FOSAMAX® and FOSAMAX® PLUS D

FDA Advisory Committees Meeting
September 9, 2011

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Merck & Co., Inc.

Summary of Responses to FDA Questions

- When alendronate is used in accordance with the prescribing information for the t*reatment of osteoporosis in postmenopausal women*†:
  - 10-year clinical trial data support a favorable benefit to risk profile in osteoporotic patients who remain at risk of fracture
  - The determination that a patient requires long-term treatment should be made by the treating physician based on the patient's individual characteristics
  - A drug holiday may be considered for patients who are no longer considered to have a sufficiently high fracture risk
  - However, neither restricting the duration of use nor implementing a drug holiday is likely to be beneficial for patients at sufficiently high fracture risk who require long-term treatment

† Other indications: treatment of osteoporosis in men, glucocorticoid-induced osteoporosis, Paget's disease.

Evidence Supporting Long-Term Use of Alendronate in the Treatment of Osteoporosis

- Two 10-year trials of alendronate have compared the effects of continuing vs. discontinuing treatment after 5 years
  - Phase III studies long-term extensions (N=350)
  - FIT Long-Term Extension study (FLEX) (N=1099)
  - In these two studies: 897 on alendronate, 587 completed 10 years

- In patients previously treated with alendronate for 5 years, continued treatment with alendronate for an additional 5 years (versus placebo) in FLEX
  - Reduced clinical vertebral fracture risk by 55%
  - Reduced non-vertebral fracture risk by 39% in a relatively high-risk subgroup of patients
  - Maintained hip BMD and increased spine BMD
  - Maintained lower bone turnover that was stable over 10 years

FIT=Fracture Intervention Trial; BMD=bone mineral density.

Evidence Supporting Long-Term Use of Alendronate in the Treatment of Osteoporosis

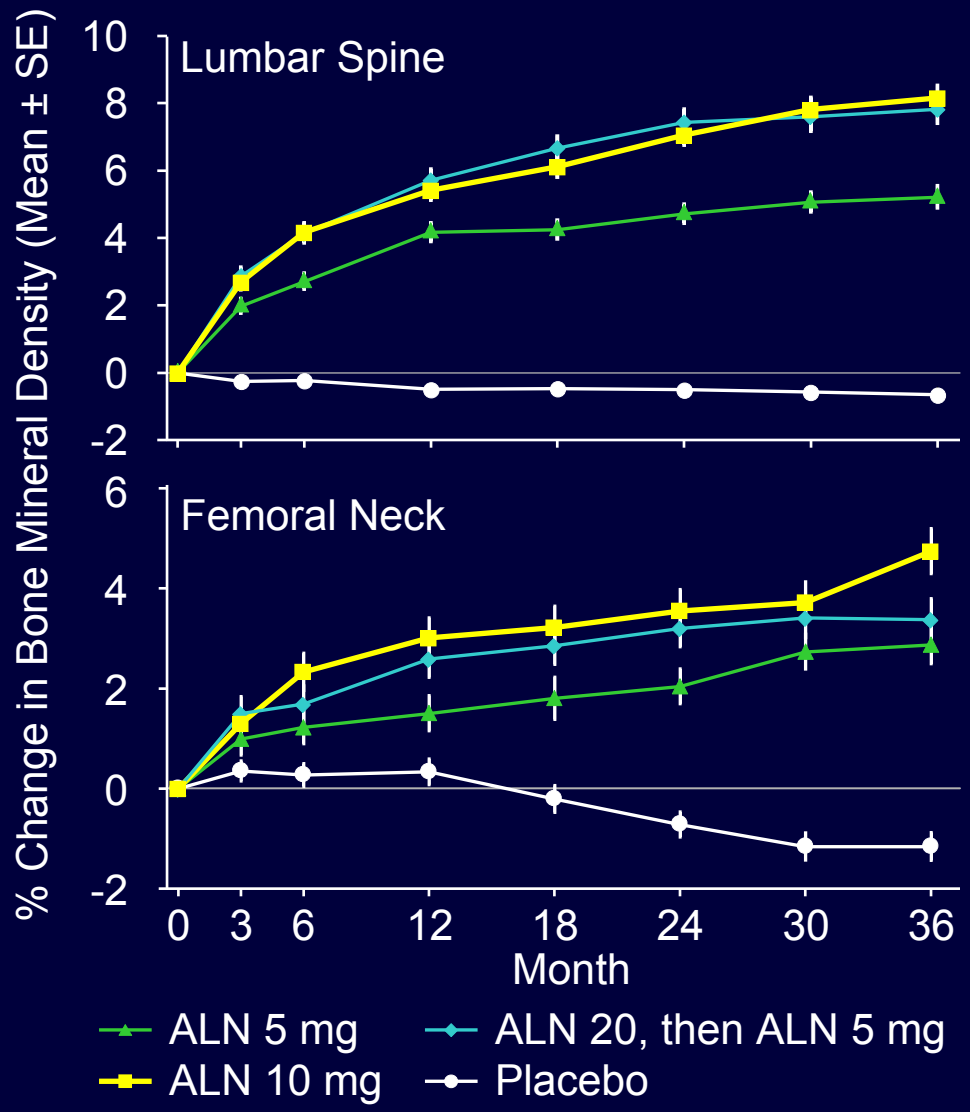
- Discontinuation of alendronate after 5 years led to:
  - Loss of hip BMD and stable spine BMD
  - Increase in bone turnover
- Safety profile for up to 10 years consistent with that established in studies ≤4 years
- In clinical studies up to 10 years:
  - No reports of osteonecrosis of the jaw
  - Subtrochanteric and diaphyseal femoral fractures infrequent with no difference in risk between drug and placebo groups
  - 2 reports of esophageal cancer, both after short-term use (<1 mo and 7 mo)

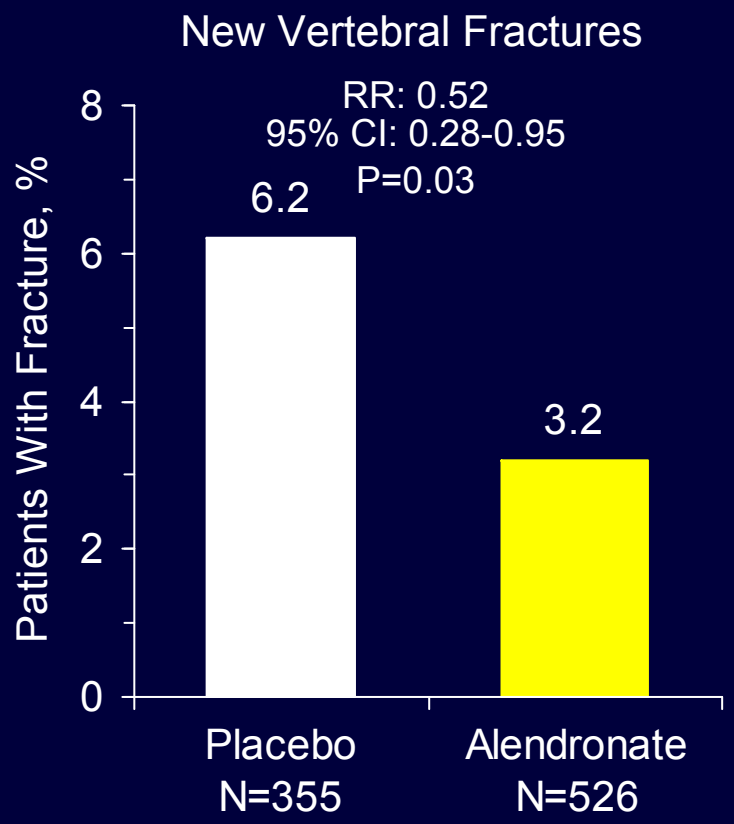
BMD=bone mineral density.

Studies ≤4 Years Duration

Phase III Studies and Fracture Intervention Trial (FIT)

3-Year Treatment with Alendronate Increased BMD and Decreased Vertebral Fracture Risk





BMD=bone mineral density; ALN=alendronate; RR=relative risk; CI=confidence interval.

Phase III Studies in
Liberman U, et al. NEJM 1995;333:1437-1443.

Fracture Intervention Trial (FIT): Design

Postmenopausal women with low femoral neck BMD

Prevalent Vertebral Fracture

Vertebral Fracture Study
(High Fracture Risk)
N=2027
Average age 71 yr
Follow-up = 3 yr

Key Endpoints
1° New Vertebral Fractures
2° Any Clinical Fracture

No Prevalent Vertebral Fracture

Clinical Fracture Study
(Lower Fracture Risk)
N=4432
Average age 67 yr
Follow-up = 4.25 yr (mean)

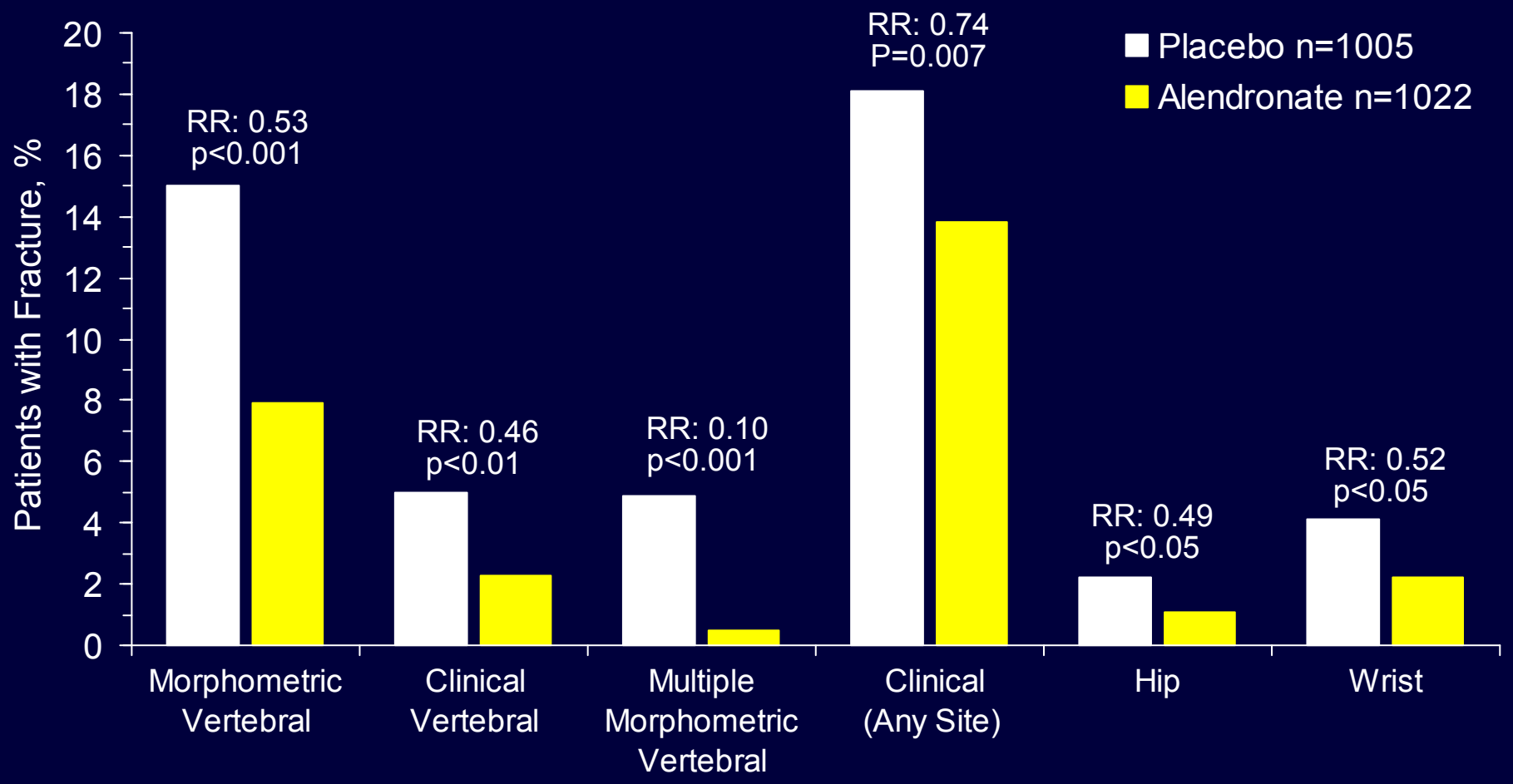
Key Endpoints
1° Any Clinical Fracture
2° New Vertebral Fractures

Black DM, et al. Lancet 1996;348:1535-1541.
Cummings SR, et al. JAMA 1998;280:2077-2082.
Low femoral neck BMD = T-score <-1.6.

Alendronate Reduced Fracture Risk at Multiple Sites

FIT 3-Year Vertebral Fracture Study

Patients with Vertebral Fracture at Baseline (High-Risk)

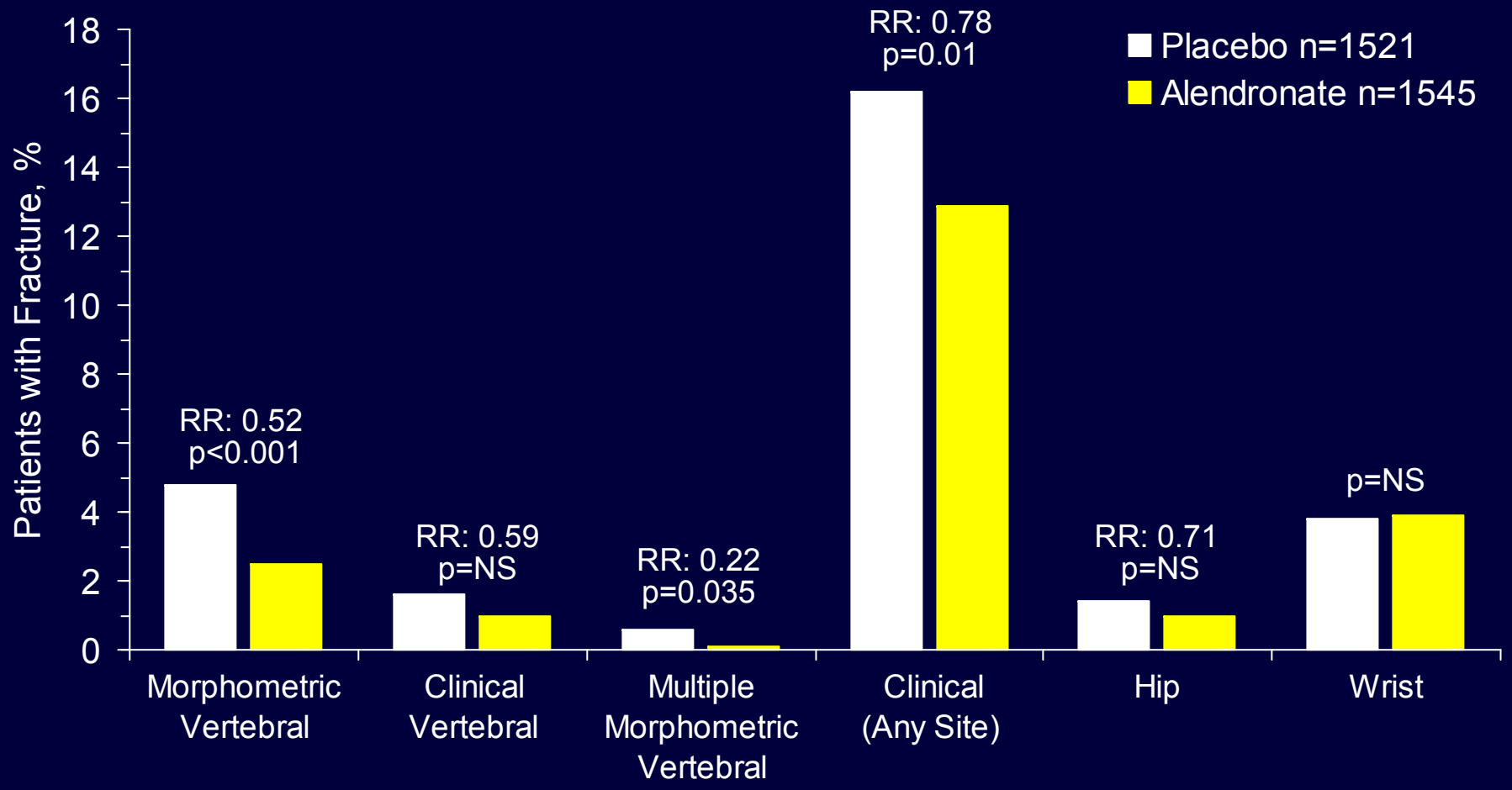


Cummings SR, et al. JAMA 1998;280:2077-2082.
RR=relative risk.

Alendronate Reduced Fracture Risk

FIT 4-Year Clinical Fracture† Study

Osteoporotic‡ Patients without Vertebral Fracture at Baseline



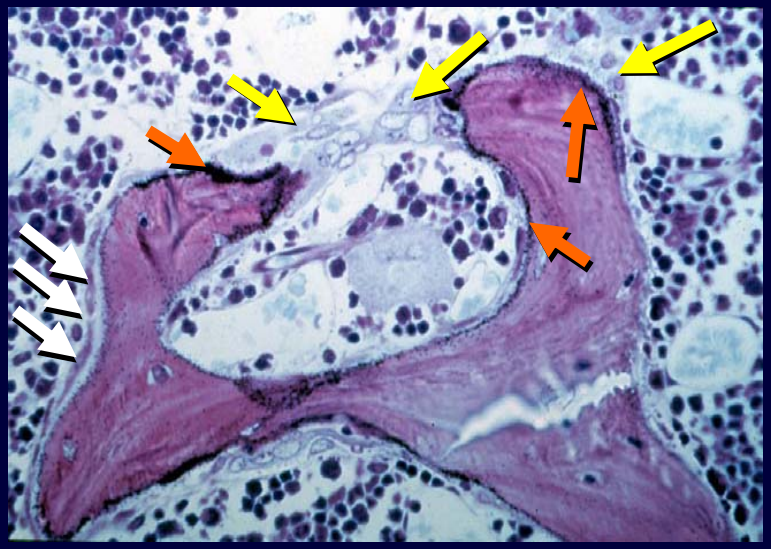
Cummings SR, et al. JAMA 1998;280:2077-2082.
† Clinical fractures defined as any fracture associated with clinical symptoms; ‡ Baseline femoral neck BMD T-score ≤-2.0;.
RR=relative risk; NS=not significant.

Pharmacokinetics of Alendronate and Implications for Long-Term Treatment

Alendronate is Active on Bone Surfaces and Inactive within Bone

- Absorbed alendronate is rapidly cleared from blood ($T_{½}$= 1-2 hr)
  - 50% rapidly excreted in urine
  - 50% on bone surfaces concentrated under osteoclasts
- Only alendronate on bone surfaces inhibits osteoclasts
- Alendronate on the surface of bone is either
  - Slowly released into blood, or
  - Trapped within newly formed bone where it does not inhibit osteoclasts
  - Estimated $T_{½}$ on the surface of bone is 2 to 5 weeks

Osteoblast **Osteoclast** **[^{3}H]Alendronate**



4 hours post-dose

Masarachia, et al. Bone 1996;19:281-290.

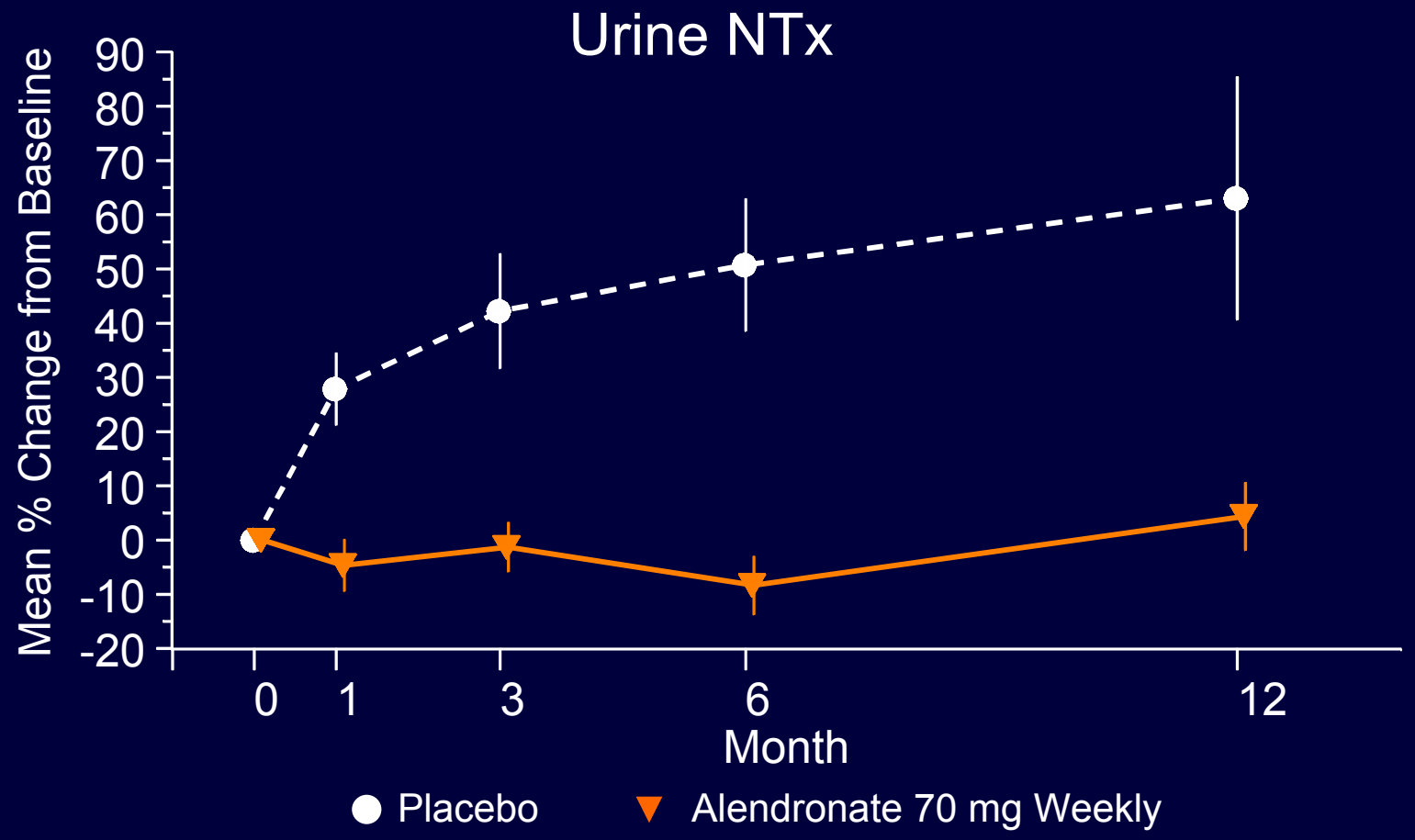
Release of Alendronate During Long-Term Dosing

- Osteoclasts may release alendronate trapped in bone
- The amount of alendronate released depends on prior dose and duration of treatment
- The amount released from bone will be insufficient to prevent bone loss if discontinued after 5 to 10 years
  - After 5 years of treatment with alendronate 10 mg daily, the amount released from bone each day is approx. the same as that absorbed after a 1.7 mg daily dose
  - After 10 years of treatment with alendronate 10 mg daily, the amount released from bone each day is approx. the same as that absorbed after a 2.5 mg daily dose

Modeled data based on Clinical Pharmacology terminal elimination kinetics.

Bone Resorption Increases Quickly After Long-Term Treatment is Discontinued

Patients Previously Treated with Bisphosphonates for ~5 Years

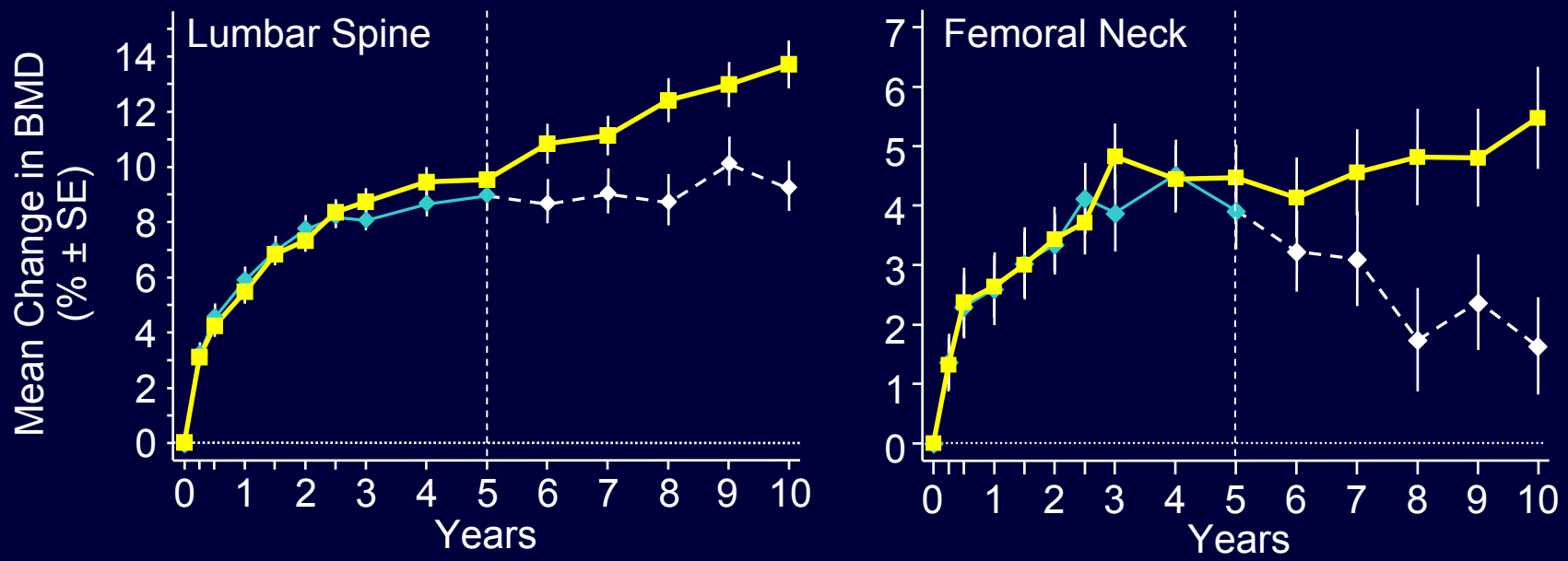


Urine NTx=urine N-Telopeptides of type 1 collagen to creatinine ratio (bone resorption marker).
The figure represents the LS Geometric Mean ± SE.
Prior use of bisphosphonates: mean 6.0 years, median 5.2 years.
Data on file.

Phase III Studies Long-Term Extensions to 10 Years

Change in BMD with Continuous Treatment vs. Discontinuation

Phase III Extension Studies to 10 Years

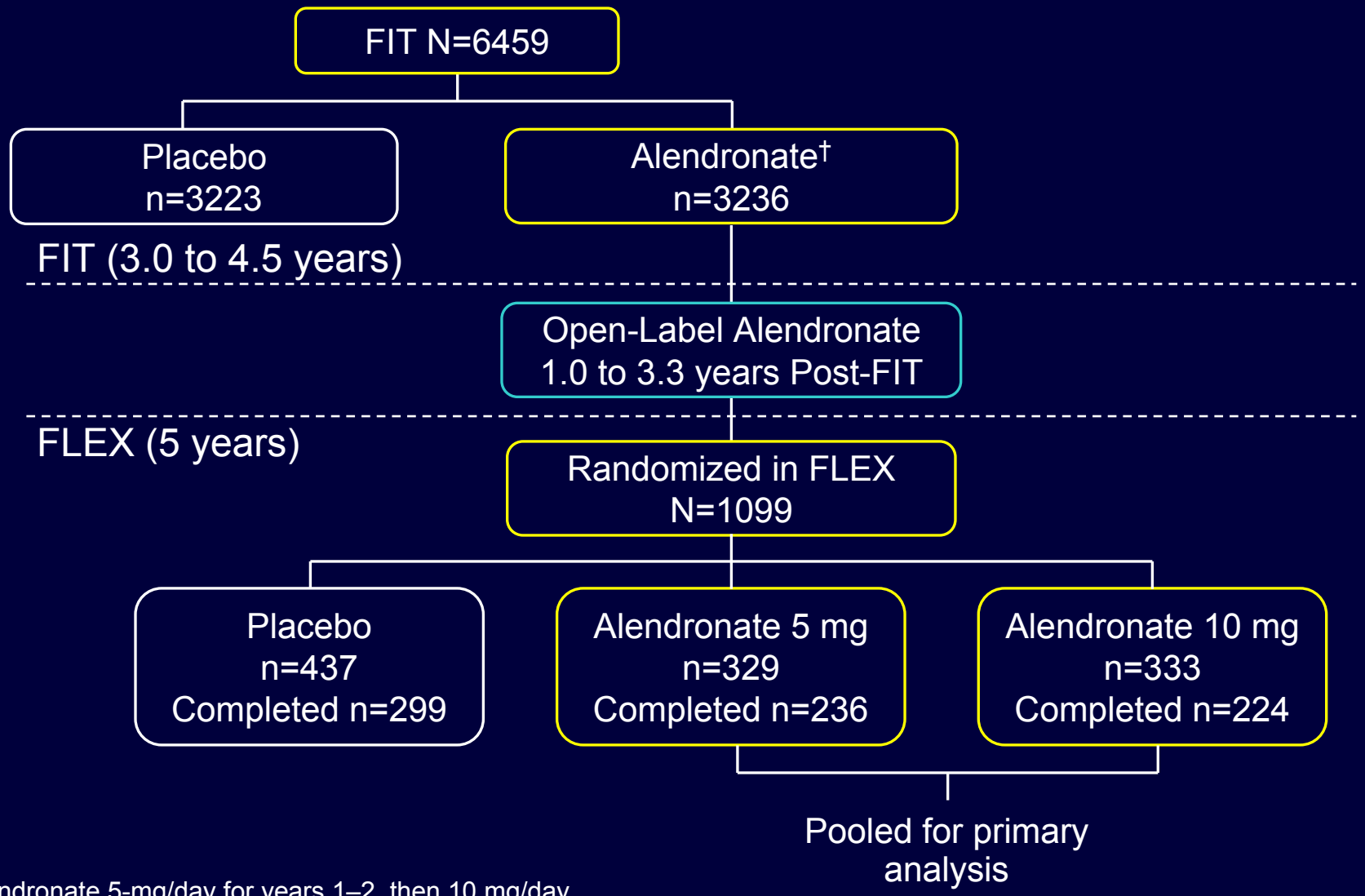


Adapted from Bone, et al. N Engl J Med 2004:350;1189-1199.
BMD=bone mineral density; ALN=alendronate.

Fracture Intervention Trial Long-Term EXtension (FLEX) Study:

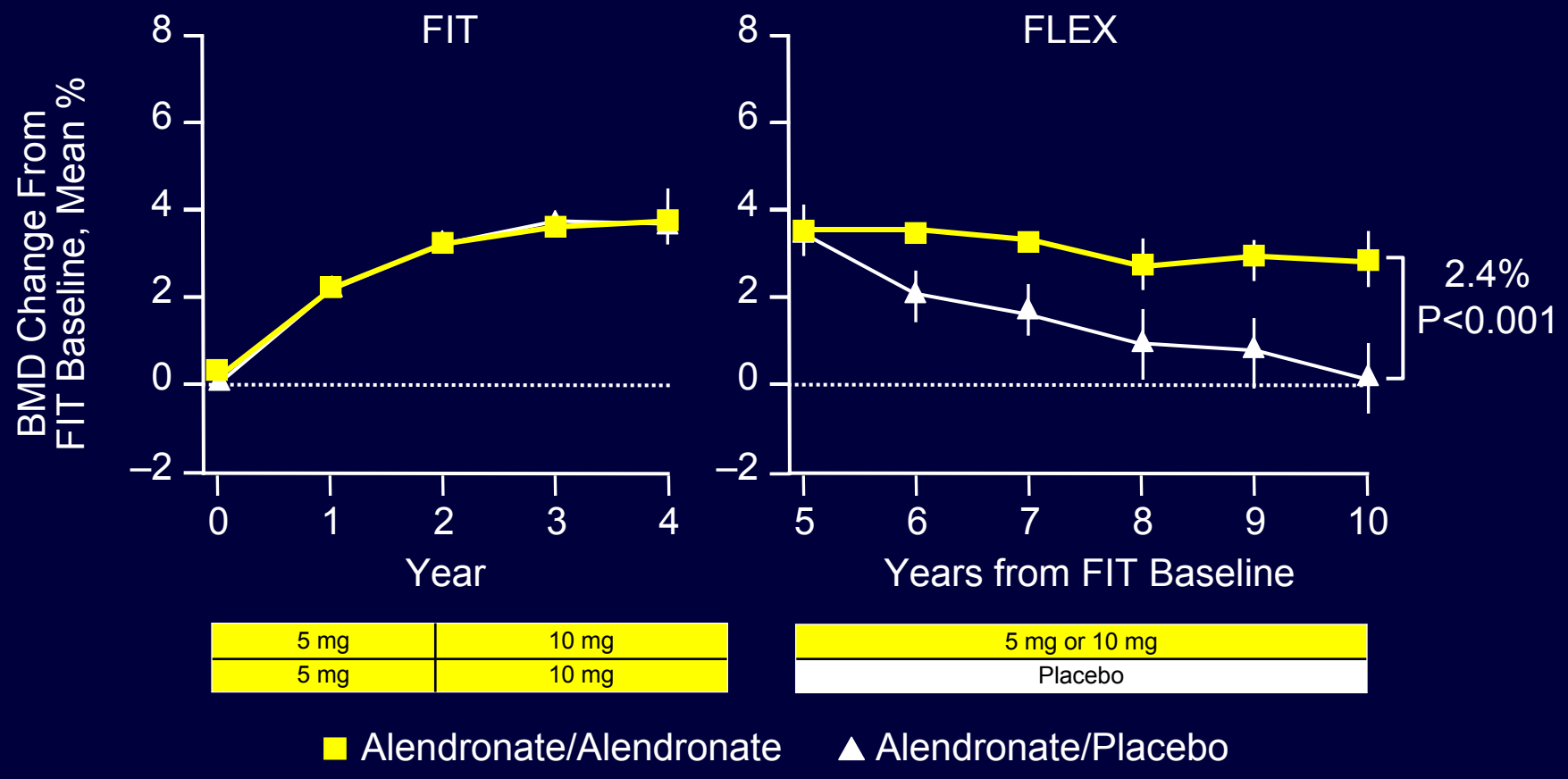
Experience with Alendronate Years 5-10

FLEX Study: Patient Enrollment



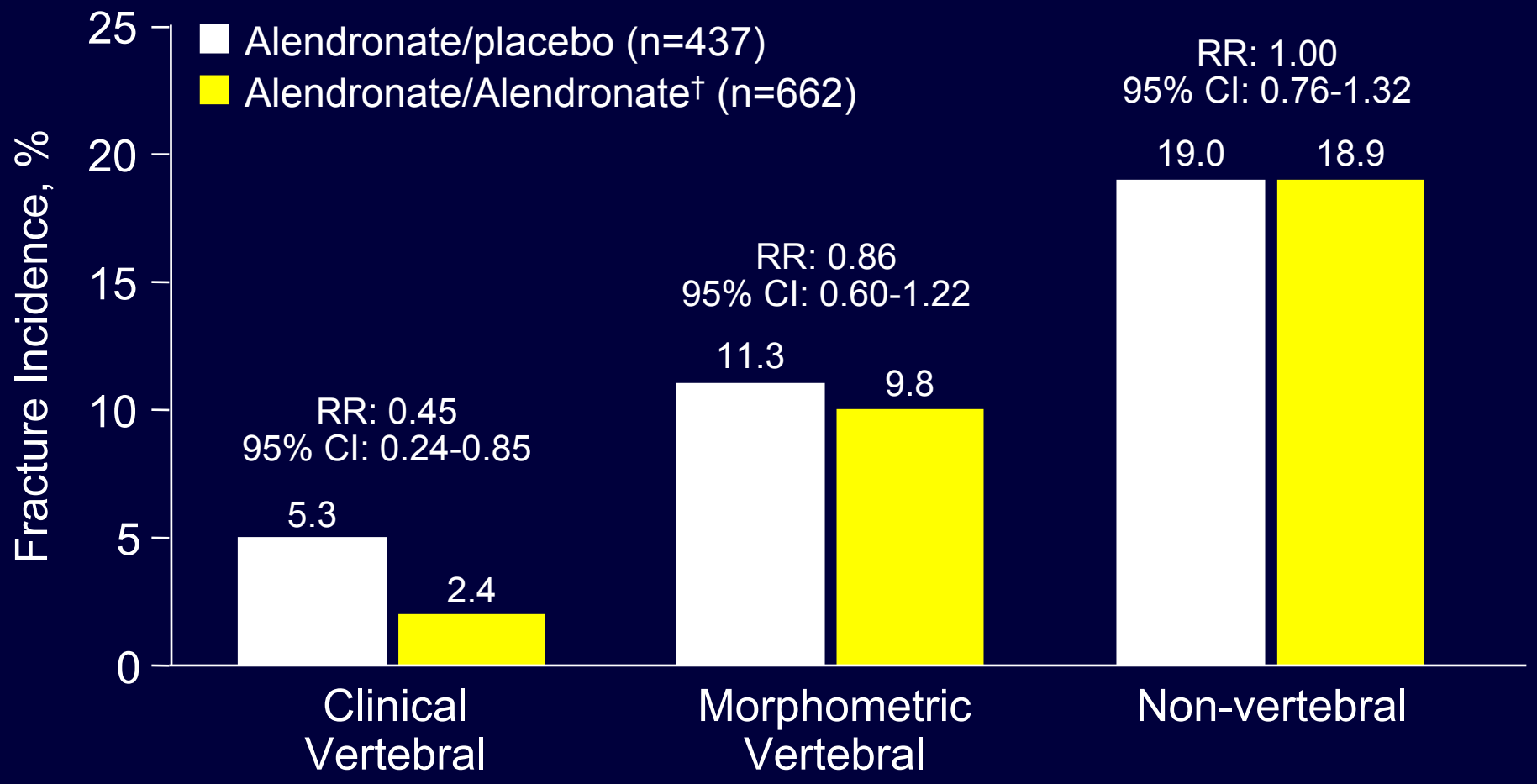
† Alendronate 5-mg/day for years 1–2, then 10 mg/day.
FLEX=FIT Long-term EXtension study; FIT=Fracture Intervention Trial.
Adapted from Black DM, et al. Osteoporos Int 1993; 3(suppl 3):S29-S39; Black DM, et al. JAMA 2006;296:2927-2938.

Change in Total Hip BMD FIT and FLEX



Pooled 5-mg and 10-mg groups; Error bars indicate 95% confidence interval.
Adapted from Black DM, et al. JAMA. 2006;296:2927-2938.
BMD=bone mineral density; FIT=Fracture Intervention Trial; FLEX=FIT Long-term EXtension study.

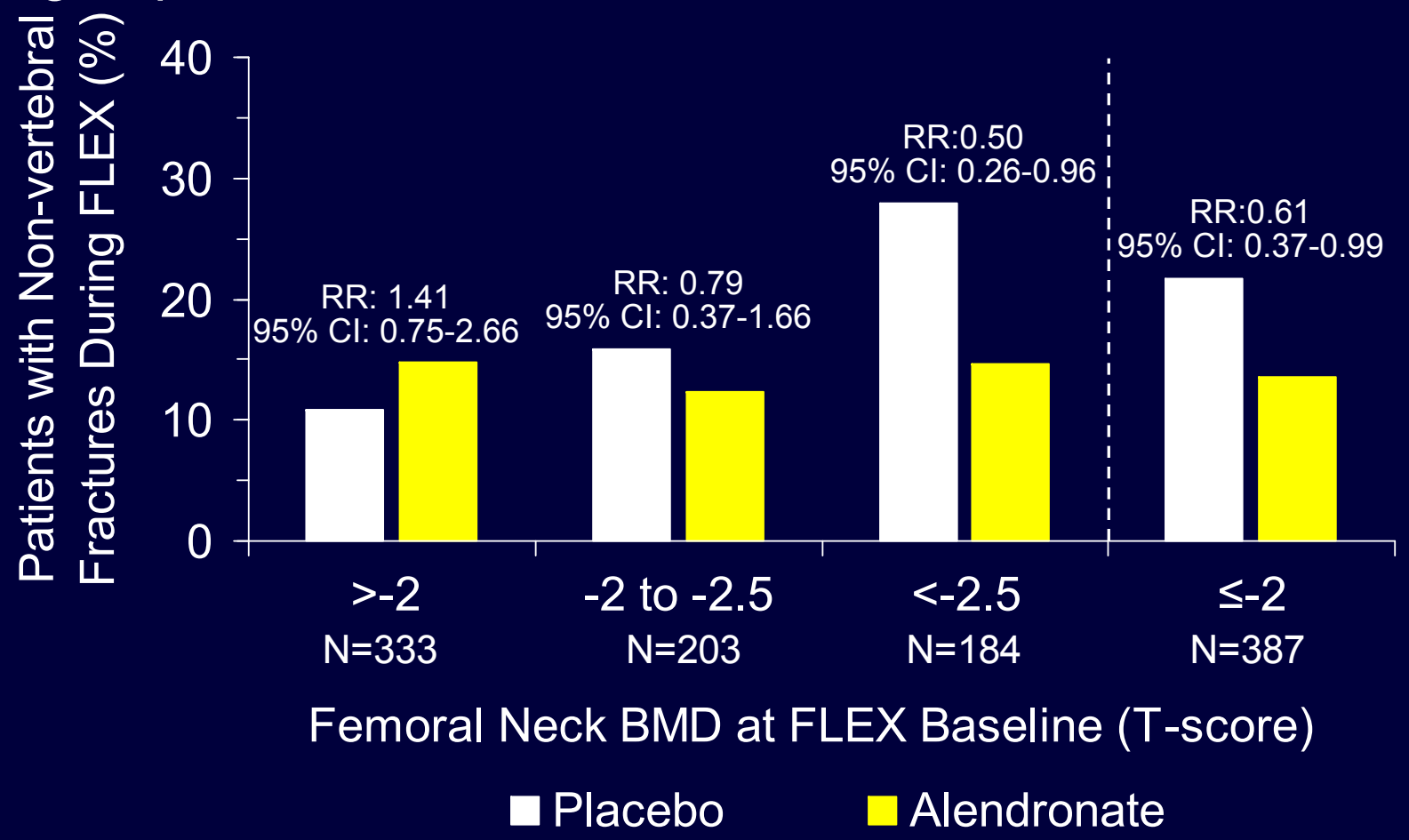
Fracture Incidence in FLEX



† Pooled 5-mg and 10-mg groups.
Adapted from Black DM, et al. JAMA. 2006;296:2927-2938.
FLEX=FIT Long-term EXtension study; RR=relative risk; CI=confidence interval.

Reduction in Non-vertebral Fracture Risk in Patients with Low FLEX Baseline BMD

Subgroup of FLEX Patients with No Prior Vertebral Fractures



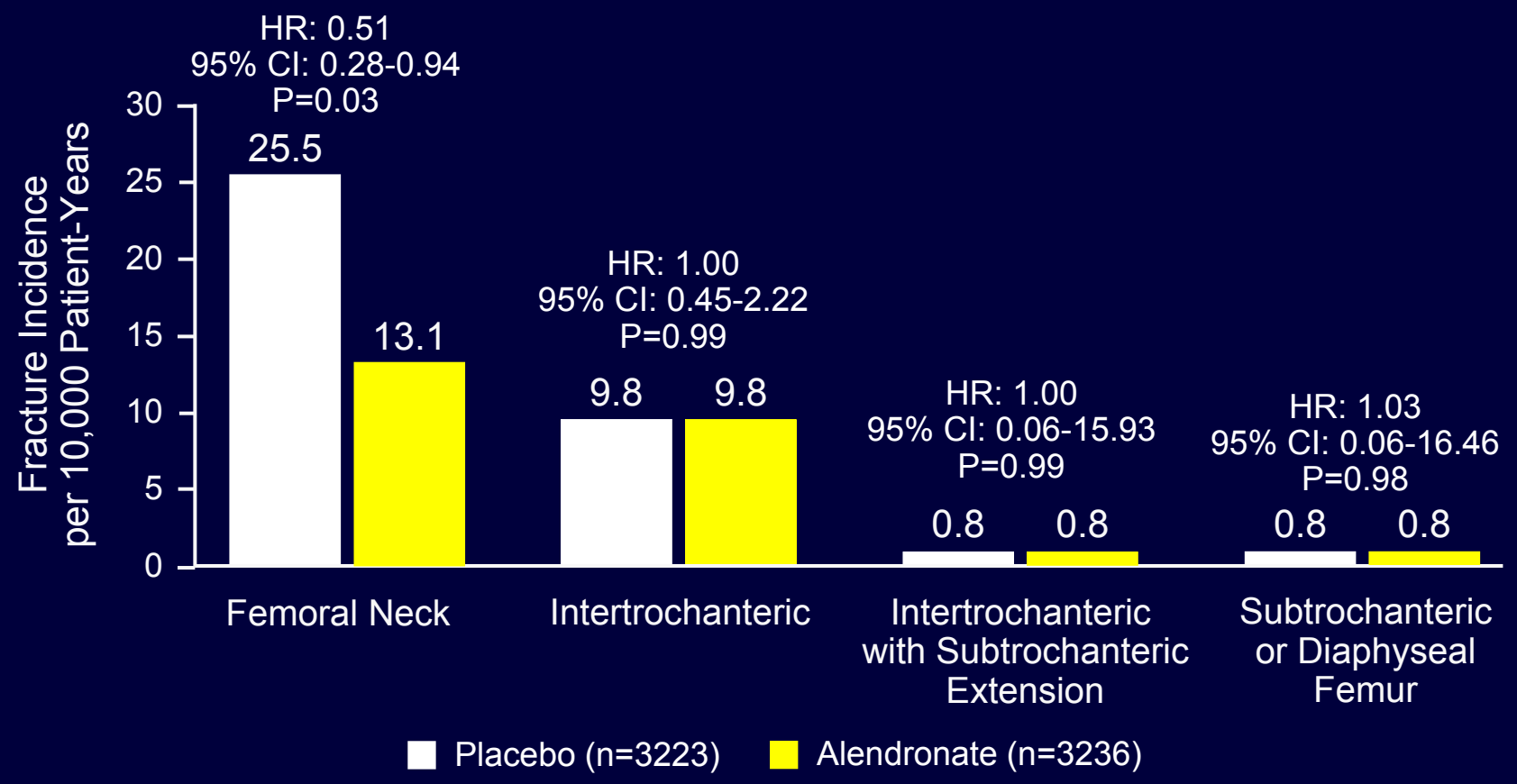
Post-hoc analysis of 720 patients.
Adapted from Schwartz, A. J Bone Min Res 2010;25:976-982.
FLEX=FIT Long-term EXtension study; BMD=bone mineral density.

Safety Concerns for Discussion at This Advisory Committee Meeting: Merck Clinical Trial Experience

- No reports of osteonecrosis of the jaw in any clinical study of alendronate conducted by Merck
- 2 Reports of esophageal cancer
  - Durations of treatment: <1 month and 7 months
- Atypical subtrochanteric and diaphyseal femoral fractures
  - Location of femoral fractures evaluated in FIT and FLEX
  - Subtrochanteric and diaphyseal femoral fractures were rare and occurred in both alendronate and placebo groups

FIT=Fracture Intervention Trial; FLEX=FIT Long-term EXtension study.

Subtrochanteric and Diaphyseal Femoral Fractures Were Rare in FIT



FIT=Fracture Intervention Trial pooled data from FIT Vertebral Fracture and Clinical Fracture Study; Black DM, et al. N Engl J Med. 2010;362(19):1761-1771.
HR=hazard ratio; CI=confidence interval.

Subtrochanteric and Diaphyseal Femoral Fractures in FIT and FLEX

	FIT		FLEX	
	Alendronate N=3236 n (%)	Placebo N=3223 n (%)	Alendronate N=662 n (%)	Placebo N=437 n (%)
Patients with subtrochanteric or diaphyseal femoral fractures	1 (<0.1)	1 (<0.1)	2 (0.3)	1 (0.2)

Black DM, et al. N Engl J Med. 2010;362 (19):1761-1771.
FIT=Fracture Intervention Trial; FLEX=FIT Long-term EXtension study.

Would either restricting the duration of use or implementing a drug holiday be beneficial for patients requiring long-term treatment?

- 10-year clinical trial data support a favorable benefit to risk profile in osteoporotic patients who remain at risk of fracture and require long-term treatment
  - A drug holiday may be considered for patients who are no longer considered to have a sufficiently high fracture risk
  - However, neither restricting the duration of use nor implementing a drug holiday is likely to be beneficial for patients at sufficiently high fracture risk who require long-term treatment
- In patients who require long-term treatment, interruption of treatment would result in:
  - Increased bone turnover within 1 month
  - Loss of BMD acquired during treatment over several years
  - Increased fracture risk versus continued treatment
- There are insufficient data to predict the effect of interruption of treatment on rare adverse events
- Each patient has unique risks of bone loss, fracture, potential adverse drug effects as well as response to prior therapy
- Each patient on bisphosphonate therapy should be re-evaluated on a periodic basis to determine the need for continued therapy

BMD=bone mineral density.