Differentiating Pharmacological Therapies for Osteoporosis

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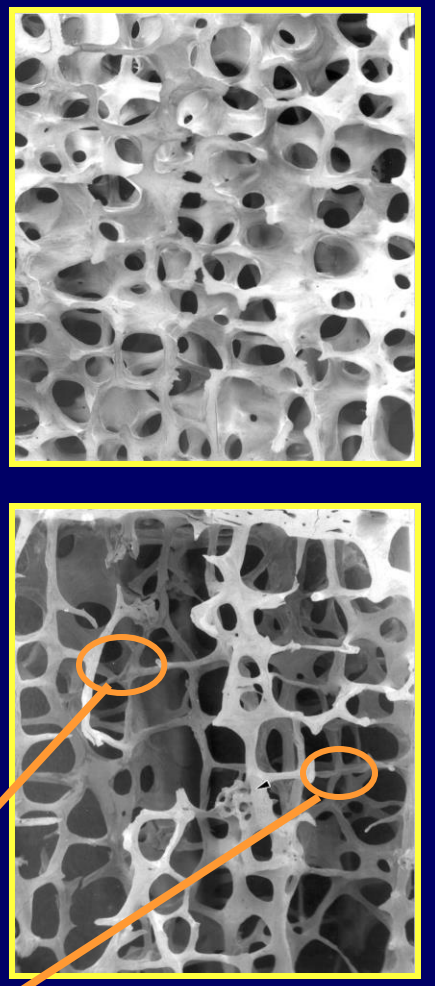
Osteoporosis

A systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture

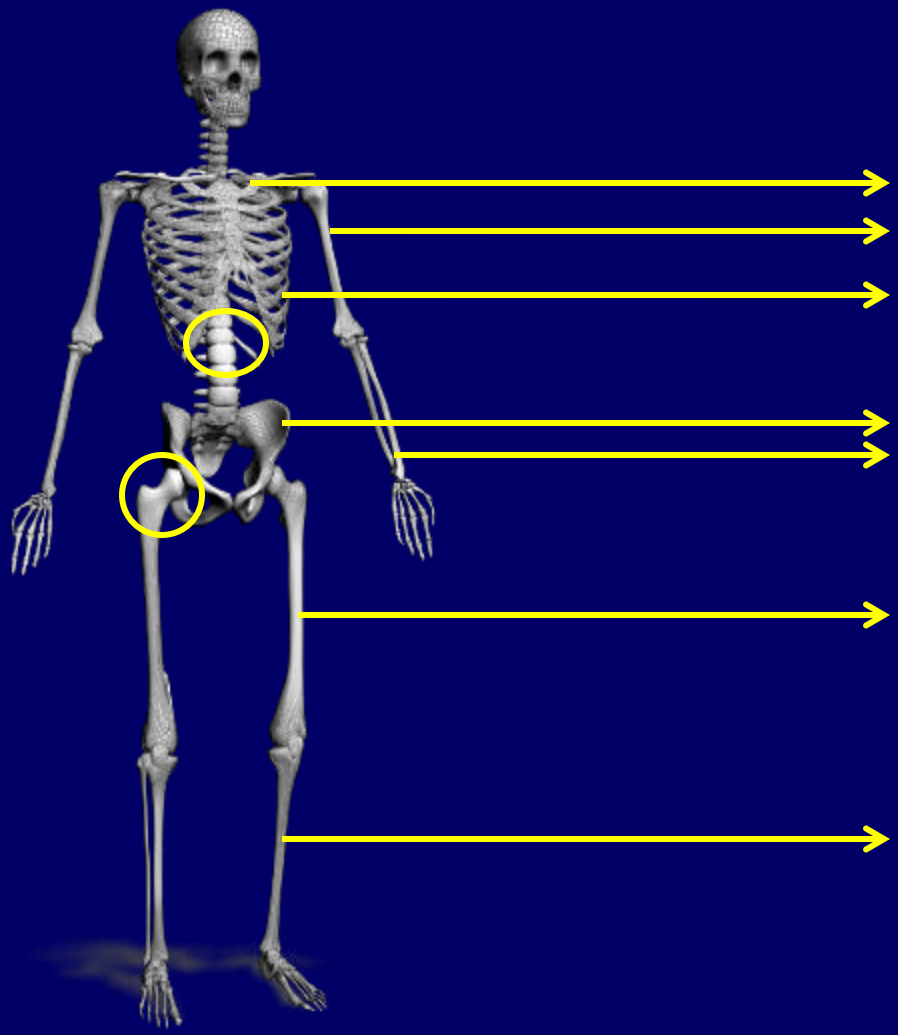
Consensus Development Conference, 1993



Horizontal Disconnections

Dempster 2000

Osteoporotic Fractures



Clavicle, scapula, sternum
Humerus
Ribs
Pelvis
Distal forearm
Femur
Tibia, fibula

WHO Scientific Technical Report 2007

Clinical Significance of Osteoporotic Fractures

- **Fractures are**:
  - frequent
  - associated with increased morbidity and deterioration of the quality of life
  - increase the risk of new fractures
  - associated with increased mortality

Fracture Prevention

- General measures
  - **vitamin D**, calcium
- Non-pharmacological interventions
  - frequency or impact of falls
- Pharmacological interventions

Pharmacological Agents for the Treatment of Osteoporosis

- Inhibitors of bone turnover
  - Bisphosphonates, Calcitonin, Denosumab Oestrogens, SERMs, Tibolone
- Stimulators of bone formation
  - Parathyroid Hormone
- Uncertain action
  - Strontium Ranelate.

Principles of Evidence-Based Medicine

- **First principle**
  - Some evidence is stronger than other
  - There is a hierarchy of evidence
  - Use evidence as high in hierarchy as possible
- **Second principle**
  - Evidence alone is never enough
  - Should be combined with clinical judgment and patient values

(Guyatt et al 1999)

EBM Antifracture Efficacy of Pharmacological Interventions

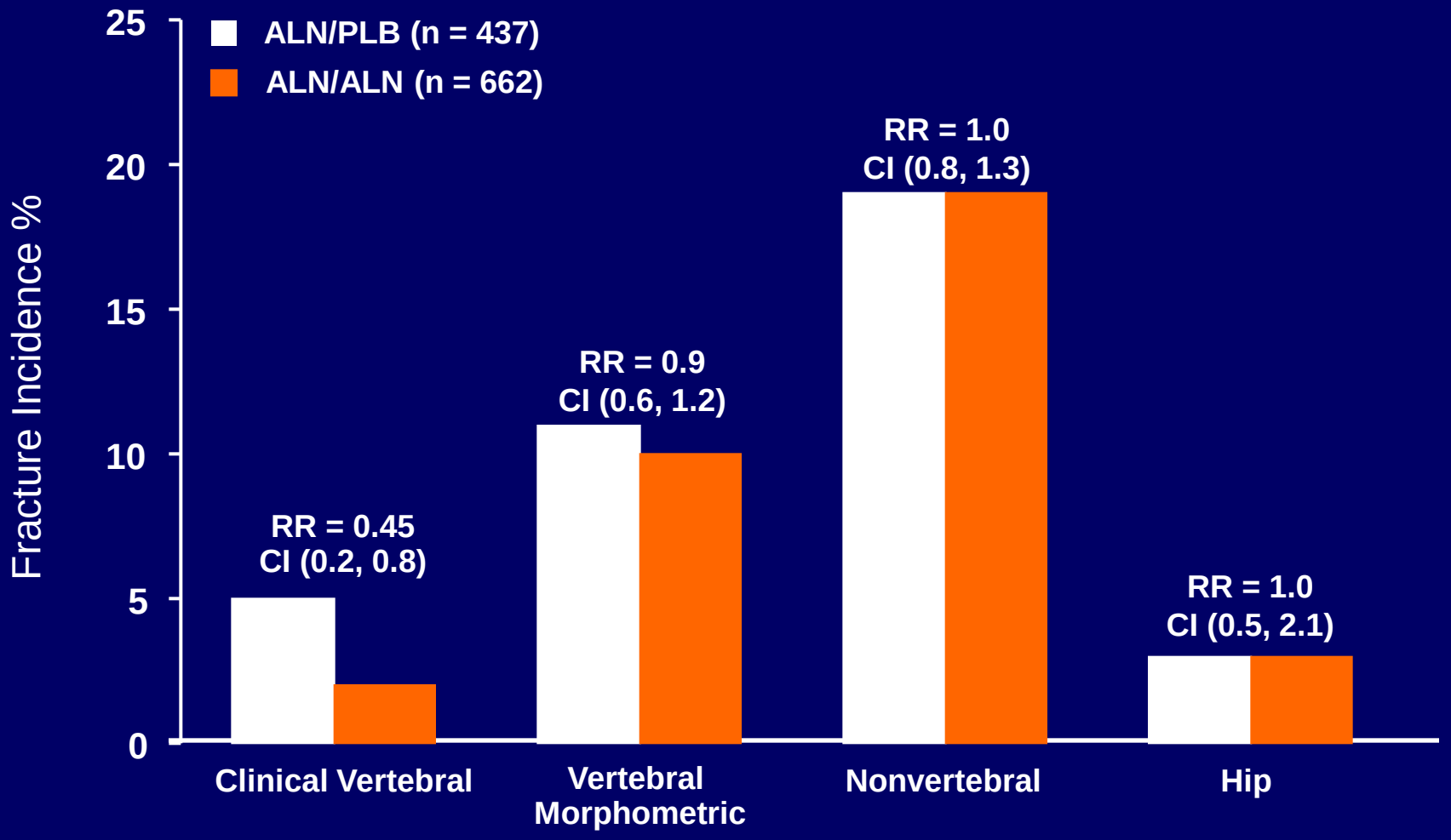
VERTEBRAL Fx	NON-VFx	HIP Fx
ALN, ETID, IBN,	ALN, IBN, RIS,	ALN, RIS
RIS, ZOL	ZOL	ZOL
Dmab	Dmab	Dmab
PTH	PTH 1-34	
SR	SR	

RCTs -Meta-analysis

Long-Term Effects

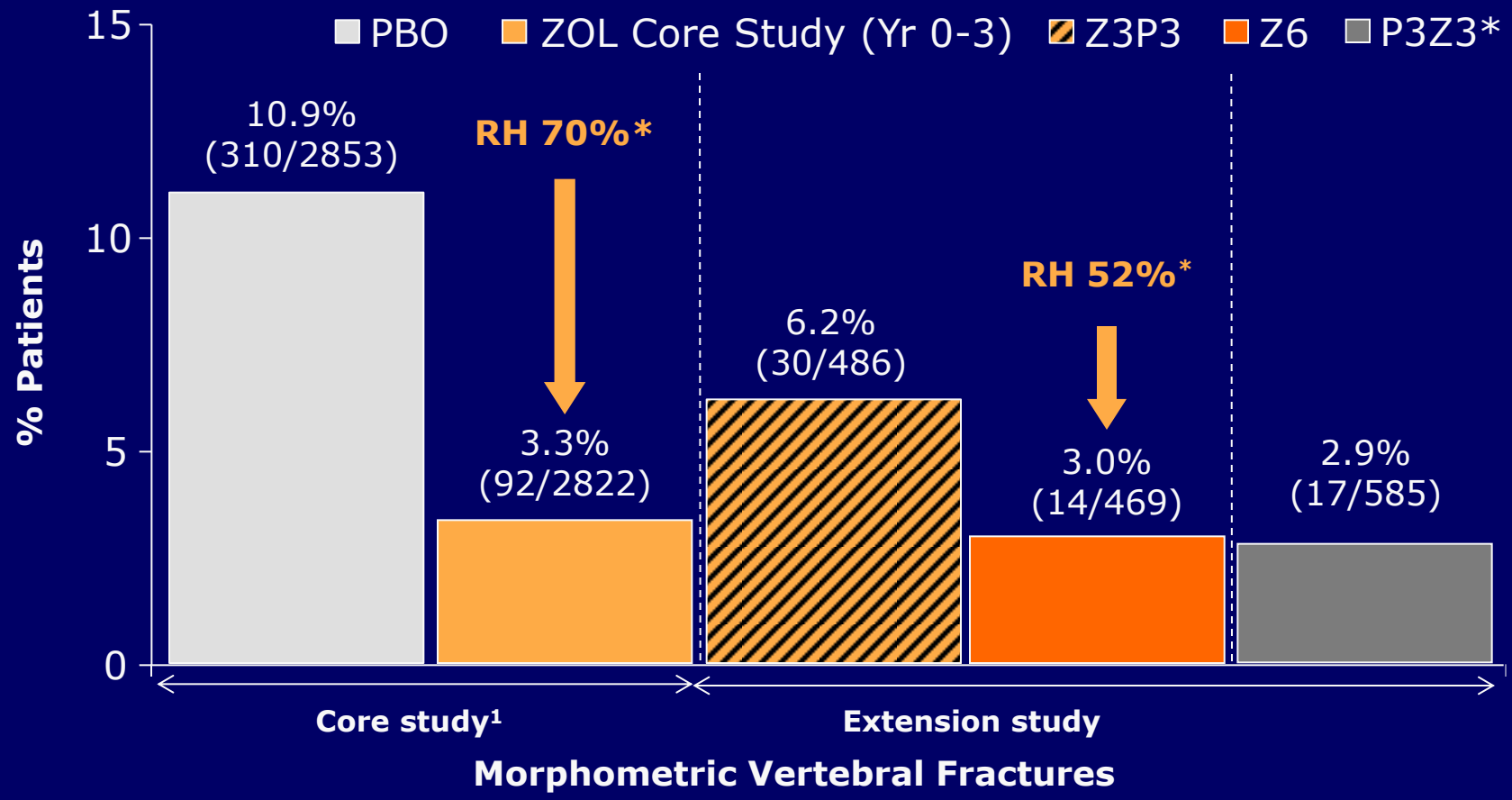
- Several drugs have proven benefits in the treatment of postmenopausal osteoporosis,
- Due to the chronic, progressive nature of the disease, therapies are likely to be prescribed for >5–10 years
- Thus, it is important to explore the efficacy of long-term treatment:
  - Sustained effect (BMD, bone turnover, fracture risk)
  - Reversibility of effect upon discontinuation

FLEX: Incidence of Fractures by Treatment Group



Black DM et al. JAMA. 2006

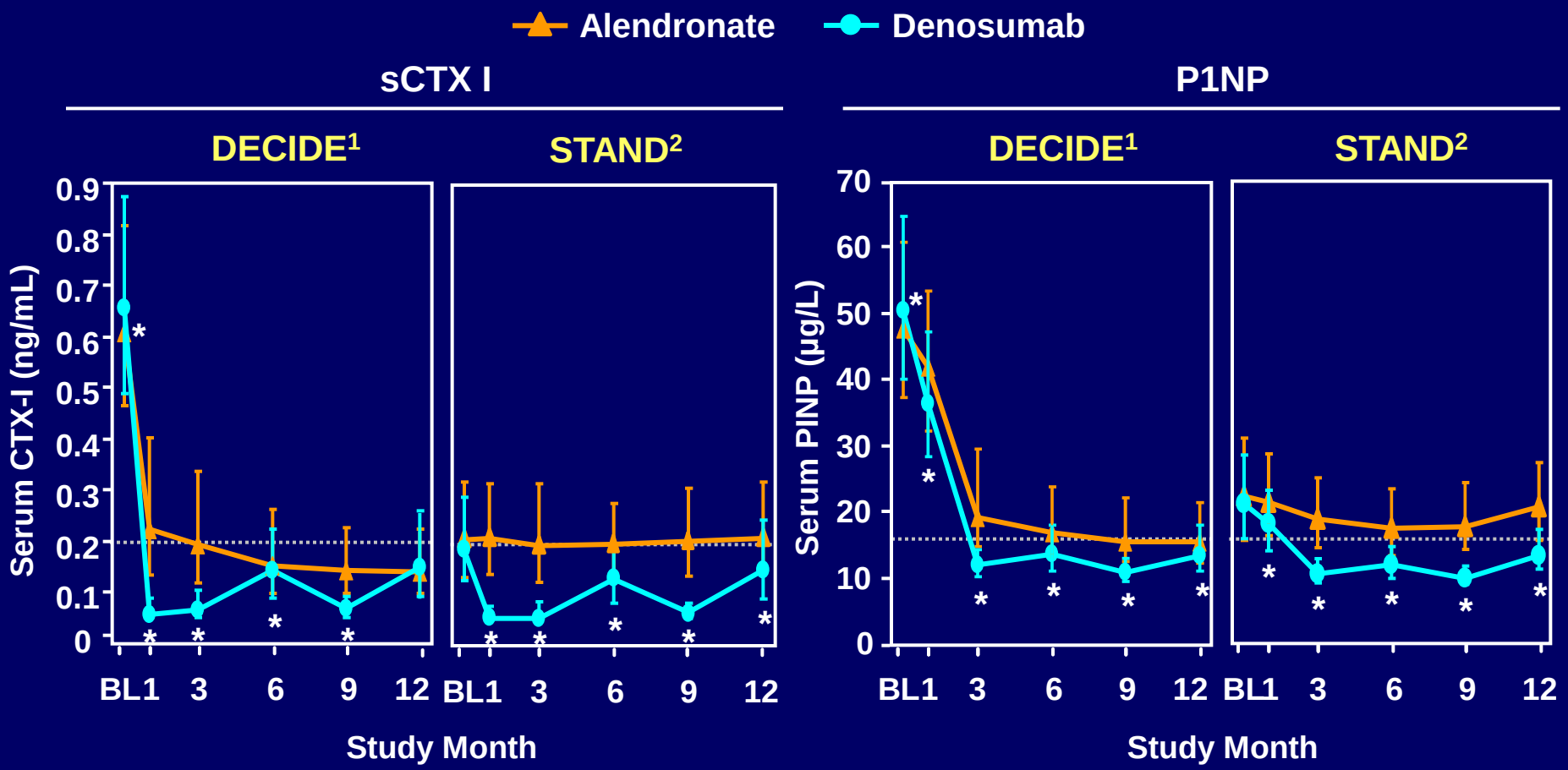
Continuous ZOL Treatment Resulted in Significantly Fewer New Morphometric VFx



*P3Z3 group included only to maintain core study blind. Patients not included in the pre-planned primary or secondary efficacy analysis. Caution should be used in interpreting the findings as approx. 500 P3Z3 patients completed the study prior to end of Year 3; P3Z3 not comparable to other arms

Black et al JBMR 2012

Serum CTX-I and P1NP Values Over Time

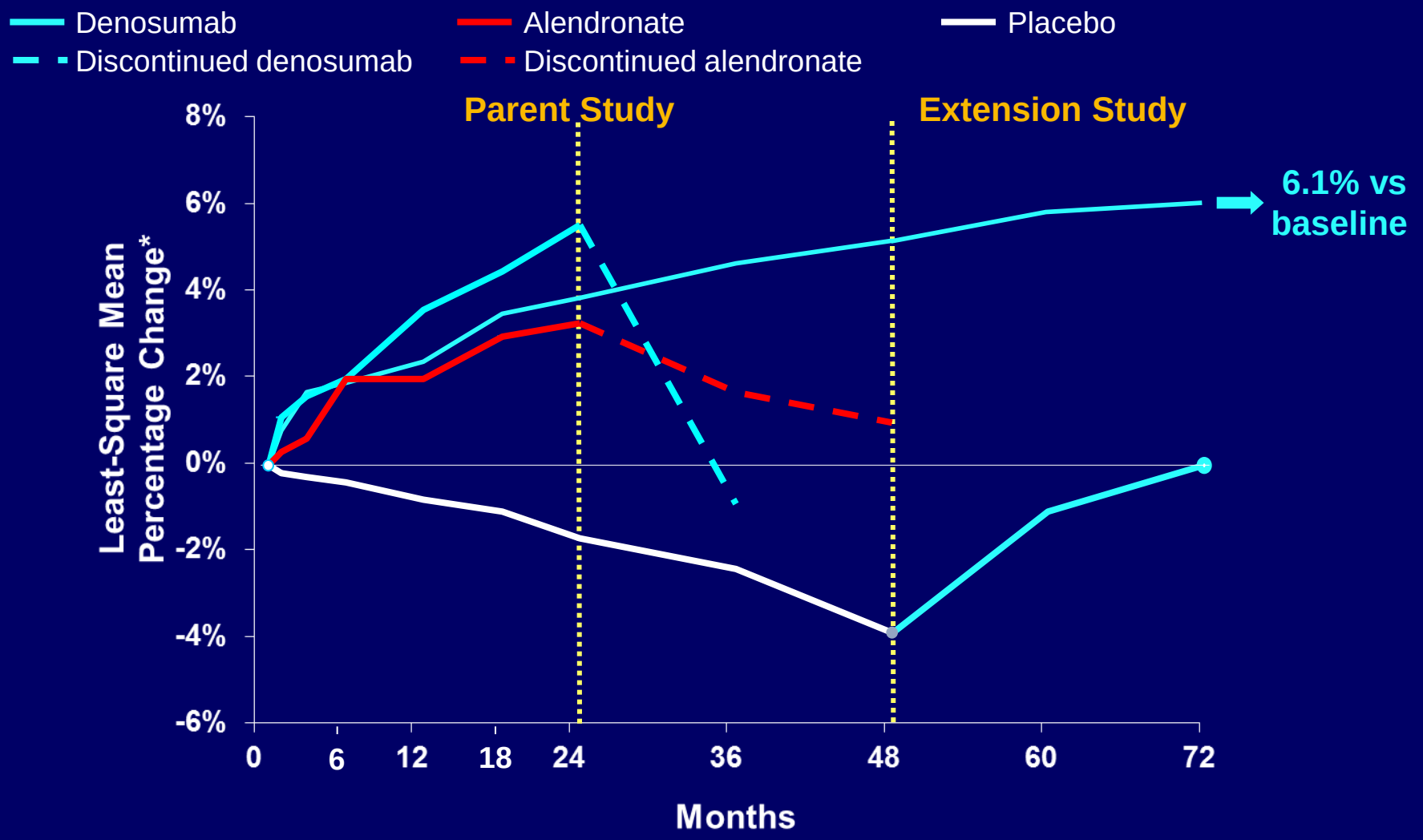


- Dotted line is lower limit of the premenopausal reference range (The University of Sheffield Bone Marker Laboratory).
- Values are medians; error bars represent the interquartile range; *P ≤ 0.01

1. Brown JP, et al. J Bone Miner Res 2009;24:153;. 2. Kendler DL, et al. J Bone Miner Res. 2010;25:72.

Effect of 6 Years of Continuous Denosumab Treatment on Total Hip BMD

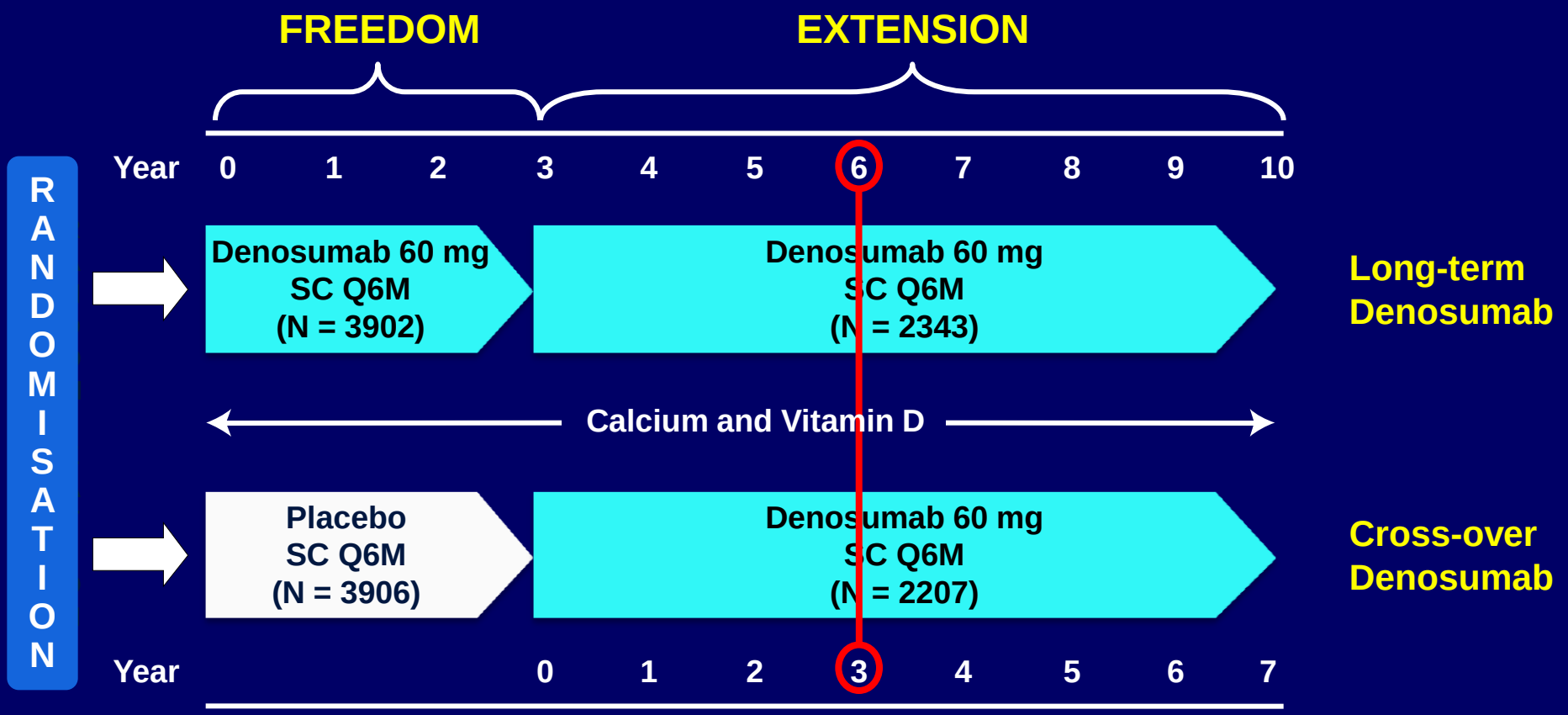
Phase 2 – Extension Study



Adapted from: Miller PD et al. J. Clin Endocrinol Metab. 2011 Feb;96(2):394-402.

FREEDOM Extension Study Design

International, multicenter, open-label, single-arm study

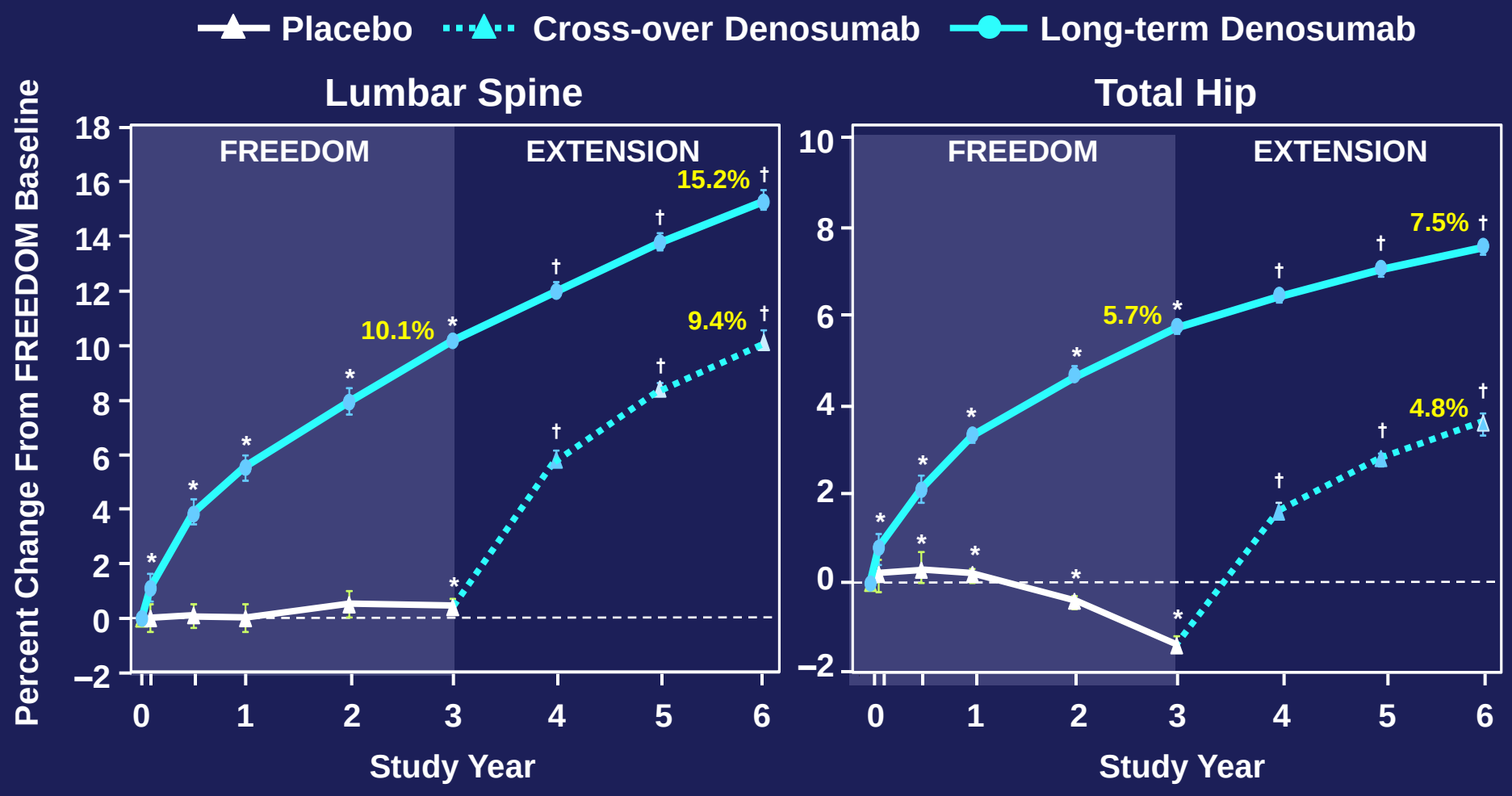


Key Inclusion Criteria

- Must have completed the FREEDOM study (received denosumab or placebo)
- Not receiving any other osteoporosis medications

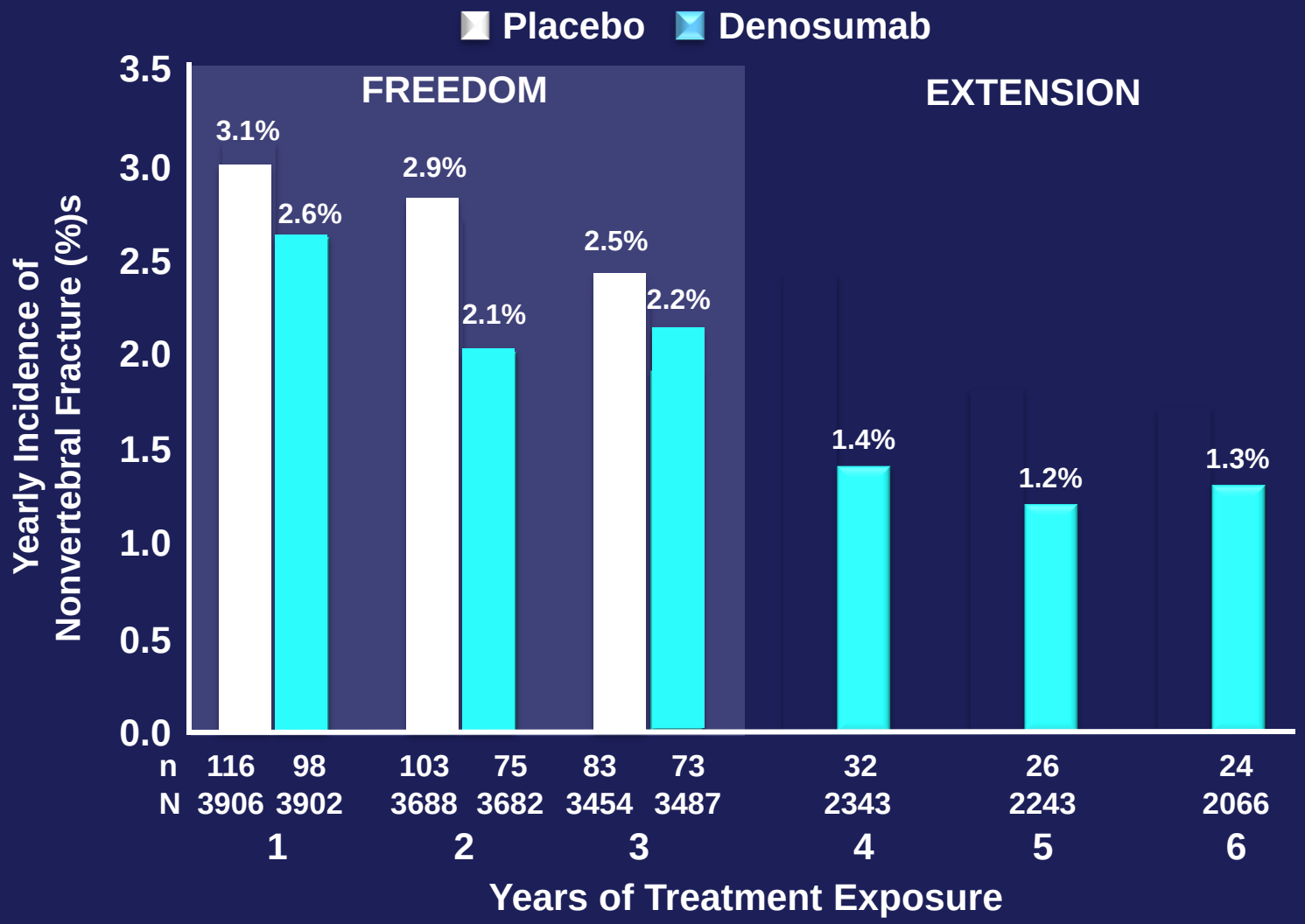
Adapted from : Cummings S et al. N Engl J Med 2009;361:756-65. ; Papapoulos S, et al. JBMR 2012; 27(3): 694-701.

Percent Change in BMD at the Lumbar Spine and Total Hip

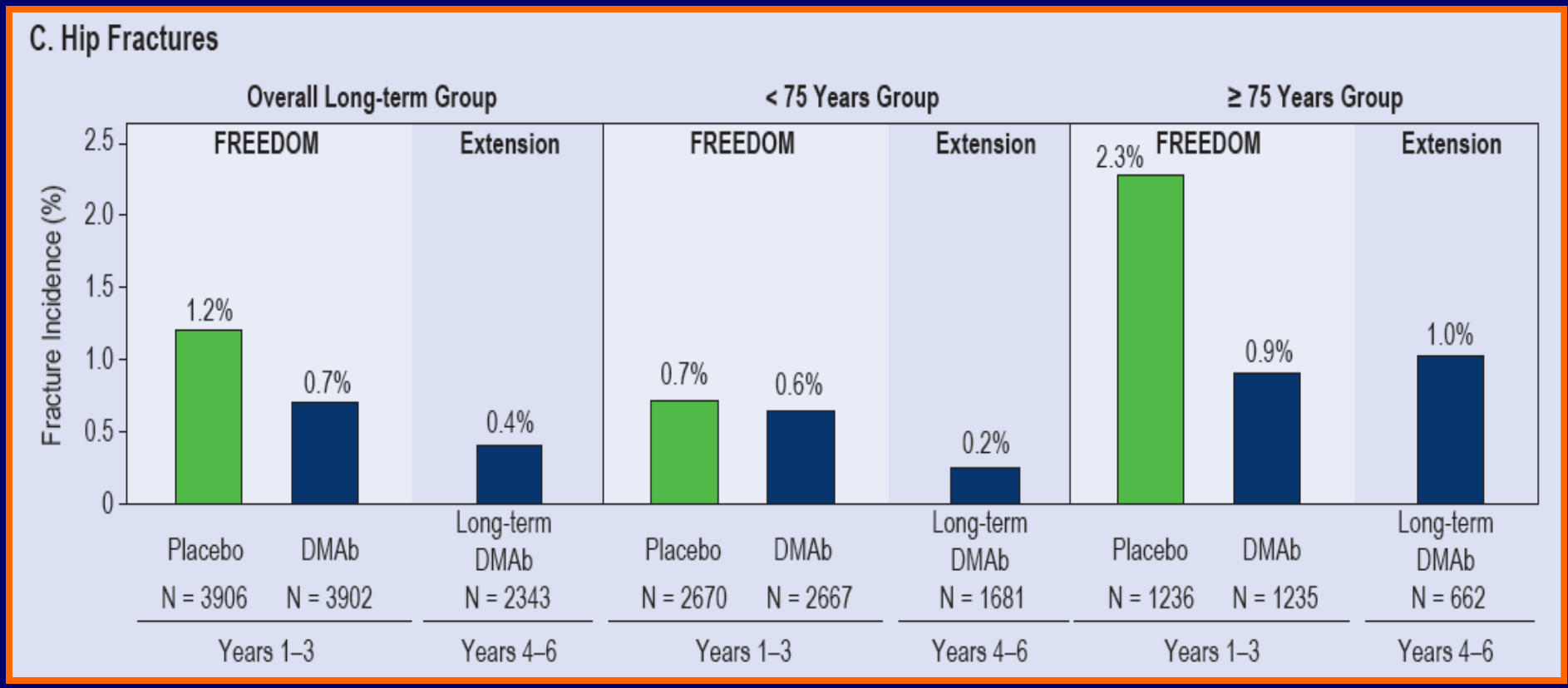


LS means and 95% confidence intervals. *$P < 0.05$ vs FREEDOM baseline; †$P < 0.0001$ vs FREEDOM baseline and Extension baseline.
Yellow numbers on the graphs represent the percent change in BMD while on denosumab treatment.

Yearly Incidence of Nonvertebral Fractures Through 6 Years: Long-term Group



Incidence of Hip Fractures Over 6 years According to Age



Papapoulos S et al ASBMR 2012

Conclusions

- Antiosteoporotic treatments are generally efficacious and well tolerated
- They have a favourable risk/benefit ratio, particularly these which reduce the incidence of hip fractures
- Knowledge of the efficacy, mechanism of action and risk profile of every treatment prescibed is essential for proper patient care