BIBLIO OS SRO
RENNES 2019

12 10 2019

P GUGGENBUHL

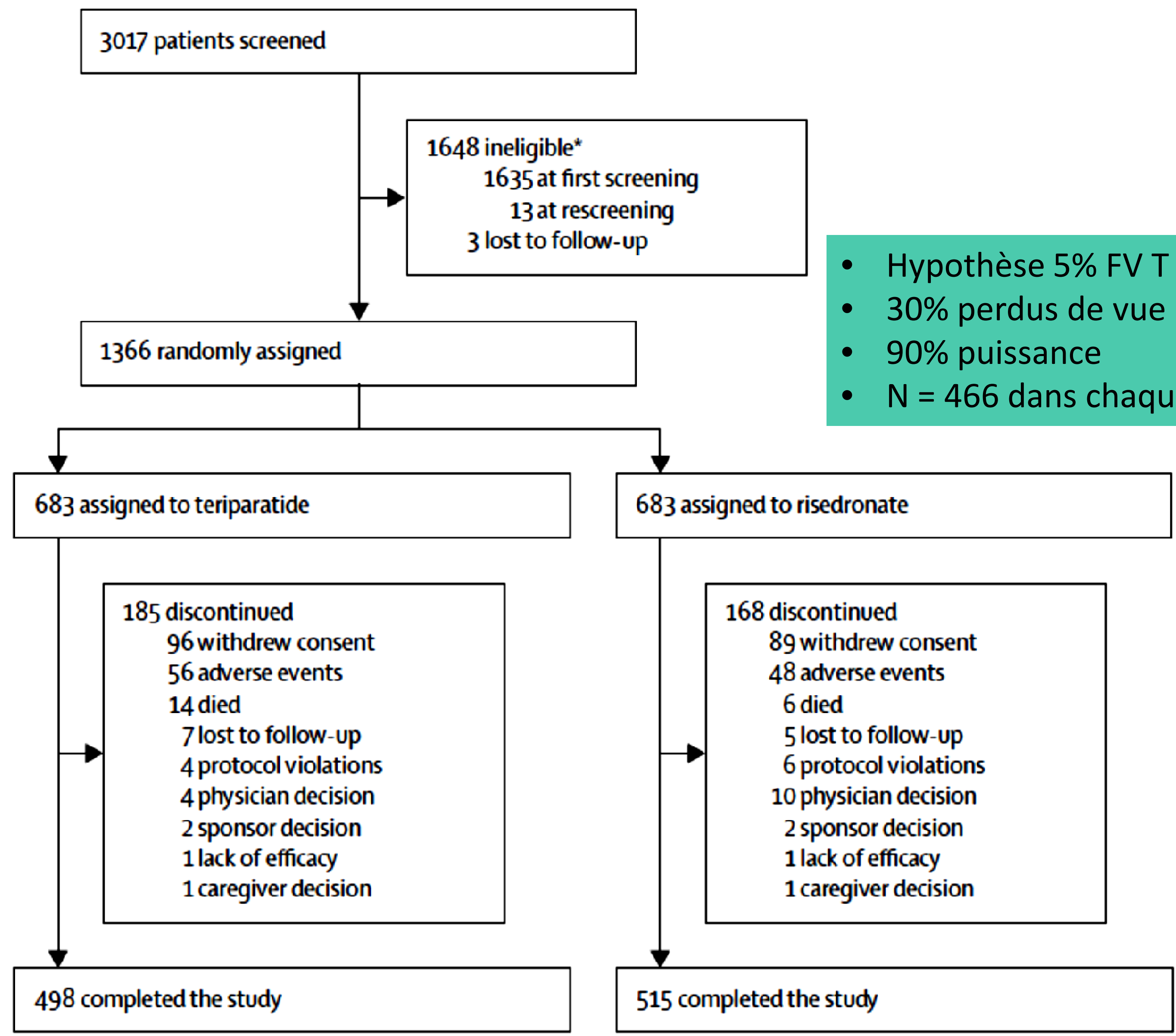
VERO VA AU BURO…

Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial

David L Kendler, Fernando Marin, Cristiano A F Zerbini, Luis A Russo, Susan L Greenspan, Vit Zikan, Alicia Bagur, Jorge Malouf-Sierra, Péter Lakatos, Astrid Fahrleitner-Pammer, Eric Lespessailles, Salvatore Minisola, Jean Jacques Body, Piet Geusens, Rüdiger Möricke, Pedro López-Romero

Lancet 2018; 391: 230–40

- RCT avec comparateur actif en groupes parallèles
- 123 centres en Europe, Amérique du nord et Afrique du sud
- Femmes ménopausées > 45 ans avec 2 FV grade 2 ou 1 FV grade 3 et T score < -1,5
- Traitement 24 mois: Tériparatide ou Risédronate 35mg hebdomadaire
- **Objectif principal: survenue de nouvelles fractures vertébrales**

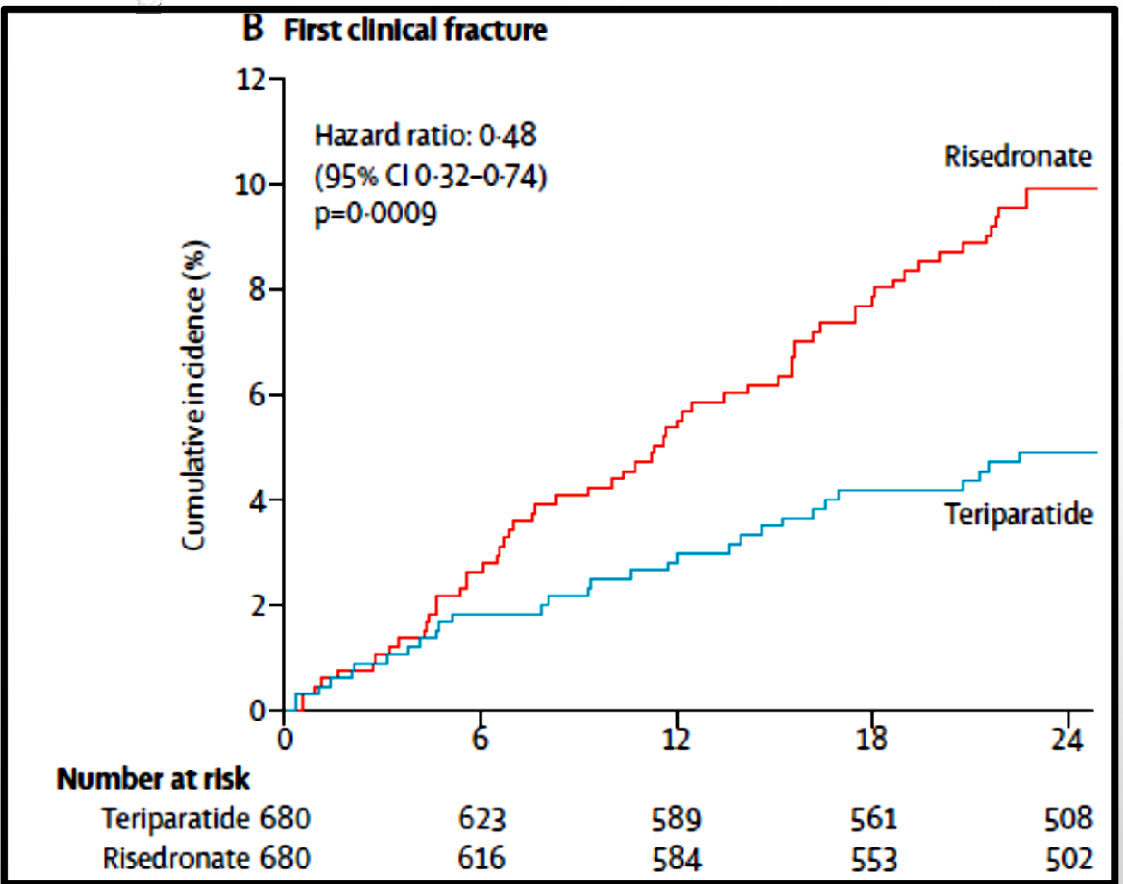


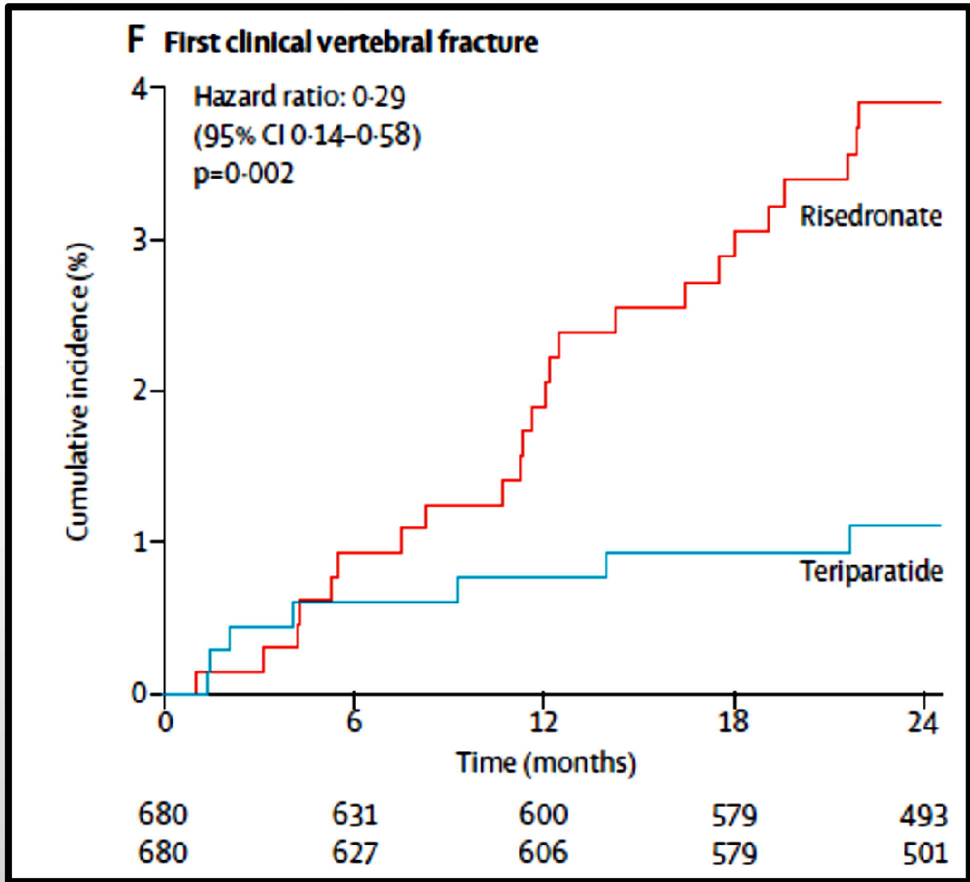
- Hypothèse 5% FV T et 10% R
- 30% perdus de vue
- 90% puissance
- N = 466 dans chaque groupe et 670 inclus

	Teriparatide group (n=680)	Risedronate group (n=680)
Age (years)		
<50	7 (1%)	2 (<1%)
50 to <65	144 (21%)	162 (24%)
65 to <80	382 (56%)	405 (60%)
≥80	147 (22%)	111 (16%)
Mean (SD)	72·6 (8·77)	71·6 (8·58)
Race		
White	670 (99%)	653 (96%)
Black or African American	5 (1%)	15 (2%)
Asian	4 (1%)	8 (1%)
Other	1 (<1%)	4 (1%)
Mean height (cm; SD)	154·7 (7·2)	155·0 (7·4)
Mean body mass index (kg/m²; SD)	26·9 (4·61)	27·1 (4·64)
Geographical region*		
North America	91 (13%)	100 (15%)
South America	142 (21%)	159 (23%)
Europe	447 (66%)	421 (62%)
Mean bone mineral density (SD)		
Lumbar spine (g/cm²)	0·86 (0·15)	0·86 (0·15)
T score†	−2·27 (1·24)	−2·29 (1·22)
Femoral neck (g/cm²)	0·66 (0·11)	0·67 (0·11)
T score†	−2·27 (0·76)	−2·24 (0·74)
Total hip (g/cm²)	0·74 (0·11)	0·74 (0·12)
T score†	−1·95 (0·87)	−1·95 (0·82)
Prevalent fractures		
Vertebral fractures‡		
≥1	679 (100%)	679 (100%)
1	231 (34%)	240 (35%)
2	178 (26%)	174 (26%)
3	104 (15%)	101 (15%)
4	60 (9%)	62 (9%)
≥5	106 (16%)	102 (15%)
Grade of the most severe vertebral fracture§		
SQ2	73 (11%)	67 (10%)
SQ3	606 (89%)	612 (90%)
Non-vertebral fractures		
Patients older than 40 years with ≥1 fracture	298 (44%)	284 (42%)
1	166 (24%)	164 (24%)
2	80 (12%)	81 (12%)
3	40 (6%)	21 (3%)
4	6 (1%)	11 (2%)
≥5	6 (1%)	7 (1%)

	Teriparatide group (n=680)	Risedronate group (n=680)
(Continued from previous column)		
Previous osteoporosis medication use		
Patients with ≥1 previous osteoporosis therapy¶	496 (73%)	485 (71%)
Antiresorptives	418 (61%)	410 (60%)
Bisphosphonates	402 (59%)	386 (57%)
Calcium or vitamin D only	64 (9%)	69 (10%)
Selective oestrogen receptor modulators	21 (3%)	26 (4%)
Hormone or oestrogen replacement therapy	9 (1%)	3 (<1%)
Other osteoporosis therapy‖	78 (11%)	80 (12%)
Median duration of previous osteoporosis therapy (years; IQR)	3·2 (1·0–6·8)	3·3 (1·0–6·3)
Any antiresorptive	3·8 (1·2–7·0)	3·7 (1·2–6·3)
Bisphosphonates	3·6 (1·1–7·0)	3·6 (1·3–6·1)
Calcium or vitamin D only	0·3 (0·1–3·1)	0·3 (0·1–2·2)
Selective oestrogen receptor modulators	4·2 (1·2–6·2)	2·5 (1·0–7·4)
Hormone or oestrogen replacement therapy	3·2 (2·8–4·0)	14·9 (7·0–22·7)
Other osteoporosis therapy‖	1·0 (0·5–2·1)	0·7 (0·1–2·3)
Median duration of previous osteoporosis therapy in recent bisphosphonate users (years; IQR)**		
Bisphosphonates (oral)	3·7 (1·8–6·7)	3·9 (2·0–5·9)
Zoledronic acid (intravenous)	1·1 (0·0–3·0)	2·0 (1·0–2·2)
Ibandronate–pamidronate (intravenous)	0·5 (0·0–2·2)	3·6 (2·9–4·2)
Patients taking glucocorticoid therapy††	71 (10%)	56 (8%)
Mean 25-hydroxy-vitamin D concentration (nmol/L, SD)	79·7 (65·8)	78·5 (47·7)

	Teriparatide group	Risedronate group	Effect size (95% CI)*	p value
Primary endpoint				
New vertebral fracture†	28 (5%)	64 (12%)	0·44 (0·29–0·68)	<0·0001
Secondary gated endpoints				
New and worsened vertebral fracture†	31 (6%)	69 (13%)	0·46 (0·31–0·68)	<0·0001
Pooled clinical fracture‡§	30 (5%)	61 (10%)	0·48 (0·32–0·74)	0·0009
Non-vertebral fragility fracture§	25 (4%)	38 (6%)	0·66 (0·39–1·10)	0·10
Major non-vertebral fragility fracture§	18 (3%)	31 (5%)	0·58 (0·32–1·05)	0·06
Secondary non-gated endpoints				
New moderate (SQ2) or severe (SQ3) vertebral fracture†	26 (5%)	63 (12%)	0·42 (0·27–0·65)	<0·001
New multiple vertebral fracture†	2 (<1%)	12 (2%)	0·16 (0·04–0·74)	0·007
Pooled fragility and traumatic non-vertebral fracture§	40 (7%)	57 (9%)	0·70 (0·46–1·05)	0·08


B First clinical fracture
Hazard ratio: 0·48
(95% CI 0·32–0·74)
p=0·0009
Risedronate
Teriparatide
Cumulative incidence (%)
0
2
4
6
8
10
12
0
6
12
18
24
Number at risk
Teriparatide 680 623 589 561 508
Risedronate 680 616 584 553 502


F First clinical vertebral fracture
Hazard ratio: 0·29
(95% CI 0·14–0·58)
p=0·002
Risedronate
Teriparatide
Cumulative incidence (%)
0
1
2
3
4
0
6
12
18
24
Time (months)
680 631 600 579 493
680 627 606 579 501

Effets indésirables

	Teriparatide group (n=680)	Risedronate group (n=680)	p value
≥1 adverse event	495 (72·8%)	500 (73·5%)	0·76
Serious	137 (20·1%)	115 (16·9%)	0·13
Related to study drug	87 (12·8%)	66 (9·7%)	0·07
Related to study procedure	4 (0·6%)	4 (0·6%)	1·000
Leading to treatment discontinuation	67 (9·9%)	48 (7·1%)	0·06
Leading to death*	15 (2·2%)	7 (1·0%)	0·13
Adverse events†			
Back pain	76 (11·2%)	83 (12·2%)	0·61
Fall	46 (6·8%)	49 (7·2%)	0·83
Arthralgia	44 (6·5%)	51 (7·5%)	0·52
Pain in hands or feet	37 (5·4%)	18 (2·6%)	0·013
Nausea	31 (4·6%)	26 (3·8%)	0·59
Nasopharyngitis	31 (4·6%)	33 (4·9%)	0·90
Dizziness	30 (4·4%)	12 (1·8%)	0·007
Osteoarthritis	29 (4·3%)	21 (3·1%)	0·31
Bronchitis	27 (4·0%)	29 (4·3%)	0·89
Hypertension	23 (3·4%)	29 (4·3%)	0·48
Hypercalcaemia	15 (2·2%)	1 (0·1%)	<0·001
Pain	10 (1·5%)	2 (0·3%)	0·038
Vitamin D concentration decreased	9 (1·3%)	1 (0·1%)	0·021
Dental caries	6 (0·9%)	0	0·031
Bone contusion	0	6 (0·9%)	0·031

Conclusion

- 1er RCT tériparatide vs bisphosphonate avec objectif principal la survenue d'une fracture vertébrale
- Diminution du risque de nouvelle fracture vertébrale de -56%
- Rapidement sur les fractures cliniques

- Quid si acide zolédronique ou denosumab comme comparateur?

ORIGINAL ARTICLE

JBMR®

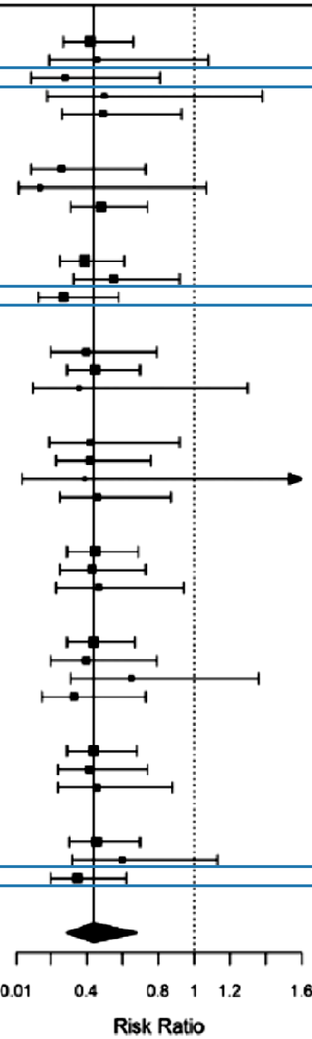
Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups of Postmenopausal Women with Severe Osteoporosis: The VERO Trial

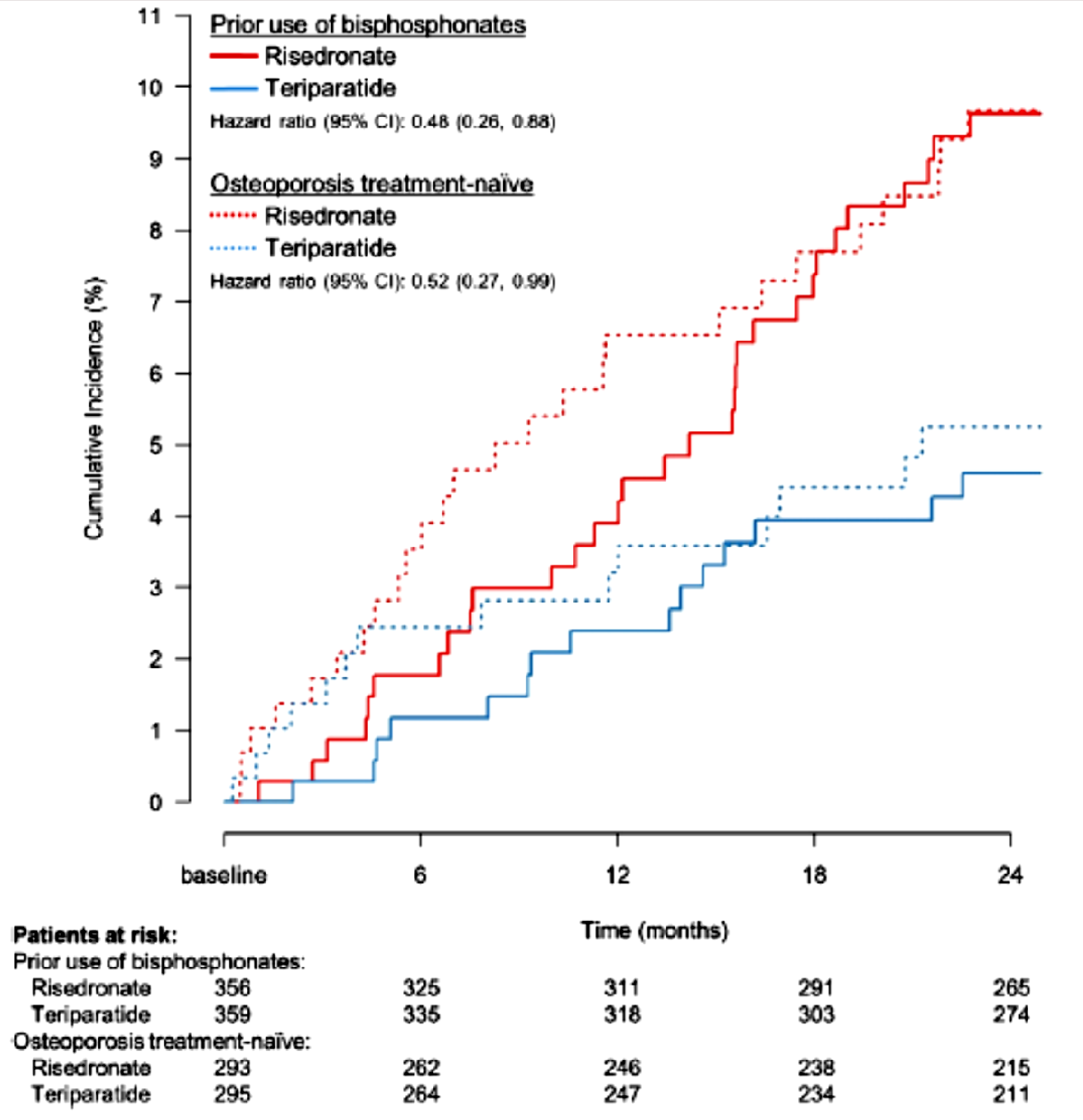
Piet Geusens,[1] Fernando Marin,[2] David L Kendler,[3] Luis A Russo,[4] Cristiano AF Zerbini,[5] Salvatore Minisola,[6] Jean Jacques Body,[7] Eric Lespessailles,[8] Susan L Greenspan,[9] Alicia Bagur,[10] Jan J Stepan,[11] Péter Lakatos,[12] Enrique Casado,[13] Rüdiger Moericke,[14] Pedro López-Romero,[2] and Astrid Fahrleitner-Pammer[15]

Journal of Bone and Mineral Research, Vol. 33, No. 5, May 2018, pp 783–794

Fractures vertébrales

Subgroup	Teriparatide n/N (%)	Risedronate n/N (%)	Interaction p value	Risk Ratio [95% CI]
Prevalent VFx (number)				
Overall			0.81	0.42 [0.27, 0.66]
1	7/180 (3.9)	16/191 (8.4)		0.46 [0.19, 1.08]
2	4/132 (3.0)	14/135 (10.4)		0.28 [0.09, 0.81]
3	5/86 (5.8)	10/82 (12.2)		0.50 [0.18, 1.38]
>3	12/118 (10.2)	24/125 (19.2)		0.49 [0.26, 0.93]
Prevalent VFx (severity)				
Overall			0.18	0.26 [0.09, 0.73]
SQ2	1/59 (1.7)	7/57 (12.3)		0.14 [0.02, 1.07]
SQ3	27/457 (5.9)	57/476 (12.0)		0.48 [0.31, 0.74]
Prior nonvertebral fracture*				
Overall			0.13	0.39 [0.25, 0.61]
no	20/355 (5.6)	38/385 (9.9)		0.55 [0.33, 0.92]
yes	8/161 (5.0)	26/148 (17.6)		0.27 [0.13, 0.58]
Glucocorticoid use				
Overall			0.76	0.40 [0.20, 0.79]
no	25/466 (5.4)	57/491 (11.6)		0.45 [0.29, 0.70]
yes	3/50 (6.0)	7/42 (16.7)		0.36 [0.10, 1.30]
Prior osteoporosis drugs**				
Overall			0.97	0.42 [0.19, 0.92]
BP	14/280 (5.0)	34/281 (12.1)		0.42 [0.23, 0.76]
non-BP	1/23 (4.3)	3/25 (12.0)		0.39 [0.04, 3.45]
treatment-naive	13/213 (6.1)	27/227 (11.9)		0.46 [0.25, 0.87]
Lowest BMD T-score				
Overall			0.86	0.45 [0.29, 0.69]
< -2.5	17/270 (6.3)	42/297 (14.1)		0.43 [0.25, 0.73]
≥ -2.5	11/246 (4.5)	22/236 (9.3)		0.47 [0.23, 0.94]
Age (tertiles), years				
Overall			0.44	0.44 [0.29, 0.67]
<68.7	10/184 (5.4)	28/202 (13.9)		0.40 [0.20, 0.79]
≥ 68.7 and < 76.8	10/152 (6.6)	18/192 (9.4)		0.65 [0.31, 1.36]
≥ 76.8	8/180 (4.4)	18/139 (12.9)		0.33 [0.15, 0.73]
Recent bisphosphonate use				
Overall			0.85	0.44 [0.29, 0.68]
no	16/309 (5.2)	39/324 (12.0)		0.42 [0.24, 0.74]
yes	12/207 (5.8)	25/209 (12.0)		0.46 [0.24, 0.88]
Recent clinical VFx				
Overall			0.22	0.46 [0.30, 0.70]
no	14/319 (4.4)	25/341 (7.3)		0.60 [0.32, 1.13]
yes	14/197 (7.1)	39/192 (20.3)		0.35 [0.20, 0.62]
Overall VERO population	**28/516 (5.4)**	**64/533 (12.0)**		**0.44 [0.29, 0.68]**



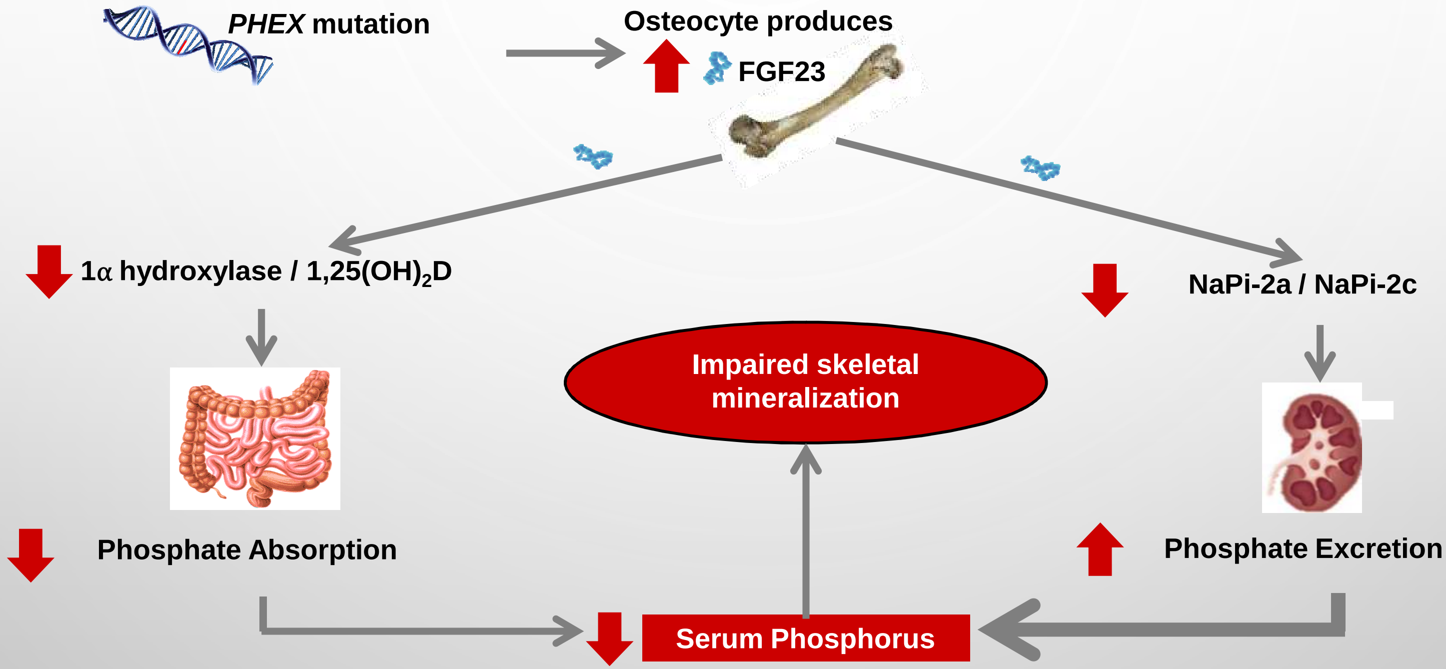

Prior use of bisphosphonates
Risedronate
Teriparatide
Hazard ratio (95% CI): 0.48 (0.26, 0.88)
Osteoporosis treatment-naïve
Risedronate
Teriparatide
Hazard ratio (95% CI): 0.52 (0.27, 0.99)
Cumulative Incidence (%)
0
1
2
3
4
5
6
7
8
9
10
11
baseline
6
12
18
24
Time (months)
Patients at risk:
Prior use of bisphosphonates:
Risedronate 356 325 311 291 265
Teriparatide 359 335 318 303 274
Osteoporosis treatment-naïve:
Risedronate 293 262 246 238 215
Teriparatide 295 264 247 234 211

XLH: hypophosphatémie liée à l’X

1- Ostéomalacie « oncogénique » → tumeur productrice
2- XLH → mutation inhibitrice PHEX
3- ADHR → mutation activatrice FGF 23
4- Dysplasie fibreuse

↑FGF 23

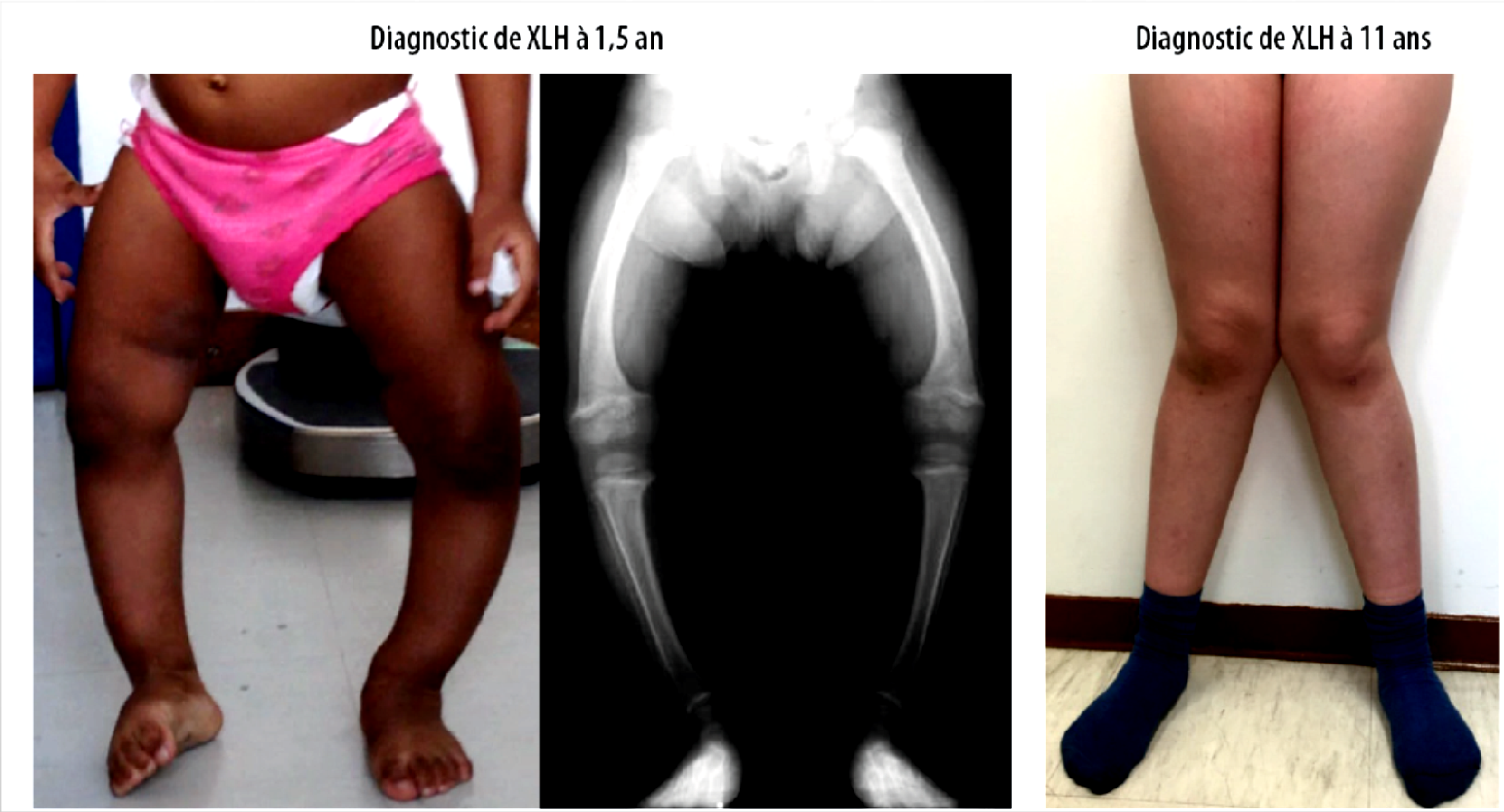
Physiopathologie de l’excès de FGF23



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.

Hypophosphatémie liée à l’X

- Transmission dominante liée à l’X
- 1-9/1000000
- **Mutation inactivatrice du gène PHEX**
- **Clinique enfant**
  - Rechercher une histoire familiale +++
  - Début dans l’enfance avec une déformation progressive des membres inférieurs
  - Ralentissement de la croissance
  - Craniosténose
  - Douleurs osseuses et/ou articulaires
  - Anomalies dentaires: abcès, anomalies de l’émail, élargissement chambre pulpaire, taurodontisme
- **Clinique adulte**
  - Déformations des membres inférieurs
  - Douleurs articulaires ou osseuses (fissures, ostéomalacie…)
  - Enthésopathies calcifiées
  - Caries



Linglart A. 2017

Collection P Guggenbuhl

G Liang 2009

Hypophosphatémie liée à l’X (XLH)

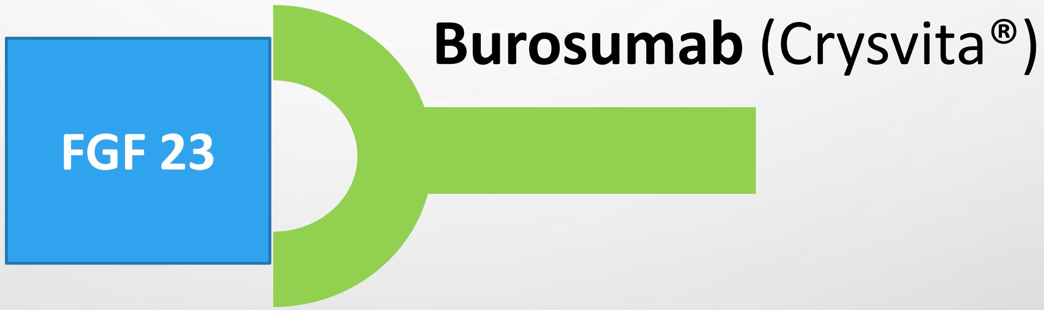
- **Examens**
  - ↓ P (attentions aux normes chez l’enfant)
  - Ca normal
  - Fuite phosphatée urinaire
  - PTH normale
  - 1-25 0H vitamine D anormalement basse ou normale +++

	< 2 ans	4-10 ans	10-18 ans	adulte
Calcémie (mmol/l)	2,25 - 2,65	2,25 - 2,55	2,25 - 2,55	2,25 - 2,55
Calcémie ionisée (mmol/l)	1,15 -1,40	1,2 - 1,35	1,15 - 1,3	1,15 -1,3
Phosphatémie (mmol/l)	1,3 - 2,2	1,2 - 1,7	1,1 - 1,8	0,8 -1,5
PTH (pg/ml) *	10 - 60	10 - 60	10 - 60	10 - 60
25-(OH)D (ng/ml)	15 - 40	15 - 40	15 - 40	15 - 40
Calciurie/créatininurie (mmol/mmol)	1,58 - 2,29	0,71 - 1,16	< 0,68	< 0,40

- **Autres atteintes**
  - Dents
  - Audition
- **Traitement conventionnel**
  - Phosphoneuros et Calcitriol
  - Corrige les déformations des MI chez l’enfant si bien pris!
  - A continuer à l’âge adulte
  - Chirurgie
- **Ac anti-FGF23: Burosumab**

Linglart A. 2017

XLH: hypophosphatémie liée à l’X

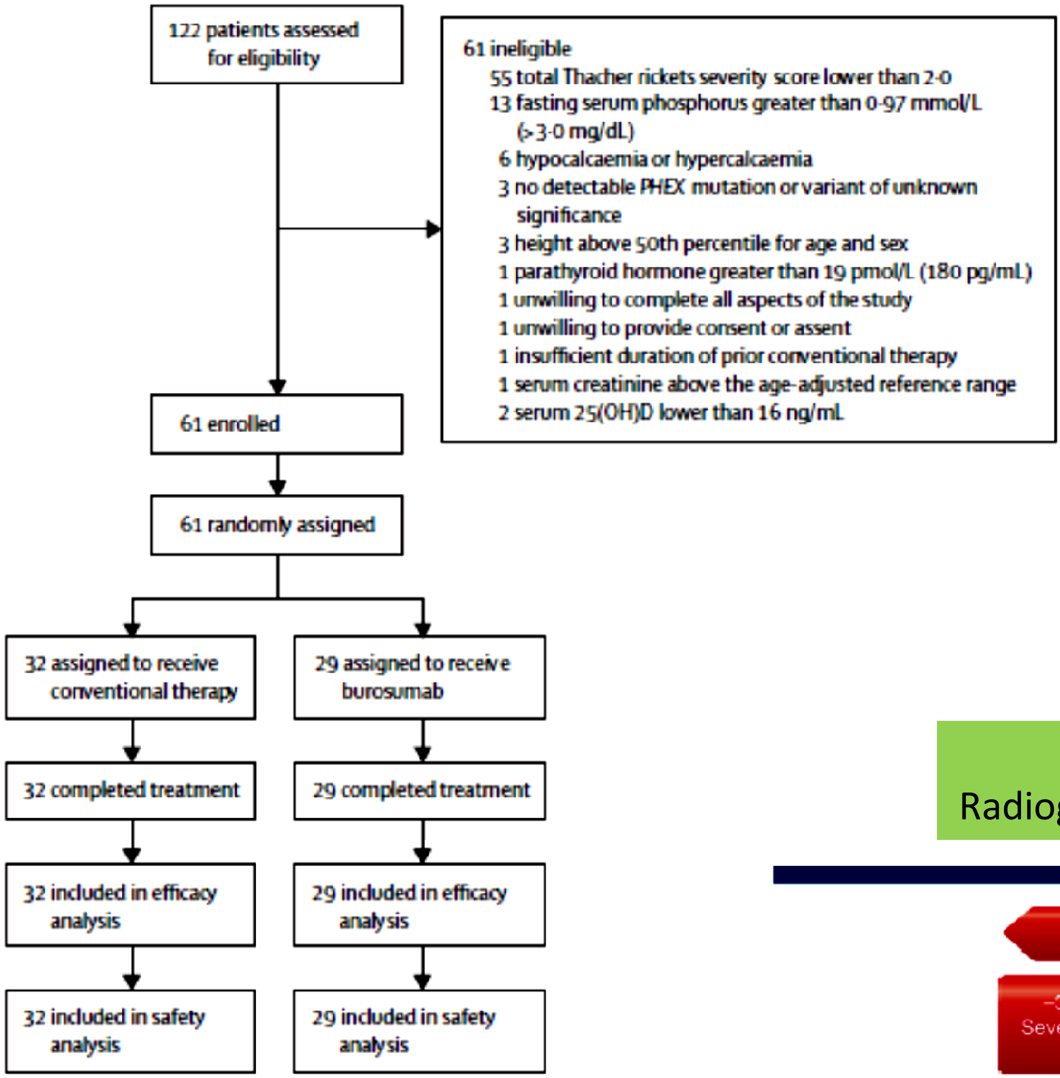


Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial

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

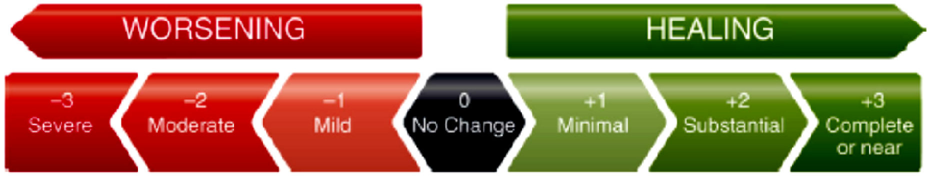
Lancet 2019; 393: 2416–27

Etude de phase 3, ouverte, randomisée, avec un contrôle actif



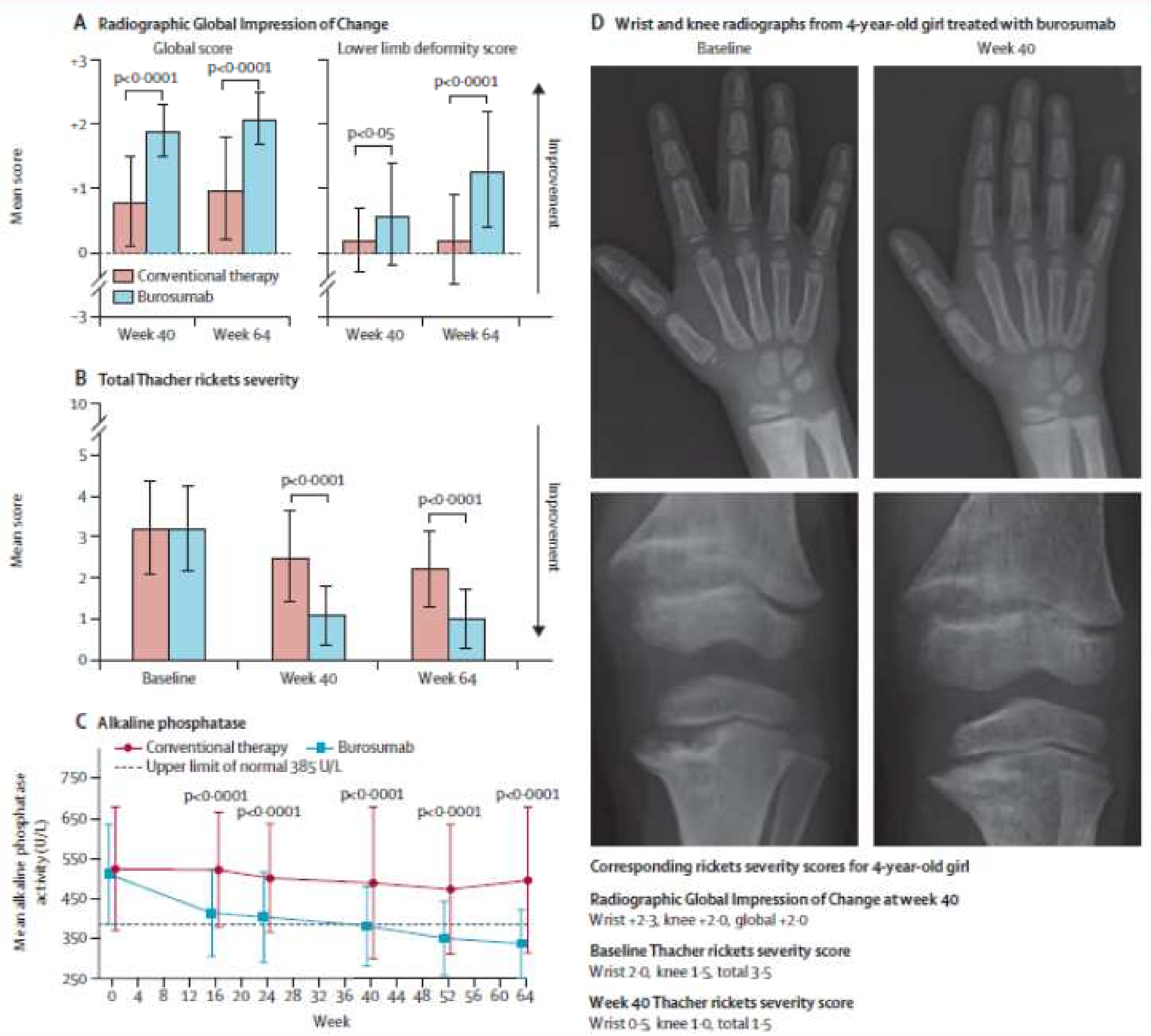
- Wash out de 7j
- **Groupe conventionnel**
  - P
  - Vitamine D active
- **Groupe Burosumab**
  - 1 sc tous les 14j avec ajustement des doses

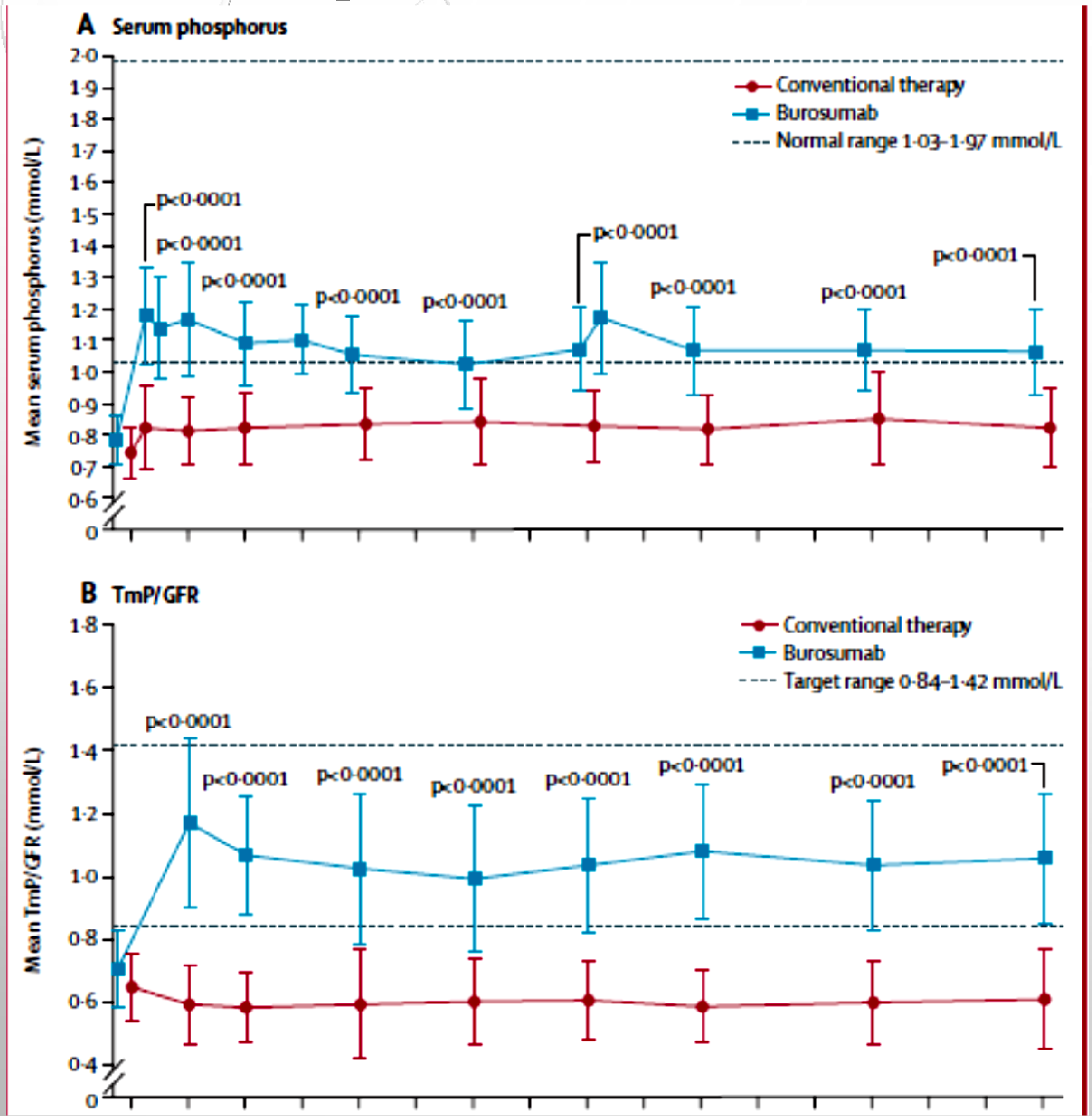
Critère principal à 40 semaines
Radiographic Global Impression of Change Global score

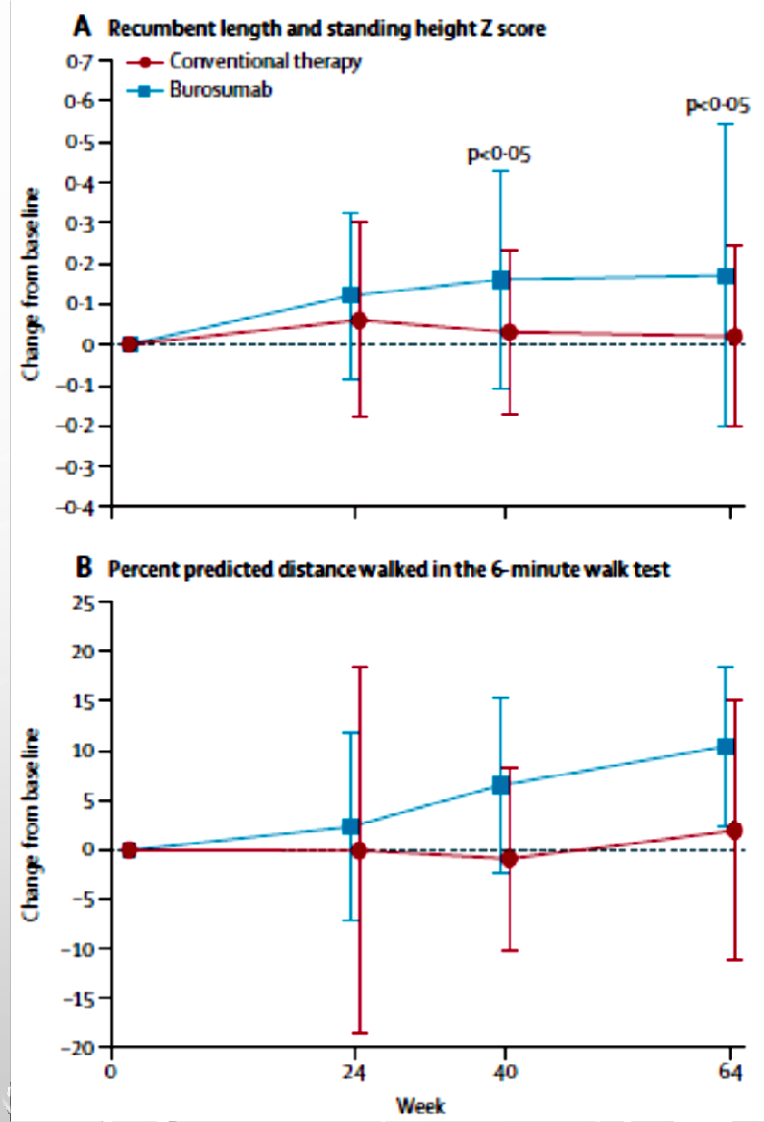


	Conventional therapy (n=32)	Burosumab (n=29)
Mean age (years)	6·3 (3·2)	5·8 (3·4)
Patients younger than 5 years	12 (38%)	14 (48%)
Girls	18 (56%)	16 (55%)
Boys	14 (44%)	13 (45%)
Ethnic origin		
White	25 (78·1%)	25 (86·2%)
Asian	6 (18·8%)	2 (6·9%)
Other	1 (3·1%)	2 (6·9%)
Geographical region		
Japan	3 (9%)	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)
Weight Z score		
Mean	−0·6 (0·9)	−0·9 (1·2)
Median	−0·7 (−1·17 to 0·05)	−0·8 (−1·75 to 0·59)
Tanner Stage		
1	31 (97%)	27 (93%)
2	1 (3%)	2 (7%)
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)$_2$D 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%)

	< 2 ans	4-10 ans	10-18 ans	adulte
Calcémie (mmol/l)	2,25 - 2,65	2,25 - 2,55	2,25 - 2,55	2,25 - 2,55
Calcémie ionisée (mmol/l)	1,15 -1,40	1,2 - 1,35	1,15 - 1,3	1,15 -1,3
Phosphatémie (mmol/l)	1,3 - 2,2	1,2 - 1,7	1,1 - 1,8	0,8 -1,5


A Radiographic Global Impression of Change
Global score
Lower limb deformity score
Mean score
p<0·0001
p<0·05
Conventional therapy
Burosumab
Week 40
Week 64
Improvement
B Total Thacher rickets severity
Mean score
Baseline
Week 40
Week 64
p<0·0001
Improvement
C Alkaline phosphatase
Conventional therapy
Burosumab
Upper limit of normal 385 U/L
Mean alkaline phosphatase activity (U/L)
p<0·0001
Week
D Wrist and knee radiographs from 4-year-old girl treated with burosumab
Baseline
Week 40
Corresponding rickets severity scores for 4-year-old girl
Radiographic Global Impression of Change at week 40
Wrist +2·3, knee +2·0, global +2·0
Baseline Thacher rickets severity score
Wrist 2·0, knee 1·5, total 3·5
Week 40 Thacher rickets severity score
Wrist 0·5, knee 1·0, total 1·5


A Serum phosphorus
Conventional therapy
Burosumab
Normal range 1·03–1·97 mmol/L
Mean serum phosphorus (mmol/L)
p<0·0001
B TmP/GFR
Conventional therapy
Burosumab
Target range 0·84–1·42 mmol/L
Mean TmP/GFR (mmol/L)
p<0·0001


A Recumbent length and standing height Z score
Conventional therapy
Burosumab
Change from base line
p<0·05
B Percent predicted distance walked in the 6-minute walk test
Change from base line
Week

CLINICAL TRIAL

JBMR®

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

Karl L Insogna,[1] Karine Briot,[2] Erik A Imel,[3] Peter Kamenický,[4] Mary D Ruppe,[5*] Anthony A Portale,[6] Thomas Weber,[7] Pisit Pitukcheewanont,[8] Hae Il Cheong,[9] Suzanne Jan de Beur,[10] Yasuo Imanishi,[11] Nobuaki Ito,[12] Robin H Lachmann,[13] Hiroyuki Tanaka,[14] Farzana Perwad,[6] Lin Zhang,[15] Chao-Yin Chen,[15] Christina Theodore-Oklota,[15] Matt Mealiffe,[15] Javier San Martin,[15] and Thomas O Carpenter[1] on behalf of the AXLES 1 Investigators

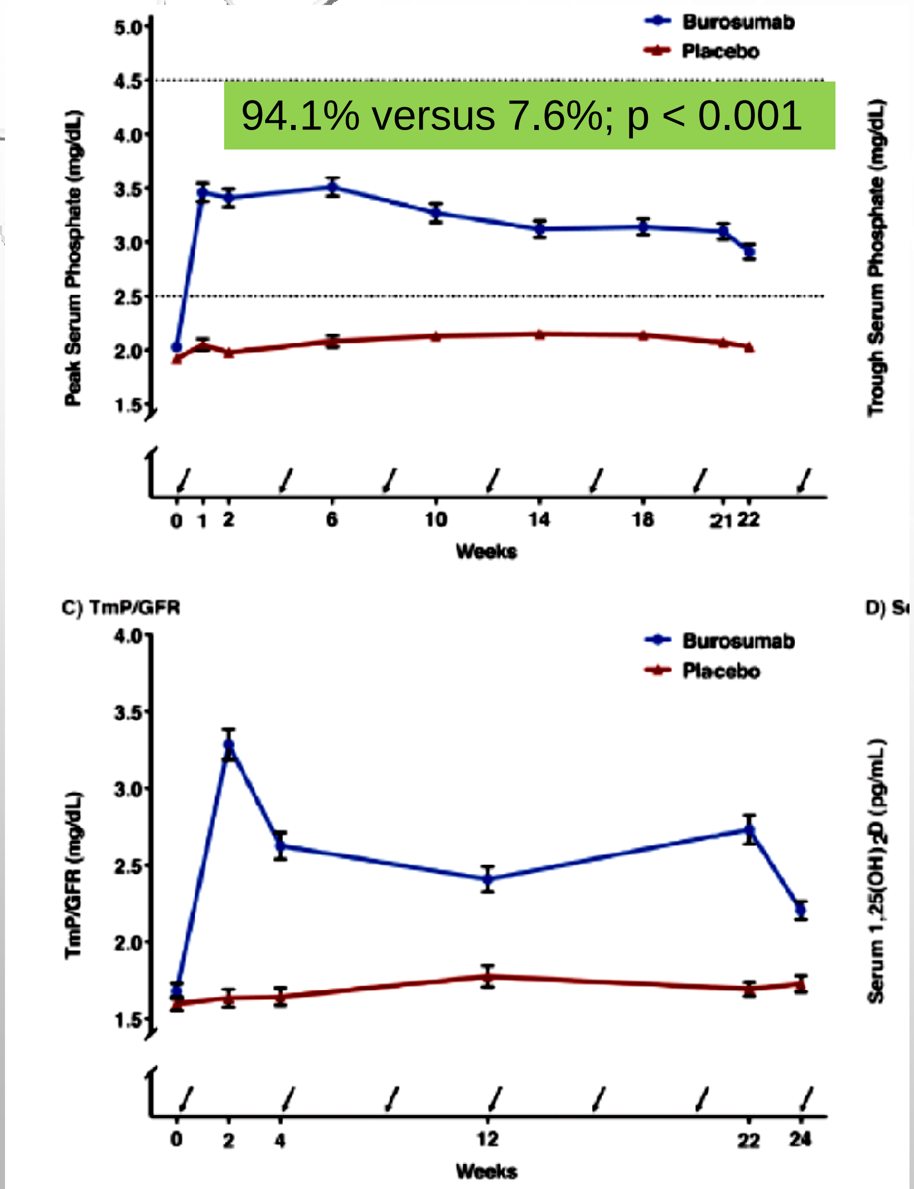
Journal of Bone and Mineral Research, Vol. 33, No. 8, August 2018, pp 1383–1393

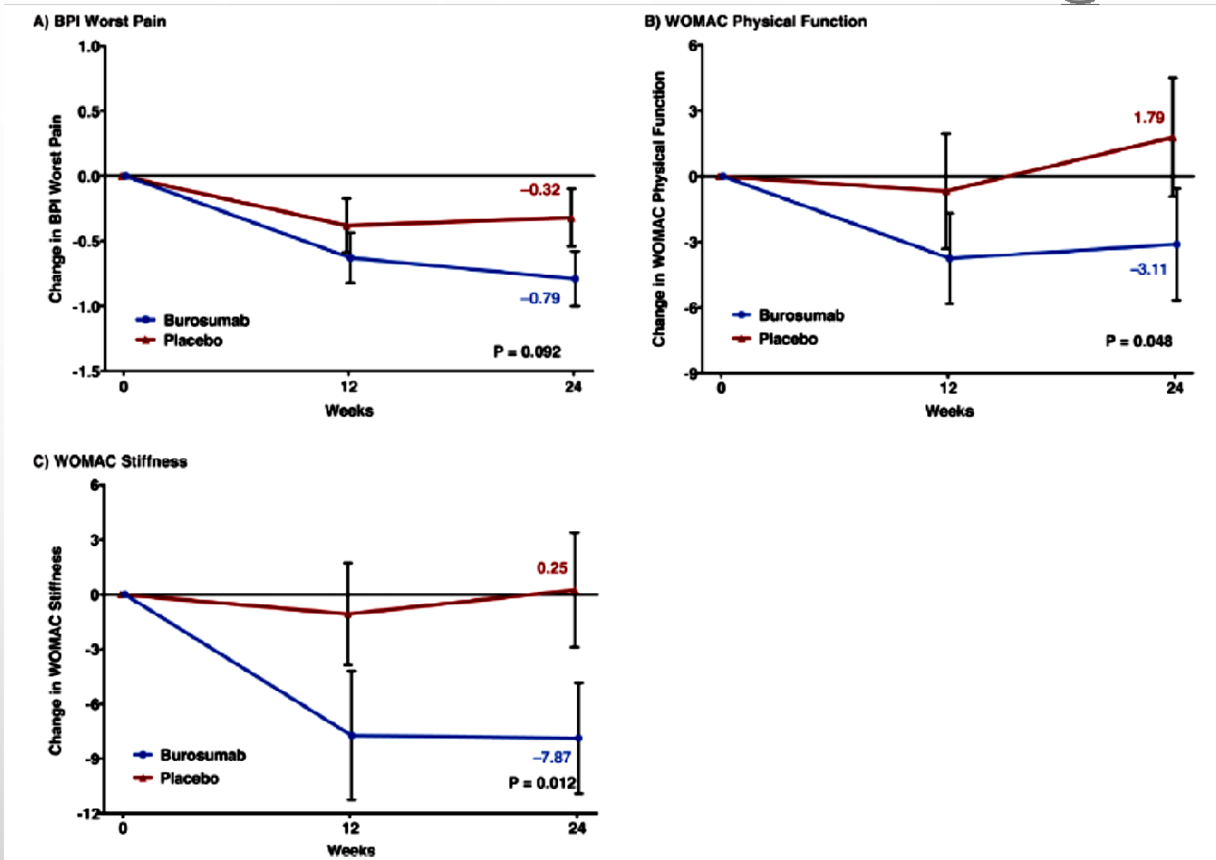
RCT, double aveugle contre placebo

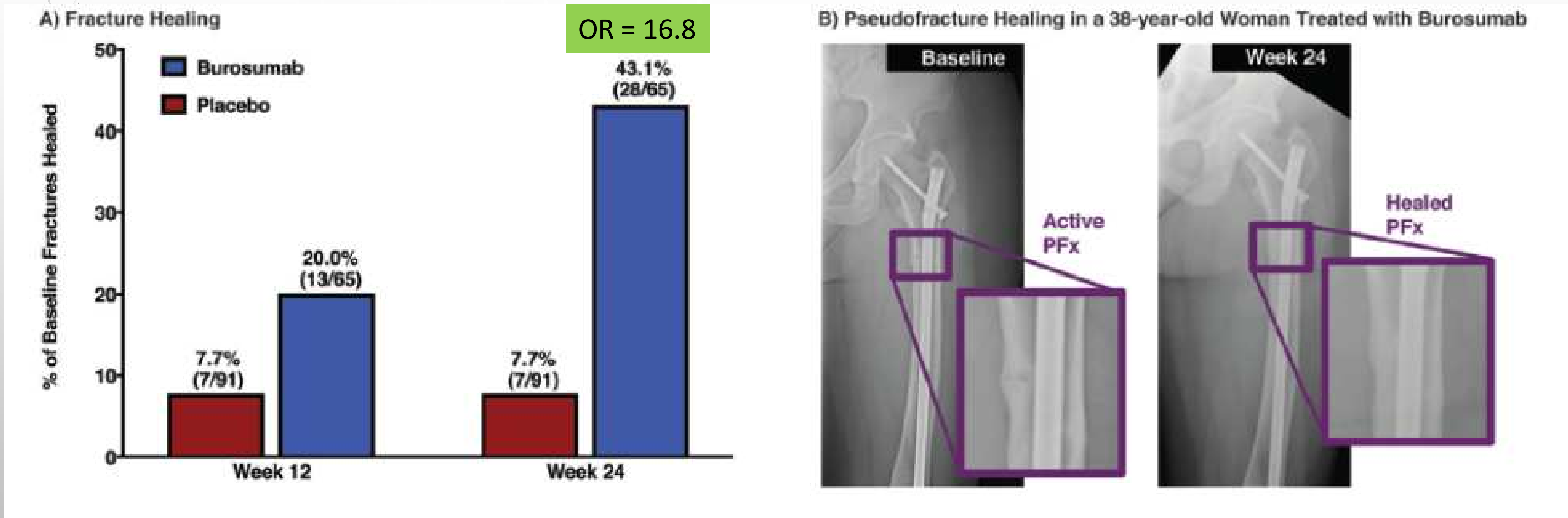
Objectif principal: phosphatémie

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

	Placebo	Burosumab
Serum phosphate (mg/dL),[c] mean ± SD	1.9 ± 0.32	2.0 ± 0.30
TmP/GFR (mg/dL),[c] mean ± SD	1.6 ± 0.37	1.7 ± 0.40
Serum $1,25(OH)_2D$ (pg/mL),[c] mean ± SD	33.5 ± 15.6	32.4 ± 13.0
Serum calcium (mg/dL),[c] mean ± SD	9.1 ± 0.41	9.2 ± 0.49
Serum iPTH (pg/mL),[c] mean ± SD	95.2 ± 38.8	98.9 ± 60.8
Conventional therapy ever, *n* (%)		
Phosphate + vitamin D metabolites or analogs	62 (93.9)	59 (86.8)
Phosphate alone	1 (1.5)	3 (4.4)
Vitamin D metabolites or analogs alone	3 (4.5)	3 (4.4)
Conventional therapy before age 18 years, *n* (%)		
Phosphate + vitamin D metabolites or analogs	48 (72.7)	45 (66.2)
Phosphate alone	2 (3.0)	5 (7.4)
Vitamin D metabolites or analogs alone	4 (6.1)	5 (7.4)
Conventional therapy duration (years), mean ± SD		
Phosphate[d]	16.2 ± 10.2	16.8 ± 10.7
Vitamin D metabolites or analogs[e]	17.5 ± 11.9	19.0 ± 10.0
BPI worst pain >6.0, *n* (%)	43 (65.2)	53 (77.9)
Any pain medication at baseline, *n* (%)	44 (66.7)	47 (69.1)
Any opioid at baseline, *n* (%)	13 (19.7)	17 (25.0)
Enthesopathy on X-ray, *n* (%)	65 (98.5)	68 (100.0)
Nephrocalcinosis score >0,[f] *n* (%)	39 (59.1)	34 (50.0)
Medical history, *n* (%)		
Orthopedic surgery	47 (71.2)	45 (66.2)
Osteoarthritis	38 (57.6)	47 (69.1)


94.1% versus 7.6%; p < 0.001
Burosumab
Placebo
Peak Serum Phosphate (mg/dL)
Trough Serum Phosphate (mg/dL)
Weeks
C) TmP/GFR
TmP/GFR (mg/dL)
D) S
Serum 1,25(OH)2D (pg/mL)


A) BPI Worst Pain
Change in BPI Worst Pain
–0.32
–0.79
P = 0.092
B) WOMAC Physical Function
Change in WOMAC Physical Function
1.79
–3.11
P = 0.048
C) WOMAC Stiffness
Change in WOMAC Stiffness
0.25
–7.87
P = 0.012
Burosumab
Placebo
Weeks



A) Fracture Healing
OR = 16.8
Burosumab
Placebo
% of Baseline Fractures Healed
0
10
20
30
40
50
7.7%
(7/91)
20.0%
(13/65)
7.7%
(7/91)
43.1%
(28/65)
Week 12
Week 24
B) Pseudofracture Healing in a 38-year-old Woman Treated with Burosumab
Baseline
Week 24
Active
PFx
Healed
PFx

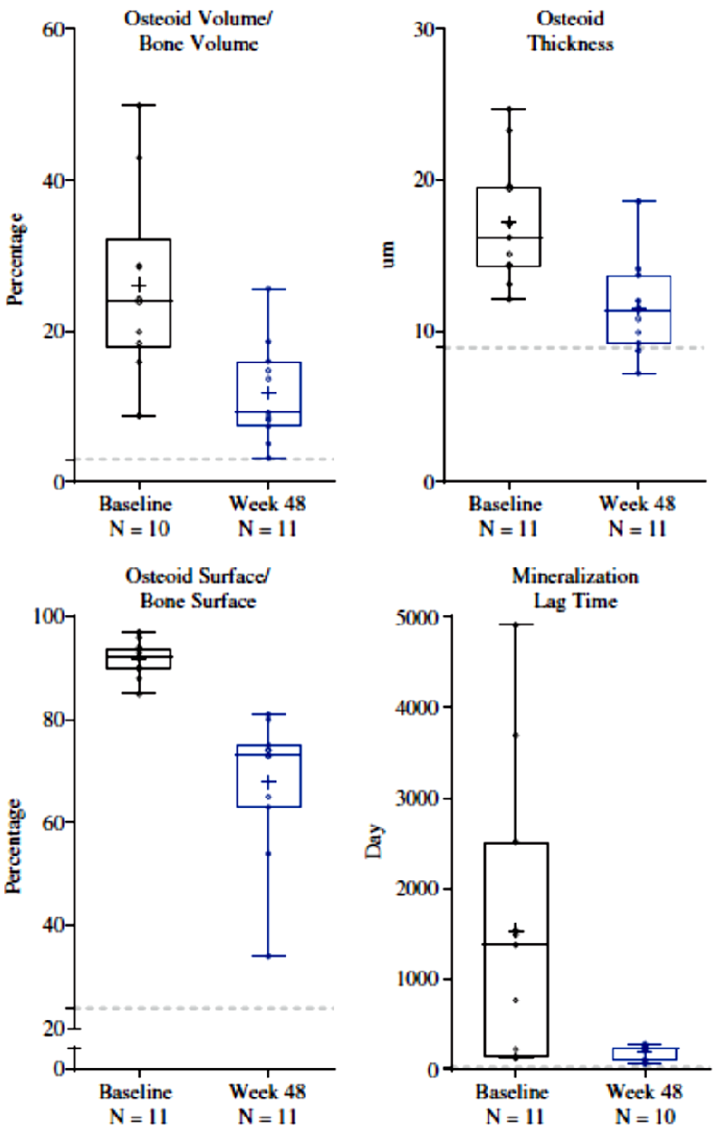
CLINICAL TRIAL

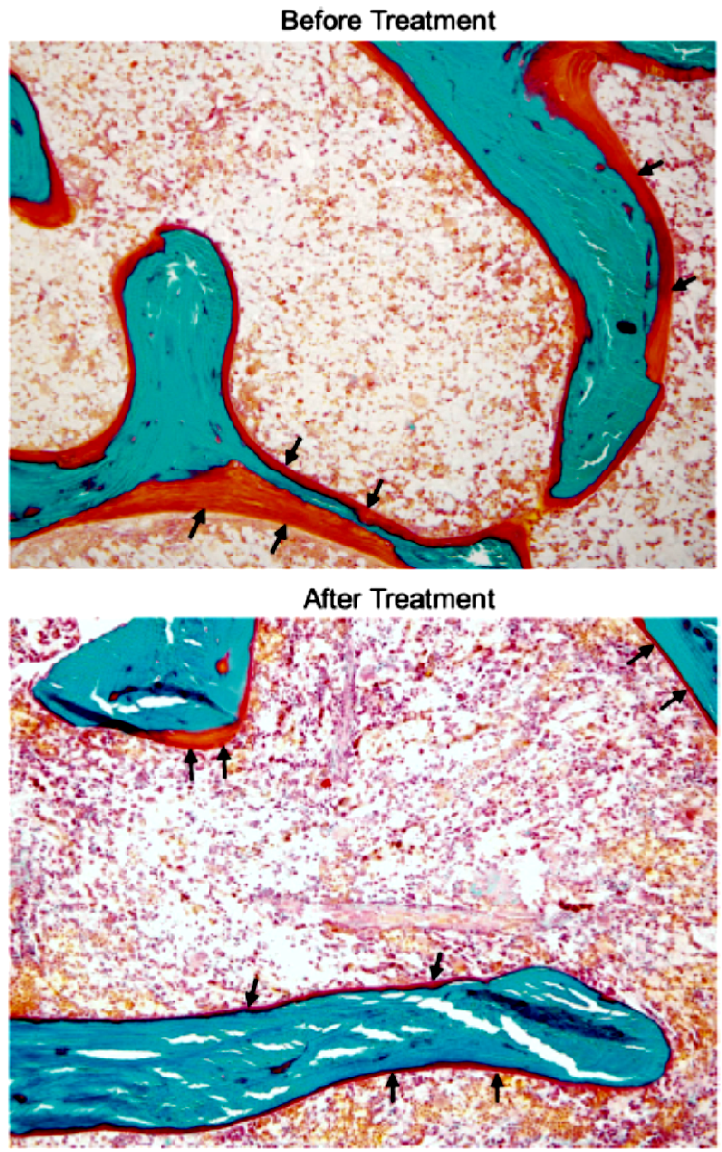
JBMR®

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. 00, No. 00, Month 2019, pp 1–9.


Osteoid Volume/
Bone Volume
Percentage
Baseline
N = 10
Week 48
N = 11
Osteoid
Thickness
um
Baseline
N = 11
Week 48
N = 11
Osteoid Surface/
Bone Surface
Percentage
Baseline
N = 11
Week 48
N = 11
Mineralization
Lag Time
Day
Baseline
N = 11
Week 48
N = 10

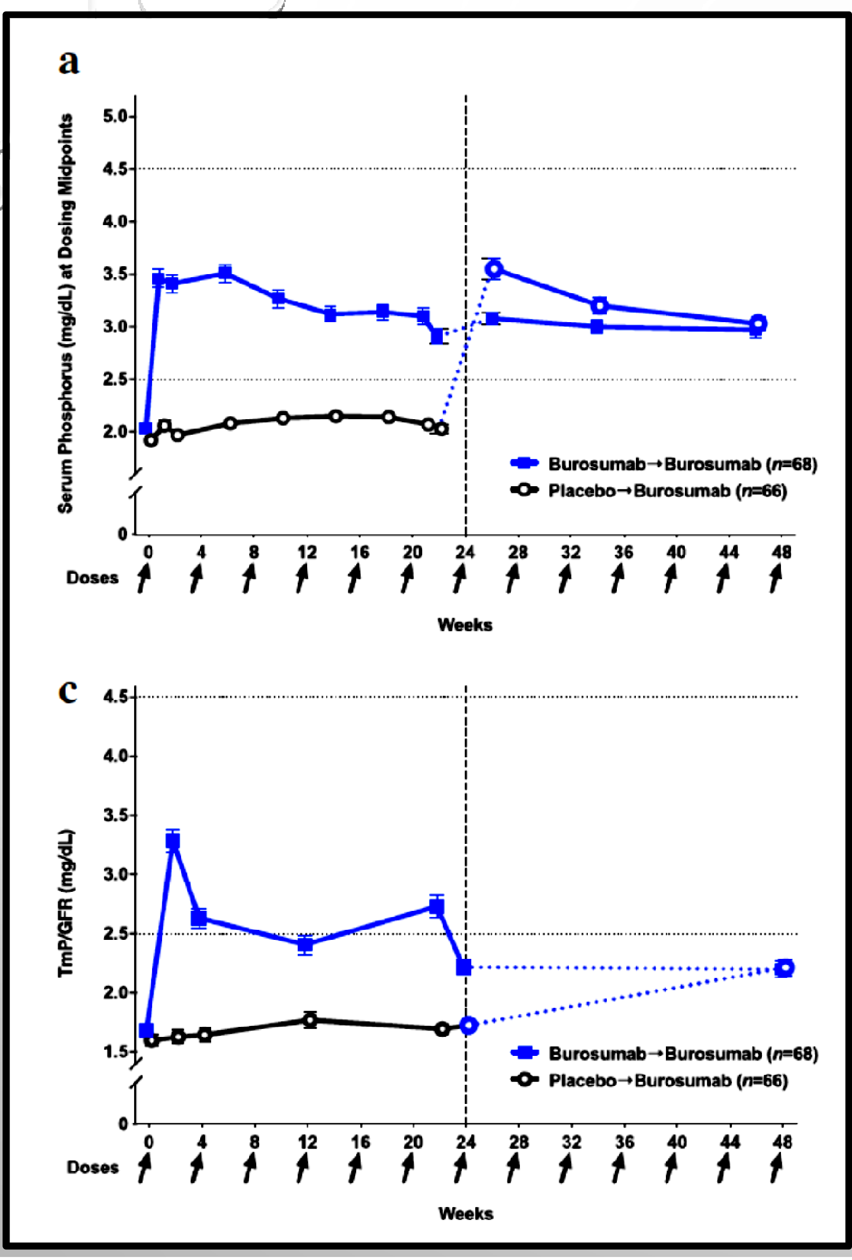

Before Treatment
After Treatment

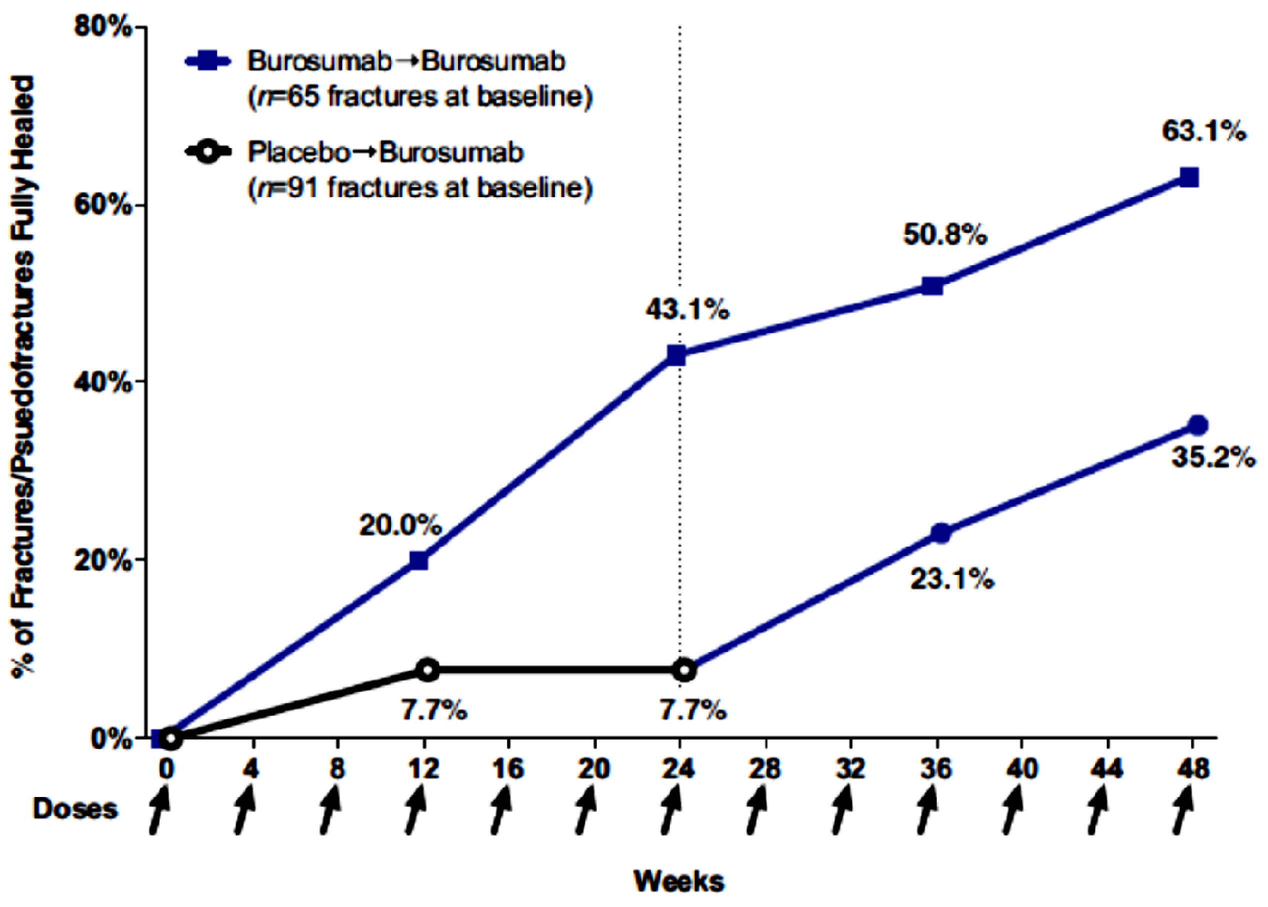
Calcified Tissue International (2019) 105:271–284
https://doi.org/10.1007/s00223-019-00568-3

ORIGINAL RESEARCH

Continued Beneficial Effects of Burosumab in Adults with X-Linked Hypophosphatemia: Results from a 24-Week Treatment Continuation Period After a 24-Week Double-Blind Placebo-Controlled Period

Anthony A. Portale[1] · Thomas O. Carpenter[2] · Maria Luisa Brandi[3] · Karine Briot[4] · Hae Il Cheong[5] · Martine Cohen-Solal[6] · Rachel Crowley[7] · Suzanne Jan De Beur[8] · Richard Eastell[9] · Yasuo Imanishi[10] · Erik A. Imel[11] · Steven Ing[12] · Nobuaki Ito[13] · Muhammad Javaid[14] · Peter Kamenicky[15] · Richard Keen[16] · Takuo Kubota[17] · Robin Lachmann[18] · Farzana Perwad[1] · Pisit Pitukcheewanont[19,26] · Stuart H. Ralston[20] · Yasuhiro Takeuchi[21] · Hiroyuki Tanaka[22] · Thomas J. Weber[23] · Han-Wook Yoo[24] · Lin Zhang[25] · Christina Theodore-Oklota[25] · Matt Mealiffe[25,27] · Javier San Martin[25] · Karl Insogna[2]


a
Serum Phosphorus (mg/dL) at Dosing Midpoints
5.0
4.5
4.0
3.5
3.0
2.5
2.0
0
0 4 8 12 16 20 24 28 32 36 40 44 48
Doses
Weeks
Burosumab→Burosumab (n=68)
Placebo→Burosumab (n=66)
c
TmP/GFR (mg/dL)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0
0 4 8 12 16 20 24 28 32 36 40 44 48
Doses
Weeks
Burosumab→Burosumab (n=68)
Placebo→Burosumab (n=66)



80%
60%
40%
20%
0%
% of Fractures/Psuedofractures Fully Healed
Burosumab→Burosumab
(n=65 fractures at baseline)
Placebo→Burosumab
(n=91 fractures at baseline)
20.0%
43.1%
50.8%
63.1%
7.7%
7.7%
23.1%
35.2%
0 4 8 12 16 20 24 28 32 36 40 44 48
Doses
Weeks

VERO VA AU BURO…ET VOUS DIT KENAVO!