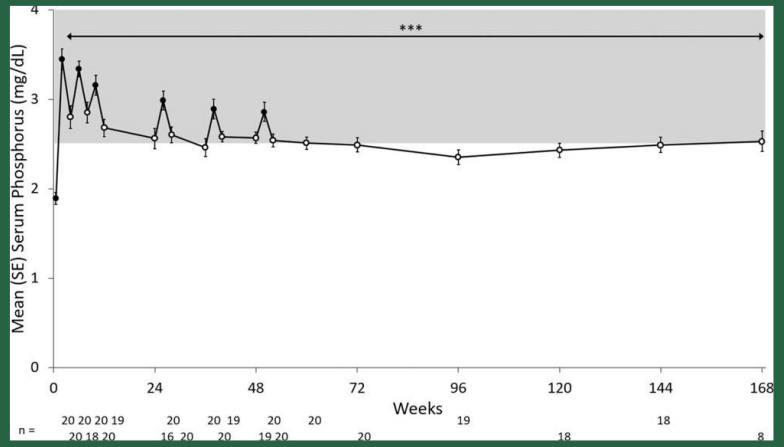
Thomas J. Weber,[1] Erik A. Imel,[2] Thomas O. Carpenter,[3] Munro Peacock,[2] Anthony A. Portale,[4] Joel Hetzer,[5] J. Lawrence Merritt II,[5] and Karl Insogna[3]

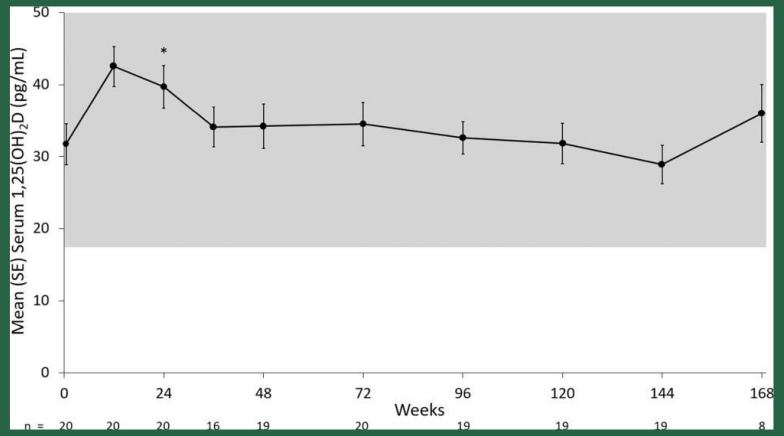
Table 1. Baseline demographics and clinical characteristics

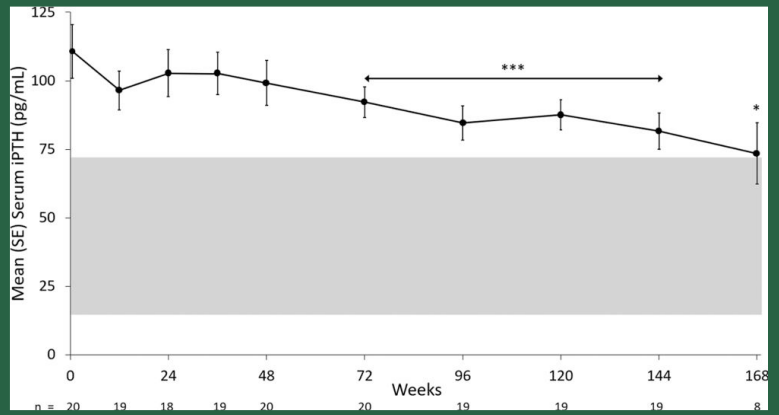
Parameter	n = 20
Age, mean (SD)	49.8 (12.9)
Sex, n (%)	
Female	14 (70%)
Race, n (%)	
White	19 (95%)
Black or African American	1 (5%)
Ethnicity, n (%)	
Not Hispanic or Latino	19 (95%)
Hispanic or Latino	1 (5%)
Height (cm), mean (SD)	147.8 (10.6)
Weight (kg), mean (SD)	78.9 (22.7)
Laboratory parameters, mean (SE)	
Serum phosphate (mg/dL)	1.9 (0.1)
Serum calcium (mg/dL)	9.1 (0.1)
Serum $1,25(OH)_2D$ (pg/mL)	32 (3)
Serum iPTH (pg/mL)	111 (10)
TmP/GFR (mg/dL)	1.6 (0.1)

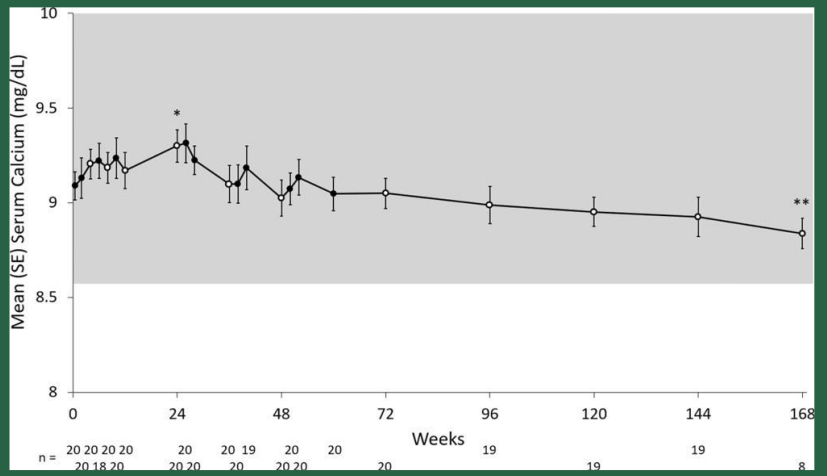
Table 2. XLH-related medical histories

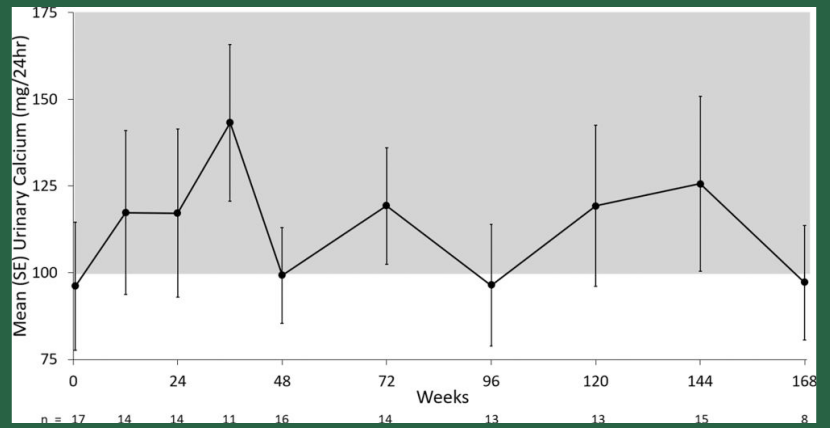
Parameter	n = 20
Time since XLH diagnosis (years), mean (SD)	40.7 (16.2)
Time since first XLH symptoms (years), mean (SD)	47.9 (13.5)
Diagnosed with, n (%)	
Short stature	19 (95%)
Bowing of lower legs	19 (95%)
Abnormal gait	17 (85%)
Dental abscesses	17 (85%)
Calcium deposits on bone	17 (85%)
Osteoarthritis	15 (75%)
Excessive cavities	14 (70%)
Bowing of upper leg	14 (70%)
Enthesopathy	12 (60%)
Widened wrists	8 (40%)
Kidney stones	7 (35%)
In-toeing	7 (35%)
Hearing loss	7 (35%)
Knock-knees	5 (25%)
Bowing of forearms	5 (25%)
Nephrocalcinosis	4 (20%)
Impaired renal function	4 (20%)
Delayed walking (first walked ≥15 months)	4 (20%)
Ribcage abnormalities	2 (10%)
Cranial synostosis	2 (10%)
Chiari malformation	2 (10%)
Other	1 (5%)
XLH symptoms in the last year, n (%)	
Joint stiffness/limited range of motion	20 (100%)
Muscle pain	16 (80%)
Muscle weakness	14 (70%)
Tingling in arms/legs	12 (60%)
Tinnitus (ringing in ears)	9 (45%)
Other	5 (25%)

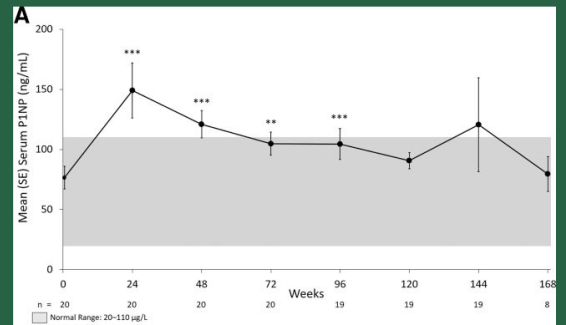

Mean (SE) Serum Phosphorus (mg/dL)
***
Weeks
n =

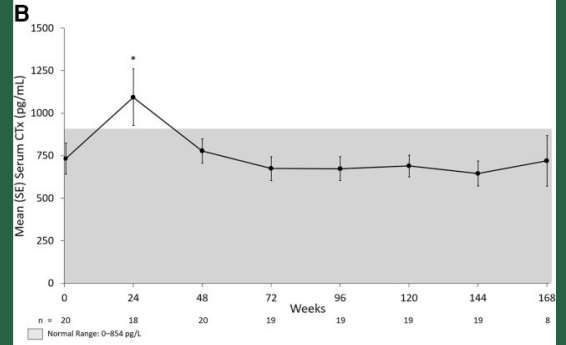

Mean (SE) Serum 1,25(OH)2D (pg/mL)
*
Weeks
n =

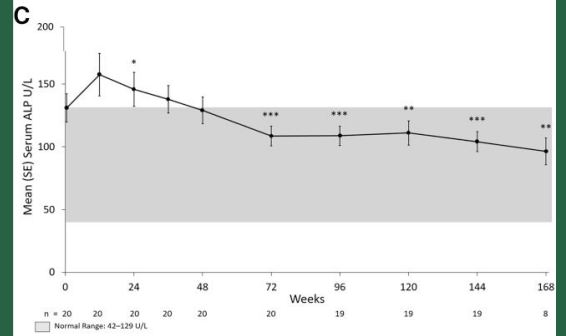

Mean (SE) Serum iPTH (pg/mL)
***
*
Weeks
n =

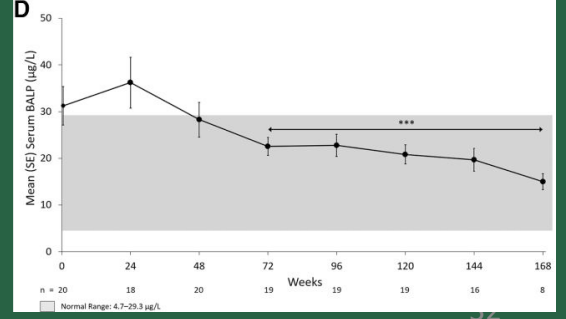

Mean (SE) Serum Calcium (mg/dL)
*
**
Weeks
n =


Mean (SE) Urinary Calcium (mg/24hr)
Weeks
n =

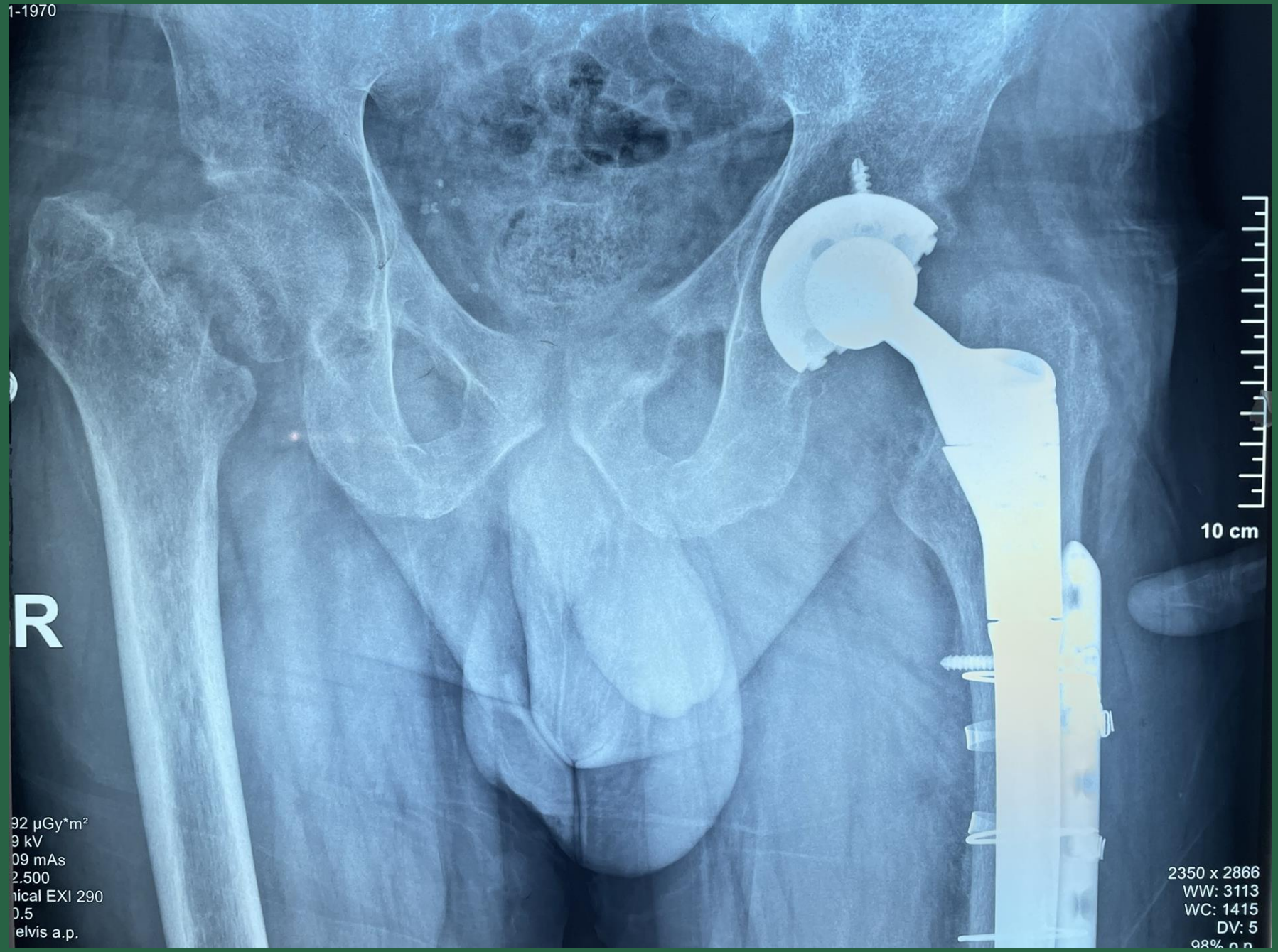

A
Mean (SE) Serum P1NP (ng/mL)
Weeks
Normal Range: 20–110 µg/L


B
Mean (SE) Serum CTx (pg/mL)
Weeks
Normal Range: 0–854 pg/L


C
Mean (SE) Serum ALP U/L
Weeks
Normal Range: 42–129 U/L


D
Mean (SE) Serum BALP (µg/L)
Weeks
Normal Range: 4.7–29.3 µg/L

	2/2020
Κρεατινίνη (mg/dl)	0,9
Ασβέστιο (mg/dl)	8,8
Φωσφόρος (mg/dl)	**1,4**
Μαγνήσιο (mg/dl)	1,9
Λευκωματίνες (gr/L)	4,4
αλ φωσφατάση (IU/L) (<150)	**260**
PTH (pg/ml)	**99**
25 D (ng/ml)	**9,1**
1,25 D (pg/ml)	Μη ανιχνεύσιμη
FGF23 (pg/ml)	> 900
TmP/GFR (mg/dl) [2.5-4.2]	**1,0159**



CLINICAL TRIAL

JBMR®

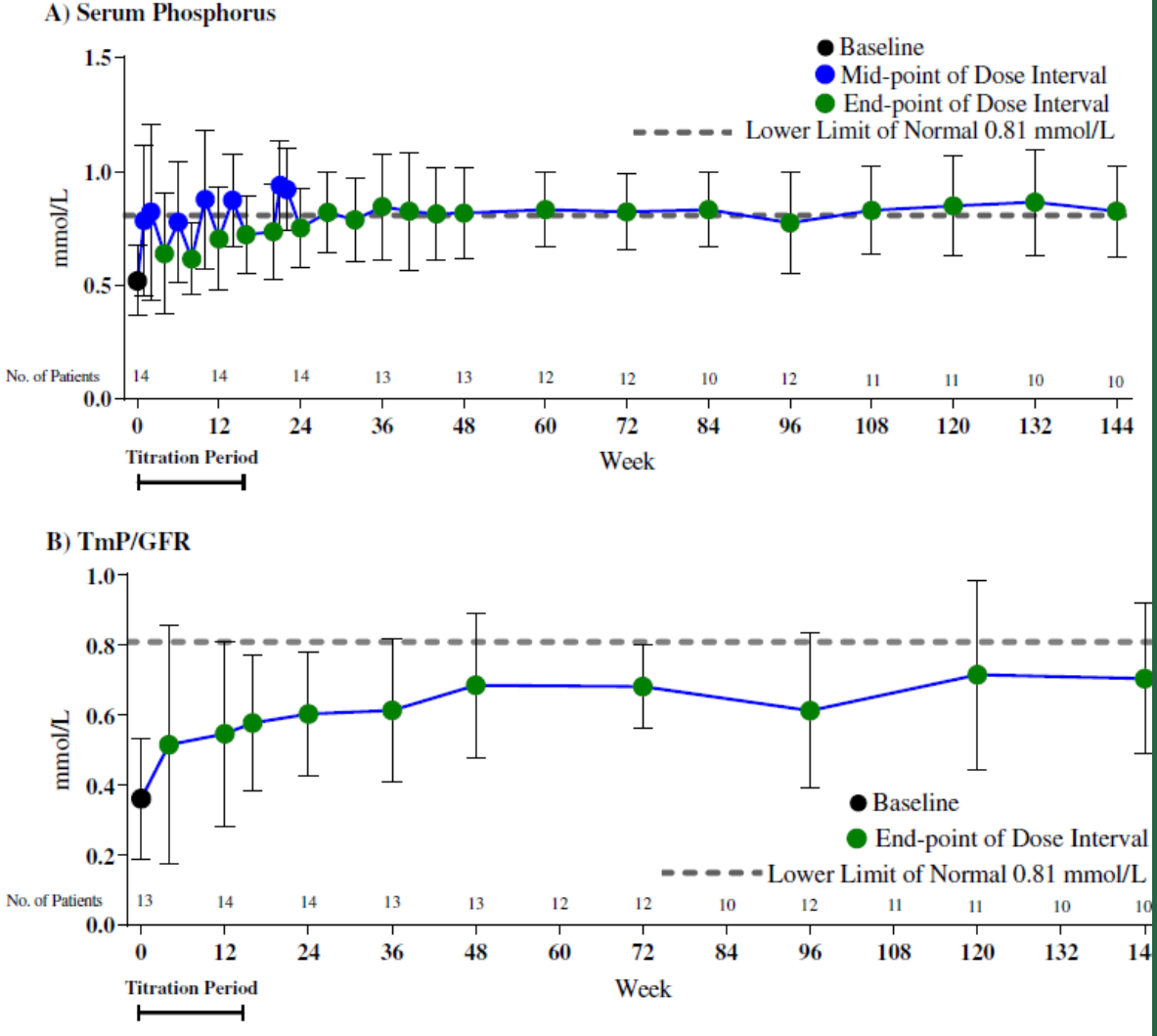
Burosumab for the Treatment of Tumor-Induced Osteomalacia

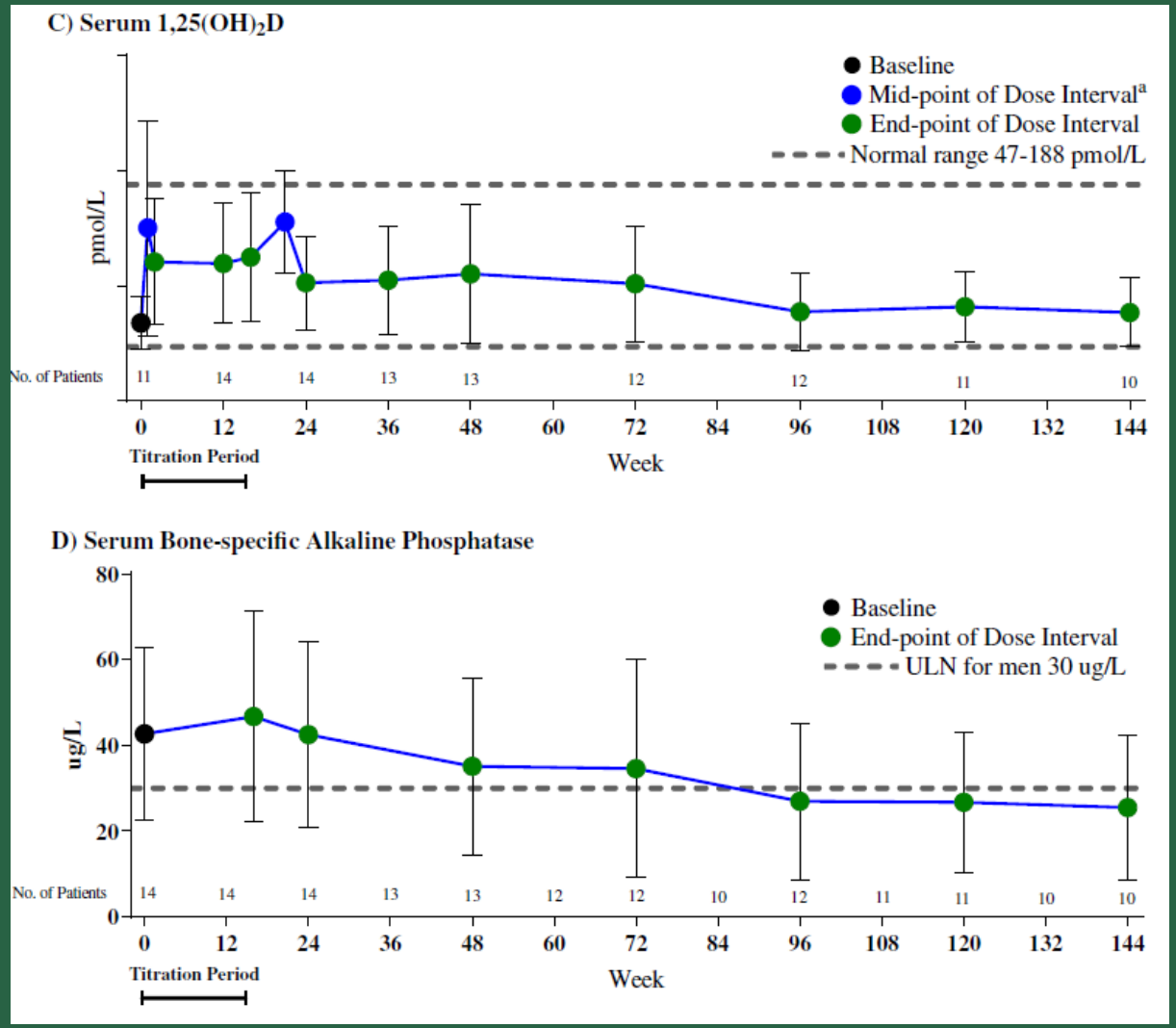
Suzanne M Jan de Beur,[1] Paul D Miller,[2] Thomas J Weber,[3] Munro Peacock,[4] Karl Insogna,[5] Rajiv Kumar,[6] Frank Rauch,[7] Diana Luca,[8] Tricia Cimms,[8] Mary Scott Roberts,[8] Javier San Martin,[8] and Thomas O Carpenter[5]

Table 1. Baseline Characteristics

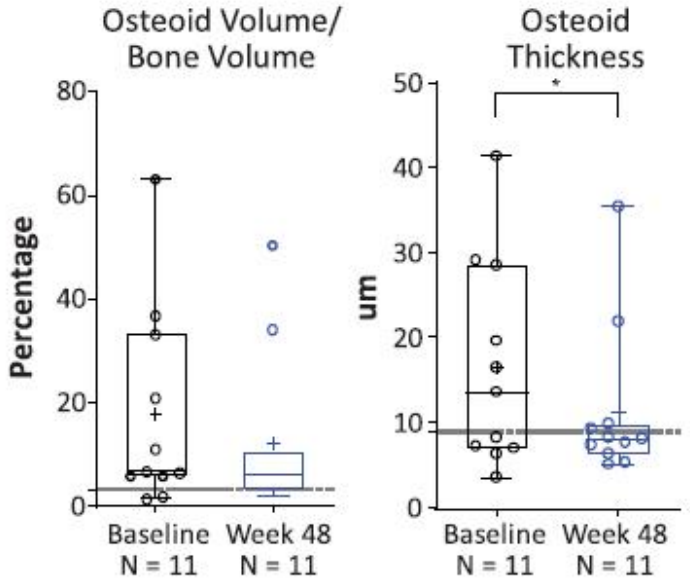
Characteristic, statistic	TIO ($N = 14$)
Male, *n* (%)	8 (57)
Age (years)	56.9 ± 10.3
Years since diagnosis	13.7 ± 13.0
Body mass index (kg/m^2)	33.8 ± 7.5
Race	
White	12 (86)
Black or African American	2 (14)
Serum phosphorus (mmol/L)	0.52 ± 0.15
Serum FGF23 (pg/mL)	416 (94, 2569)
TmP/GFR (mmol/L)	0.36 ± 0.17
1,25(OH)$_2$D (pmol/L)	68 ± 23
25(OH)D (nmol/L)	77 ± 29
Serum iPTH (pmol/L)	9 (1, 54)
Received prior phosphate treatment	13 (93)
Received prior active vitamin D	14 (100)
History of hyperparathyroidism	2 (14)
History of nephrolithiasis	3 (21)
Tumor located at baseline[a]	6 (43)

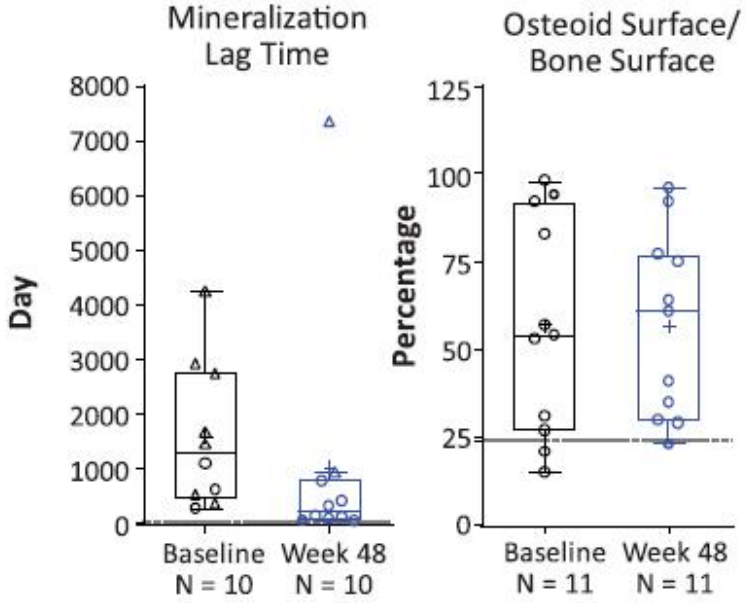
1 mg/dl= 0,323 mmol/L


A) Serum Phosphorus
Baseline
Mid-point of Dose Interval
End-point of Dose Interval
Lower Limit of Normal 0.81 mmol/L
mmol/L
1.5
1.0
0.5
0.0
No. of Patients
14 14 14 13 13 12 12 10 12 11 11 10 10
0 12 24 36 48 60 72 84 96 108 120 132 144
Titration Period
Week
B) TmP/GFR
mmol/L
1.0
0.8
0.6
0.4
0.2
0.0
Baseline
End-point of Dose Interval
Lower Limit of Normal 0.81 mmol/L
No. of Patients
13 14 14 13 13 12 12 10 12 11 11 10 10
0 12 24 36 48 60 72 84 96 108 120 132 14
Titration Period
Week

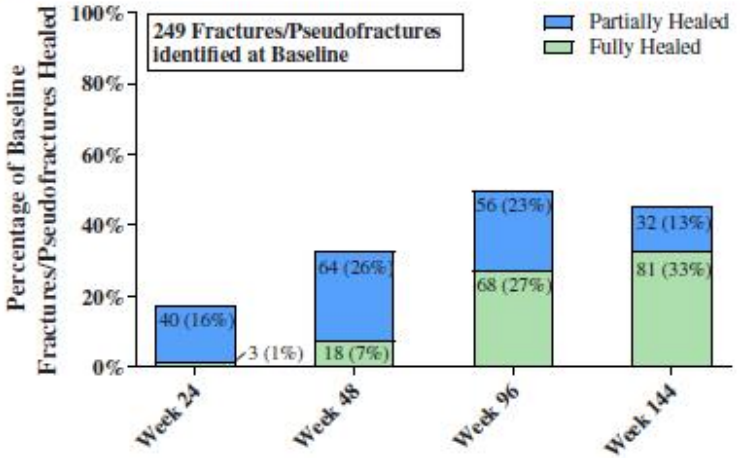

C) Serum 1,25(OH)2D
Baseline
Mid-point of Dose Interval[a]
End-point of Dose Interval
Normal range 47-188 pmol/L
pmol/L
No. of Patients
11 14 14 13 13 12 12 11 10
0 12 24 36 48 60 72 84 96 108 120 132 144
Titration Period
Week
D) Serum Bone-specific Alkaline Phosphatase
Baseline
End-point of Dose Interval
ULN for men 30 ug/L
ug/L
80
60
40
20
0
No. of Patients
14 14 14 13 13 12 12 10 12 11 11 10 10
0 12 24 36 48 60 72 84 96 108 120 132 144
Titration Period
Week

A) Histomorphometric Analysis

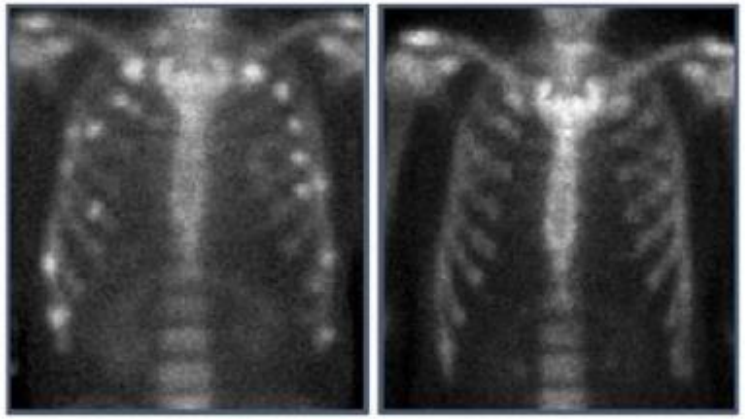




B) Fracture Healing



C) Chest from Full-body Bone Scan



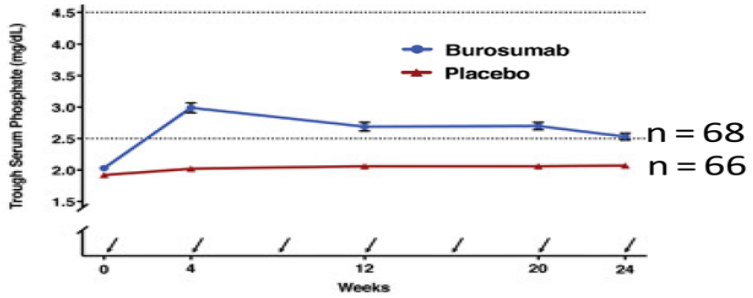
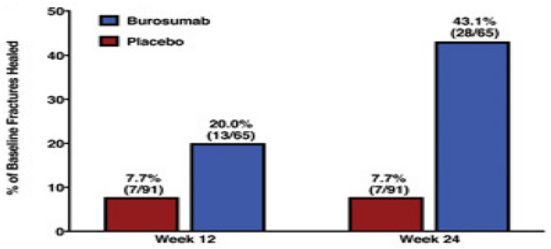
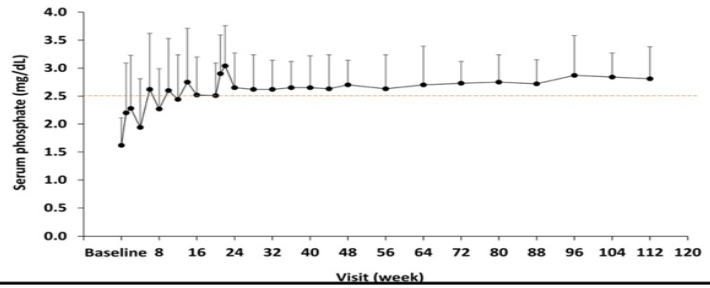
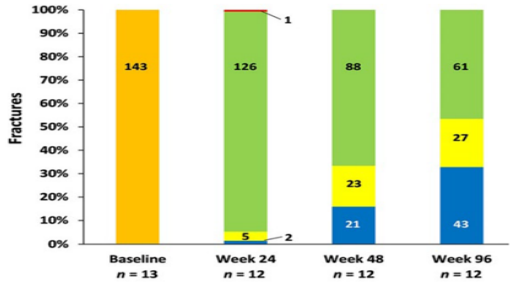
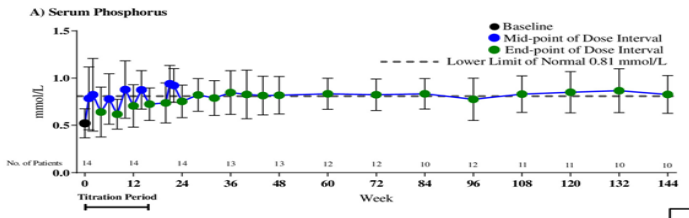
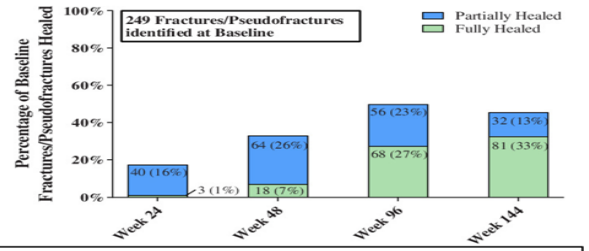
LETTER TO THE EDITOR

JBMR

Burosumab for Tumor-Induced Osteomalacia: Not Enough of a Good Thing

Iris R Hartley and Michael T Collins

National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA

	Study	Blood Phosphate	Fracture Healing
XLH	Insogna, JBMR, 2018 n=68 on Burosumab $\bar{x}$ baseline Pi = 1.9 mg/dL Starting dose = 1 mg/kg Maximum dose = 1 mg/kg			57% fractures remain at 24 weeks
TIO	Imanishi, JBMR, 2020 n=13 on Burosumab $\bar{x}$ baseline Pi =1.6 mg/dL $\bar{x}$ length disease = 10y $\bar{x}$ dose = 1.0 mg/kg @144w			67% fractures 71% pseudofractures remain at 96 weeks
TIO	Jan De Beur, 2020, JBMR n=14 on Burosumab $\bar{x}$ baseline Pi = 1.6 mg/dL $\bar{x}$ length disease = 14y $\bar{x}$ dose = 0.8 mg/kg at week 96; 0.7 mg/kg at week 144		 New fractures: 19 17 3 3	Up to 67% fractures/ pseudofractures remain at 144 weeks

JBMR

Reply to: Burosumab for Tumor-Induced Osteomalacia: not Enough of a Good Thing

Suzanne M. Jan de Beur,[1] Paul D. Miller,[2] Thomas J. Weber,[3] Munro Peacock,[4] Karl Insogna,[5] Rajiv Kumar,[6] Frank Rauch,[7] Diana Luca,[8] Tricia Cimms,[8] Mary Scott Roberts,[8] Javier San Martin,[8] and Thomas O. Carpenter[5]

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To the Editor:

We appreciate that Dr Hartley and Dr Collins recognize the importance of burosumab as a treatment for patients with tumor-induced osteomalacia (TIO) and X-linked hypophosphatemia (XLH). Burosumab is the only US Food and Drug Administration (FDA)-approved therapy for patients with TIO who have unresectable or unlocalizable tumors. Up until the approval of burosumab, treatment with active vitamin D and phosphate was the standard of care for medical treatment of TIO. However, treatment with these agents must be carefully monitored and titrated to avoid side effects such as secondary hyperparathyroidism, hypercalciuria, and nephrocalcinosis. For these reasons, clinicians aim for blood phosphate levels that are just within the lower limit of normal. The registrational TIO study[1] was designed in the context of this traditional approach to treatment and was implemented prior to the availability of robust, long-term safety data of burosumab in adult patients with XLH.[2–4] As such, burosumab was initially given at a conservative dose (0.3 mg/kg every 4 weeks) and then titrated to a maximum dose of 2.0 mg/kg every 4 weeks to achieve a serum phosphate level just above the lower limit of normal. Some patients required higher doses to reach the lower limit of normal, and these doses were well tolerated. Based on these data, the FDA has approved burosumab for patients with TIO with doses ranging from 0.5 mg/kg every 4 weeks up to 2.0 mg/kg every 2 weeks.

Although XLH and TIO have the commonality of fibroblast growth factor 23 (FGF23)-mediated hypophosphatemia, they are different diseases with different underlying etiologies and clinical manifestations. TIO symptoms and physical signs can be more debilitating. As such, it is difficult to directly compare burosumab efficacy across disease states and across clinical studies with different assessments and endpoints. Compared to patients enrolled in the adult XLH Phase 3 clinical trials,[2,3] TIO patients had lower serum phosphate, higher FGF23, and more variable histomorphometric parameters of osteomalacia upon study entry. The latter may be explained by differences in study enrollment criteria in which TIO patients continued to receive phosphate/active vitamin D until 2 weeks prior to study entry, whereas XLH patients in the bone biopsy subset were ineligible to participate if they received phosphate/active vitamin D within 2 years prior to study entry.[3]

Patients with TIO treated with burosumab experienced significant improvements across multiple measures, including some measures of osteomalacia, fracture healing, and patient-reported pain, fatigue, and physical functioning. Of note, significant changes were seen in the setting of a small study population of 14 patients, and despite the fact that most patients did not reach an effective burosumab dose until the end of the 16-week titration period. Because of the titration period, patients were on an effective burosumab dose for only 32 weeks at the time of the second bone biopsy, which may explain why significant improvements in some, but not all, osteomalacia parameters were observed. With longer burosumab treatment, we would expect to see greater improvements in these measures as well. Similarly, 33% of fractures were fully healed after 144 weeks of treatment. In this study, fractures were assessed by full-body bone scan, whereas the XLH studies[2,3] used

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This letter comments on the clinical trial article by Jan de Beur et al.
[The copyright line for this article was changed on 11 November 2021 after original online publication]
Journal of Bone and Mineral Research, Vol. 36, No. 12, December 2021, pp 2455–2456.
DOI: 10.1002/jbmr.4317

Συμπεράσματα

- Η χορήγηση Burosumab σε ασθενείς με XLH και TIO
  - Αποκαθιστά τις βιοχημικές διαταραχές της νόσου
  - Αποκαθιστά τις ραχιτικές αλλοιώσεις - οστεομαλακία
  - Βελτιώνει το ρυθμό ανάπτυξης, τις οστικές παραμορφώσεις και τον πόνο
  - Βελτιώνει την πώρωση των καταγμάτων
  - Βελτιώνει τη φυσική δραστηριότητα

Ενδείξεις

- Θεραπεία XLH σε παιδιά και εφήβους ηλικίας 1-17 ετών με ακτινολογικά επιβεβαιωμένη οστική νόσο και σε ενήλικες.
- Θεραπεία FGF23 επαγώμενης υποφωσφοραιμίας λόγω φωσφατουρικού όγκου (TIO) που δεν μπορεί να αντιμετωπισθεί χειρουργικά ή δεν εντοπίζεται σε παιδιά και εφήβους ηλικίας 1-17 ετών και σε ενήλικες.