Bone, Calcium and Phosphate - News from the ENDO 2022 Atlanta, Georgia

Universitätsspital Basel

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Overview

Denosumab discontinuation – Bente Langdahl, Aarhus, DK

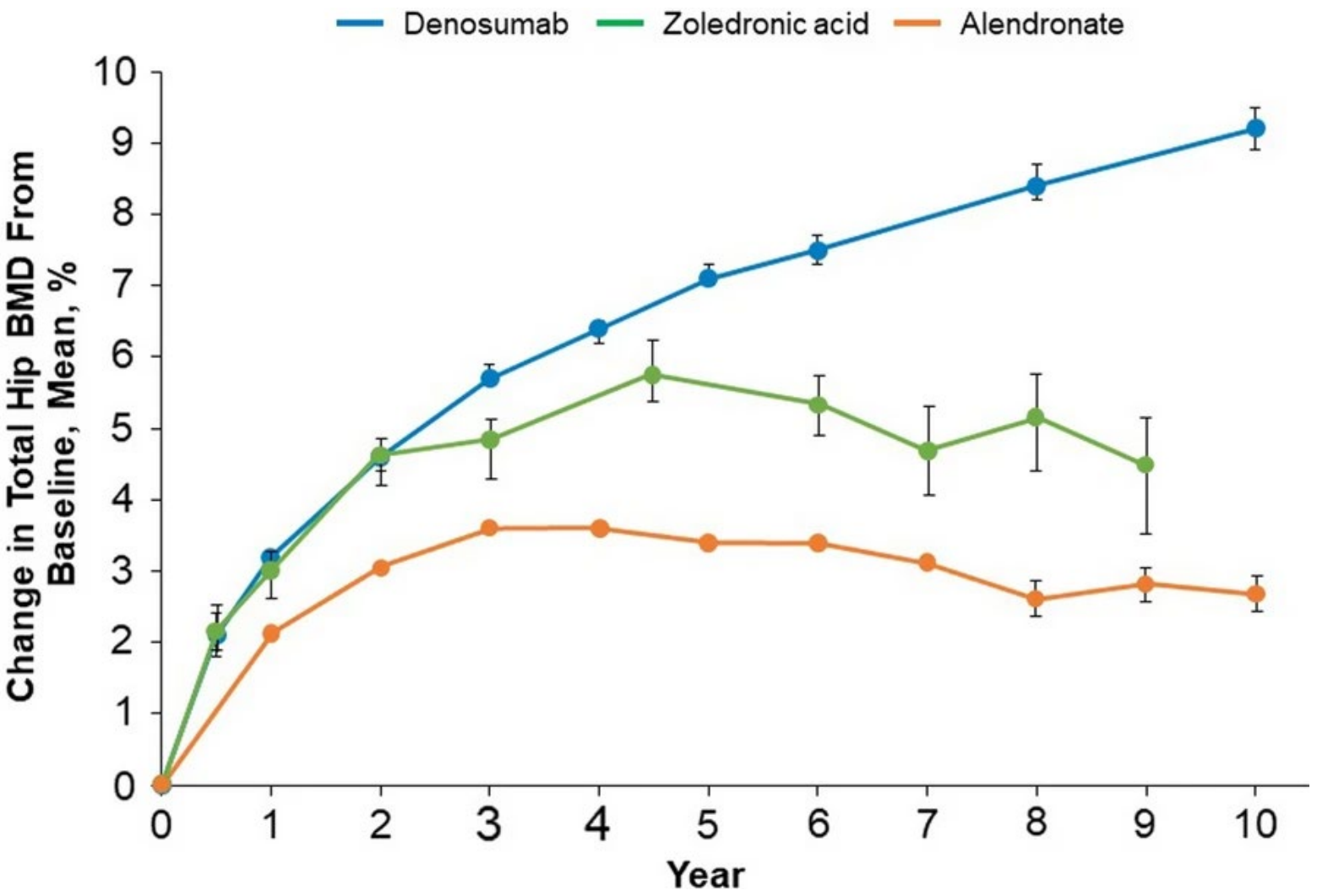
What's new in primary hyperparathyroidism – John P. Bilezikian, New York, USA

Hypophosphatemia after iron infusion – Erik Imel, Indianapolis, USA

Discontinuation of Denosumab

Bente L. Langdahl
University of Aarhus, Denmark

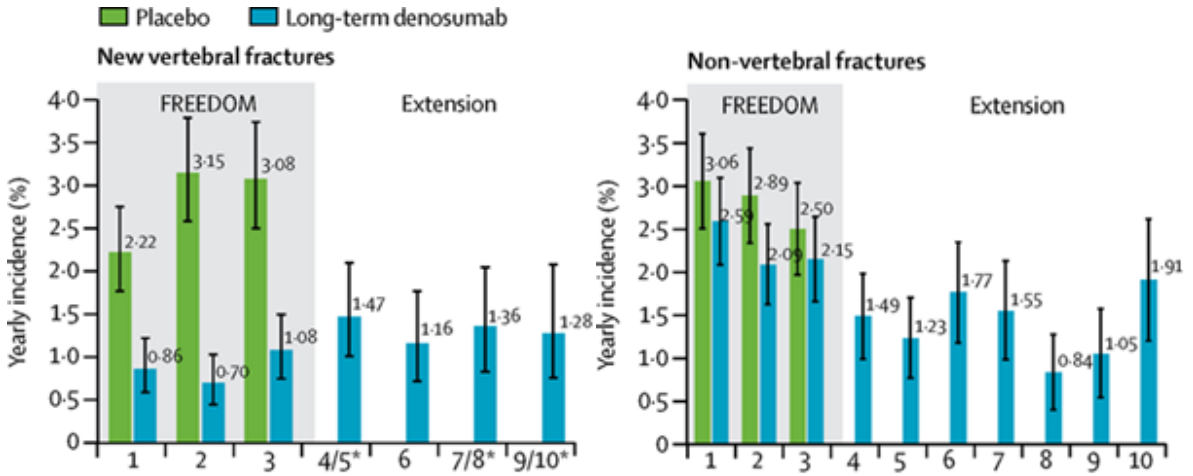
Why should we use denosumab?

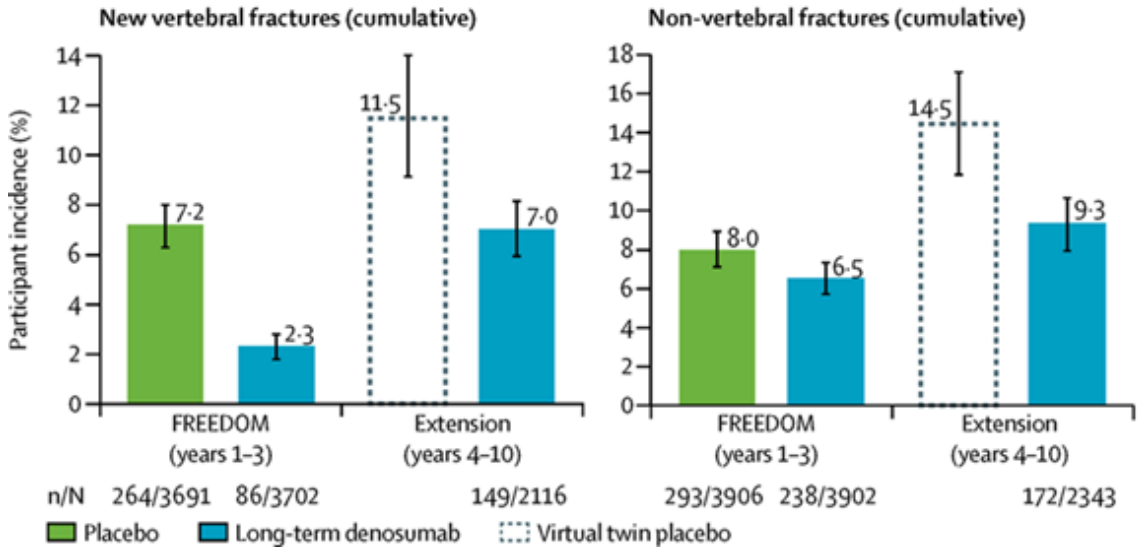


Kendler, D.L. et al. Denosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review. Adv Ther 39, 58–74 (2022). https://doi.org/10.1007/s12325-021-01936-y

What have we learned?

- Long-term denosumab increases BMD and reduces fracture risk





BMD = bone mineral density

Bone HG, et al.,10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension, The Lancet Diabetes & Endocrinology, 2017
https://doi.org/10.1016/S2213-8587(17)30138-9

Benefit and risk of long-term denosumab therapy

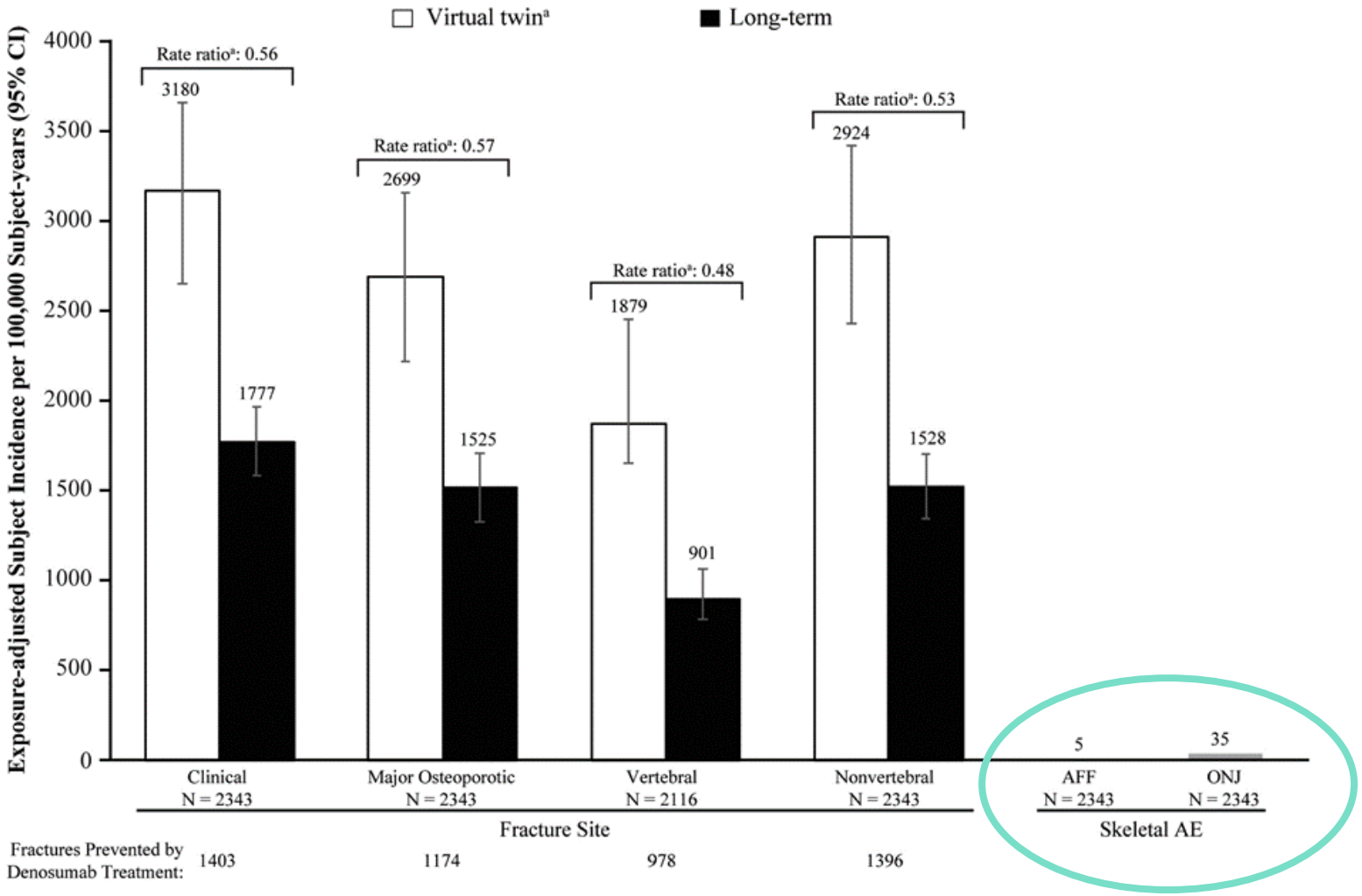
Data from the Freedom trial

Virtual Twin model

Skeletal benefit/risk ratio:

ONJ/Fx: 1:40

AFF/Fx: 1:288



ONJ = Osteonecrosis of the jaw

AFF = atypical femur fracture

Ferrari S, et.al. A virtual-twin analysis of fractures prevented relative to skeletal safety events observed. *Bone*. 2020;134:115287. doi:10.1016/j.bone.2020.11528

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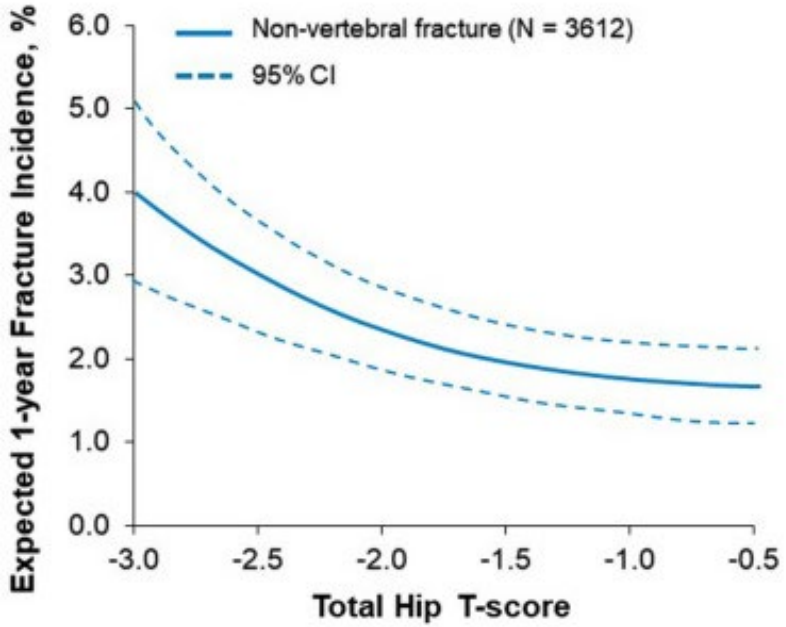
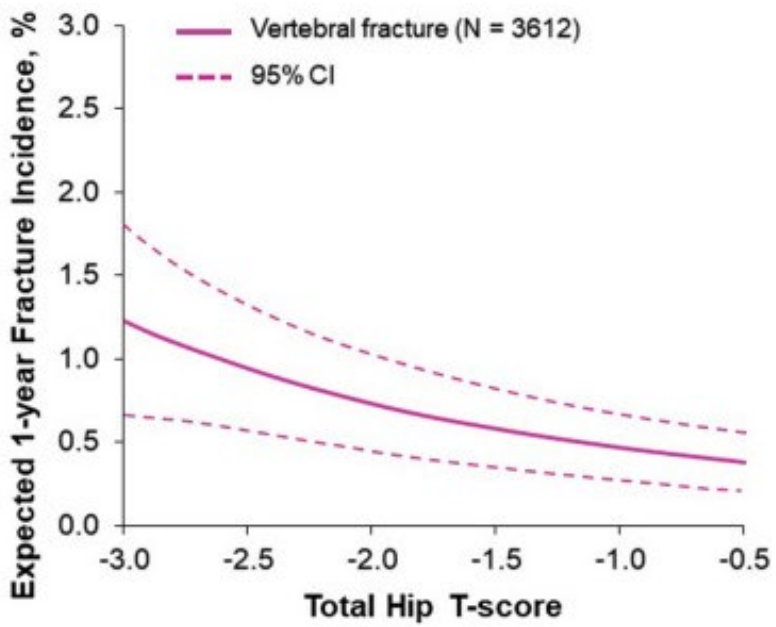
What are our treatment targets?

- Absence of fracture
- Increase BMD
- Lower bone turnover





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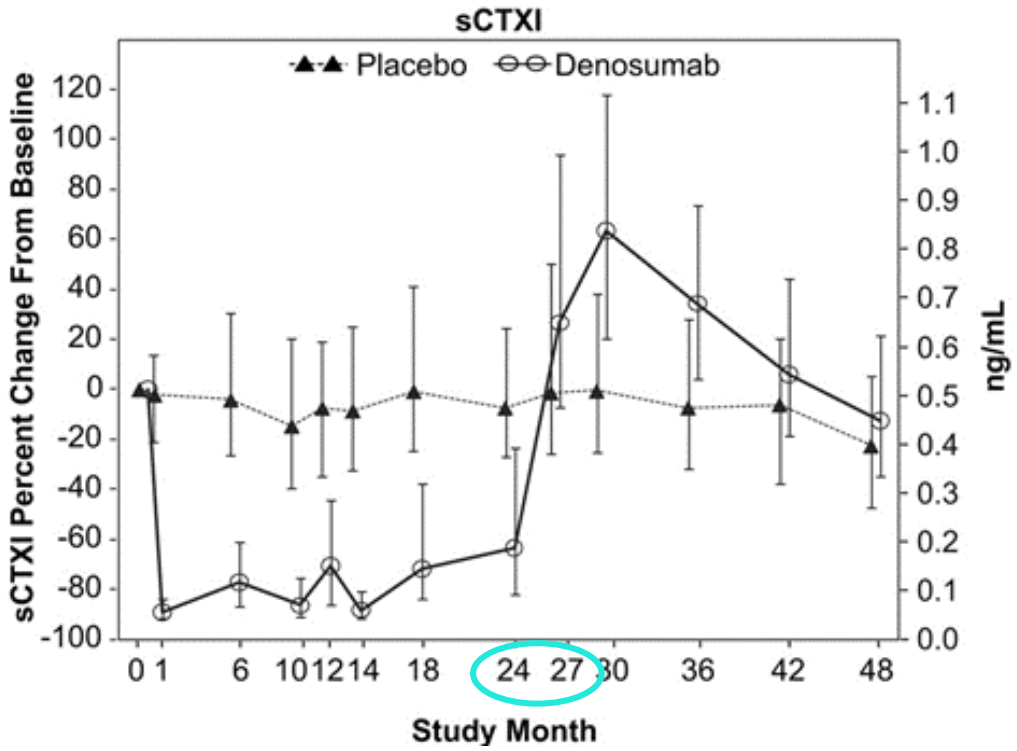
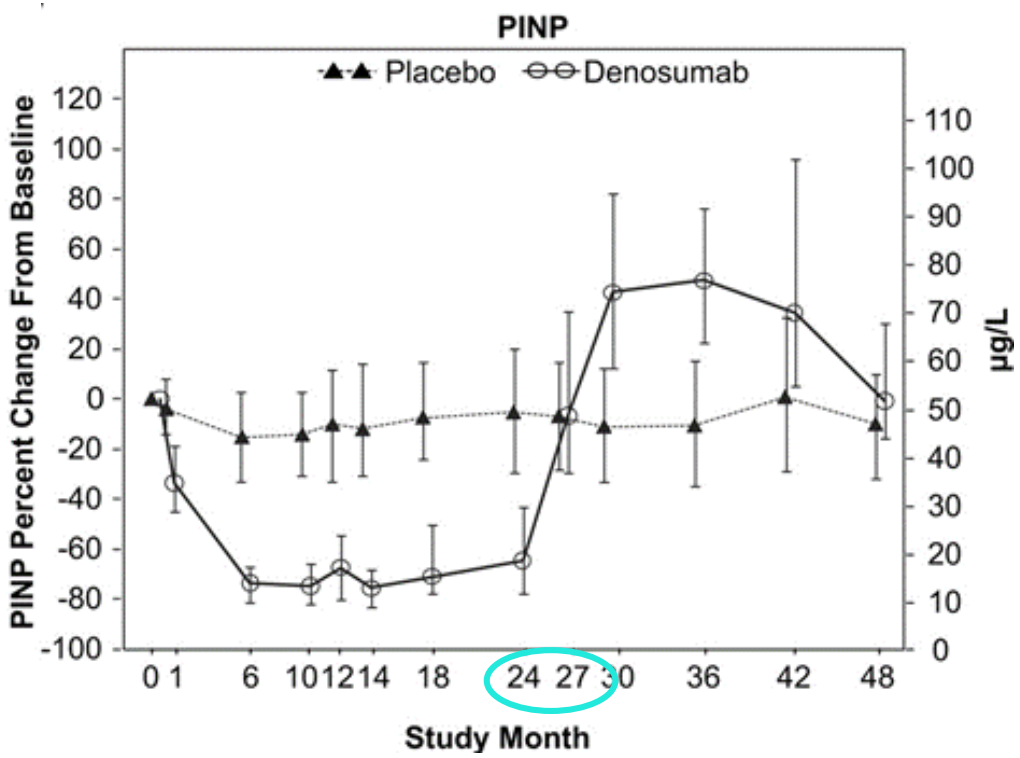
What happens when we discontinue Denosumab?





Bone, H. G., et al. Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass. JCEM (2011), 96(4): 972-980. doi: 10.1210/jc.2010-1502

How can we prevent a rebound?

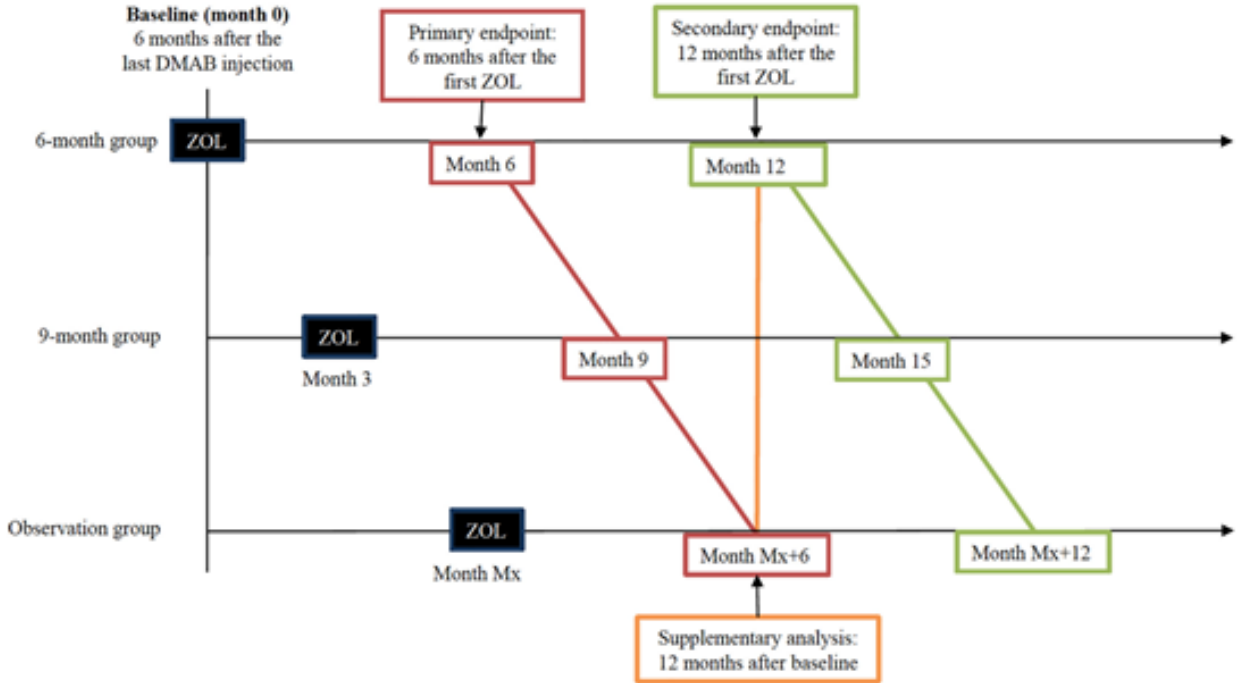
ZolarMab Study – University Hospital in Aarhus

Inclusion

- 61 Patients
- T-Score > -2.5 SD
- Stop denosumab was planned

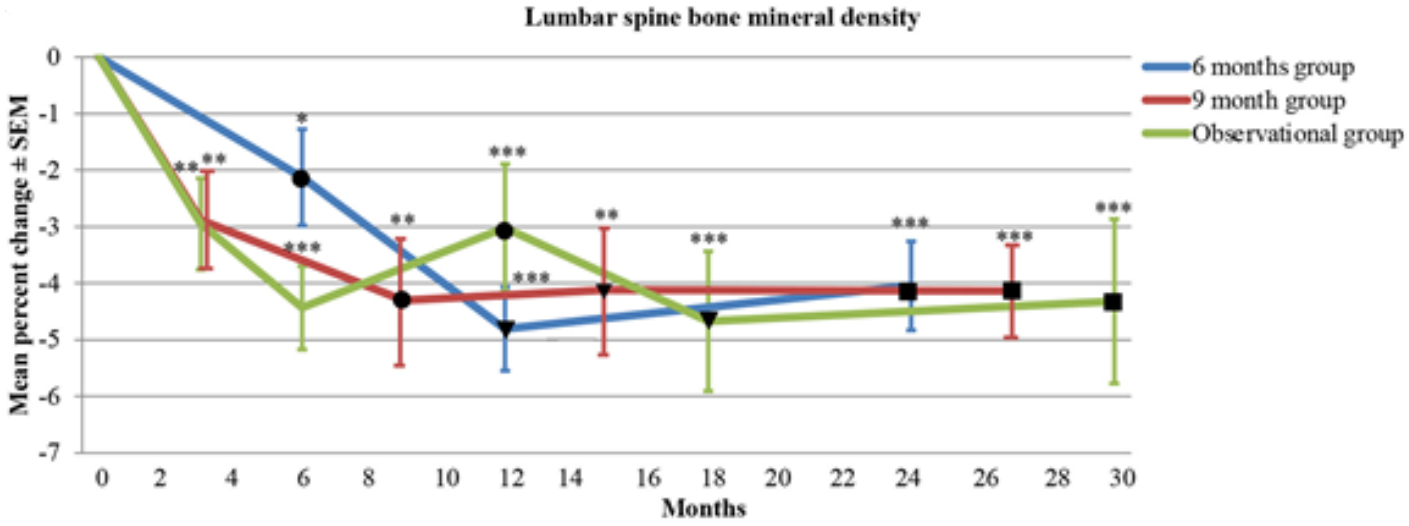
Design

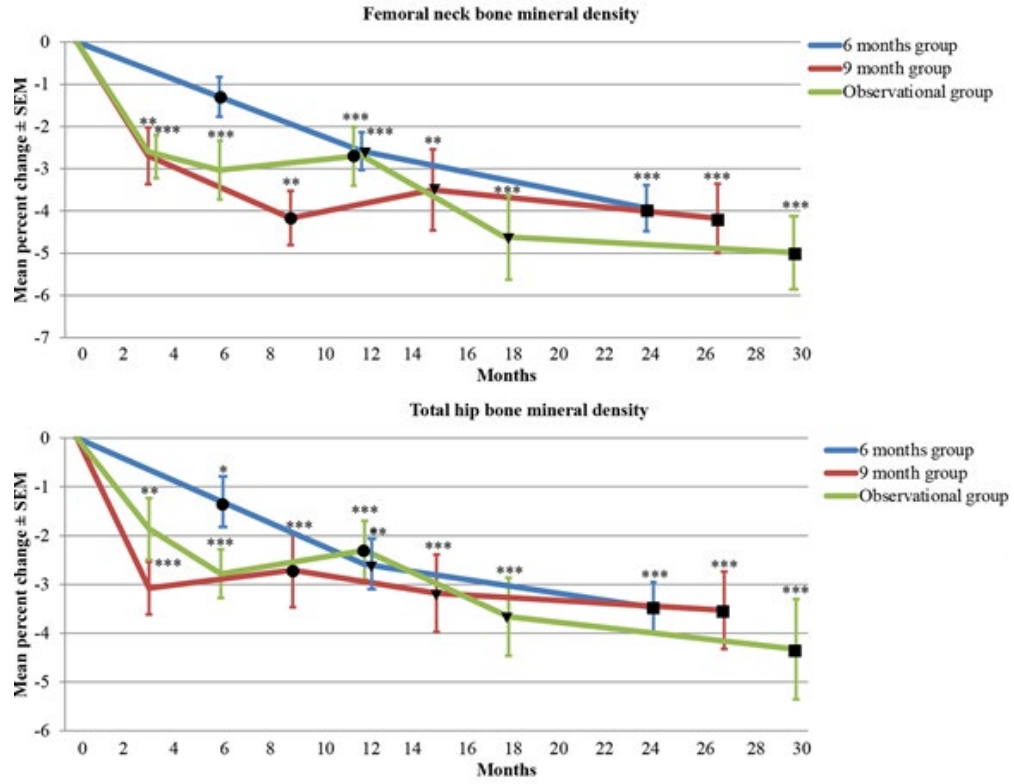
- Open-label, interventional study – randomized in 3 study groups (1:1:1)
- Zoledronat 6, 9 or max. 12 months after last denosumab
- Monthly check for CTX
- DXA 6 months after zoledronate



Sølling, A.S., et al. Treatment with Zoledronate Subsequent to Denosumab in Osteoporosis: a Randomized Trial. JBMR (2020), 35: 1858-1870. https://doi.org/10.1002/jbmr.4098

Results from the ZolarMab-Study – BMD

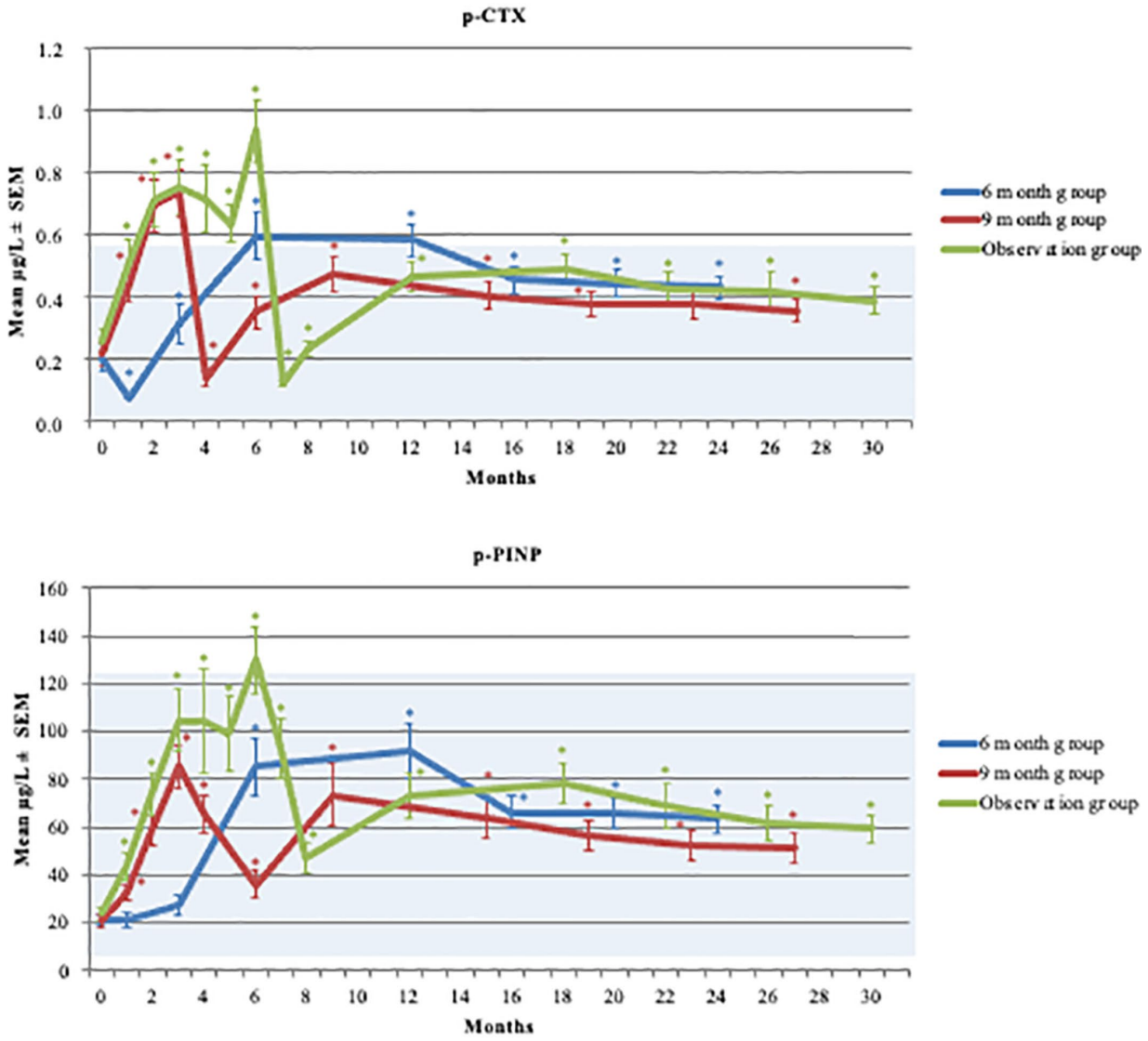




BMD= bone mineral density

Sølling, A.S.,et al. (2021), Treatment With Zoledronate Subsequent to Denosumab in Osteoporosis: A 2-Year Randomized Study. JBMR, 36: 1245-1254. https://doi.org/10.1002/jbmr.4305

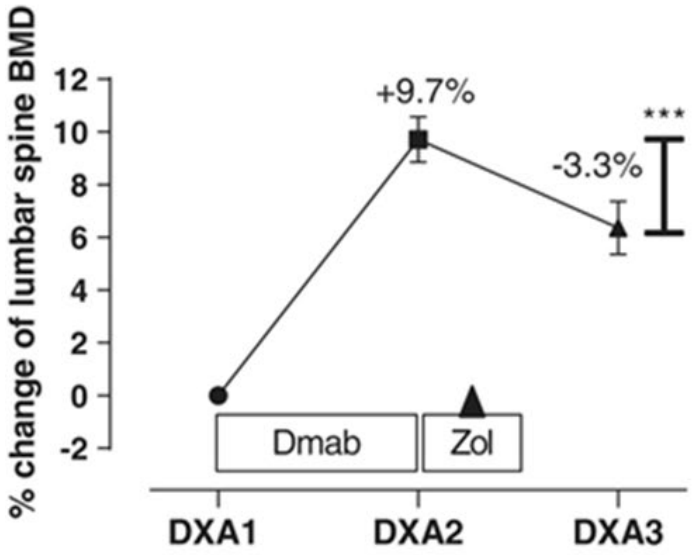
Results from the ZolarMab-Study – bone turnover

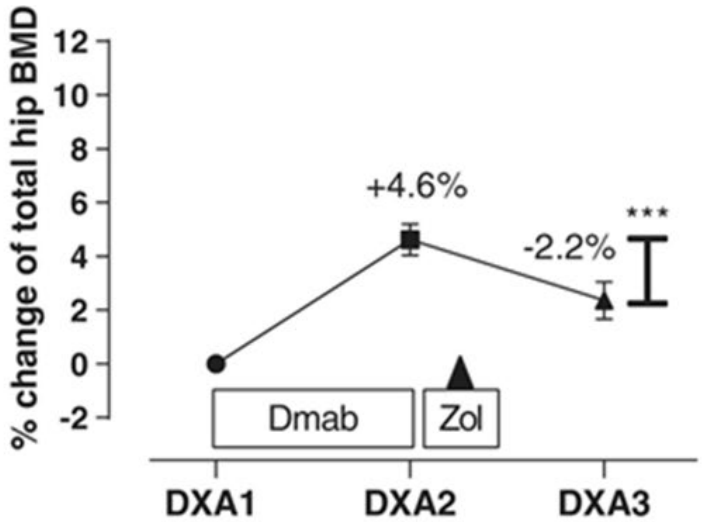


Sølling, A.S.,et al. (2021), Treatment With Zoledronate Subsequent to Denosumab in Osteoporosis: A 2-Year Randomized Study. JBMR, 36: 1245-1254. https://doi.org/10.1002/jbmr.4305

Observational study from Bern

- Observational study
- 120 postmenopausal women
- 65.6 (49-85) years
- Denosumab for 2-5y
- 1 infusion of zoledronate





Everts-Graber, J., et al. (2020), A Single Infusion of Zoledronate in Postmenopausal Women Following Denosumab Discontinuation Results in Partial Conservation of Bone Mass Gains. J Bone Miner Res, 35: 1207-1215. https://doi.org/10.1002/jbmr.3962

Managing the patient after denosumab

- Expect loss of BMD after long-term treatment
- Aim for higher BMD before stopping denosumab
- Slightly different approach for:
  - Short-term treatment with denosumab (up to 2.5y)
  - Long-term treatment with denosumab (>2.5y)

Managing the patient after Denosumab

Short-term (up to 2.5y)

- Alendronate for (1)-2y possible
- Monitor CTX!

- Zoledronate 5mg six months after last denosumab

Long-term (>2.5y)

- Zoledronate 5mg six months after last denosumab
- Monitor CTX after 3, 6 and 12 months
  - If CTX elevated, repeat zoledronate infusion
  - If unable to monitor CTX, repeat zoledronate infusion after 6 months

CTX = bone turnover marker

Tsourdi,E., et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS,Bone,Volume 105,2017,Pages 11-17, https://doi.org/10.1016/j.bone.2017.08.003.

Maintenance of BMD beyond the first year

- No long-term protection after bisphosphonate
- Expect further age-related bone loss
- Consider bisphosphonates

Tsourdi,E., et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS,Bone,Volume 105,2017,Pages 11-17, https://doi.org/10.1016/j.bone.2017.08.003.

Summary - 1

Denosumab

- BMD continously increases over 10 years
  - Risk of any osteoporotic fracture is significantly reduced and maintains so for up to 10 years
- Risk associated with long-term treatment is low (e.g. atypical femur fracture and osteonecrosis of the jaw)
- Benefit/risk ratio is positive in patients with osteoporosis and increased risk of fractures

Summary - 2

- Discontiunation of denosumab results in most cases in rebound activation of bone resorption, bone loss and perhaps risk of vertebral fracture

- Optimal time point for transition from denosumab to bisphosphonates still unclear
  - Bisphophonates can reduce but not completely prevent increased bone turnover and BMD loss
  - If you want to stop the treatment, aim for a higher BMD to allow minor loss

- After discontiuning denosumab probably no long-term protection against bone loss
  - Close follow-up and monitoring needed

5th International Workshop on Primary Hyperparathyroidism

John P. Bilezikian
Columbia University, New York, USA

Three phenotypes of primary hyperparathyroidism

- Symptomatic PHPT
  - Overt disease
- Asymptomatic PHPT
  - Meanwhile the most common form of PHPT
  - Two forms of asymptomatic PHPT:
    - WITH or WITHOUT target organ involvement
- Normocalcemic PHPT
  - Normal adjusted calcium levels AND elevated PTH
  - Alternative cause für 2° HPT ruled out:
    - Vitamin D deficiency (25-OH D <50 (- 75) nmol/l)
    - Renal insufficiency (eGFR <60ml/min)
    - Medication (Lithium, Thiazid)
    - Hypercalcuria
    - Malabsorption

PHPT = primary hyperparathyroidism

Normocalcemic PHPT

Very limited data

- Higher prevalence of multi-gland disease
- In some studies BMD increased after PTX
- Effect on renal, cardiovascular and QoL uncertain

Management

- Referral to experienced experts
- Imaging: Localization less successful

NO guidelines due to limited data

PTX = parathyroidectomy
QoL = Quality of life

«2022» Guidelines for surgery in asymptomatic PHPT

Index	Guidelines (any one of the following)
Increased calcium level	>0.25mmol/l ULN
Skeletal involvement	Fracture DXA (T-Score <-2.5 SD) any site
Renal	eGFR <60ml/min Kidney stone or nephrocalcinosis **Urinary calcium (mg/d), >300 for men, >250 for women**
Age	<50 years

	1990	2002	2008	2013
Measurement[b]				
Serum calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: Z-score <−2.0 (site unspecified)	BMD by DXA: T-score <−2.5 at any site[b]	BMD by DXA: T-score <−2.5 at any site[b]	A. BMD by DXA: T-score < −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius[b]
			Previous fragility fracture[c]	B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. eGFR reduced by >30% from expected B. 24-h urine for calcium >400 mg/d (>10 mmol/d)	A. eGFR reduced by >30% from expected B. 24-h urine for calcium >400 mg/d (>10 mmol/d)	A. eGFR < 60 cc/min B. 24-h urine for calcium not recommended	A. Creatinine clearance < 60 cc/min B. 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis[d]
				C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age, y	<50	<50	<50	<50

Bilezikian JP, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. JCEM 2014;99(10):3561-3569. doi:10.1210/jc.2014-1413

Hypophosphatemia after iv iron

Erik Imel
Indiana University, Indianapolis, USA

Hypophosphatemia

Causes

- Low intestinal absorption
  - Inadequate intake
  - Medication (PPI)
- Internal redistribution
  - Refeeding
  - Hungry bone syndrome
  - Respiratory Alkalosis
- Increased urinary excertion
  - 1° and 2° Hyperparathyroidism
  - High levels of FGF23 (e.g. XLH)

Symptoms

- Muscle pain and weakness
- Neurological symptoms (e.g. paresthesia)
- Osteomalacia
- Hematologic dysfunction

A quick look at FGF23

- FGF23 is a peptide hormone
  - Highest expression in bone
- Intact FGF23
  - Reduces renal tubular phosphate reabsorption
  - Downregulates activation of 1,25(OH)vitamin D
  - Lowers PTH levels in plasma
- Iron deficiency leads to an increase of FGF23

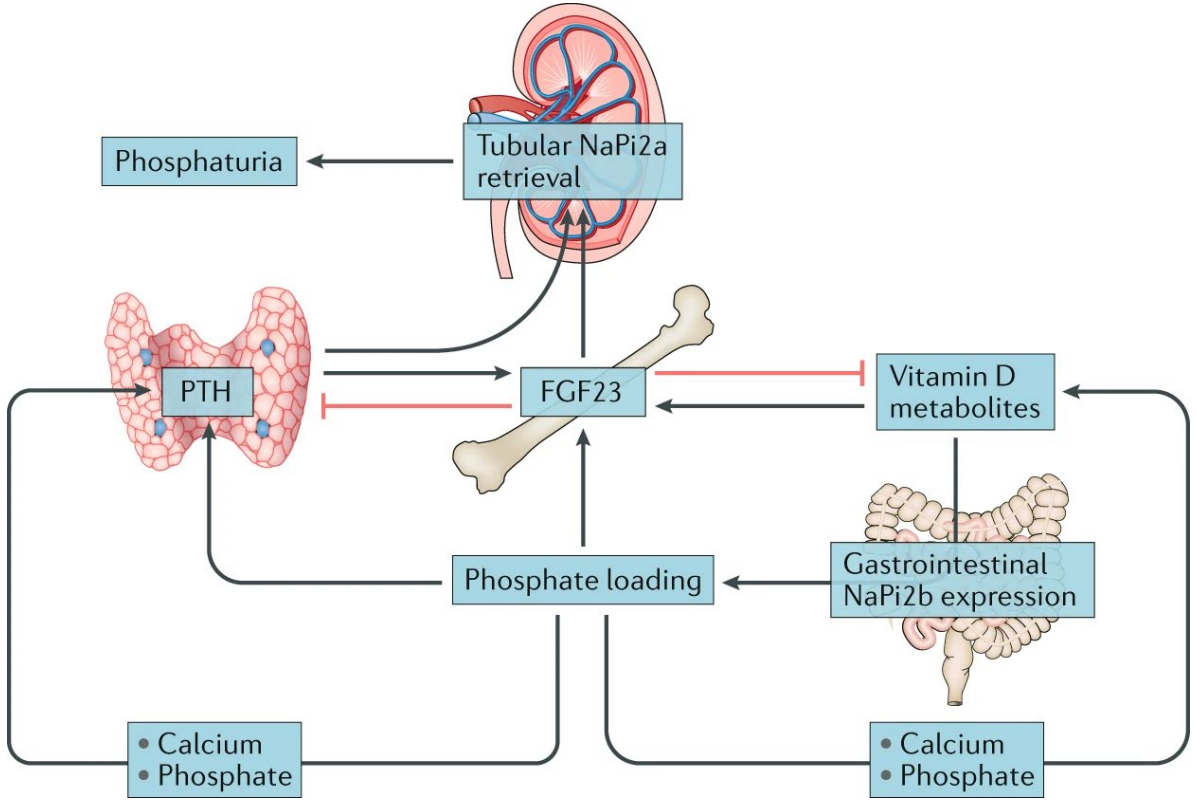
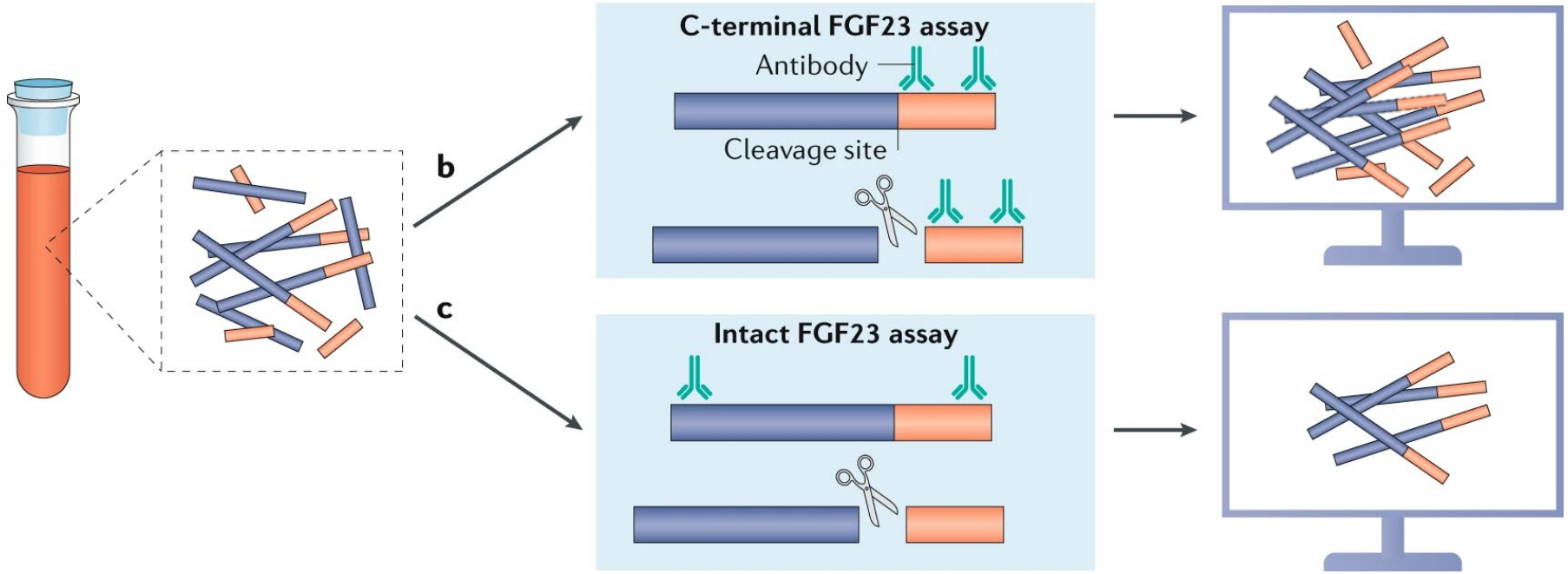


Figure: Vervloet, M. Renal and extrarenal effects of fibroblast growth factor 23. Nat Rev Nephrol 15, 109–120 (2019). https://doi.org/10.1038/s41581-018-0087-2

Rausch, S., Föller, M. The regulation of FGF23 under physiological and pathophysiological conditions. Pflugers Arch - Eur J Physiol 474, 281–292 (2022). https://doi.org/10.1007/s00424-022-02668-w

FGF23 assay



Edmonston, D., Wolf, M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. Nat Rev Nephrol 16, 7–19 (2020), doi.org/10.1038/s41581-019-0189-5

FGF23 – the link between iv iron and hypophosphatemia

Iron carboxymaltose

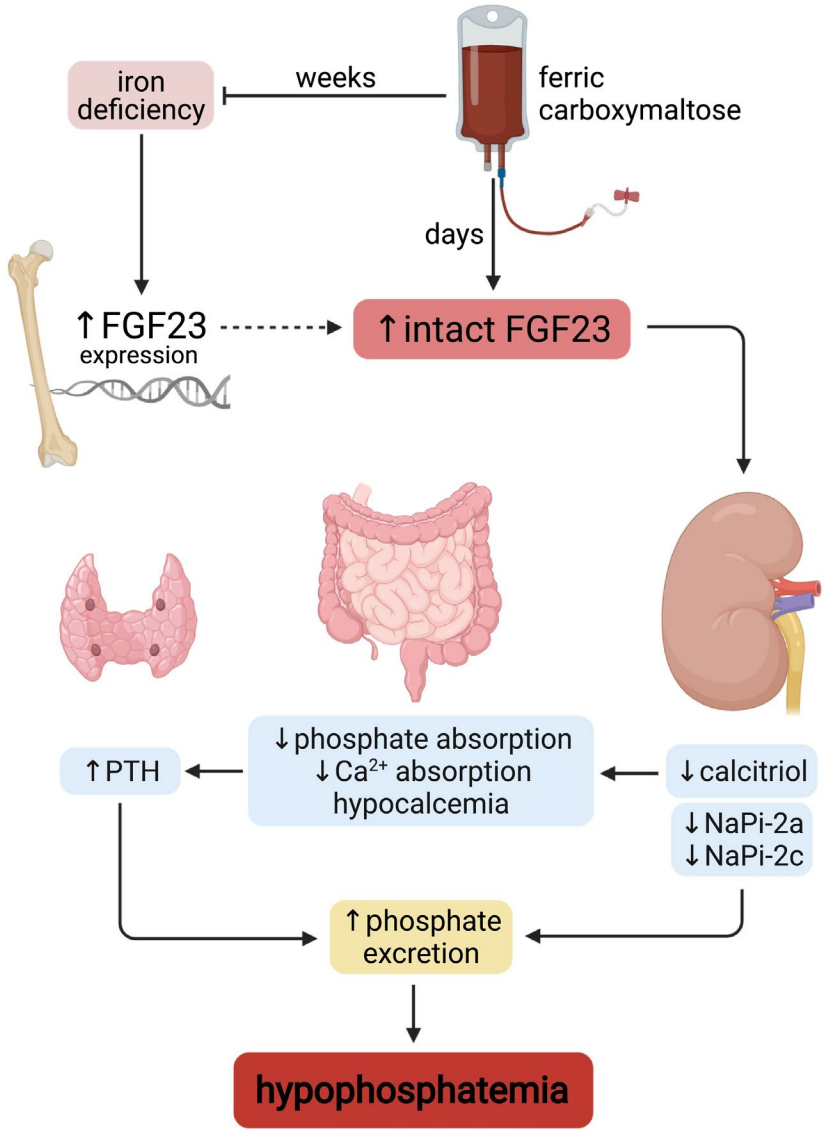
- Ferinject®

Iron sucrose

- Venofer®

Iron isomaltoside

- FerMed®
- MonoFer®



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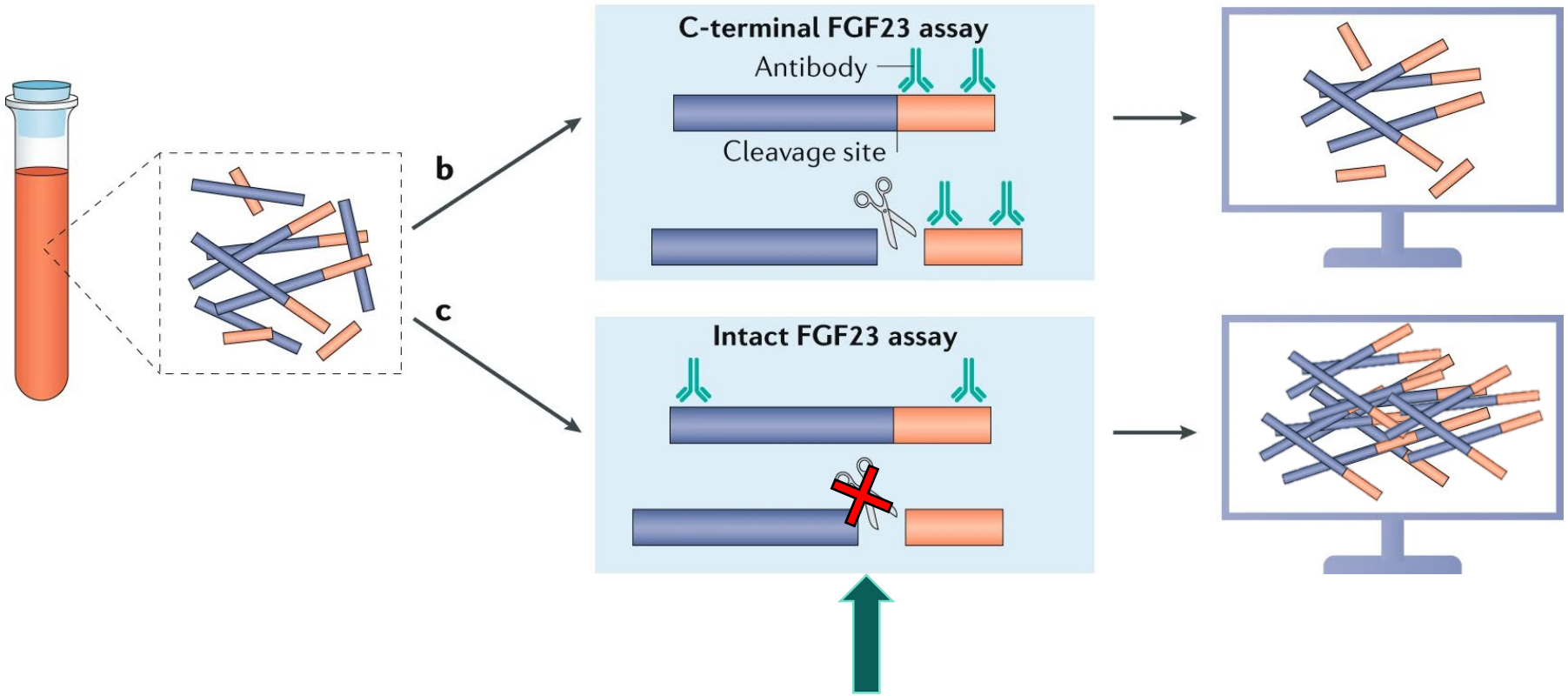
Effect of iron carboxymaltose on FGF23



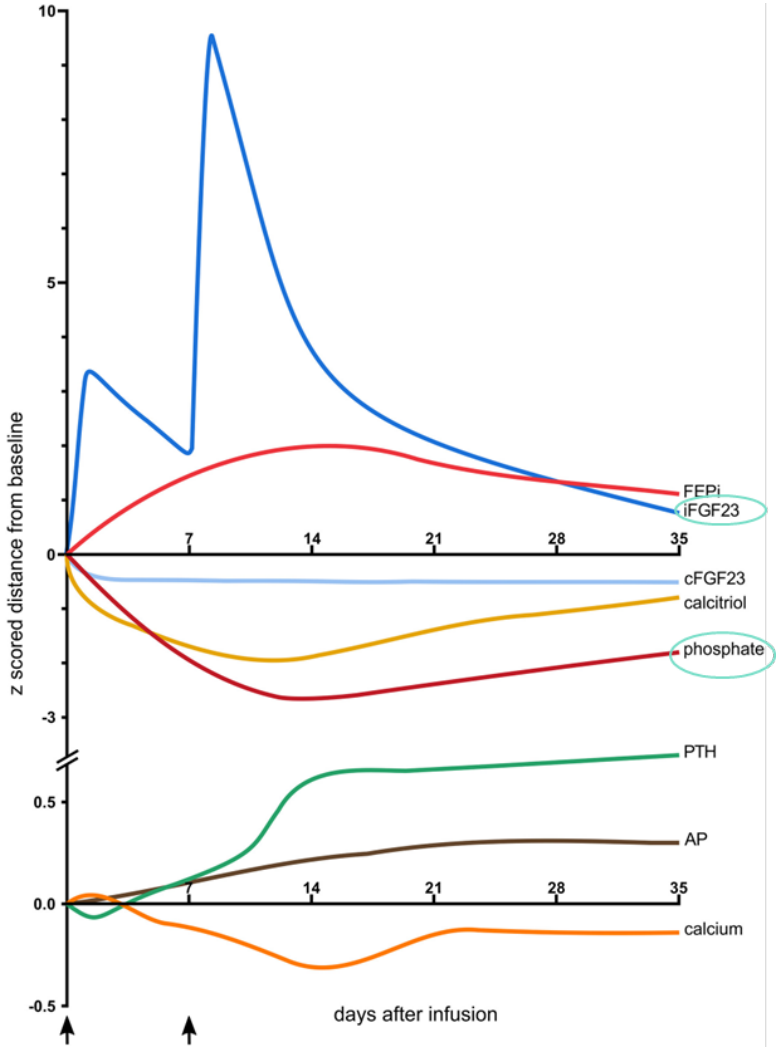
Iron carboxymaltose inhibits the cleavage of intact FGF23

Adapted from
Edmonston, D., Wolf, M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. Nat Rev Nephrol 16, 7–19 (2020), doi.org/10.1038/s41581-019-0189-5

Iron infusion and hypophosphatemia

- After iron carboxymaltose (Ferinject®) highest risk for hypophosphatemia
  - In some studies >90% of patients had low phosphate levels
  - Most patients asymptomatic

- Risk factors:
  - Pre-existing hypophosphatemia
  - Low vitamin D-levels
  - Malnutrition



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Duration and treatment of hypophosphatemia after iv iron

- Duration
  - Low phosphate levels resolve in most cases after a month
  - In some patients hypophosphatemia persists up to 5 months
- Treatment
  - Symptomatic
  - >90% of cases resolve without treatment
  - Severe, symptomatic hypophosphatemia should be treated
    - Orally (0.3-0.8 mmol/l)
    - Intravenously (<0.3 mmol/l)

Rausch, S., Föller, M. The regulation of FGF23 under physiological and pathophysiological conditions. Pflugers Arch - Eur J Physiol 474, 281–292 (2022). https://doi.org/10.1007/s00424-022-02668-w

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Vielen Dank für Ihre Aufmerksamkeit!