מרכז שניידר לרפואת ילדים בישראל
مركز شنايدر لطب الأطفال في إسرائيل
Schneider Children's Medical Center of Israel

כללית 100 שנה
הכי טובה למשפחה

"האיזון העדין"

החלטות טיפוליות ב-BUROSUMAB בחולי XLH

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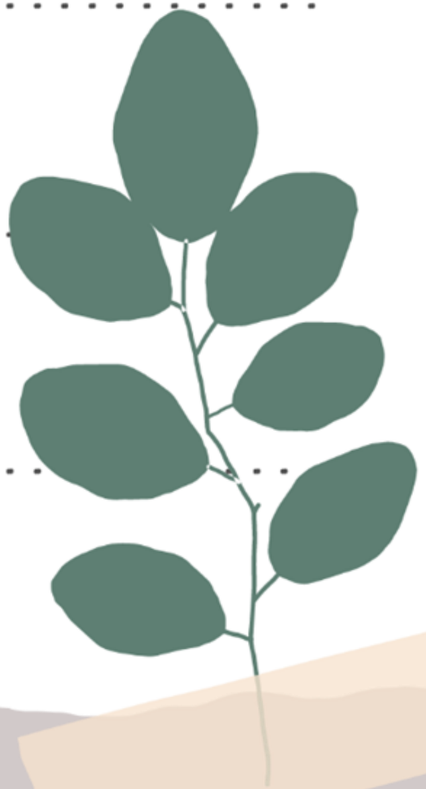
Pediatric Nephrology Institute

Dr. Rachel Bello
The Jesse and Sara Lea Shafer Institute
of Endocrinology and Diabetes



(XLH

phos

endo

Clini

Shor

Gen

Rickets

Laboratory abnormalities:

Nephrolithiasis

Impaired renal function

SC Burosumab= Crysvita

התוויה

CRYSVITA is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and paediatric patients 6 months of age and olderTumor-induced OsteomalaciaCRYSVITA is indicated for the treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older.

התוויות הכלולות במסגרת הסל

התוויה	תאריך הכללה	תחום קליני	Class Effect	מצב מחלה
חולים ללא לוחיות גדילה פעילות העונים על אחד מאלה: א. רמת זרחן נמוכה מ-2 מ"ג/דצ"ל; ב. שברים ופסאודו שברים ספונטניים; ג. רמת alkaline phosphatase מוגברת; ד. כאב עצמות חמור; ה. טיפול מקדים (חצי שנה) לפני ניתוח אורטופדי.	03/02/2022	אנדוקרינולוגיה		X-linked hypophosphatemia
טיפול ב-X-linked hypophosphataemia בחולים עם עדות רדיוגרפית למחלת עצם ולוחיות גדילה פעילות - לילדים מגיל שנה ועד לאיחוי לוחיות הגדילה.	16/01/2019	אנדוקרינולוגיה		X-linked hypophosphataemia

B.T. – Presentation 03/2019

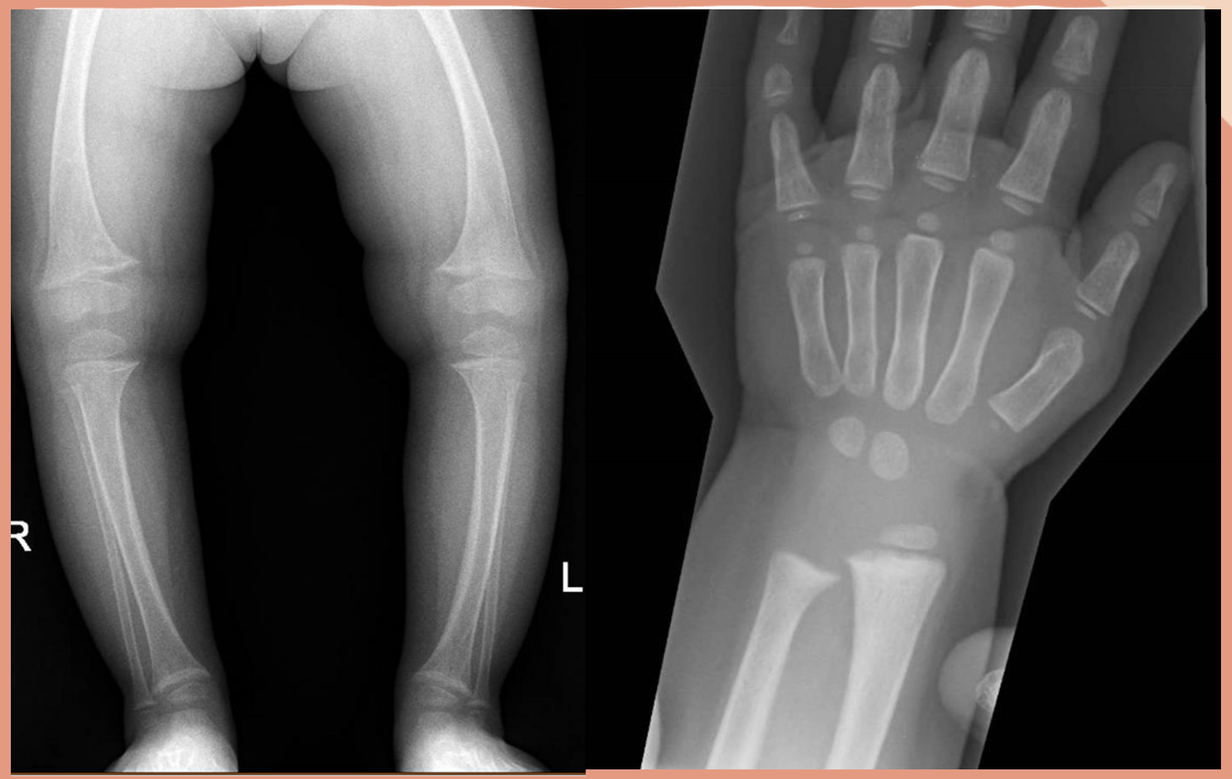
Symptoms

- 2.2 yrs old girl
- Presented to orthopedic unit with bowing, waddling gate, rec falls
- Growth deceleration from 50 to 15 percentile
- No family history

Signs

- Genu varum
- Widened metaphysis

Imaging



Fraying: indistinct margins of the metaphysis
Splaying: widening of metaphyseal ends
Cupping: concavity of metaphysis

B.T. – confirming the diagnosis of XLH

Investigation

Hypophosphatemia 2.9mg/dl

Elevated ALP 565 U/L

Normocalcemia

Vitamin 25OHD 70nmol/l

Vitamin 1,25OH_2D 122pmol/l

PTH 46 (14-53pg/ml)

Normal TRP 87% (85-95%)

Low TMP/GFR 2.52 mg/dl (3.25-5.5)

Confirmation

Elevated intact FGF-23 96pg/ml (29-61)

PHEX gene - de novo mutation c.1601C>T

Treatment

- [ ] Oral phosphate
- [ ] Alpha –D3
- [ ]
- [ ]
- [ ]

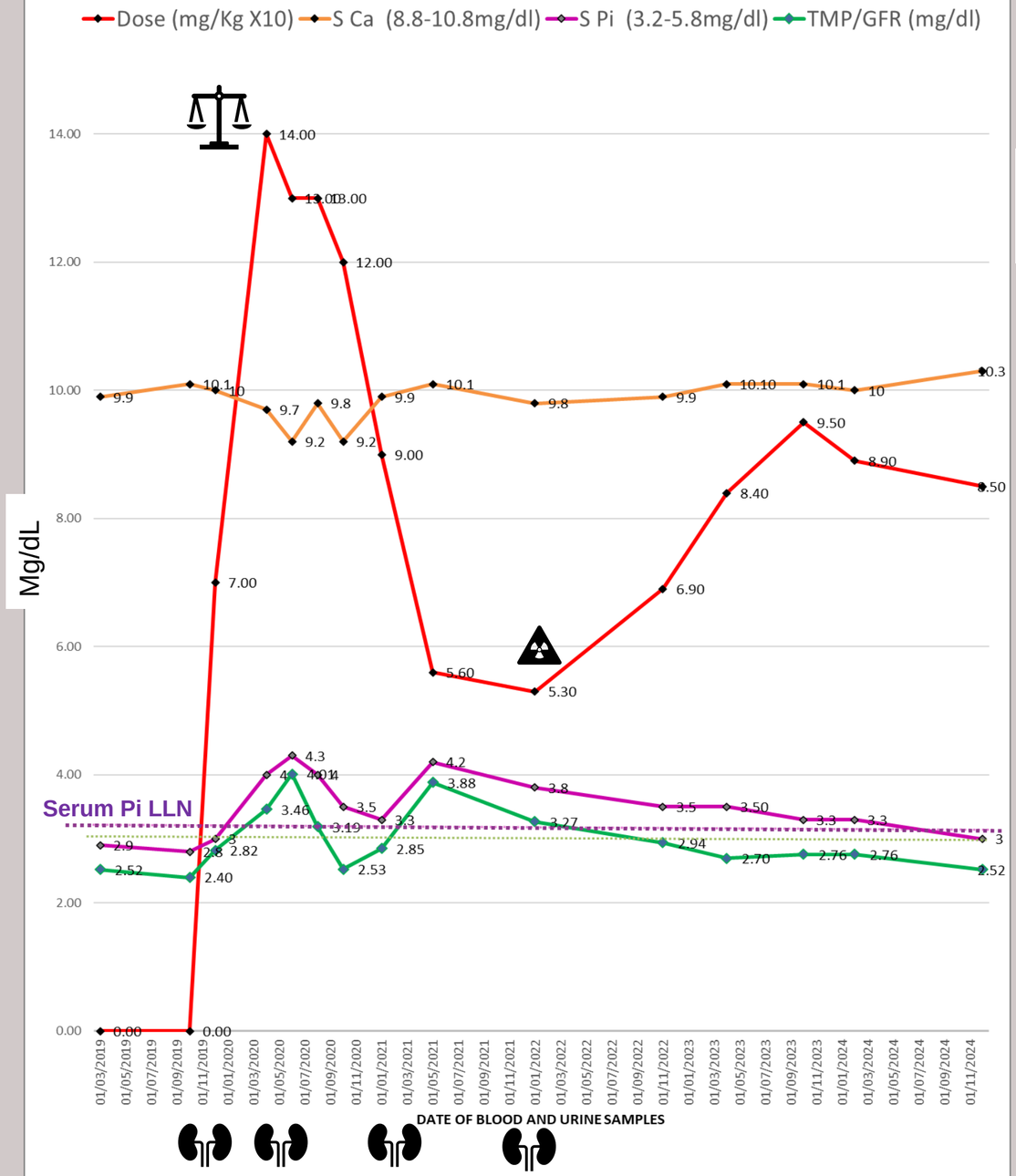
Follow-up laboratory & imaging

	Normal range	3/2019	**6/2019**
Calcium (mg/dl)	8.8-10.8	9.9	10
Phosphorus (mg/dl)	3.2-5.8	2.9	2.6
Albumin (gr/dl)	3.8-5.4	4.4	4.5
Alk Phos (U/L)	96-297	565	537
Creatinine (mg/dl)	0.15-0.37	0.26	0.19
Vitamin D 25OH (nmol/l)	75-250	69.9	68
Vitamin D 1,25 OH_2 (pmol/l)	50-190	122	174
PTH (pg/ml)	14-53	46	42
Urine Creatinine (mg/dl)		32	23.9
Urine Phosphor (mg/dl)	40-137	46.5	38.9
Urine Calcium/Creatinine		0.12	0.09

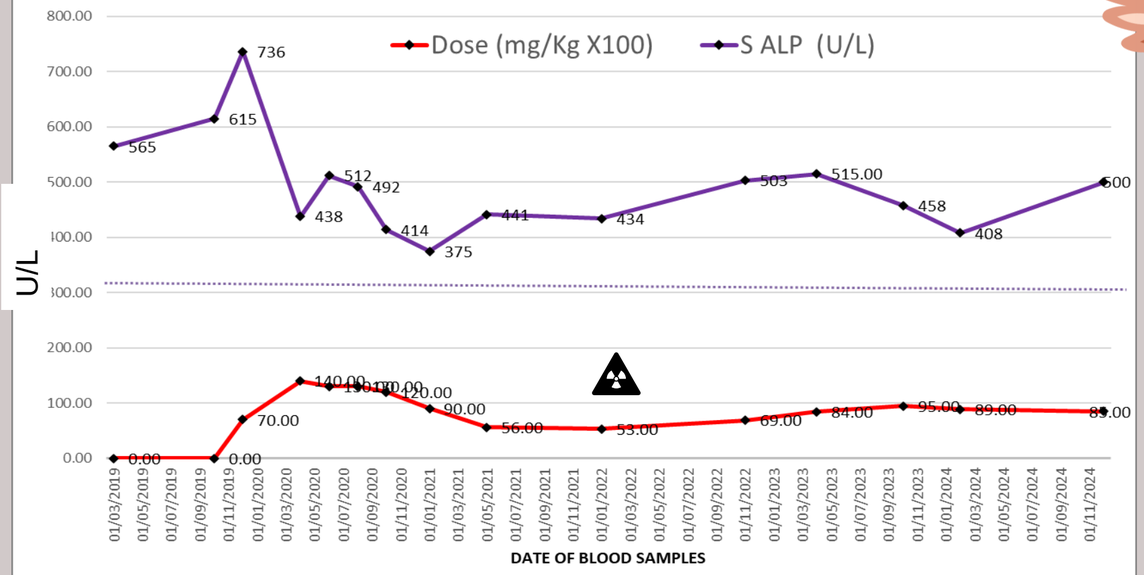
Treatment

- [ ] Oral phosphate
- [ ] Alpha D3
- [ ] Switch to burosumab
- [ ] Dec 2019
- [ ]

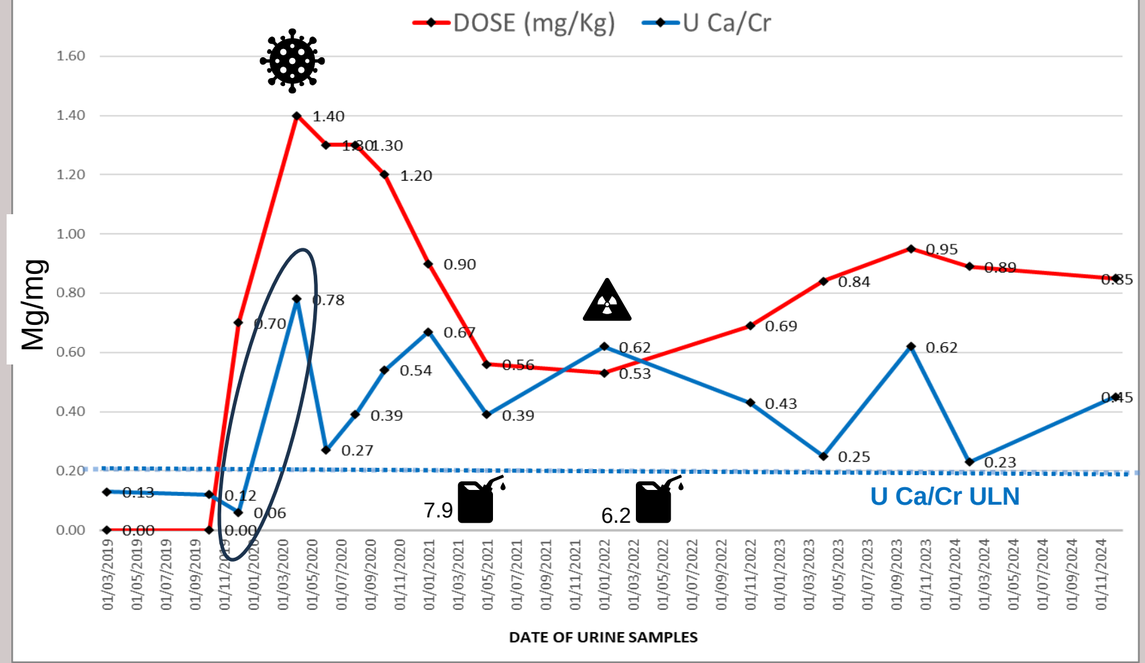
BUROSUMAB DOSE, SERUM CA & P, URINARY TMP/GFR OVER 5 YEARS OF TX



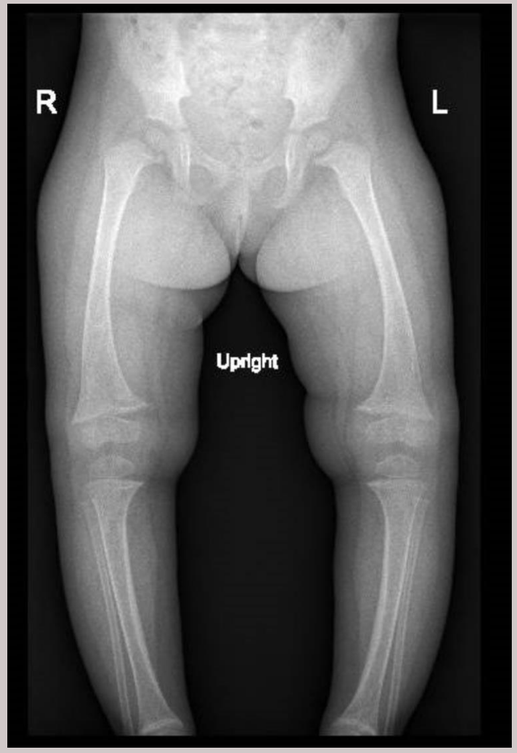
BUROSUMAB DOSE & SERUM ALP OVER 5 YEARS OF TX



BUROSUMAB DOSE & URINARY CA/CR RATIO OVER 5 YEARS OF TX

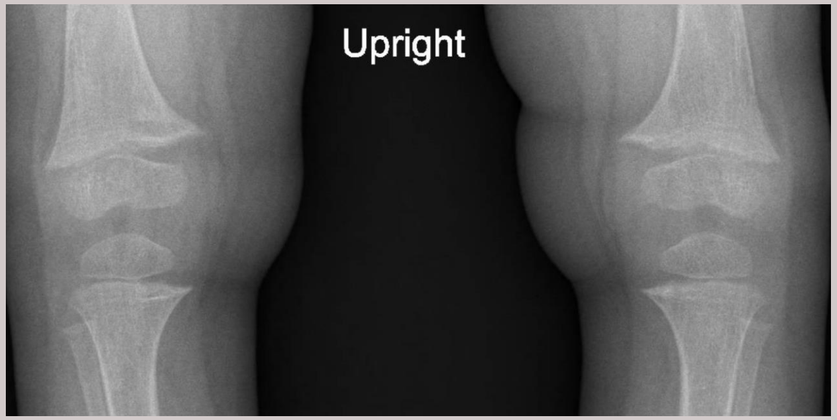


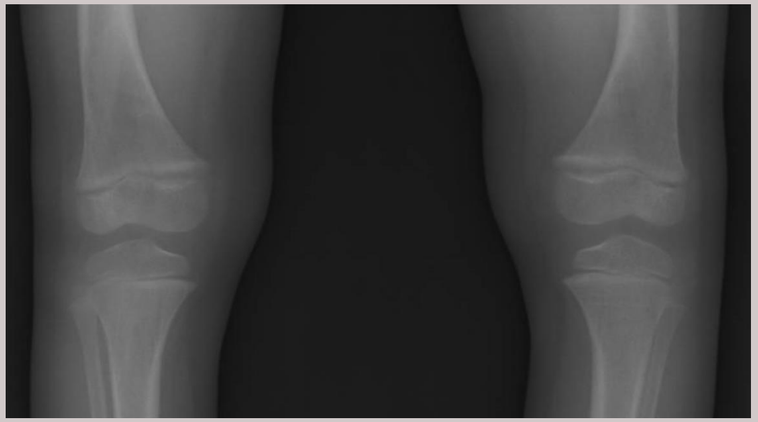
03/2019 - presentation



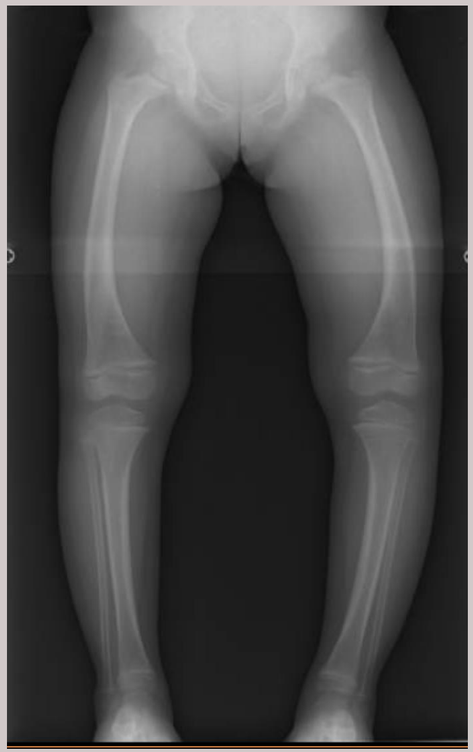
02/2020 – 3 mo Bur

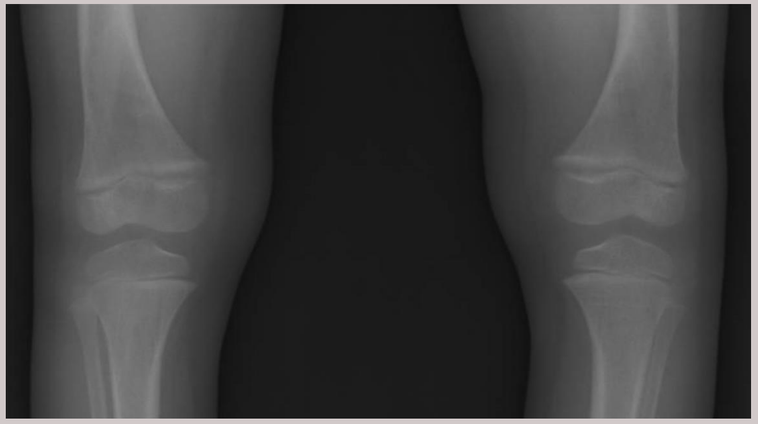
01/2021 – 13 mo Bur



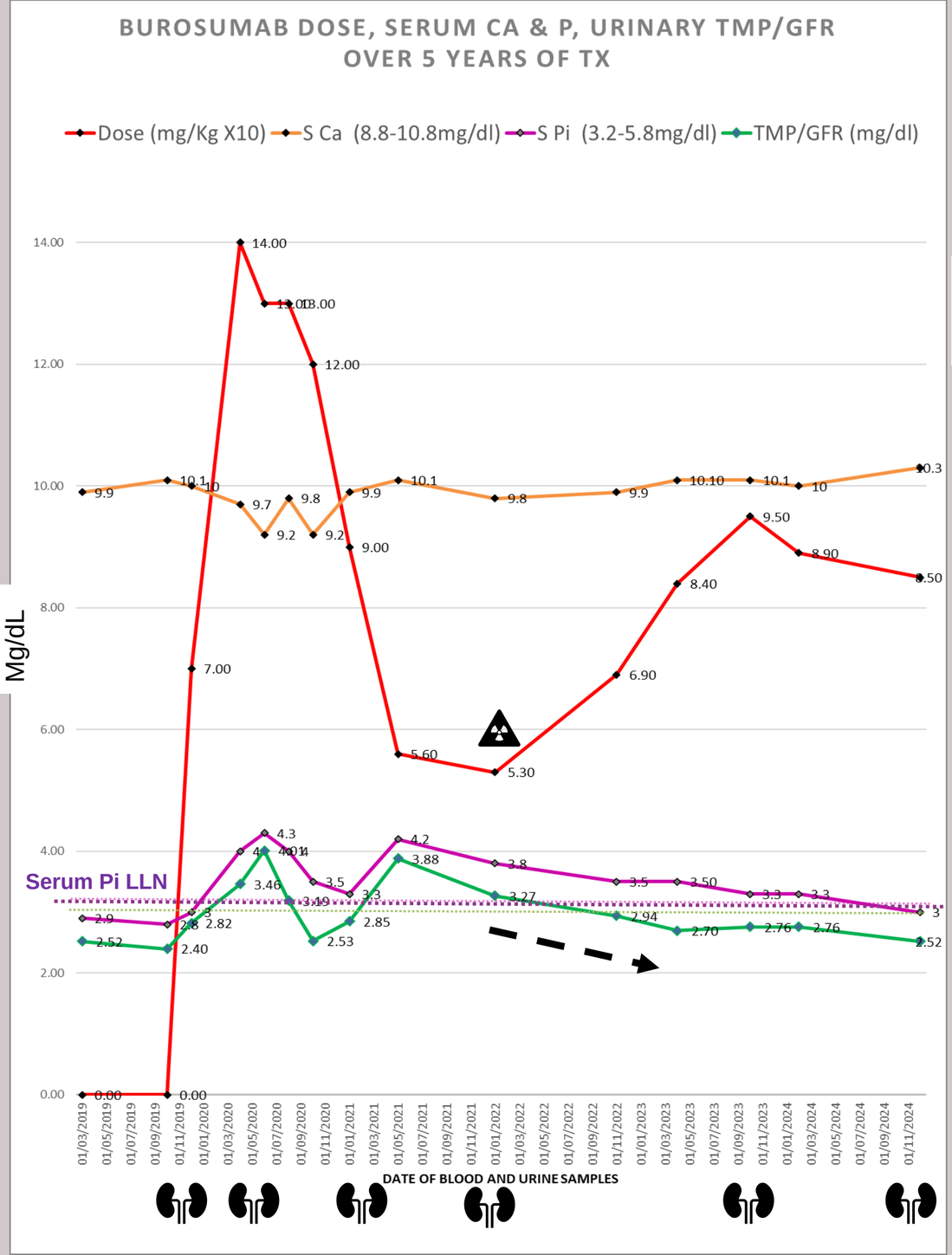


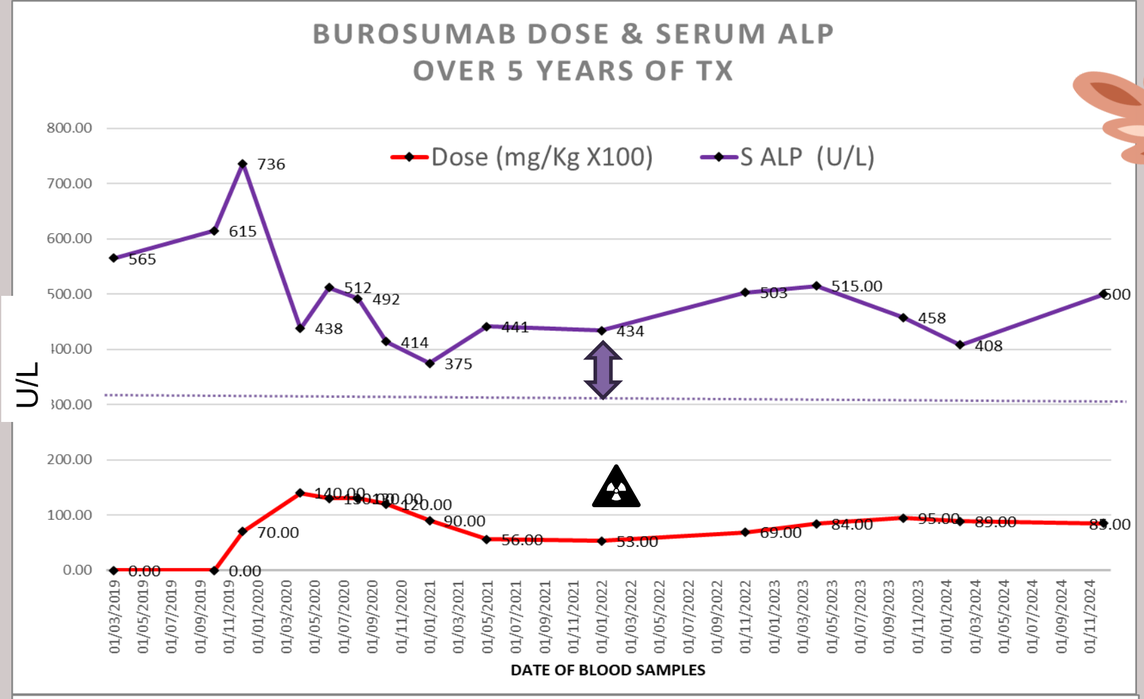
01/2021 – 13 mo Bur

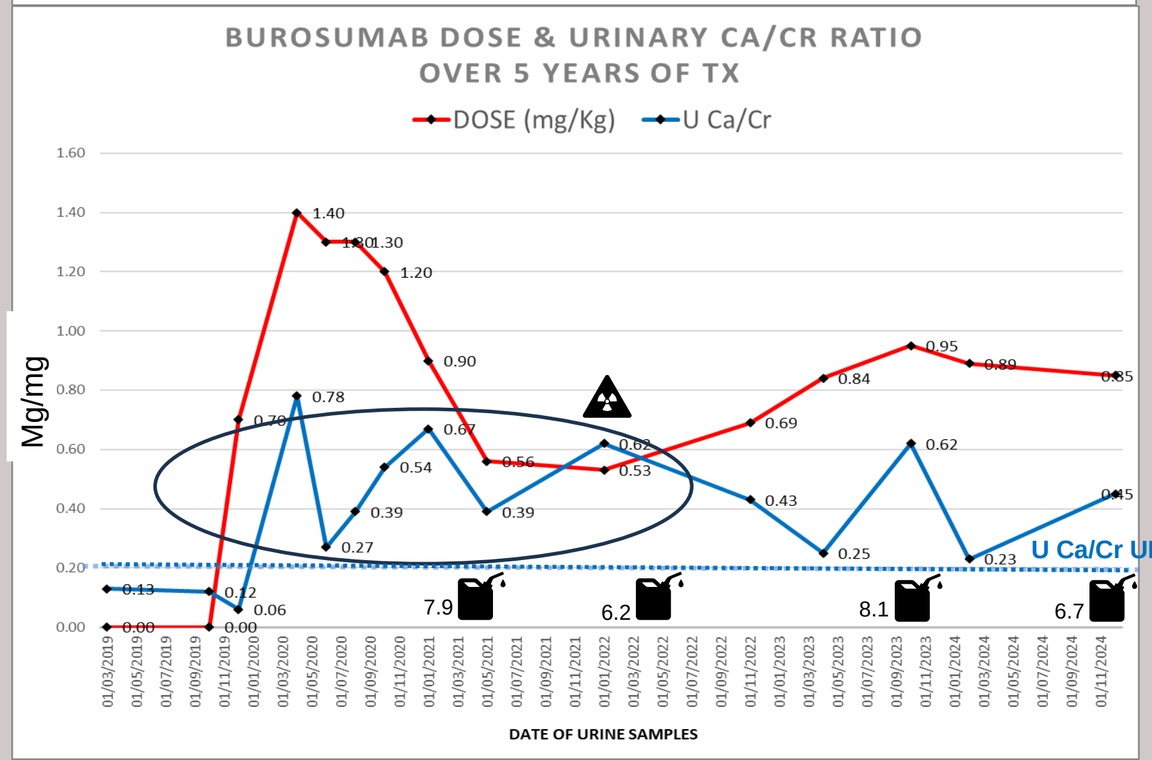




01/2022 - 25 mo Bur


BUROSUMAB DOSE, SERUM CA & P, URINARY TMP/GFR
OVER 5 YEARS OF TX
Dose (mg/Kg X10)
S Ca (8.8-10.8mg/dl)
S Pi (3.2-5.8mg/dl)
TMP/GFR (mg/dl)
Mg/dL
Serum Pi LLN
DATE OF BLOOD AND URINE SAMPLES

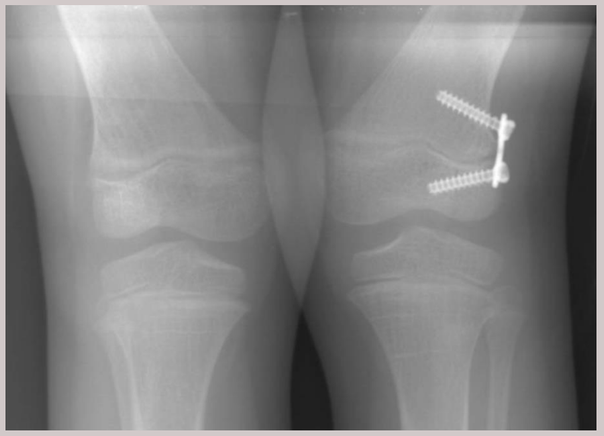

BUROSUMAB DOSE & SERUM ALP
OVER 5 YEARS OF TX
Dose (mg/Kg X100)
S ALP (U/L)
U/L
DATE OF BLOOD SAMPLES

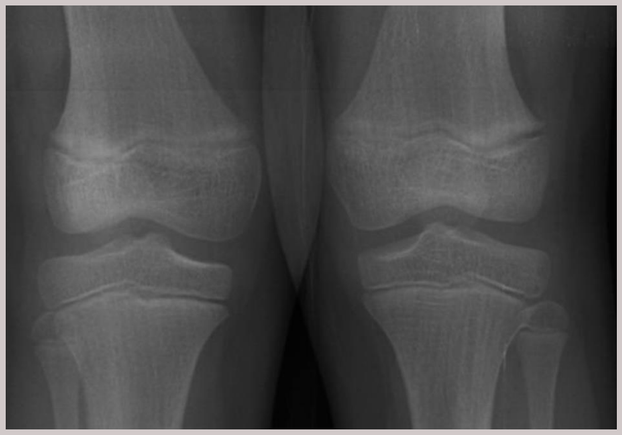

BUROSUMAB DOSE & URINARY CA/CR RATIO
OVER 5 YEARS OF TX
DOSE (mg/Kg)
U Ca/Cr
Mg/mg
U Ca/Cr ULN
DATE OF URINE SAMPLES

01/2022 - 25 mo Bur

12/2022 - 36 mo Bur

11/2024 - 59 mo Bur





Hypercalciuria

Urine Collection:

- Adult >200mg/day
- Children> 4mg/kg/day

Spot - Urine Calcium/Creatinine Ratio

Normal urinary solute value in children based on measurements of solutes and creatinine from a single random urine collection

	Age	mg/mg	Age	mmol/mmol
Calcium/creatinine	0 to 6 mo	<0.8	0 to 6 mo	<2.24
	6 to 12 mo	<0.6	6 to 12 mo	<1.68
	2 to 18 yr	<0.2	2 to 18 yr	<0.56

Up To Date

Table 2 Random urine solute-to-creatinine ratio[a] by age [79, 114, 121] (Modified with permission from Wiley-Blackwell)

Urinary solute	Age	Solute-to-creatinine ratio	
		mmol/mmol	mg/mg
Calcium	0–1 years	2.29	0.81
	1–2 years	1.58	0.56
	2–3 years	1.41	0.50
	3–5 years	1.16	0.41
	5–7 years	0.85	0.30
	7–10 years	0.71	0.25
	10–17 years	0.68	0.24

Ped Neprol. Avner. 7th edition

Hypercalciuria (HC) & Nephrocalcinosis (NC) in XLH patients

Historically-

Side effect of supplemental therapy (up to 60%!!)

Caused by :

Hyperparathyroidism - PTH stimulation associated with oral phosphate supplementations

Active vitamin D >> can prevent hyperparathyroidism but may increase risk of HC and NC

Maria Goretti M. G. Penido & Uri S. Alon. Ped Neprol 2012

Normal kidney parenchyma

Medullary nephrocalcinosis (started 1 yr post supplemental Tx)

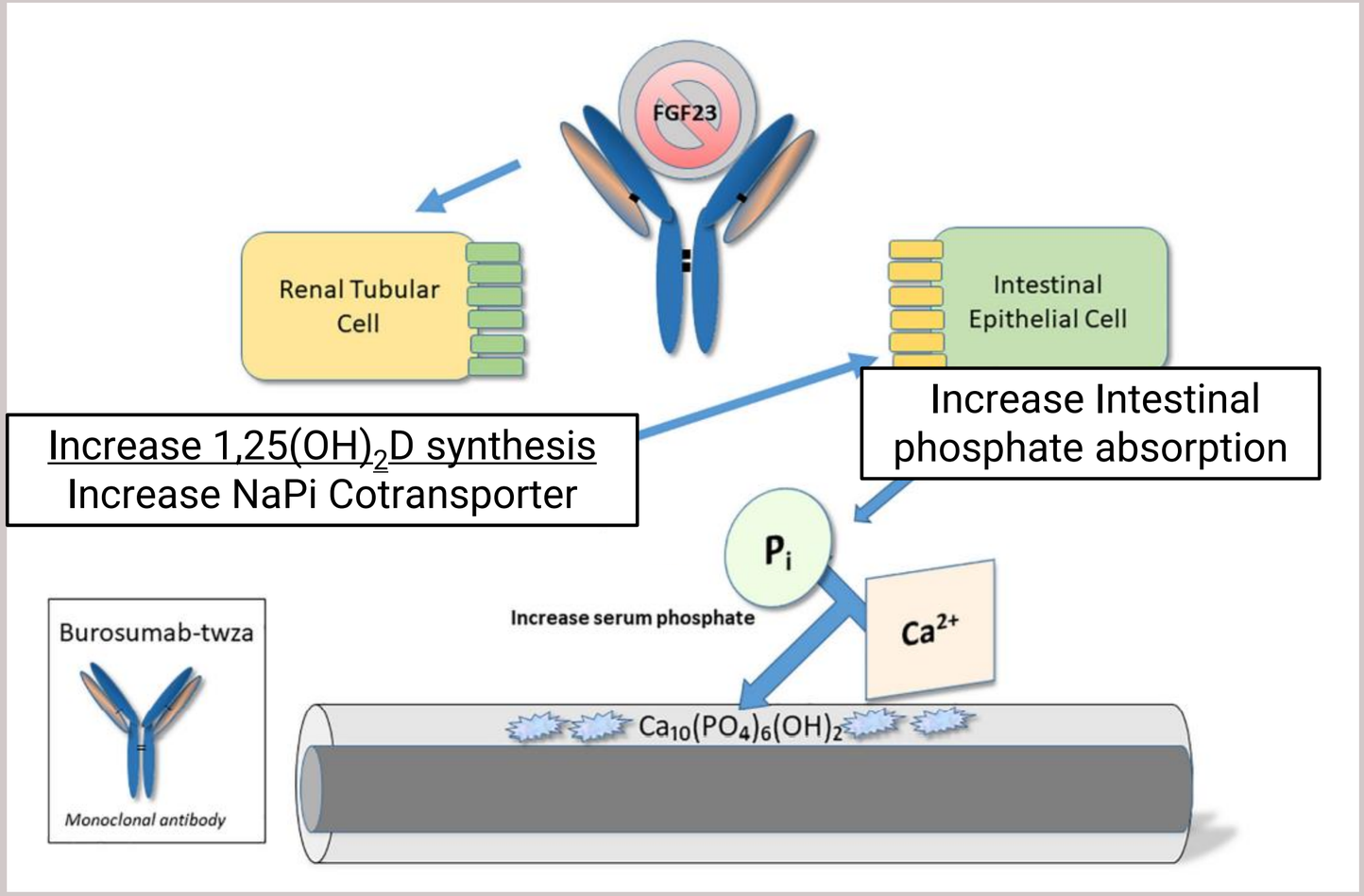
DE GRUYTER J Pediatr Endocrinol Metab 2021; 34(6): 791–798

Daisuke Harada*, Kaoru Ueyama, Kyoko Oriyama, Yoshihito Ishiura, Hiroko Kashiwagi, Hiroyuki Yamada and Yoshiki Seino

Switching from conventional therapy to burosumab injection has the potential to prevent nephrocalcinosis in patients with X-linked hypophosphatemic rickets

Burosumab and potential risk for HC/ NC

Goal- to restore phosphate balance



Inhibition of FGF23 may potentially cause →
Uncontrolled elevation in $1,25(OH)_2D$ levels→
Increasing intestinal calcium absorption →
Leading to hypercalcemia, HC and NC

Kathryn M. Et al. frontier in ped. 2022

Burosumab and risk for HC/NC
Summary of clinical trails (Conflicting results)

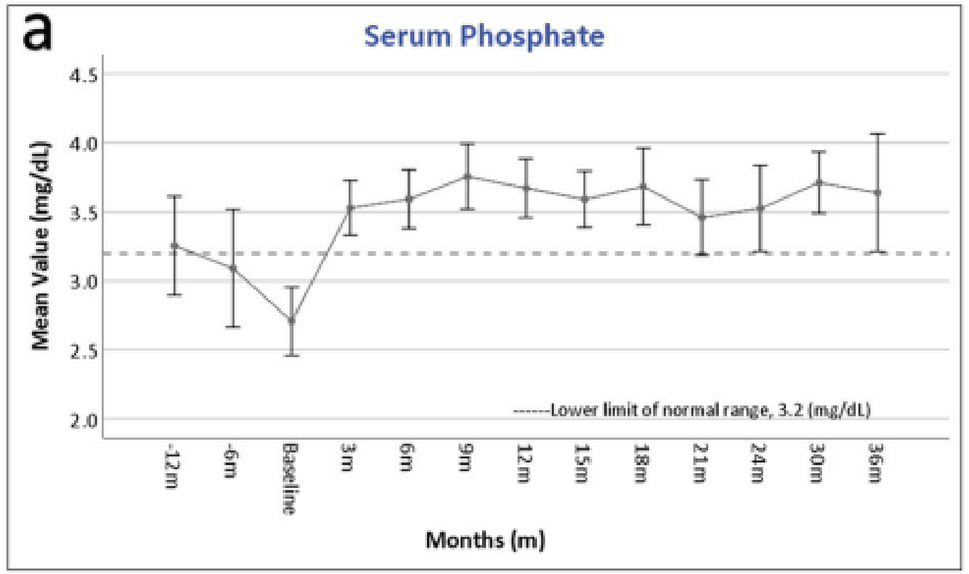
	Carpenter TO et al. NEJM 2018 Linglart A et al. JCEM 2022	**Imel EA et al. Lancet. 2019 (Phase 3 trail)**	**Neil J Paloian et al. Frontier in Ped 2024 Real word data!**
Number of patients	52	61 (32 conventional + 29 burosumab)	13
Age	5-12 years	5-12 years	Mean 5.6 (±5)
Burosumab Tx duration	64w>> (extension) 160w	64w	6 years in 3 patients with NC
Serum Ca	No significant change	No significant change	N/A
Urinary Ca	No significant change	No significant change	N/A
Change in NC grading	stable in 39, -1 in 3, +1 in 9, +2 in 1 patients	No deterioration	+1 in 1 after 5 years of burosumab

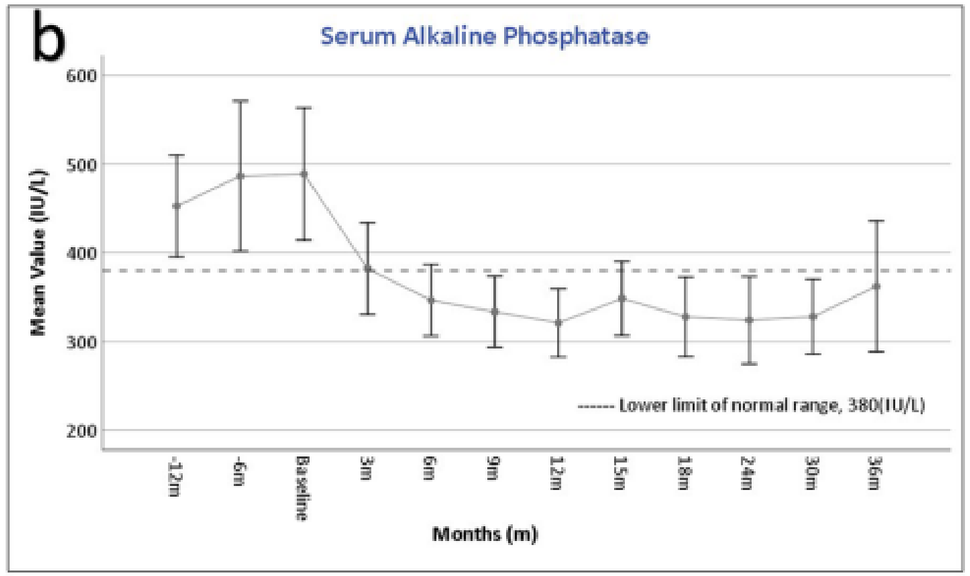
Nephrocalcinosis tendency does not worsen under burosumab treatment for XLH rickets: a multicenter pediatric study

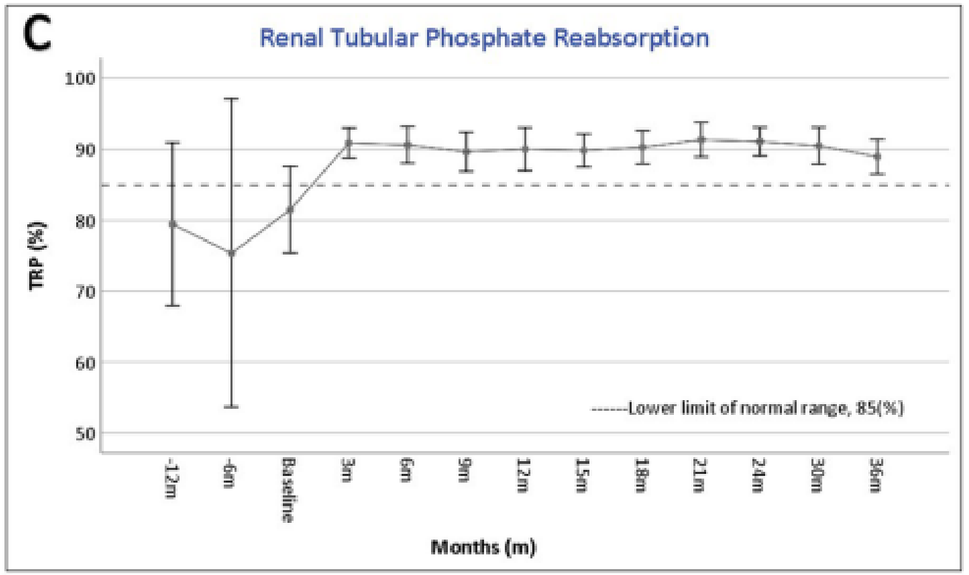
Shelly Levi, Mika Shapira-Rotman, Daniel Landau, Miriam Davidovits, Avivit Brener, Shoshana Gal, Yael Borovitz, Ori Goldberg, Rachel Bello, Roxana Cleper, Yael Lebenthal, Yael Levy-Shraga, Adi Chezana, Ravit Regev, Dov Tiosano, Leonid Zeitlin.

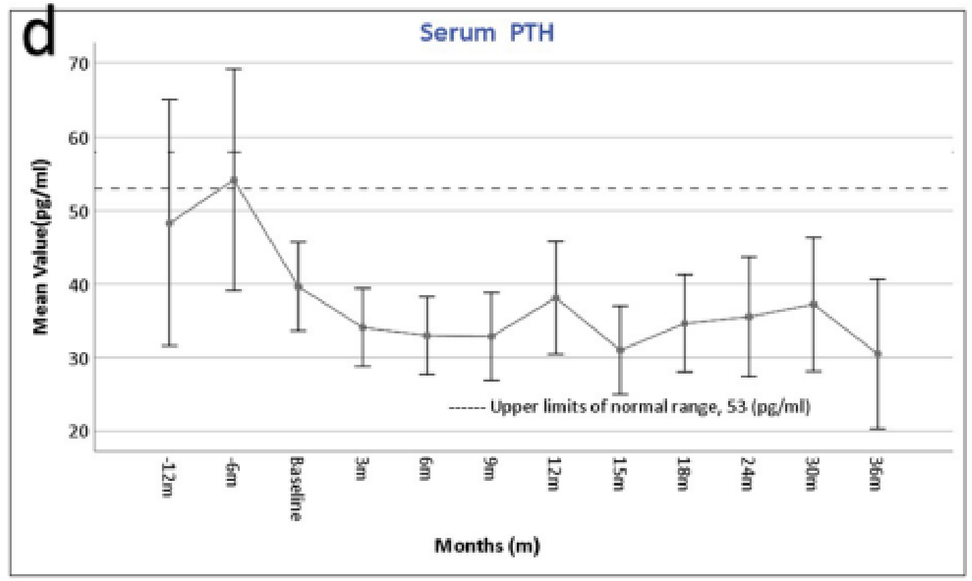
Front Pediatr. 2024 Dec

Results- Efficacy

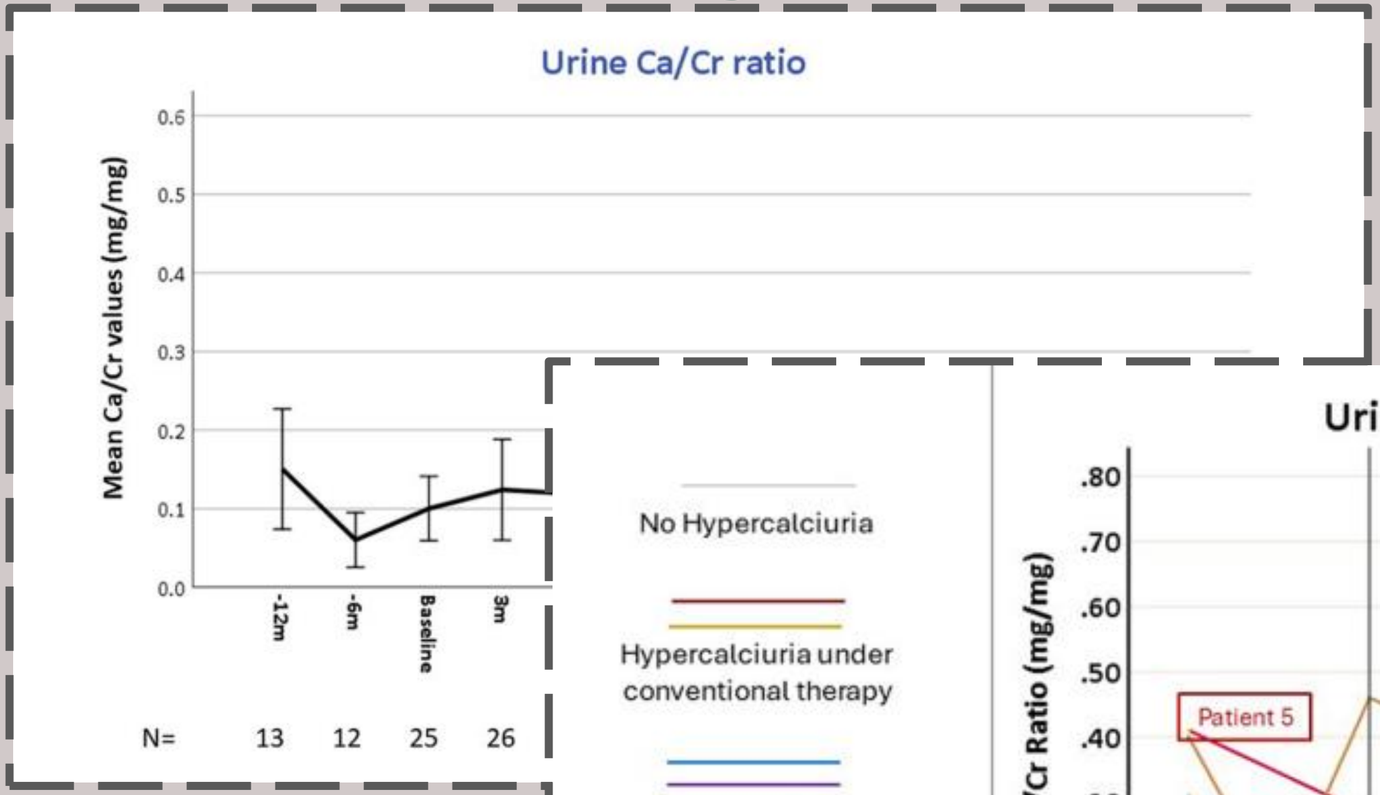


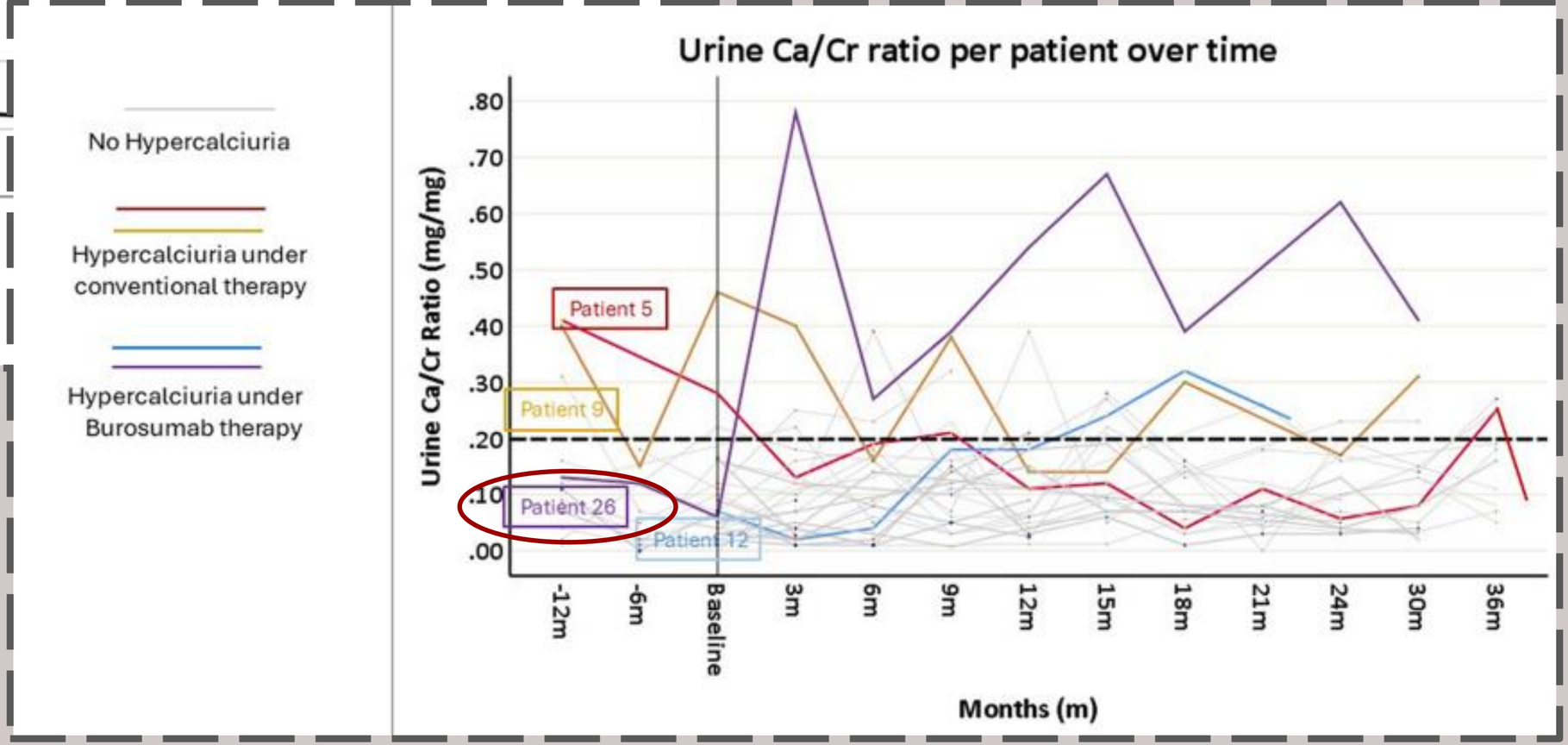






Results- Urinary Ca





Results- NC

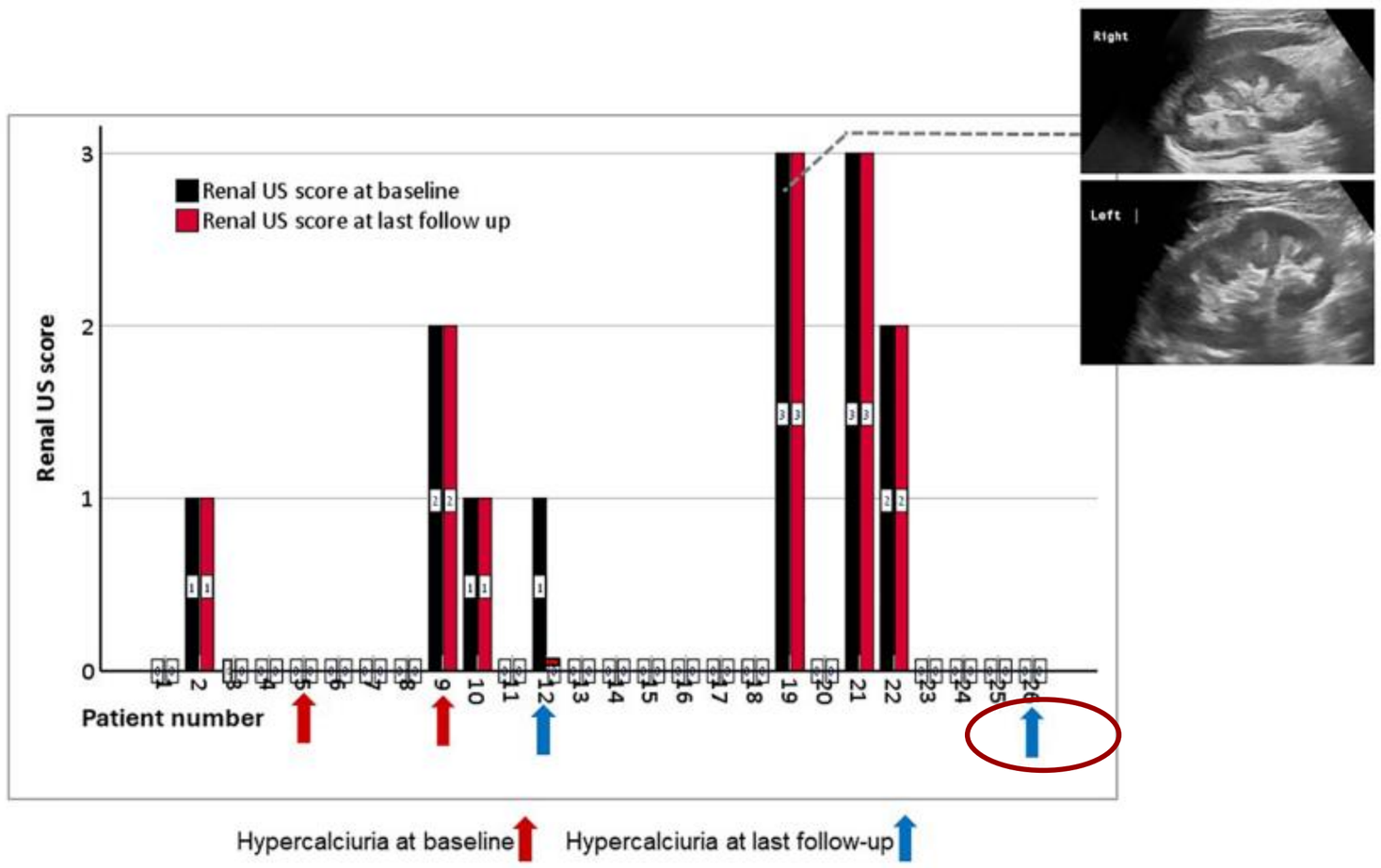


FIGURE 4
Bar chart of NC scores for each of the 26 patients, measured before (black column) and at the last follow up (red column) after burosumab treatment. The arrows represent the patients with hypercalciuria before (red arrows) and after (blue arrows) burosumab initiation. The figure inserts show examples of grade 3 medullary NC in the right and left kidneys of one patient. US, ultrasound.

Evidence-based guidelines

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

- ✓ <u>Follow-up under burosumab</u>:
- ✓ In patients without previous long-standing treatment with active vitamin D and phosphate supplements, the risk of developing HC, NC and hyperparathyroidism is probably very low.
- ✓ Monitor 1,25$(OH)_2$D levels at least yearly (as they may increase above the normal range, which may promote hypercalciuria).
- ✓ Kidney US- Every 2 years or annually in patients with pre-existing NC or HC.

Dieter Haffner et al. Nature review Jan 2025

Evidence-based guidelines

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

- ✓ Clinical trials- burosumab dose was tailored to raise serum phosphate into the lower normal range.
- ✓ German XLH registry & UK cohort- Hypophosphataemia persisted in about half of patients, but serum ALP normalized in the vast majority.
- ✓ Patients with subnormal plasma phosphate levels had a higher TRP arguing against ongoing urinary phosphate wasting.

Ewert, A. et al. J. Clin. Endocrinol. Metab. 108 (2023)
Walker, E. Y. X. et al. Arch. Dis. Child. 108, 379–384 (2023)

Conclusions

- Burosumab is safe and effective treatment in pediatric XLH.
- During treatment we may observe a low incidence of HC and no increase in NC.
- Maintaining phosphate levels in the lower range of normal, as recommended in the guidelines, as well as close surveillance of kidney safety parameters is important for the prevention of this low, but existing, risk of HC.

Thank you!

BUROSUMAB DOSE, SERUM PTH & 1,250H$_2$D OVER 5 YEARS OF TX