Osteoporosis Rx: Clinical Decisions Today

Robert A. Adler, MD
McGuire Veterans Affairs Medical Center, Richmond
Virginia Commonwealth University

Disclosures

- Research Support (to institution)
  - Amgen
  - Eli Lilly
  - Genentech
  - Merck
  - Novartis

Osteoporotic Fractures

- > 1,500,000 Osteoporotic Fractures Annually
- Bisphosphonates →
  - ↓ Vertebral Fracture 41-70%
  - ↓ Non-vertebral fracture 25-39%
  - ↓Hip fracture 40-51%

Modified from O'Connell & Vondracek in Pharmacotherapy 7th Edition, 2008

Bisphosphonates: FDA-Approved Indications

Agent	Osteoporosis: Women	Osteoporosis: Men	Glucocorticoid-induced Osteoporosis	Secondary Fracture Prevention
Alendronate	X	X	X	
Risedronate	X	X	X	
Ibandronate	X			
Zoledronic acid	X	X	X	X

Patient 1: 71 yo man

- Compression fx, rib fx on x-ray
- COPD, still smoking, EtOH > 3 units daily
- H/o Zenker's diverticulum, GERD
- 170 cm/ 67.4 kg
- Spine T -1.4, FN -2.2 Forearm -2.9
- FRAX: 17% any fx; 8.1% hip fracture/10 yrs.
- Garvan: 55.5% any fx; 11.4% hip fx/10 yrs.

SK Sandhu, Osteoporos Int 21:863, 2010

Patient 2: 60 yo Woman

- BSO age 30, Gastric Bypass age 52
- ~400 lbs to 190 lbs, now 240 lbs
- Femoral neck -2.8
- No other risk factors for FRAX calculation
- FRAX: Any fx: 12%; hip 3.1% in 10 years
- Life expectancy > 10 years

Dilemma Facing the Clinician

- People with osteoporosis & ↑fracture risk
- Bisphosphonates decrease fracture risk
- Some treatments are inexpensive
- Rx is for a long time; optimal length of Rx is unknown
- What to do about side effects:
  - Who will get them?
  - Not enough data!
  - Does concern for side effects → ↓ adherence?

PN Sambrook Med J Aust 193:154, 2010

Compliance and Fractures

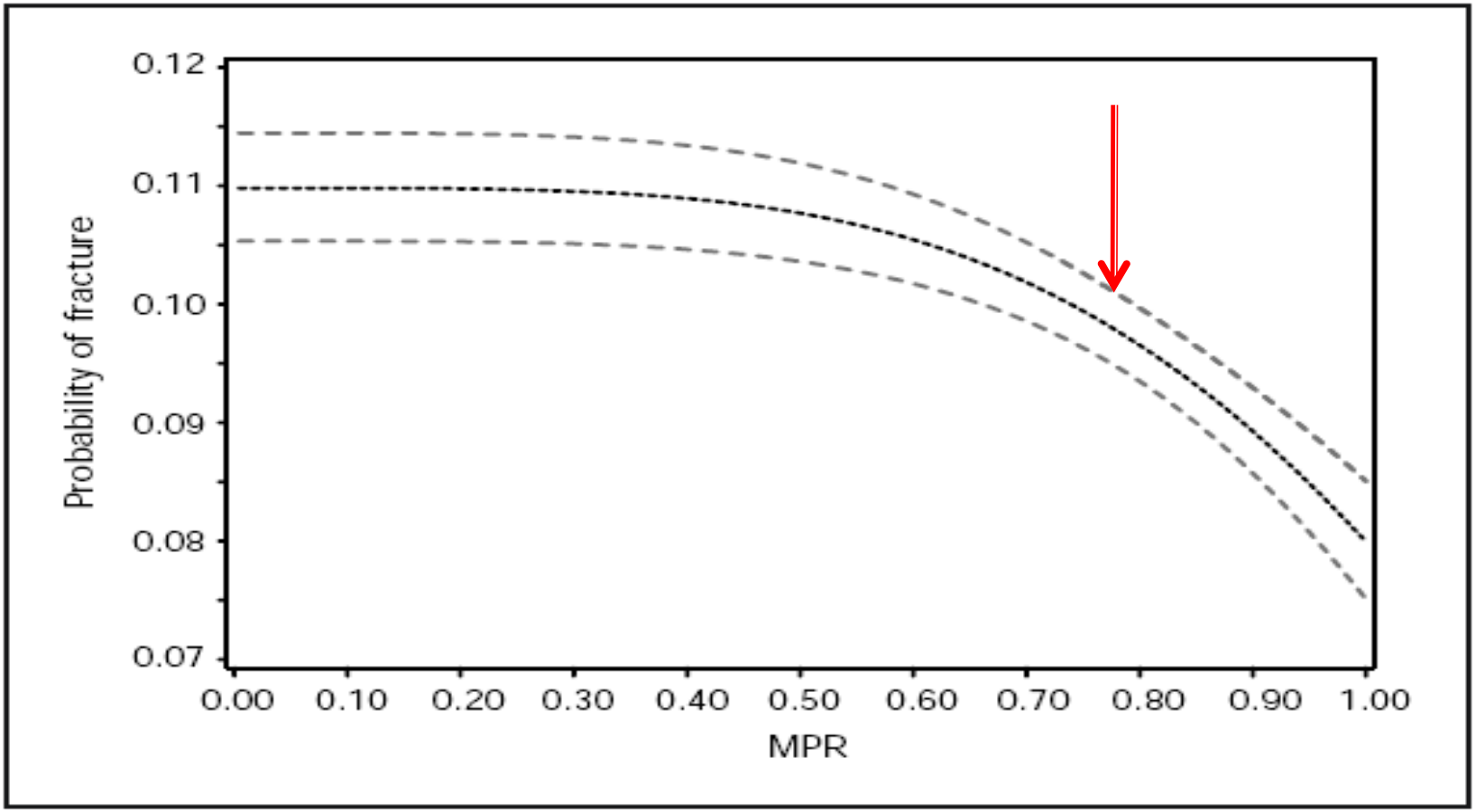


FIGURE 2. Probability of fracture in 24 months in the bisphosphonate-treated patients. MPR = medication possession ratio.

Siris ES, Mayo Clin Proc 81:1013, 2006

Nonadherence

- Population based studies: must take 75-80% of tx in order to benefit from fx ↓
- Review of compliance and persistence data from randomized and observational trials
  - 16-53% of patients have satisfactory compliance
  - ~50% of patients discontinue tx within 1 yr
- Cost, asymptomatic nature of disease, adverse effects and complex dosing regimens may contribute

Williams & Petkov in Adler, ed, Osteoporosis-Pathophysiology & Clinical Management 2nd Ed, 2010.

Side Effects: Mild or Avoidable

- Worsening of GERD: take Rx correctly, have GERD under control first
- Don't use oral Rx in esophageal mobility disorders
- Acute Phase Reaction: mostly with first IV dose; hydration and acetaminophen help
- Hypocalcemia: unusual but assure adequate calcium and vitamin D
- Renal toxicity: use in patients with adequate renal function: safety testing

Atrial Fibrillation

- Unexpected ↑in serious AEs – a. fib. in zoledronic acid registration trial
- Found rarely in other major trials
- Age is common risk factor
- Meta-analyses not consistent
- Korean study: bisphosphonates protective! [HR 0.52 (0.29-0.91]

CW Rhee, OI on line 3/24/2011; B Abrahamsen J Intern Med 265:581, 2009

Osteonecrosis of the Jaw (ONJ)

- Common in cancer patients on high dose/high frequency I.V. bisphosphonates
- Probably between 1/10,000-1/100,000 in osteoporosis doses
- Mechanism still unclear

S. Khosla, J Bone Miner Res 22:1479, 2007

American Dental Association Recommendations

- Attention to teeth before Rx
- Good dental hygiene for all
- Avoid invasive dental procedures if possible
- No need to stop Rx if procedures needed
- Worst case incidence: 1/1,000
- ADA prefers term ARONJ: Anti-resorptive associated osteonecrosis of the jaw

J Hellstein et al, JADA November 2011

Esophageal Cancer & Oral Bisphosphonates

- UK:↑Risk 1.30 (1.02-166), higher with longer Rx
- UK: No ↑Risk 1.07 (0.77-1.49)
- Probably no ↑ risk in years 1-3
- 5 extra cases/10,000 pt-yrs in years 4-7
- Risks of osteoporosis AND esophageal carcinoma:
  - Age
  - Alcohol excess
  - Smoking

J Green BMJ 2010;341:c4444, CR Cardwell JAMA 2010;304:657; Dixon & Solomon Nat Rev Rheumatol 7:369, 2011

Atypical Subtrochanteric Fractures

- Unusual
- Mechanism unclear
- Need to know background incidence – are osteoporosis patients at ↑risk before Rx?
- Probably 5 cases/10,000 patient-years
- Probably 30-100 typical fractures prevented for every atypical fracture

E Shane, JBMR 25:2267, 2010, J Schilcher NEJM 364:1728, 2011, P Vestergaard, OI online 12/17/2010

Bisphosphonate Half-Life

- "The gift that keeps on giving"
- Half-life estimated in years
- Recent study of discontinuation for ~14 mos.
  - 41% of women had detectable alendronate in urine
  - 0% of women had detectable risedronate in urine

P Peris, Bone doi:10.1016/j.bone2011.06.027

Risedronate Discontinuation after 3 years

- 3 Years of Risedronate + 1 year Discontinuation:
  - ↓BMD
  - ↑Bone Turnover Markers
  - Fracture risk still less than placebo group

NB Watts, Osteoporos Int 19:365, 2008

Risedronate Discontinuation after 7 Years

- Small numbers
- 7 years of Risedronate + 1 year discontinuation
  - ↓Total hip, Trochanter
  - Stable Femoral neck, spine
  - ↑BTMs

R Eastell, J Clin Endocrinol Metab on line Aug 24, 2011

Bisphosphonates: ↓Mortality

- IV-Post-hip fracture: 28% ↓relative risk
- PO-Post-hip fracture: ~63% ↓relative risk/year of Rx
- Dubbo Trial: ↓Mortality in women, possibly in men
- Institutionalized elders: HR [0.73 (0.56-0.940)]

Lyles, NEJM 357:1799, 2007; Beaupre OI 22:983, 2011; Center JCEM 96:1006, 2011; Sambrook OI 22:2551, 2011

Bisphosphonate Rx: Summary

- Patients are at risk and bisphosphonates decrease fracture risk!
  - Adherence necessary: need to monitor
- Long term use: 5-10 years for most patients
- Optimal treatment length unclear
- Despite rare side effects, ↓Fractures and ↓Mortality with bisphosphonates
  - This finding needs to be shared with patients
  - General public needs to know this

Bisphosphonates

Regulatory History

Theresa Kehoe, M.D.
Medical Officer, Team Leader
Division of Reproductive and Urologic Products
Office of New Drugs, CDER, FDA

Postmenopausal Osteoporosis

- Osteoporosis is defined as a systemic skeletal disorder of compromised bone strength, predisposing an individual to an increased risk of fracture
- Currently, an estimated 10 million people in the US have osteoporosis (8 million women, 2 million men)
- An estimated 34 million people have low bone mass and are at risk for developing osteoporosis

WHO Criteria for Diagnosis based on Bone Mineral Density

T score*	Classification
Greater than –1	Normal
–1 to –2.5	Osteopenia (low bone mass)
–2.5 or less	Osteoporosis

*T score indicates the SDs below or above the average peak bone mass in young adults

FRAX

- Tool developed by the WHO to evaluate fracture risk
- Integrates clinical risk factors as well as femoral neck BMD
- Reported as 10-year probability of hip fracture and 10-year probability of major osteoporotic fracture

Osteoporosis Treatment Guidelines*

- **1998**:
  - BMD T-score ≤ -2.0
  - BMD T-score ≤ -1.5 with other risk factors
- **2008**:
  - hip or vertebral fracture
  - BMD T-score ≤ -2.5
  - BMD T-score ≤ -1.0 <u>and</u> a 10-year probability of hip fracture ≥ 3% or a 10-year probability of major osteoporotic fracture ≥ 20% based on US adapted WHO algorithm (FRAX)

*from the National Osteoporosis Foundation

Therapies Seeking an Indication for Treatment of Osteoporosis

- Must demonstrate nonclinical evidence of bone quality including biomechanical testing of bone strength
- Must demonstrate fracture reduction efficacy in a 3-year clinical trial.
- Must demonstrate bone quality and normal mineralization on bone biopsy (bone histomorphometry)
- Once fracture efficacy is established, subsequent indications or new dose regimens are based on BMD non-inferiority

Bisphosphonate Products Available for Treatment of Osteoporosis

- Currently, there are four bisphosphonate products available for the treatment of osteoporosis:
  - **Alendronate** (Fosamax, Fosamax Plus D, generics)
  - **Risedronate** (Actonel, Actonel with Calcium, Atelvia, generics)
  - **Ibandronate** (Boniva tablets, Boniva injection, generics)
  - **Zoledronic acid** (Reclast)
- Daily to once yearly dosing regimens available

Bisphosphonates and Bone

- Bisphosphonates are pyrophosphate analogs
- Bind to hydroxyapatite crystals and are incorporated into bone mineral
- Bisphosphonate remains in the bone until there is osteoclast activity
- As the osteoclast breaks down bone, the bisphosphonate is released and causes osteoclast cell death

Bisphosphonate Regulatory History

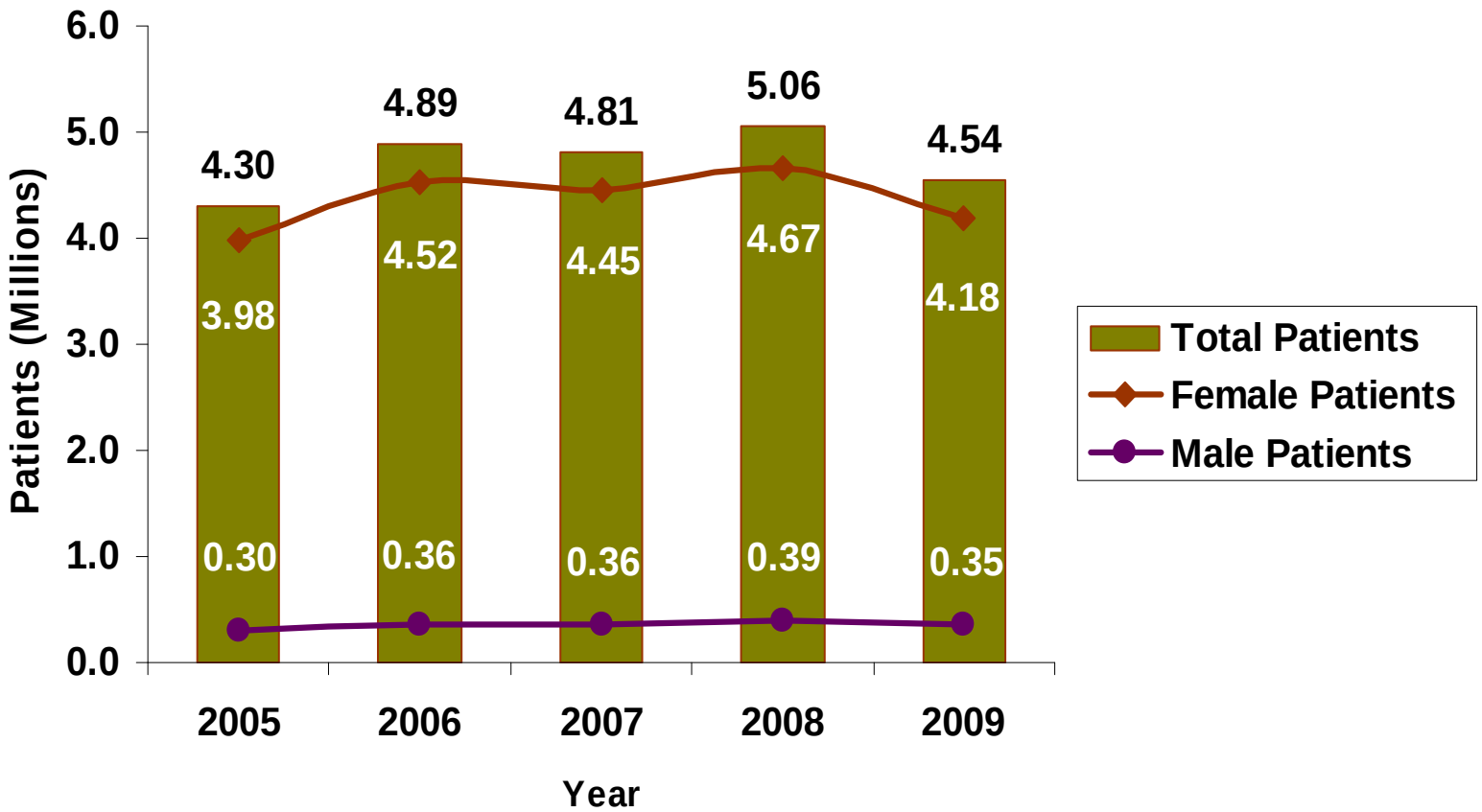
- The first bisphosphonate approval in the US occurred in 1977 (etidronate)
- The first bisphosphonate approval for osteoporosis indications occurred in 1995
  - Fosamax (alendronate): 1995
  - Actonel (risedronate): 2000
  - Boniva (ibandronate): 2003
  - Reclast (zoledronic acid): 2007

Bisphosphonate Efficacy

Drug	N	% Subjects MVF		ARR	RRR
		Drug	Placebo		
Fosamax	994	3.2	6.2		49
	2027	7.9	15.0	7.1	47
	3066	2.5	4.8	2.3	48
Actonel	1374	11.3	16.3	5.0	41
	690	18.1	29.0	10.9	49
Boniva	1952	4.7	9.6	4.9	52
Reclast	7736	3.3	10.9	7.6	70

MVF = morphometric vertebral fracture
ARR = actual risk reduction; RRR = relative risk reduction

Total patients age 55+ years who filled a prescription for bisphosphonates in U.S. outpatient retail pharmacies



Source: SDI Total Patient Tracker. Data Extracted 4/2010.

Bisphosphonate Efficacy

- Robust efficacy seen in the fracture trials, many patients receiving these drugs.

- National Hospital Discharge Survey
  - Hospital discharge rates*
    - 1996: Hip 598 per 100,000 persons
    - 2006: Hip 428 per 100,000 persons

*Nieves 2010. Osteoporosis Int 21:399-408

Bisphosphonate Regulatory History: Safety

- **Mineral Metabolism: Hypocalcemia**
- **Gastrointestinal Adverse Reactions**
- **Musculoskeletal Adverse Reactions**
- **Renal Adverse Reactions**
- **Osteonecrosis of the jaw**
- **Atypical Subtrochanteric and Femoral Diaphyseal Fractures**

Mineral Metabolism: Hypocalcemia

- Preexisting hypocalcemia is a Contraindication
- Hypocalcemia is a Warning and Precaution
- Hypocalcemia adverse reactions in the clinical trials were low – all patients received calcium and vitamin D supplementation
- Hypocalcemic tetany attributed to bisphosphonates has been reported postmarketing

Gastrointestinal Adverse Reactions

- Oral bisphosphonates well known to cause gastroesophageal adverse reactions
  - Attributed to mucosal irritation, mainly esophagus
- Initially labeled as a Precaution at the time of Fosamax approval in 1995
- Upgraded to a Contraindication and a Warning in 1997.
- In 2009, the Gastrointestinal Adverse Reactions Warning and Precaution was updated to class labeling

Gastrointestinal Adverse Reactions Contraindication

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 (60) minutes

Gastrointestinal Adverse Reactions

Warning and Precaution

[Drug], like other bisphosphonates administered orally, **may cause local irritation of the upper gastrointestinal mucosa**. Because of these possible irritant effects and a potential for worsening of the underlying disease, **caution should be used when [drug] is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers)**

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. **Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue [drug] and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn**.

Gastrointestinal Adverse Reactions

Warning and Precaution, cont'd

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6 to 8 oz) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, **it is very important that the full dosing instructions are provided to, and understood by, the patient.** In patients who cannot comply with dosing instructions due to mental disability, therapy with [drug] should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

Musculoskeletal Adverse Reactions

- Bone, joint and muscle pain reported with bisphosphonate use postmarketing
- Etiology unclear. No clear temporal relationship to dosing
- Initially labeled in postmarketing adverse reactions.
- Upgraded to a Warning and Precaution in 2004

Renal Adverse Reactions

- Concerns regarding renal toxicity emerged during the zoledronic acid oncology program (Zometa)
- Risk is dose dependent and increased with more rapid infusion time
- Dosing recommendations: Infusion <u>no less</u> than 15 minutes.

Renal Adverse Reactions

- Reclast postmarketing: adverse reactions of renal failure reported - requiring dialysis, some with fatal outcome
  - Warning and Precaution updated in March, 2009
  - Contraindication added in August, 2011
    - Reclast is contraindicated in patients with creatinine clearance < 35 ml/min and in those with evidence of acute renal impairment due to an increased risk of renal failure

Osteonecrosis of the Jaw

- Clinical entity known to occur in patients with head and neck irradiation for cancer therapy.
- First noted in the cancer patients with no irradiation but with iv zoledronic acid or iv pamidronate exposure
- Oncology Drugs Advisory Committee meeting March 4, 2005
- Warning and Precaution for oncology products in 2005

Osteonecrosis of the Jaw

- Osteoporosis Population:
  - Although ONJ was first noted in the oncology population, there was concern regarding ONJ risk in the osteoporosis population
  - **Warning and Precaution** added to osteoporosis labels in 2005.

Atypical Subtrochanteric and Femoral Diaphyseal Fractures

- FDA began receiving reports of subtrochanteric hip fractures in 2008
- Subtrochanteric hip fractures account for 10 -30% of hip fractures, mainly seen in 2 populations:
  - Younger patients with high energy trauma
  - Elderly patients with minor trauma
- A review of bisphosphonate clinical trial data was conducted, a total of 19 subtrochanteric fractures were reported.
- It became clear during our review that the features of the fracture being reported were not typical

Atypical Subtrochanteric Fractures ASBMR definition

- Major features:
  - Located along femur from distal to lesser trochanter to proximal to supracondylar flare
  - No or minimal trauma associated with fracture
  - Transverse or short oblique configurations
  - Non-comminuted
  - Complete fractures – through both cortices, may have medial spike
  - Incomplete fractures – lateral cortex only

Subtrochanteric femoral fracture in an osteoporotic patient

Normal Femur

Subtrochanteric femoral fracture in a patient on bisphosphonate

Atypical Fracture, Warning and Precaution

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are traverse or short oblique in orientation without evidence of comminution. **Causality has not been established** as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. **They may be bilateral and many patients report prodromal pain in the affected area**, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Bisphosphonate Postmarketing Safety

- Other events noted and labeled:
  - Acute Phase Reactions
  - Inflammatory eye disease
  - Atrial fibrillation

Bisphosphonate Regulatory History

- Bisphosphonates are highly efficacious in reducing the risk for fracture and are widely prescribed for the prevention and/or treatment of osteoporosis
- Recent events have raised questions regarding long term use of these drugs
- In January, 2011, language highlighting this concern was added to the bisphosphonate product labels

Bisphosphonate Regulatory History

- **Important Limitations of Use**

The safety and effectiveness of [drug] for the treatment of osteoporosis are based on clinical data of [xx] years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

[xx] = range from 1 to 4 years, depending on the labeled clinical trials

Bisphosphonate Regulatory History

- We have continued to evaluate all available data concerning the duration of use for bisphosphonates.
- Both long term safety and long term efficacy will be discussed
- Long term safety is derived mainly from epidemiology studies
- Long term efficacy is derived from available clinical trial data

Long-Term Use of Bisphosphonates in the Prevention/Treatment of Osteoporosis: Safety

Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee
September 9, 2011

Fatmatta Kuyateh, M.D., M.S.
Medical Officer, Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

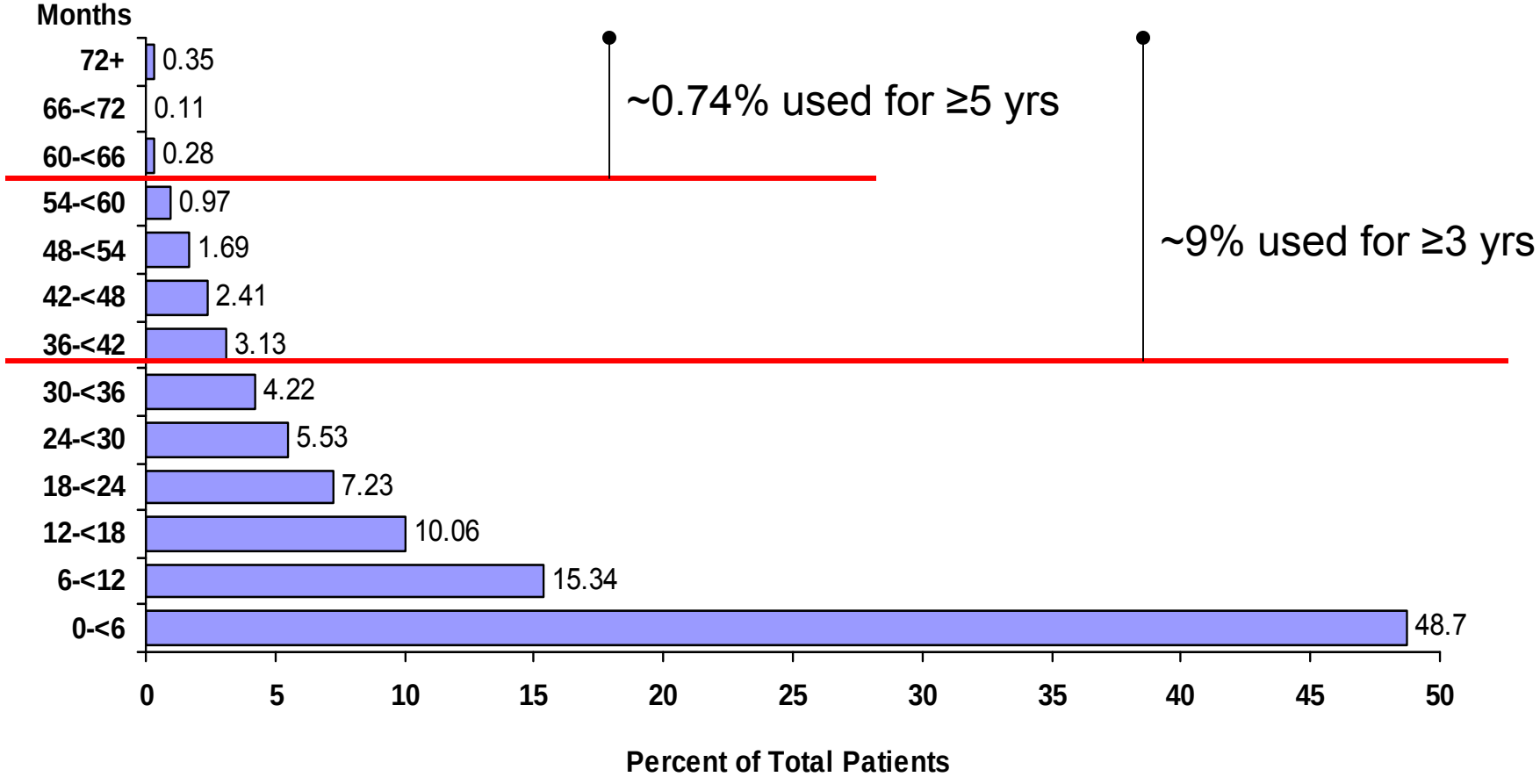
Outline

- Duration of Use Analysis
- Overview of the Long-term Safety Issues
  - Atypical Fractures
  - ONJ
  - Esophageal Cancer
- Utility of FDA Adverse Event Reporting System Data
- Epidemiology Review
- Conclusions

Long-Term Drug Utilization

- SDI Vector One®
- Bisphosphonate prescriptions dispensed from retail pharmacies
  - Includes IV and oral
  - years 2005 through 2010
- Restricted to incident users (n=369,156)
  - Age >60 years n=262,545
  - Age 35-60 years n=106,611
- Sample not nationally projected

Duration of Therapy for Patients Receiving a Bisphosphonate Indicated for Osteoporosis, SDI Vector One, 2006-2010



Overview of Safety Issues Atypical Femoral Fractures

- Differing case definitions led to difficulties in aggregating case counts across studies
- In 2010, an American Society for Bone and Mineral Research (ASBMR) Task Force published a case definition:
  - Located below lesser trochanter of femur and supracondylar flare
  - No or minimal trauma associated with fracture
  - Specific radiographic features (Transverse/short oblique, non-comminuted, medial spike, beaking/flaring*, generalized cortical thickness*)

*Not required for case definition

Overview of Safety Issues: Osteonecrosis of the Jaw (ONJ)

- Established association with intravenous bisphosphonates in cancer patients
- Incidence in general population unknown
- 2007 American Association of Oral and Maxillofacial Surgeons (AAOMS) Task Force case definition of bisphosphonate-related ONJ:
  - Current or previous treatment with a BP
  - Exposed bone in the maxillofacial region >8weeks
  - No history of radiation to the jaws

Overview of Safety Issues Esophageal Cancer

- Esophagitis and esophageal ulcer are well-known adverse events associated with oral bisphosphonates
- More recently reports of esophageal cancer have surfaced
- 23 U.S. cases following BP exposure reported between 1995 and 2008*
- Incidence of esophageal cancer in general population
  - 3-6 cases per 100,000 population in 2008 (age-adjusted)**

**Wysowski, DK. Reports of Esophageal Cancer with Oral Bisphosphonate Use. N Engl J Med 2009;360:1*
***American Cancer Society*

Utility of FDA AERS Data

- FDA AERS
  - Computerized passive surveillance reporting system
  - Reports from industry, consumers, and others
  - Cannot calculate incidence rates
- Major limitations for bisphosphonate adverse events
  - Reports generally lack clinical information meeting case definitions
  - Duration of exposure data absent or frequently uncertain
  - Long latency of outcomes of interest
- Unable to characterize the association of adverse event outcomes to bisphosphonate exposure

Epidemiology Review Summary

Atypical Fractures

- Radiographic findings consistent with ASBMR Atypical fracture case definition appear to be associated with bisphosphonate use
  - Relationship with duration of use unclear
  - Causality uncertain

Osteonecrosis of the Jaw

- Prevalence of ONJ may increase with increased duration of exposure to oral bisphosphonate
  - Causality not established

Esophageal Cancer

- Available evidence inconsistent concerning esophageal cancer and bisphosphonate use

Atypical Femoral Fractures

Epidemiology Review

Literature Review

- Published studies from 1995 to 2011
- Search Strategy
  - All approved bisphosphonates in U.S.
  - Femoral fracture
  - Subtrochanteric
- Included
  - Randomized clinical trials (or secondary analyses)
  - Longitudinal observational studies
- Excluded
  - Case reports and case series

Studies Finding No Association

Author (year)	Study Design	N Exposed (cases)/ control (cases)	Radiographs or Reports	Risk
Abraham-sen (2009)	Cohort	5187 (35)/ 10375 (41)	No	Hazard Ratio [HR] (95% CI) =1.46 (0.91-2.35) BP >6 yr: HR (95%CI) =1.37 (0.22-8.62)
Kim (2011)				
Vestergaard (2011)				
Black (2010)				

Studies Finding No Association

Author (year)	Study Design	N Exposed (cases)/ control (cases)	Radiographs or Reports	Risk
Abraham-sen (2009)	Cohort	5187 (35)/ 10375 (41)	No	Hazard Ratio [HR] (95% CI) =1.46 (0.91-2.35) BP >6 yr: HR (95%CI) =1.37 (0.22-8.62)
Kim (2011)	Cohort	17028 (57) / 16787 (47)	No	HR (95%CI) = 1.03 (0.70-1.52) BP >5yrs: HR (95%CI) =2.02 (0.41-10)
Vestergaard (2011)				
Black (2010)				

Studies Finding No Association

Author (year)	Study Design	N Exposed (cases)/ control (cases)	Radiographs or Reports	Risk
Abraham-sen (2009)	Cohort	5187 (35)/ 10375 (41)	No	Hazard Ratio [HR] (95% CI) =1.46 (0.91-2.35) BP >6 yr: HR (95%CI) =1.37 (0.22-8.62)
Kim (2011)	Cohort	17028 (57) / 16787 (47)	No	HR (95%CI) = 1.03 (0.70-1.52) BP >5yrs: HR (95%CI) =2.02 (0.41-10)
Vestergaard (2011)	Cohort	55090 (161) / 165270 (148)	No	Post-exposure OR(95% CI) = 2.41(1.78-3.27) Pre-exposure HR (95%CI) = 2.36(2.05-2.72)
Black (2010)				

Studies Finding No Association

Author (year)	Study Design	N Exposed (cases)/ control (cases)	Radiographs or Reports	Risk
Abraham-sen (2009)	Cohort	5187 (35)/ 10375 (41)	No	Hazard Ratio [HR] (95% CI) =1.46 (0.91-2.35) BP >6 yr: HR (95%CI) =1.37 (0.22-8.62)
Kim (2011)	Cohort	17028 (57) / 16787 (47)	No	HR (95%CI) = 1.03 (0.70-1.52) BP >5yrs: HR (95%CI) =2.02 (0.41-10)
Vestergaard (2011)	Cohort	55090 (161) / 165270 (148)	No	Post-exposure OR(95% CI) = 2.41(1.78-3.27) Pre-exposure HR (95%CI) = 2.36(2.05-2.72)
Black (2010)	RCT (2º analysis)	3236 (1) / 3223 (1) 3875 (4)/ 3861 (2) 662 (3)/ 437 (1)	Yes	RCT1: HR (95%CI) =1.03 (0.06-16.43) RCT 2: HR (95%CI) =1.5 (0.25-9) RCT 2: HR (95%CI) =1.33 (0.12-14.67)

Studies with Positive Findings

Author (Year)	Study Design	N	Radiographs or Reports	Risk	Duration of Use in Cases
Abra-hamsen (2010)	Cohort	Exposed (cases) 39,567 (412) Unexp (cases) 158,268 (637)	No	HR (95%CI) =2.02 (1.77-2.32) IR per 10,000 p-y at 0.2, 1.1, 3.7, and 8.7 years of use = 47.3, 30, 42.3, and 31 respectively (trend test p=0.22)	Not reported
Giusti (2010)					
Lenart (2009)					
Wang (2011)					

Studies with Positive Findings

Author (Year)	Study Design	N	Radiographs or Reports	Risk	Duration of Use in Cases
Abra-hamsen (2010)	Cohort	Exposed (cases) 39,567 (412) Unexp (cases) 158,268 (637)	No	HR (95%CI) =2.02 (1.77-2.32) IR per 10,000 p-y at 0.2, 1.1, 3.7, and 8.7 years of use = 47.3, 30, 42.3, and 31 respectively (trend test p=0.22)	Not reported
Giusti (2010)	Case-Control	Cases (exposed) 10 (4) Controls (unexp) 53(2)	Yes	OR (95%CI) =17 (2.55-113.26)	Mean 3.75 years
Lenart (2009)	Case-Control	13(10) 41(15)	Yes	OR (95%CI) =15.33 (3.06-76.90)	Mean 7.3 yrs
Wang (2011)					

Studies with Positive Findings

Author (Year)	Study Design	N	Radiographs or Reports	Risk	Duration of Use in Cases
Abra-hamsen (2010)	Cohort	Exposed (cases) 39,567 (412) Unexp (cases) 158,268 (637)	No	HR (95%CI) =2.02 (1.77-2.32) IR per 10,000 p-y at 0.2, 1.1, 3.7, and 8.7 years of use = 47.3, 30, 42.3, and 31 respectively (trend test p=0.22)	Not reported
Giusti (2010)	Case-Control	Cases (exposed) 10 (4) Controls (unexp) 53(2)	Yes	OR (95%CI) =17 (2.55-113.26)	Mean 3.75 years
Lenart (2009)	Case-Control	13(10) 41(15)	Yes	OR (95%CI) =15.33 (3.06-76.90)	Mean 7.3 yrs
Wang (2011)	Trend Analysis	N/A	No	Increase in proportion of ST by 2.1%; Increase in drug use by 14.9% Increase in bisphosphonate use preceded increase in ST fracture	Not reported

Positive Findings with Long-term Use

Author (Year)	Study Design	**N Cases (exposed) / controls (exposed)**	**Radiographs or records**	**Risk**	**Duration of Use Among AFx Cases**
Park-Wyllie (2011)	Nested Case-control	716/3580 (all exposed)	No	***Bisphosphonate Use ≥5yrs vs. <100 days:*** OR(95%CI)=2.74(1.25-6.02) ***Bisphosphonate use 3 to 5 yrs vs. <100 days:*** OR(95%CI)=1.59(0.80-3.15)	Median 4 years
Schilcher (2011)					

Positive Findings with Long-term Use

Author (Year)	Study Design	**N Cases (exposed) / controls (exposed)**	**Radiographs or records**	**Risk**	**Duration of Use Among AFx Cases**
Park-Wyllie (2011)	Nested Case-control	716/3580 (all exposed)	No	***Bisphosphonate Use ≥5yrs vs. <100 days:*** OR(95%CI)=2.74(1.25-6.02) ***Bisphosphonate use 3 to 5 yrs vs. <100 days:*** OR(95%CI)=1.59(0.80-3.15)	Median 4 years
Schilcher (2011)	Case-Control	59 (46)/263 (26)	Yes	Overall OR(95%CI)=33.3(14.3-77.8) ***Bisphosphonate use <1yr*** OR(95%CI)=9.8(1.9-49.9) ***Bisphosphonate use 1-1.9 yrs*** OR(95%CI)=7.1(1.6-30.7) ***Bisphosphonate use ≥2 yrs*** OR(95%CI)=51.1(20.3-128.2)	3yrs

Atypical Fractures Conclusions

- Mixed evidence concerning subtrochanteric and femoral shaft fractures in general
- Radiographic findings consistent with ASBMR case definition appear to be associated with bisphosphonate use
  - Causality not established
  - Relationship between atypical fracture and duration of use unclear

Osteonecrosis of the Jaw (ONJ)

Epidemiological Review

ONJ Literature Review

- Previous studies mostly evaluate IV formulations in the setting of malignant disease
  - Except one Cohort of Osteoporotic patients*: OR = 4.01 (2.06-7.78)
- Earlier studies done before ICD-9 code for ONJ established
- Mavrokokki et al †
  - 1 ONJ case per 8470 treated with oral bisphosphonates

*Cartsos VM, et al. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc. 2008 Jan;139(1):23-30.

† Mavrokokki T, Cheng A, Stein B, et al: Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 65:415, 2007

Predicting Risk of Osteonecrosis with Bisphosphonate Exposure (PROBE) Study

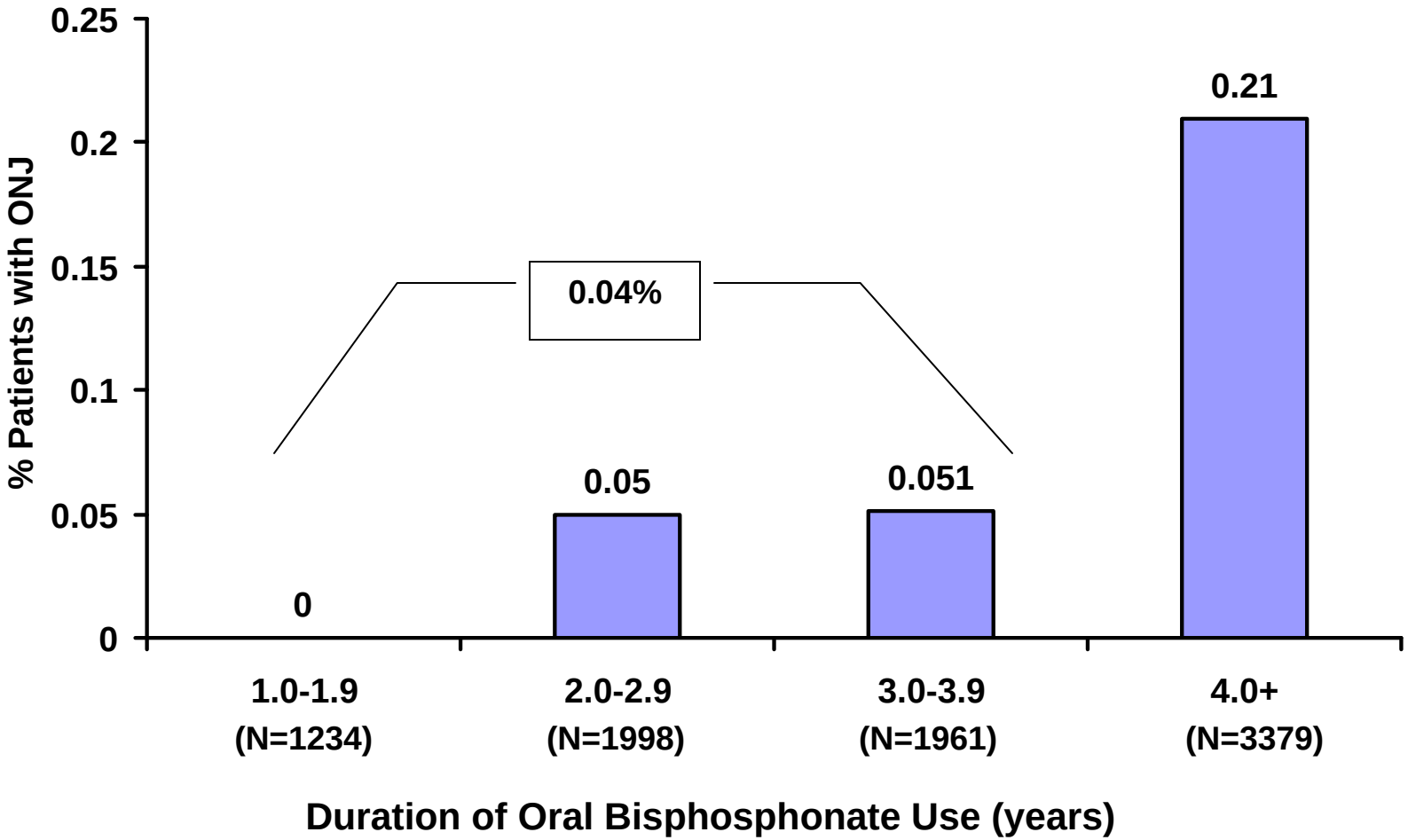
- Objectives
  - To determine the prevalence of ONJ among patients with chronic oral bisphosphonate exposure
  - To examine the risk factors for ONJ among patients with chronic oral bisphosphonate exposure
- Design
  - Cross-Sectional Observational Study
    - Kaiser Permanente Northern California
  - Mailed survey of oral bisphosphonate users followed by oral exams (or dental record review) in the subset with dental symptoms.
- Inclusion Criteria
  - Active member, age 21-90 years old with ≥ 1 year of oral BP exposure
- Exclusion Criteria
  - Any documented IV BP use
  - History of oral malignancy

ONJ PROBE Summary of Findings* (I)

- 9 cases of ONJ out of 8572 respondents
  - Overall prevalence of ONJ = 0.1%
  - 95% Confidence Interval (CI) = 0.05 – 0.20
  - 28 cases per 100,000 person-years of exposure

* Lo JC, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010 Feb;68(2):243-53.

Prevalence of ONJ by Bisphosphonate Duration (n=9)



Association of Bisphosphonate Treatment Duration and ONJ

	ONJ* Adjusted OR (95%CI)
BP use <4 yrs	Ref
BP use ≥4 years	4.45 (0.92-21.54) p=0.06

* Adjusted for age and history of rheumatoid arthritis

PROBE Study Conclusions

- Prevalence of ONJ may increase with increased duration of exposure to oral bisphosphonate
- Highest prevalence at 4 or more years of use
- Limitations to study
  - No control population unexposed to bisphosphonates
  - Pre-exposure dental health unknown
  - Not all symptomatic patients evaluated
  - Number of ONJ cases small

Esophageal Cancer

Epidemiology Review

Study Findings

- Large cohort study* did not find an association (n=83652)
  - Relative Risk (RR) = 0.96, 95%CI 0.74-1.25
- Large case-control study† found an increased risk (n=17675)
  - RR=1.30, 95%CI 1.02-1.66
  - ≥10 prescriptions: RR=1.93, 95%CI 1.37-2.70

** Cardwell CR et al. Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer. JAMA 2010;304:657-663*

† Green J et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010;341:c4444. doi: 10.1136/bmj.c4444

Study Findings (II)

- Three additional studies
  - No difference IRR = 0.55, 95% CI (0.06-4.72)*
  - No difference RR = 0.81, 95%CI (0.18-3.72)†
  - Decreased risk HR = 0.35, 95%CI (0.14-0.85)‡

**Solomon DH et al. More on reports of esophageal cancer with oral bisphosphonate use. N Engl J Med. 2009;360:1789-90*
†Nguyen DM et al. Oral Bisphosphonate Prescriptions and the Risk of Esophageal Adenocarcinoma in Patients with Barrett's Esophagus. Dig Dis Sci 2010;55:3404-07
‡ Abrahamsen B et al. More on reports of esophageal cancer with oral bisphosphonate use. N Engl J Med. 2009;360:1789

Esophageal Cancer Conclusions

- Available evidence inconclusive
  - Conflicting results
  - Variation in case definition
  - Role of potential confounding factors unclear
    - History of Barrett's esophagus and esophagitis

Overall Conclusions

AERS

- AERS data could not be used to assess the associations of safety issues to long-term use of bisphosphonates

Atypical Femoral Fractures

- Radiographic findings consistent with ASBMR atypical fracture case definition associated with bisphosphonate use
  - Causation uncertain and relationship with duration of use unclear

Osteonecrosis of the Jaw

- Prevalence of ONJ may increase with increased duration of exposure to oral bisphosphonate
  - Causality not established

Esophageal Cancer

- Available evidence inconclusive concerning esophageal cancer and bisphosphonate use

Thank You

Long-Term Use of Bisphosphonates Used in the Treatment of Osteoporosis: Efficacy

Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee
September 9, 2011

Marcea Whitaker, M.D.
Medical Officer
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research

Duration of Use Overview

Available data (treatment of osteoporosis)

- Fosamax (alendronate)
- Actonel (risedronate)
- Reclast (zoledronic acid)
- Boniva (ibandronate)

Study criteria:

- Duration > 3 years
- Systematic and complete capture of fracture data
- Comparator group

Overview of Long-term Studies

Timeline (years)									
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**
Fosamax									
Core - FIT (Years 0-4)					**Extension - FLEX (Years 0-5)**				
Alendronate (ALN)					ALN 5 mg				
					ALN 10 mg				
					Placebo				
Placebo									

Reclast	
Core (Years 0-3)	**EXT (Years 4-6)**
Zoledronic acid (ZOL) 5 mg	ZOL 5 mg
	Placebo
Placebo	ZOL 5 mg

Overview of Long-term Studies (con't)

Timeline (years)									
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Actonel									
Core			**Extension**						
Years 0-3			**Years 4-5**		**Years 6-7**		**Year 8**	**Years 9-10**	
Risedronate (RIS) 5 mg					RIS 5 mg		OFF	RIS 5 mg	
Placebo									

- All long-term studies included calcium and vitamin supplementation

Limitations

- Post-hoc analyses
- Power: Studies not powered for fracture
- Selection bias
- Small sample size
- Differences in time points selected for morphometric vertebral fracture assessment

BMD Results

Fosamax Study Design

Cohort 1	Cohort 2
3-year	4-year
+VF	No VF
N=2027	N=4432

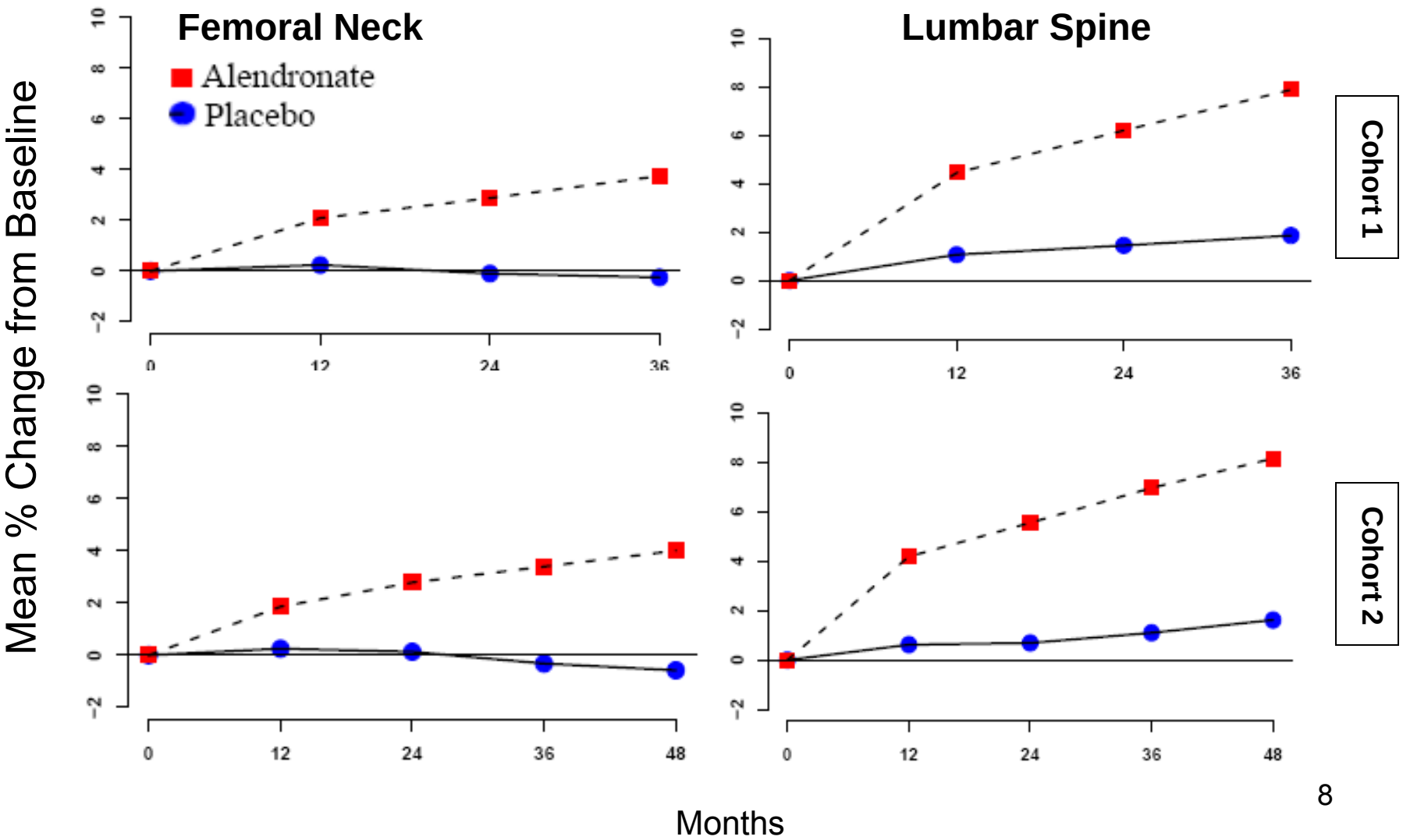
Re-randomization

FIT (years 0 to 4)	Post FIT	FLEX (years 0 to 5)	
Alendronate (ALN) 5 mg → 10 mg	Active Drug	ALN 10 mg (n=333)	N=1,099
		ALN 5 mg (n=329)	
		PBO (n=437)	
Placebo (PBO)			

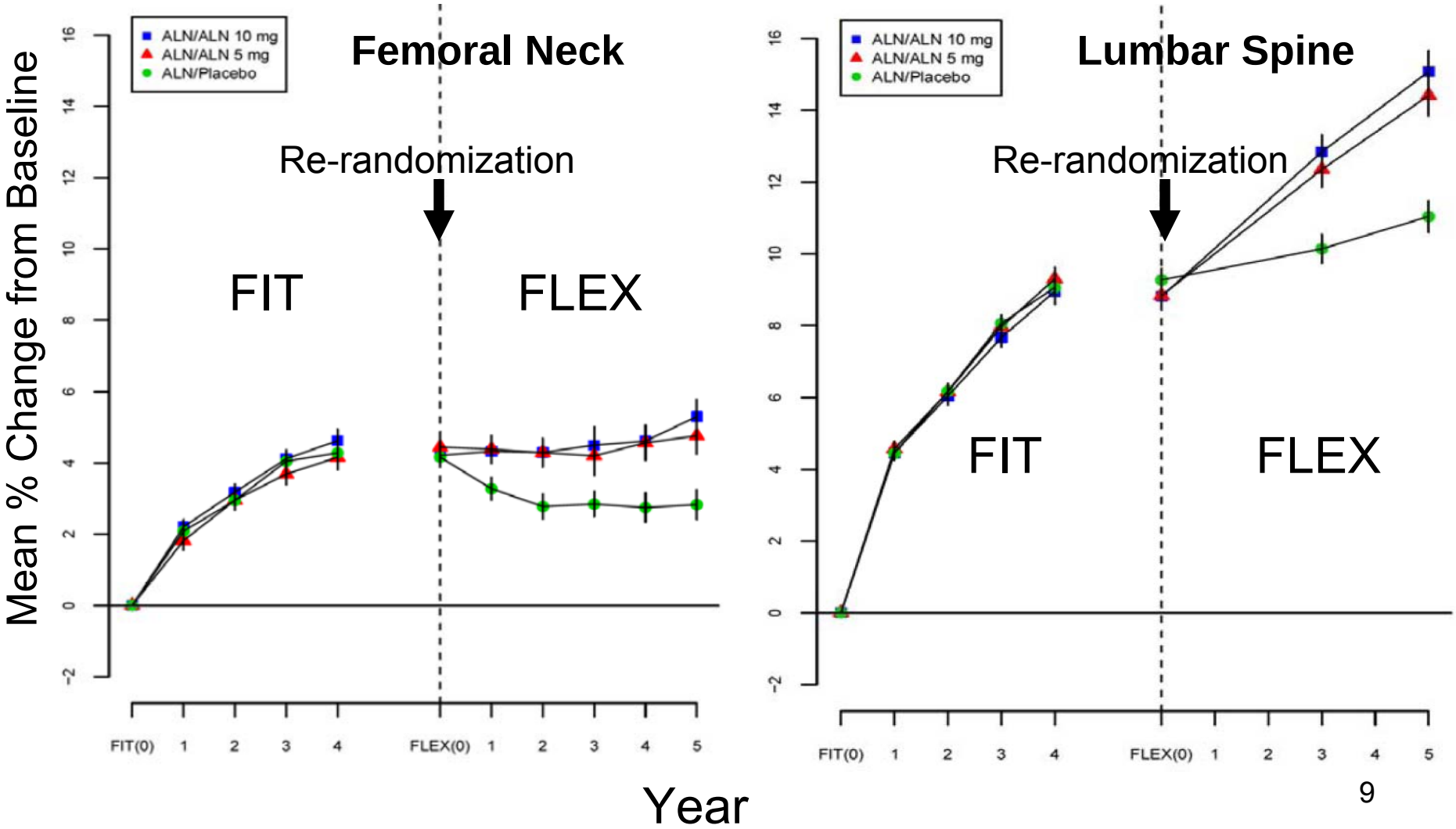
Patient Characteristics (FIT baseline)

- Postmenopausal women, n=6,459 (FIT), n=1,099 (FLEX)
- Femoral Neck BMD ≤0.68g/cm2 (T-score, ≤-1.6)
- Mean age = 71 yrs

FIT 3- and 4-year BMD Results



FIT/FLEX BMD


Mean % Change from Baseline
ALN/ALN 10 mg
ALN/ALN 5 mg
ALN/Placebo
Femoral Neck
Re-randomization
FIT
FLEX
FIT(0)
FLEX(0)
Lumbar Spine
Re-randomization
FIT
FLEX
Year

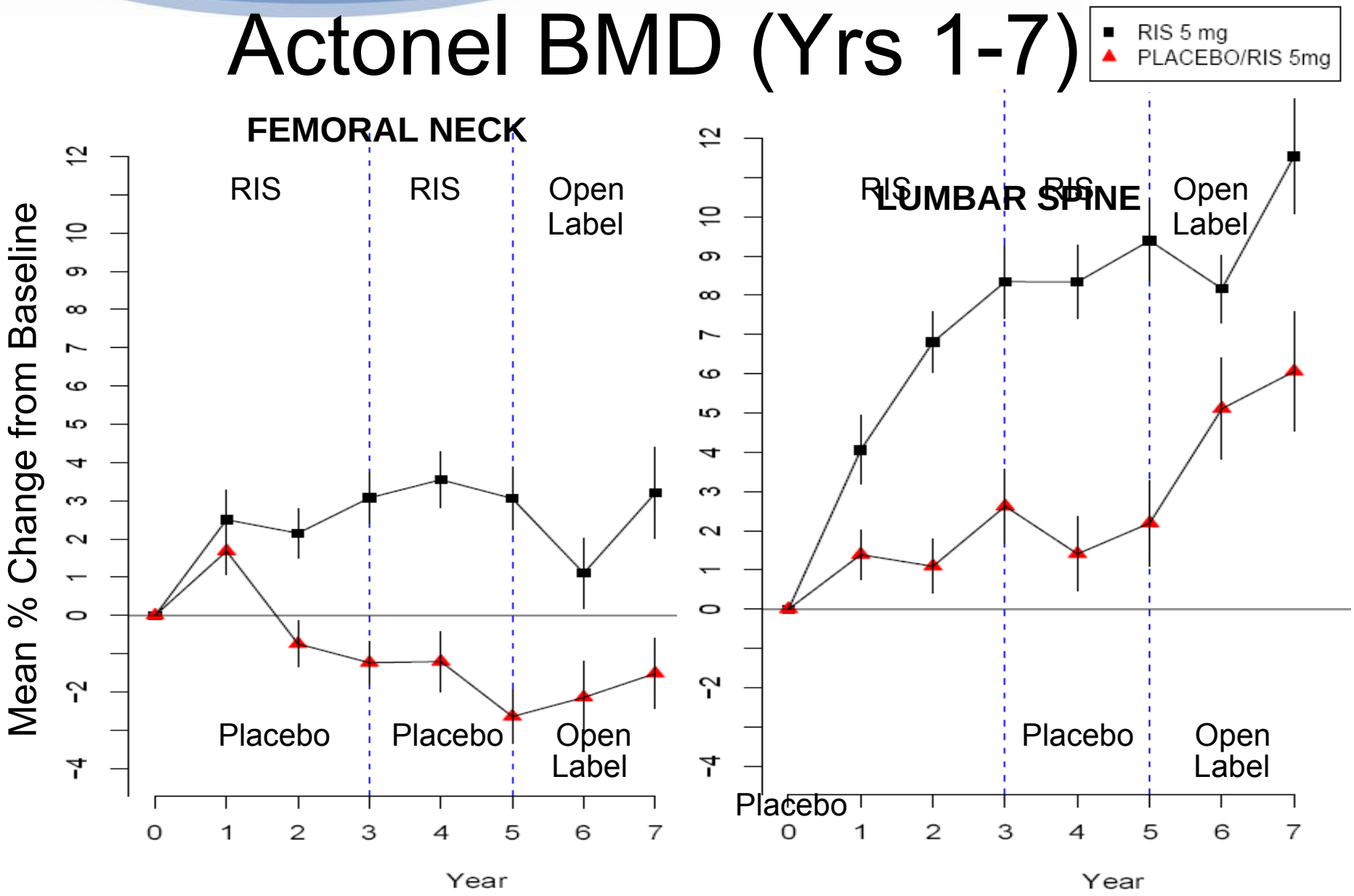
Actonel Study Design

Core	Extension Studies			
Years 0 - 3	**Years 4 - 5**	**Years 6 – 7 Open-Label**	**Year 8**	**Years 9 – 10 Open-Label**
Risedronate (RIS) 2.5 mg (n=410)				
RIS 5 mg (n=408)	**RIS 5 mg** (n=135)	**RIS 5 mg** (n=83)	**OFF**	**RIS 5 mg** (n=14)
Placebo (PBO) (n=408)	**PBO** (n=130)	**RIS 5 mg** (n=81)	**OFF**	**RIS 5 mg** (n=18)

Patient Characteristics (Baseline)

- Postmenopausal women, n=1226 (Core), n=164 (Year 7)
- + Vertebral Fracture (multiple), mean T-score -2.7
- Mean age = 70 yrs

Actonel BMD (Yrs 1-7)



Reclast Study Design

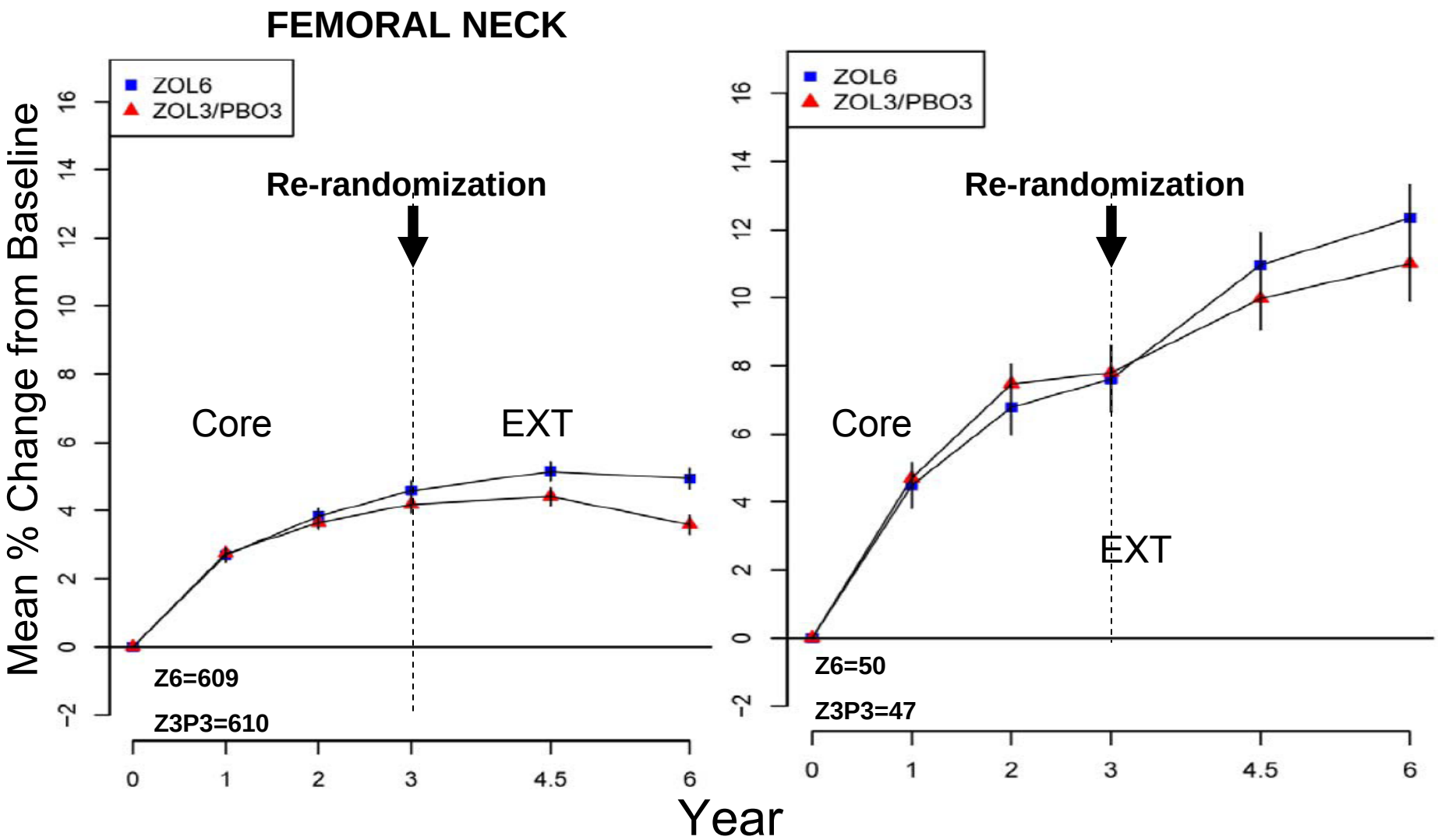
Re-randomization

Core Years 0 - 3	Extension Years 4 - 6
Zoledronic acid (ZOL) 5 mg (n=3875)	**ZOL 5 mg** (n=616)
	PBO (n=617)
Placebo (PBO) (n=3861)	**ZOL 5 mg**

Patient Characteristics (Baseline)

- Postmenopausal women, n=7736 (Core), n=1233 (EXT)
- + Vertebral Fracture or T-score ≤ -2.5 (+/- Vertebral Fx)
- Mean age = 73 yrs

BMD - Reclast


FEMORAL NECK
ZOL6
ZOL3/PBO3
Re-randomization
Core
EXT
Z6=609
Z3P3=610
Mean % Change from Baseline
Year
ZOL6
ZOL3/PBO3
Re-randomization
Core
EXT
Z6=50
Z3P3=47
Year

BMD Summary

- Continued drug therapy (0 to 5 years)
  - Similar BMD Response for all bisphosphonate products
- Continued drug therapy (Beyond 5 years)
  - Maintenance at Femoral Neck
  - Increases at Lumbar Spine (drug effect vs other)
- After 3 – 5 years of therapy, re-randomized to placebo
  - Decrease followed by plateau above baseline at Femoral Neck
  - Small increases at Lumbar Spine (drug effect vs other)

Suggests:

- ➢ Maintenance of BMD with continued therapy
- ➢ BMD benefit persists after drug discontinuation

Fracture Results

New Vertebral Fractures – Fosamax (FLEX)

Patients with at least 1 Vertebral Fracture in FLEX [N (%)]

Treatment	Vertebral Fracture			
	Any	Clinical	Morphometric	Total No. in FLEX
ALN / Alendronate 10 mg	28 (8.4%)	5 (1.5%)	24 (7.2%)	333
ALN / Alendronate 5 mg	18 (5.5%)	5 (1.5%)	13 (4.0%)	329
ALN / Placebo	35 (8.0%)	18 (4.1%)	21 (4.8%)	437

Relative Risk = 0.87 (0.57-1.32)

Relative Risk = 0.39 (0.17-0.77)

Source: FDA Analysis of Sponsor Data

All Osteoporotic Fractures - Fosamax

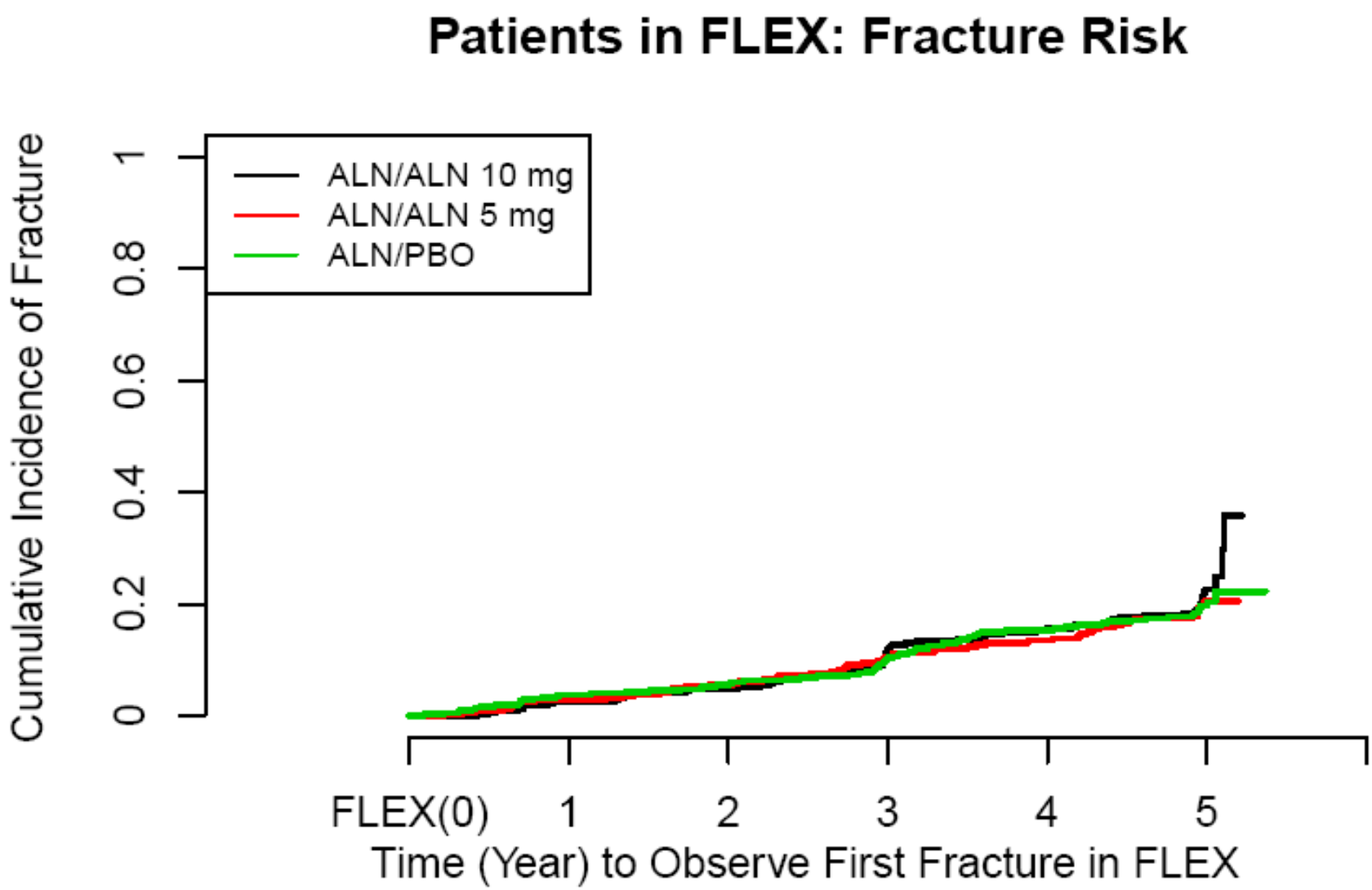
Percent of Patients[a] with at least 1 osteoporotic fracture
% (n patients with fracture / N total patients)

FIT Treatment / FLEX Treatment	FIT (Years 0 – 4)	FLEX (Years 0 – 5)
ALN* / ALN 10 mg	**12.6%** (42/333)	**18.6%** (62/333)
ALN / ALN 5 mg	**9.7%** (32/329)	**16.7%** (55/329)
ALN / Placebo	**9.8%** (43/437)	**16.9%** (74/437)

All ALN / Any Treatment	**10.6%** (117/1099)	
Background Placebo	**21%**	

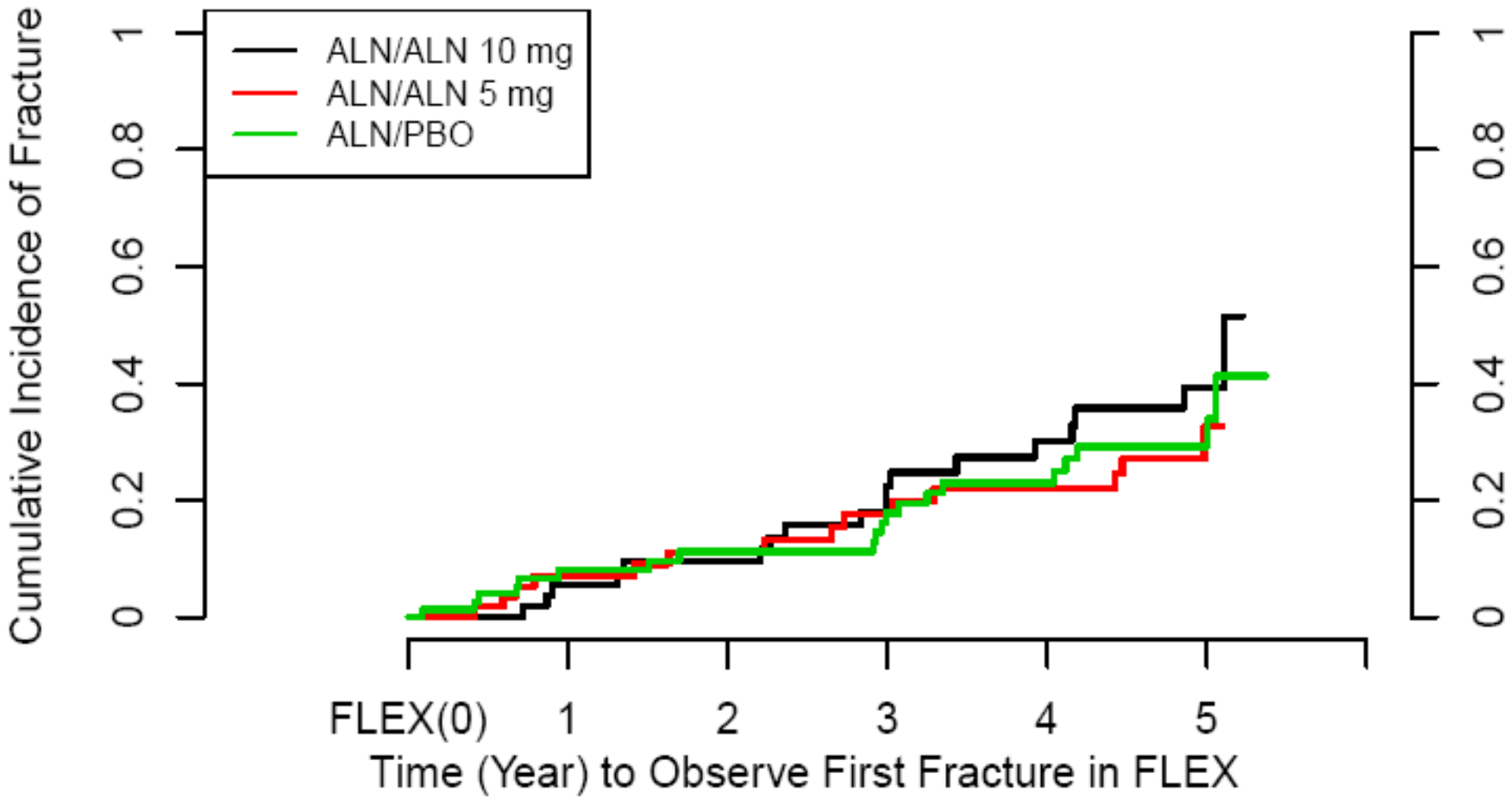
ALN / ALN 5 + ALN / ALN 10 mg (combined)		**17.7%** (117/662)

[a]Patients who were enrolled in both FIT and FLEX
*ALN = alendronate



At Risk:						
ALN/ALN 10 mg	333	306	285	243	220	85
ALN/ALN 5 mg	329	301	270	245	226	83
ALN/PBO	437	397	369	330	290	115

Osteoporotic range[Tscore <= −2.5 Total Hip] at baseline



At Risk:						
ALN/ALN 10 mg	56	49	45	34	26	10
ALN/ALN 5 mg	59	50	44	37	32	5
ALN/PBO	76	62	57	50	39	15

FLEX post-hoc analysis

- Interaction of Femoral Neck T-score and fracture occurrence

➢ Nonvertebral Fracture Benefit
  - Subjects
    - Without a baseline vertebral fracture; and
    - T-score < -2.5

Source: Schwartz et al, 2010. Efficacy of Continued Alendronate for Fractures in Women with and without Prevalent Vertebral Fractures. JBMR, 25(5):976-982

Osteoporotic Fractures - Actonel

Percent of patients with at least 1 osteoporotic fracture
% (n patients with fracture/ N total patients)

Treatment Year 0-3/Year 4-5/Year 6-7	Year 0 - 3	Year 4 - 5	Year 6 - 7
Ris* 5mg/Ris 5mg/ Ris 5mg	20.5% (17/83)	19.3% (16/83)	13.2% (11/83)
Placebo/Placebo/Ris 5mg	32.1% (26/81)	32.1% (26/81)	16.0% (13/81)

***Ris=Risedronate**

New Vertebral Fractures - Reclast

Percent of subjects with at least 1 vertebral fracture
% (n patients with vertebral fracture/ N total patients)

Vertebral Fracture Type	Reclast/Reclast (Yr 0-3/Yr 4-6)	Reclast/Placebo (Yr 0-3/Yr 4-6)	Relative Risk
Morphometric Vertebral	3.0% (14/469)	6.2% (30/486)	RR 0.48 (0.26, 0.90) P=0.035
Clinical Vertebral	1.1% (7/616)	0.6% (4/617)	RR 1.51 (0.53, 6.19) P=0.34

Source: FDA Analysis of Sponsor Data

All Osteoporotic Fractures - Reclast

Percent of patients with at least 1 osteoporotic fracture
% (n patients with fracture/ N total patients)

Treatment	CORE Years 0-3	EXTENSION Years 4-6
Reclast/Reclast	10.1% (62/616)	8.6% (53/616)
Reclast/Placebo	9.6% (59/617)	12.0% (74/617)
Background Placebo	20%	

Difference 3.4% (p=0.0502)

Pooled Fractures

Percent of patients with at least 1 fracture per time period
% (n patients with fracture / N total patients)

	Year 0-3	Year 4-5	Year 6-9	Year >9
Active Therapy (ALN + ZOL + RIS)*	**9.7%** (116/1200)	**6.0%** (72/1200)	**10.6%** (62/585)	**9.3%** (48/517)
3 Years Active then Placebo[1] (ALN/Placebo + ZOL/Placebo)	**8.2%** (79/968) On active drug	**8.6%** (83/968)	**8.8%** (31/351)	**8.0%** (28/351)
Background Placebo	**20.4%**			

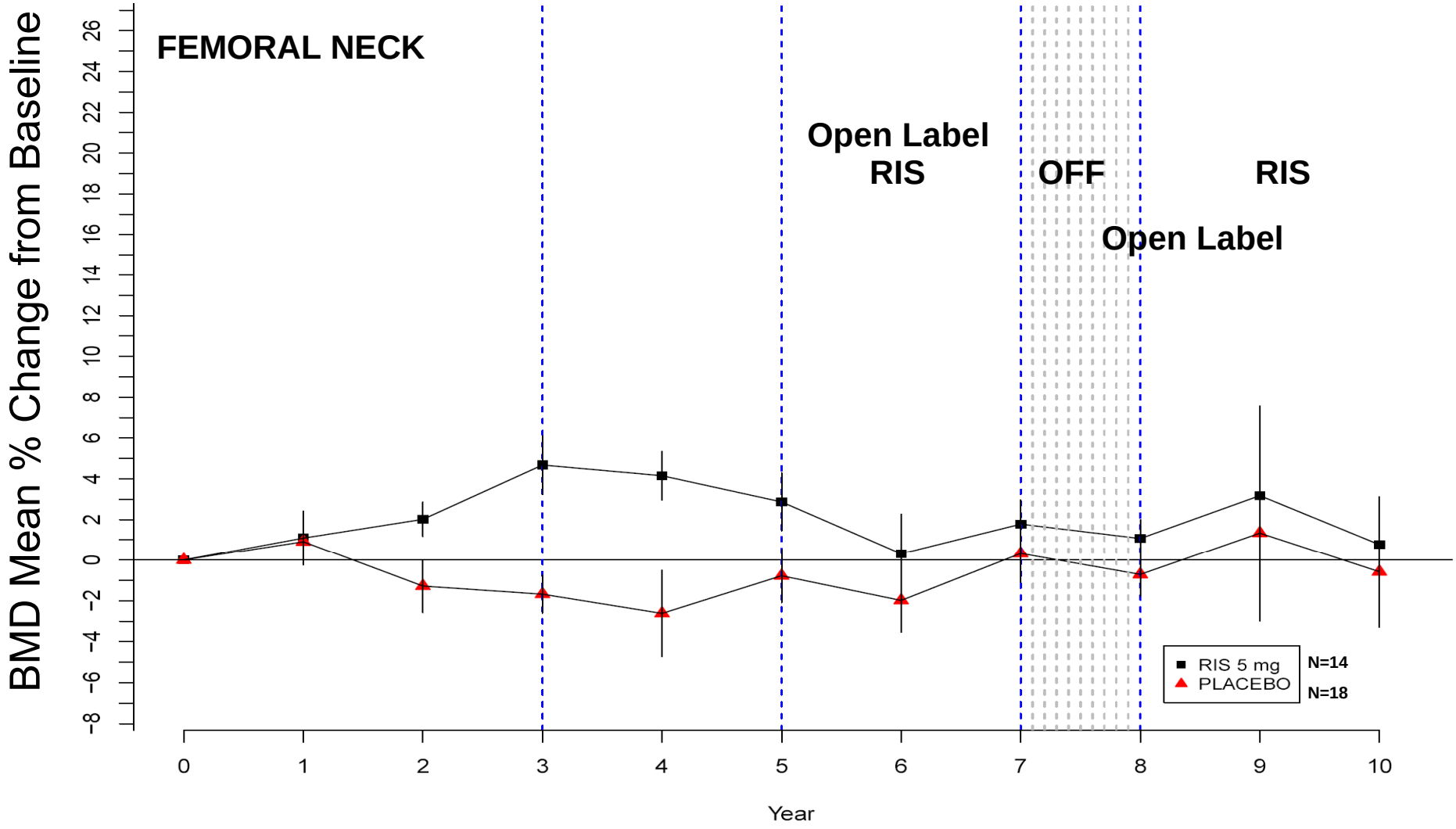
[1] Includes only patients from alendronate and zolendronic acid trials because there was no risedronate/placebo group studied
* ALN = alendronate, ZOL = zolendronic acid, RIS = risedronate

Fracture Summary

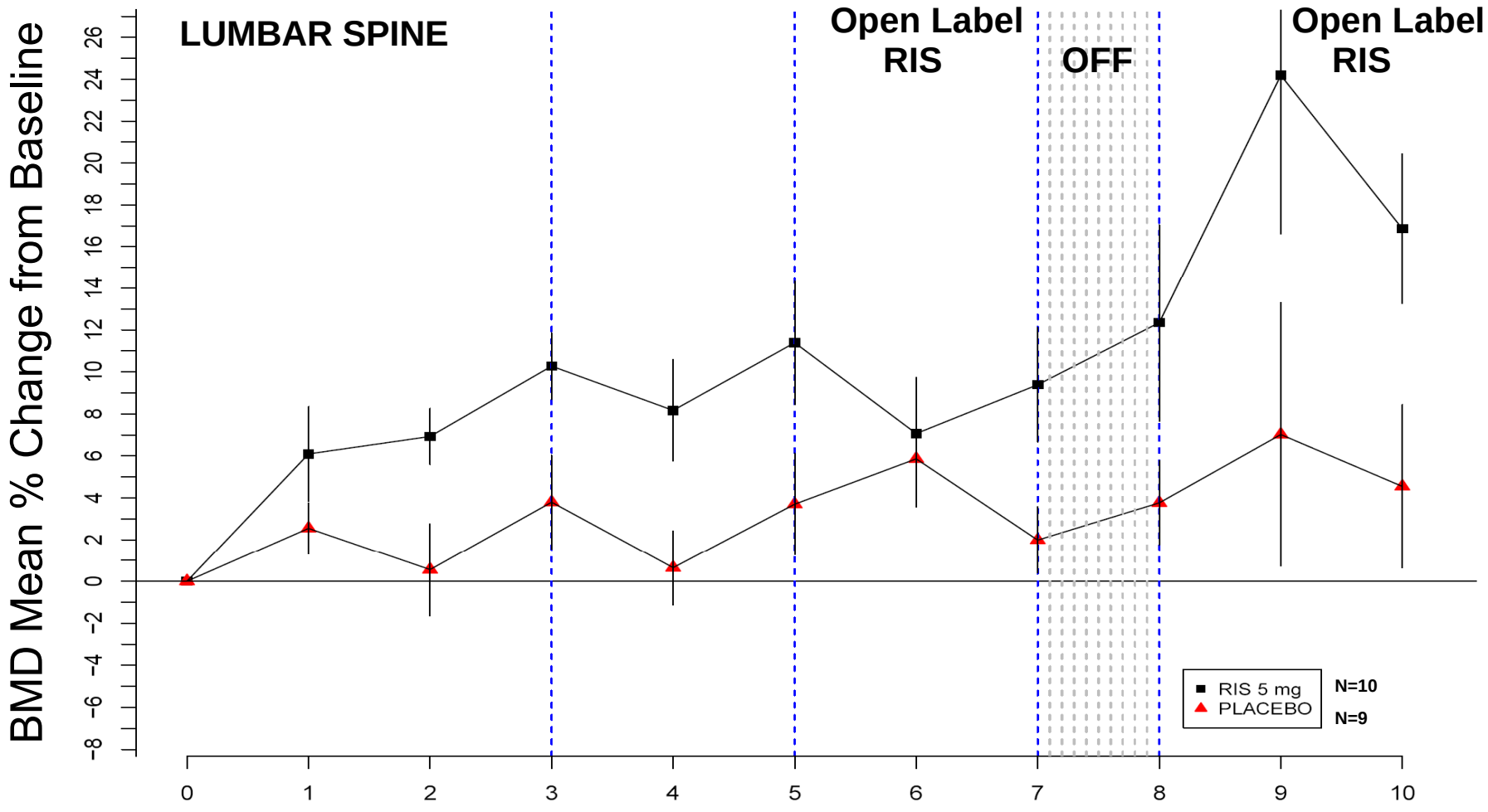
- Continued Drug Exposure
  - No clear benefit or harm for overall osteoporotic fractures
  - No subset with clear and consistent fracture benefit
- Re-randomized to Placebo
  - No difference in rates compared to active therapy
  - Stable fracture incidence
  - Possible maintenance of benefit after 3 – 5 years of exposure

Drug Holiday

Drug Holiday –Actonel 10-yr BMD



Drug Holiday –Actonel 10-yr BMD



Drug Holiday - Actonel 10-yr Fracture

Percent of subjects with at least one fracture during each time period
% (n patients with fractures / N total patients)

	Year 1 – 3	Year 4 – 5	Year 6 – 7	Year 8	Year 9 – 10
Risedronate 5 mg	RIS 5mg	RIS 5mg	RIS 5mg	OFF	RIS 5mg
	28.6% (4/14)	**21.4%** (3/14)	**0%** (0/14)	**7.1% (1/14)**	**14.3% (2/14)**
Placebo/RIS 5mg	PBO	PBO	RIS 5mg	OFF	RIS 5mg
	22.2% (4/18)	**27.8%** (5/18)	**22.2%** (4/18)	**0% (0/18)**	**16.7% (3/18)**

Drug Holiday- Published data

1. Femoral neck BMD after the intial 5 years of alendronate treatment predicted future alendronate efficacy (Subset with no baseline VF and T-score≤ -2.5)[1]
   - BMD changes and, therefore BMD monitoring, are not useful in predicting who will most likely benefit from continued alendronate therapy
2. Hip BMD at the time of alendronate discontinuation strongly predicted the risk of clinical fractures over the next five years[2]
   - Following BMD changes over 1- and 2- year intervals after alendronate discontinuation were not useful

[1]Schwartz, A, et al. (2006) *JBMR*. 25 (5):976-982

[2]Bauer, D.,et al. Abstract presented to ASBMR Annual Meeting, Toronto 2010.

Bone Turnover Markers

Bone Turnover Markers

Randomized Withdrawal Studies:

- Active Therapy: Bone turnover markers stable while on active therapy
- Re-randomized/Placebo: Increases in markers after discontinuation but levels remained below baseline.

Bone Histomorphometry

Fosamax
Bone Histomorphometry

- Quantitative: No differences in histomorphometry parameters
- Qualitative: No woven bone, marrow fibrosis, abnormal osteoid, marrow dyscrasia or osteomalacia

Duration of Use Conclusions

- Bone Mineral Density:
  - Data on bisphosphonate exposure out to 10 years appears to demonstrate maintenance of BMD at the femoral neck and continued increases in BMD at the lumbar spine
  - In patients who discontinue bisphosphonate exposure after 3-5 years, small decreases followed by a plateau at the femoral neck and small increases in BMD at the lumbar spine are seen
  - Change in BMD after bisphosphonate discontinuation is not predictive of future fracture

Duration of Use Conclusions

- Fracture :
  - Data on bisphosphonate exposure out to 10 years appears to demonstrate:
    - No clear evidence of harm or increase in overall osteoporotic fractures
    - No clear subset with continued fracture benefit
    - For those with a BMD T-score < -2.5, there is no apparent benefit for continued therapy
  - In patients who discontinue bisphosphonate exposure after 3-5 years, fracture incidence rates appear relatively constant over time

Duration of Use Conclusions

- Bone Turnover Markers / Bone Histomorphometry
  - Bone turnover markers levels tend to follow bisphosphonate exposure
  - No concerning findings on bone quality studies

Duration of Use Conclusions

- Drug Holiday:
  - Data are sparse
  - BMD results show maintenance of BMD at the femoral neck and increases at the lumbar spine
  - Remaining Questions
    - Who is a candidate?
    - What factors should be considered?
    - Who should resume therapy?
    - When should therapy be resumed?

Duration of Use Conclusions

- In light of risk-benefit challenges, the available data suggest that therapy can be safely discontinued without loss of efficacy
- Additional data would be needed to further define the appropriate duration of drug cessation and to determine interim monitoring

Fracture Outcomes and Monitoring After Discontinuation of Bisphosphonate Therapy

Douglas C. Bauer, MD
University of California, San Francisco

Disclosures

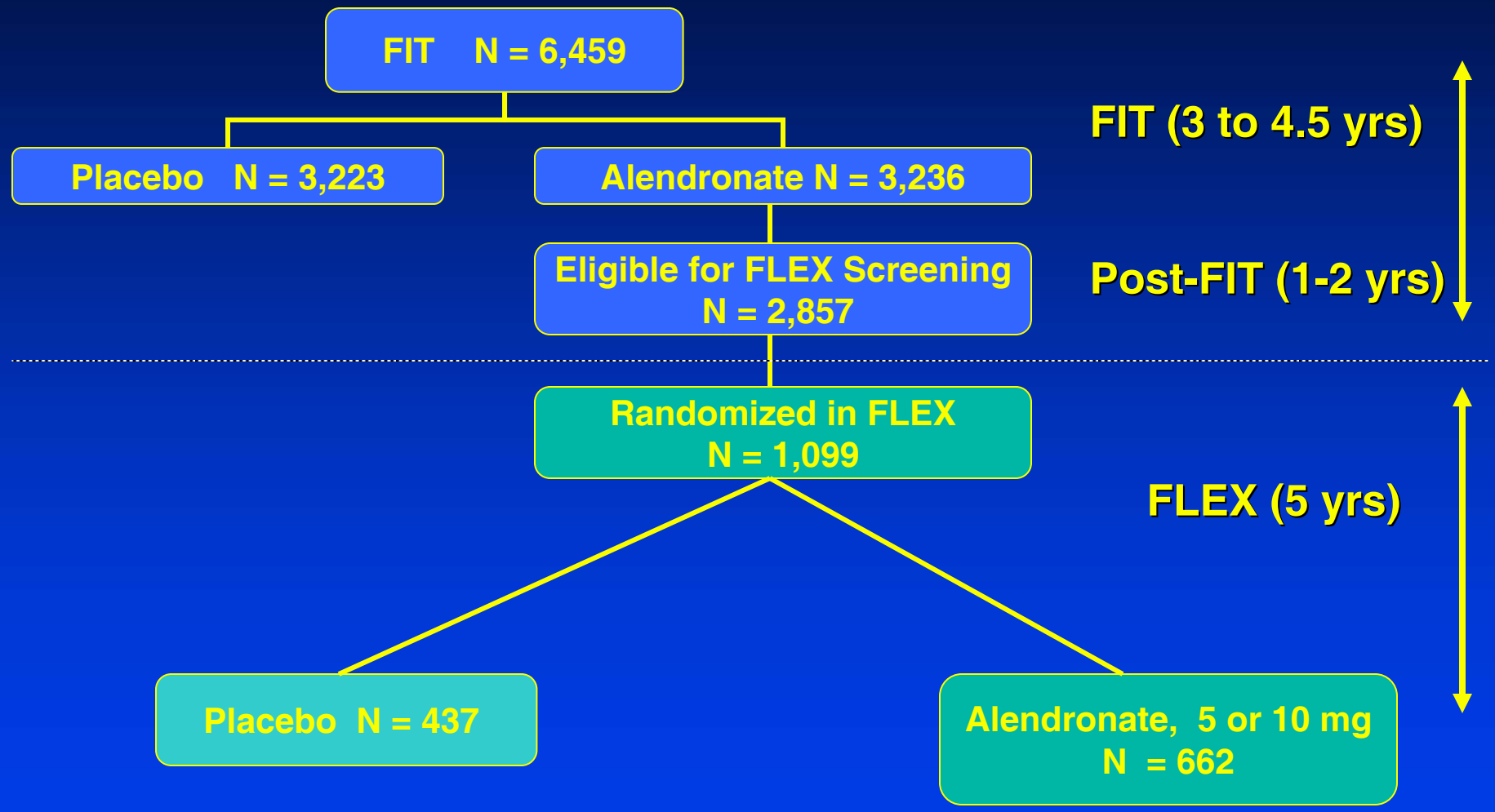
- Research support to UCSF
  - Amgen, Novartis (both for endpoint adjudication)
- No consultancies, stock ownership or speakers bureaus
- FIT and FLEX were funded by Merck but independently coordinated by the UCSF Coordinating Center
- Corporate sponsor had no role in the analysis or interpretation of these data

Background

- Some experts suggest a drug holiday and monitoring after 5 years of bisphosphonate[1,2]
- Key questions:
  - Compared to continued bisphosphonate therapy, what is the risk of fracture after discontinuation?
  - What factors predict fracture among those who have discontinued?
  - Is monitoring after discontinuation useful?
- Ideal study: after prolonged bisphosphonate therapy, individuals are randomized to continue or stop then followed for fracture outcomes

[1]Watts et al, JCEM, 2010
[2]Ott, Clev Clin J Med, 2011

Design of the FIT and FLEX Trials



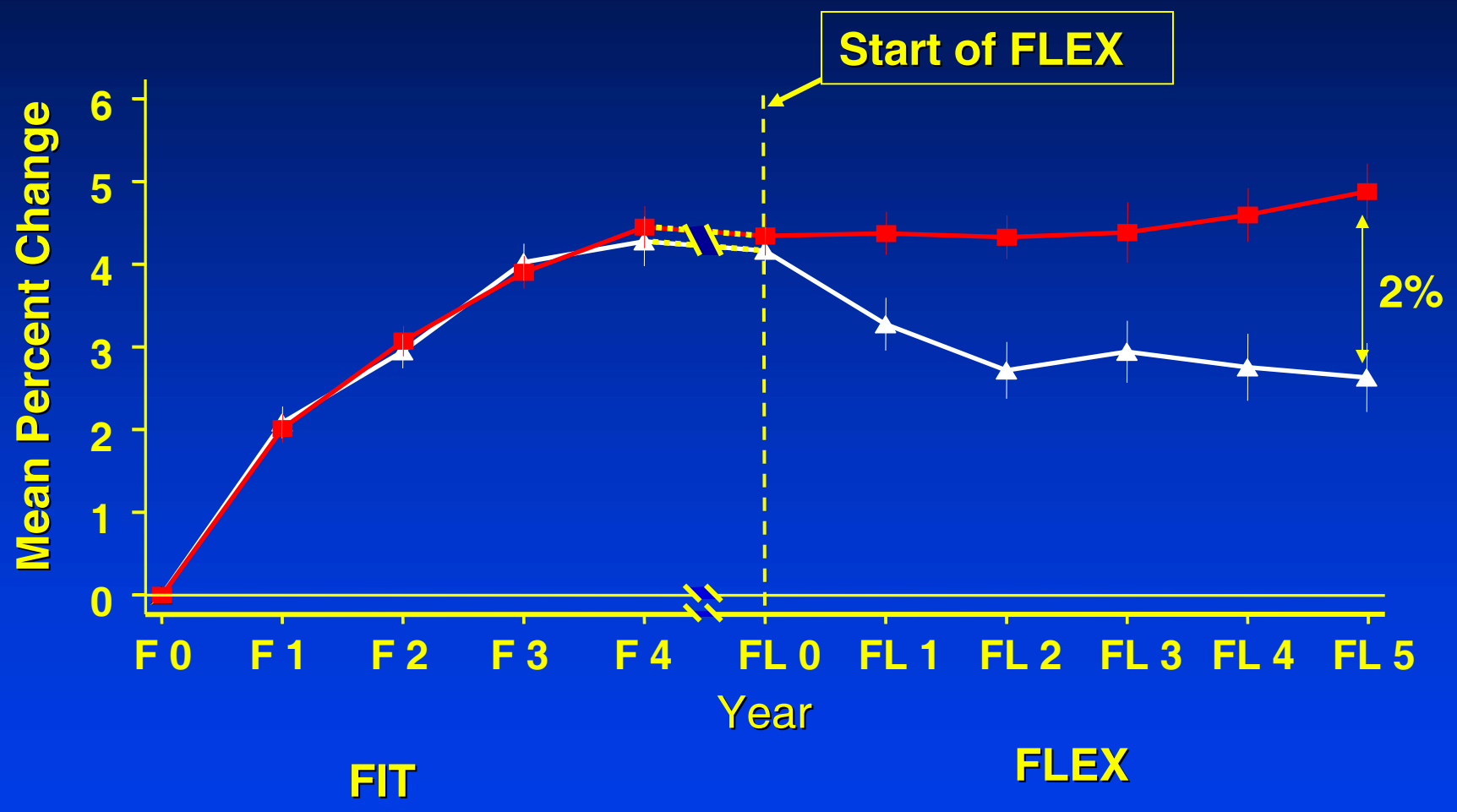
FLEX Eligibility

- Received alendronate during FIT
  - 5 mg/d for 2 years, then 10 mg/d
  - At least 3 years of prior ALN
- Total hip BMD at FLEX baseline
  - T-score >–3.5 and
  - > FIT baseline
- Willing to be randomized to ALN or PBO
- 10 of 11 original FIT clinics

FLEX Treatment and Endpoints

- **Randomized for 5 more years to:**
  - Placebo (PBO) (40%)
  - ALN 5 or 10 mg/day (ALN) (60%)
- **Calcium (500 mg/day) + vitamin D (250 IU)**
- **Primary Endpoint**
  - Total hip BMD
- **Other Endpoints**
  - Fractures (vertebral and non-spine)
  - Bone turnover markers (urine NTX, serum Bone ALP)

FLEX Change in Femoral Neck BMD: % Change from FIT Baseline

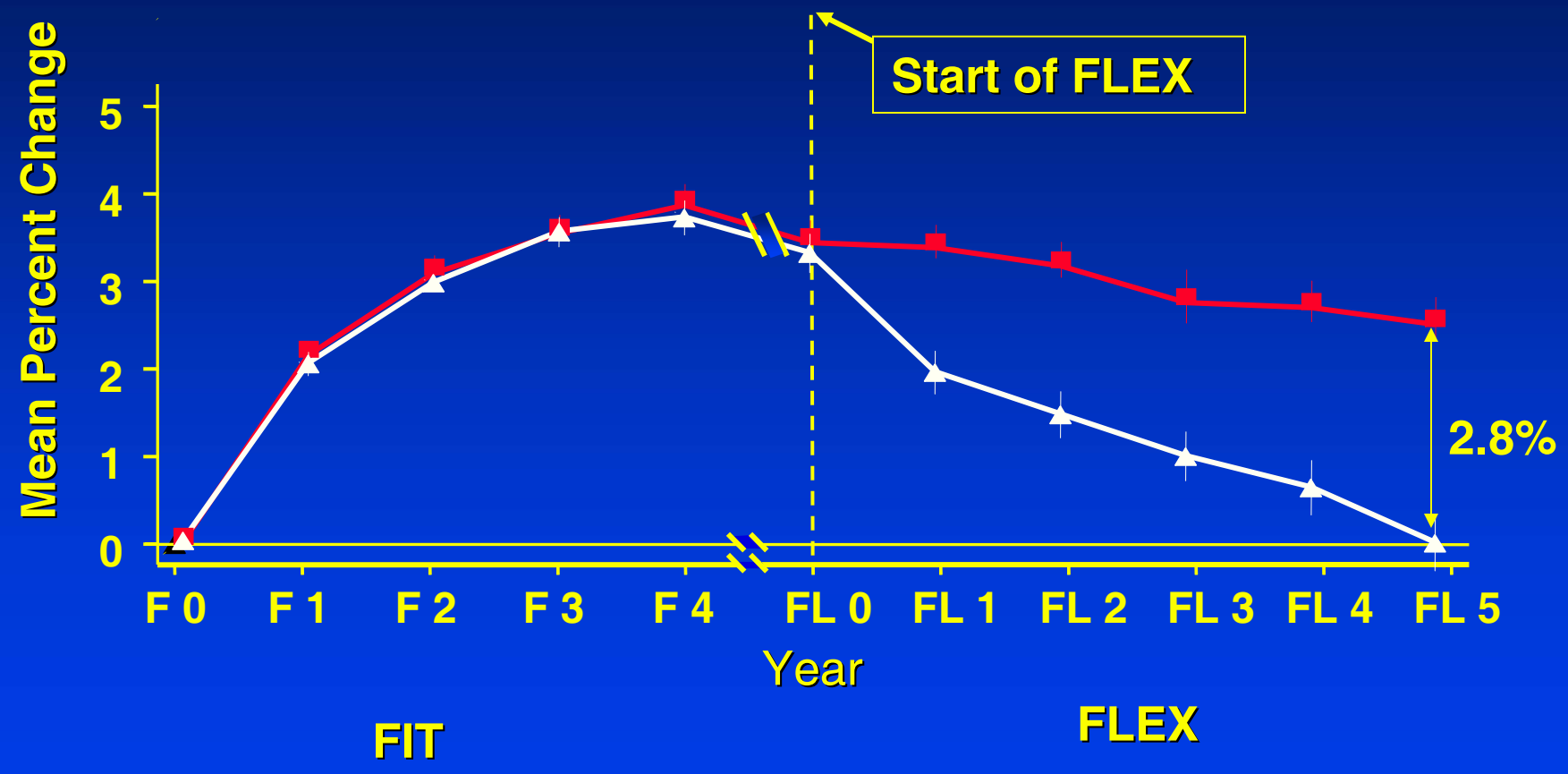


= Placebo

= ALN (Pooled 5 mg and 10 mg groups)

P<0.001 ALN vs PBO

FLEX Change in Total Hip BMD: % Change from FIT Baseline

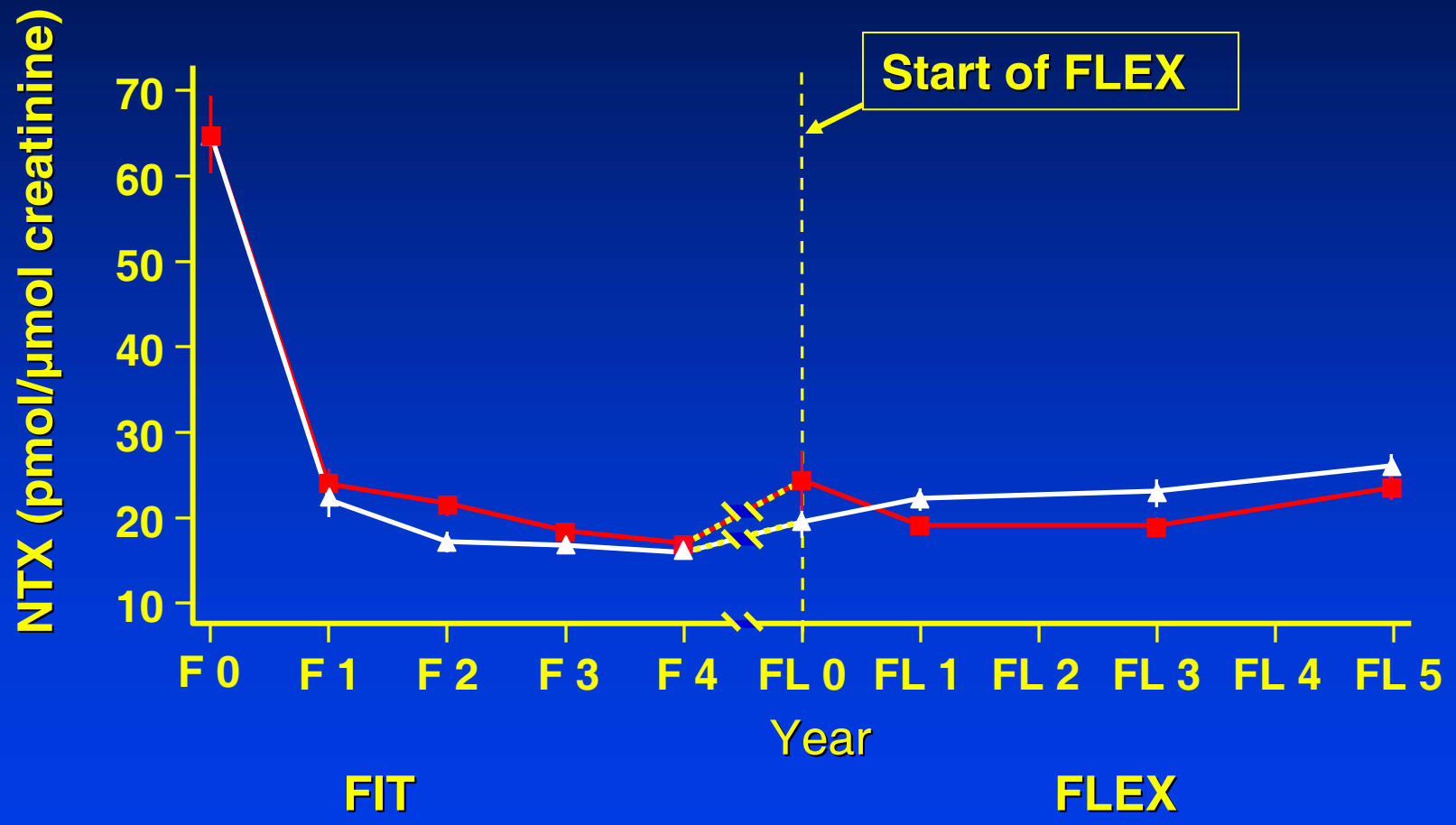


= Placebo

= ALN (Pooled 5 mg and 10 mg groups)

P<0.001 ALN vs PBO

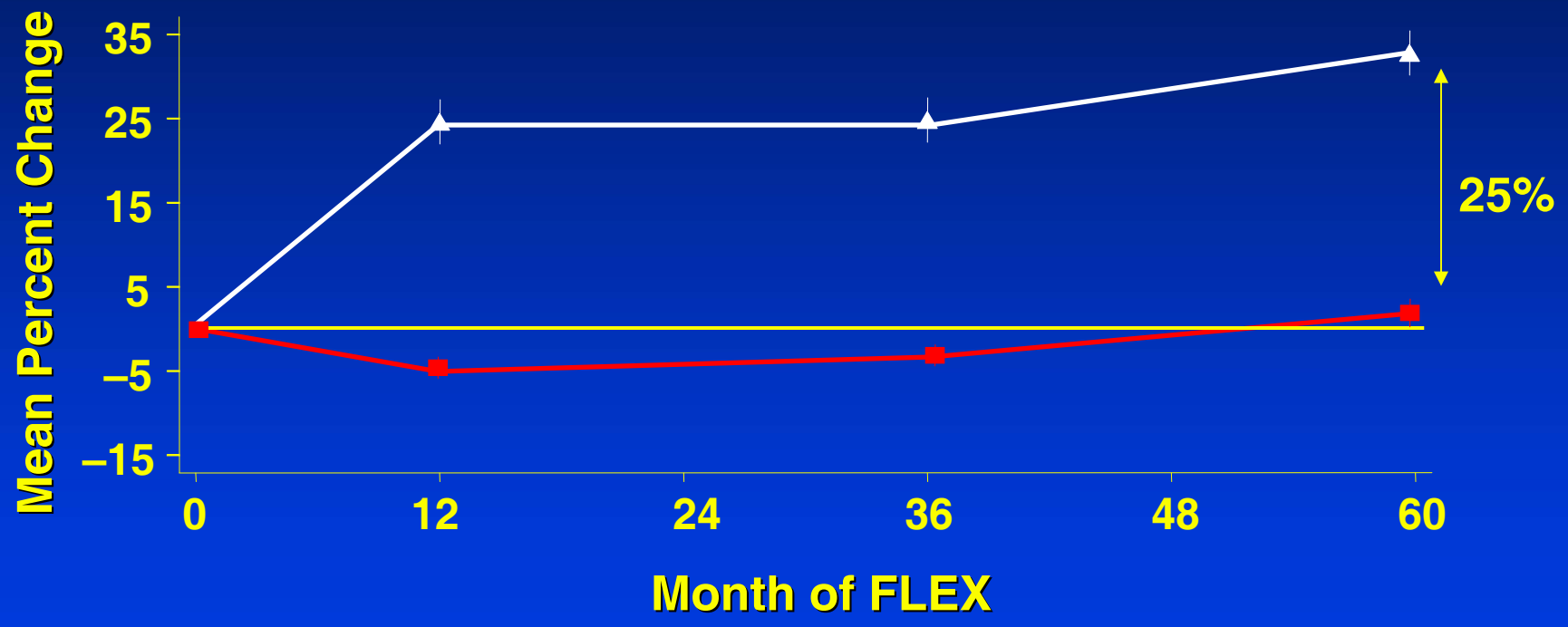
FLEX Change in Urinary NTX: Absolute Change from FIT Baseline



▲ = Placebo
■ = ALN (Pooled 5 mg and 10 mg groups)

Black et al, JAMA, 2006

Percent Change in Urinary NTX During FLEX



▲ = Placebo

■ = ALN (Pooled 5 mg and 10 mg groups)

P<0.001 ALN vs PBO

Cumulative Incidence of Fractures During FLEX

	PBO (N = 437)	ALN (N = 662)	RR (95% CI)
Non-spine			
Non-vertebral	20%	19%	1.0 (0.8, 1.4)
Hip	3%	3%	1.1 (0.5, 2.3)
Vertebral			
Morphometric	11%	10%	0.9 (0.6, 1.2)
Clinical	5%	2%	0.5 (0.2, 0.8)

FLEX Placebo Group: Characteristics at FLEX Baseline

	No FLEX Fracture (N=343)	FLEX Fracture (N=94)
Prior years ALN	5.0 ± 0.8	4.9 ± 0.6
Age (y)	73.0 ± 5.7	76.2 ± 6.0*
Vert fx at FLEX BL	111 (32%)	39 (42%)*
Total Hip BMD (g/cm2)	0.73 ± 0.09	0.68 ± 0.08*
Total Hip T-score ≤-2.5	66 (19%)	36 (38%)
Bone ALP	9.0 ± 3.4	9.5 ± 3.7
NTX/Cr	19.7 ± 13.3	19.3 ± 11.5

Bauer et al, ASBMR, 2010

*$p<0.05$ compared to no fracture

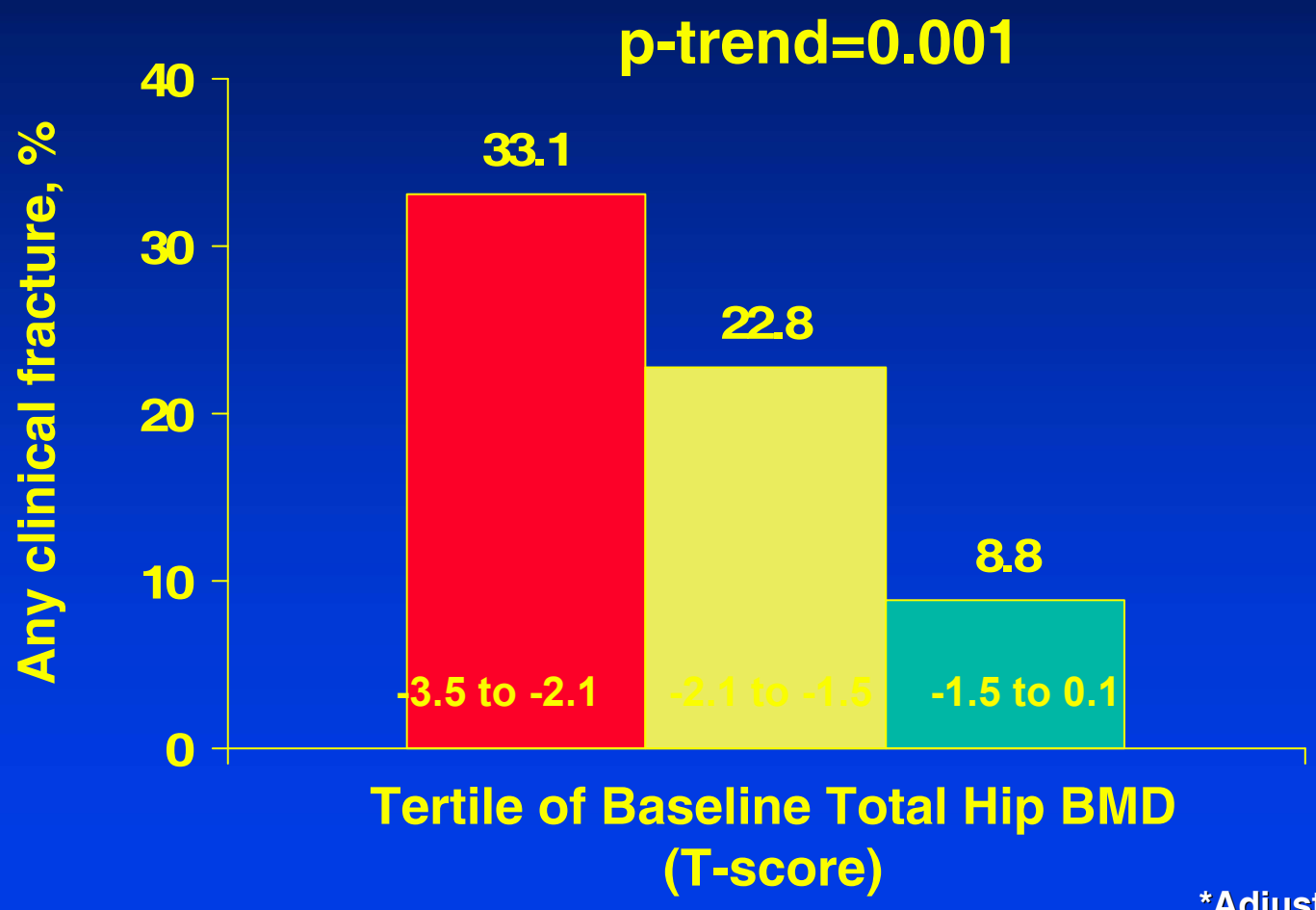
Slide 12

db1 Combine ALN groups

ADD % with vertebral fx at FLEX BL
dbauer, 10/7/2010

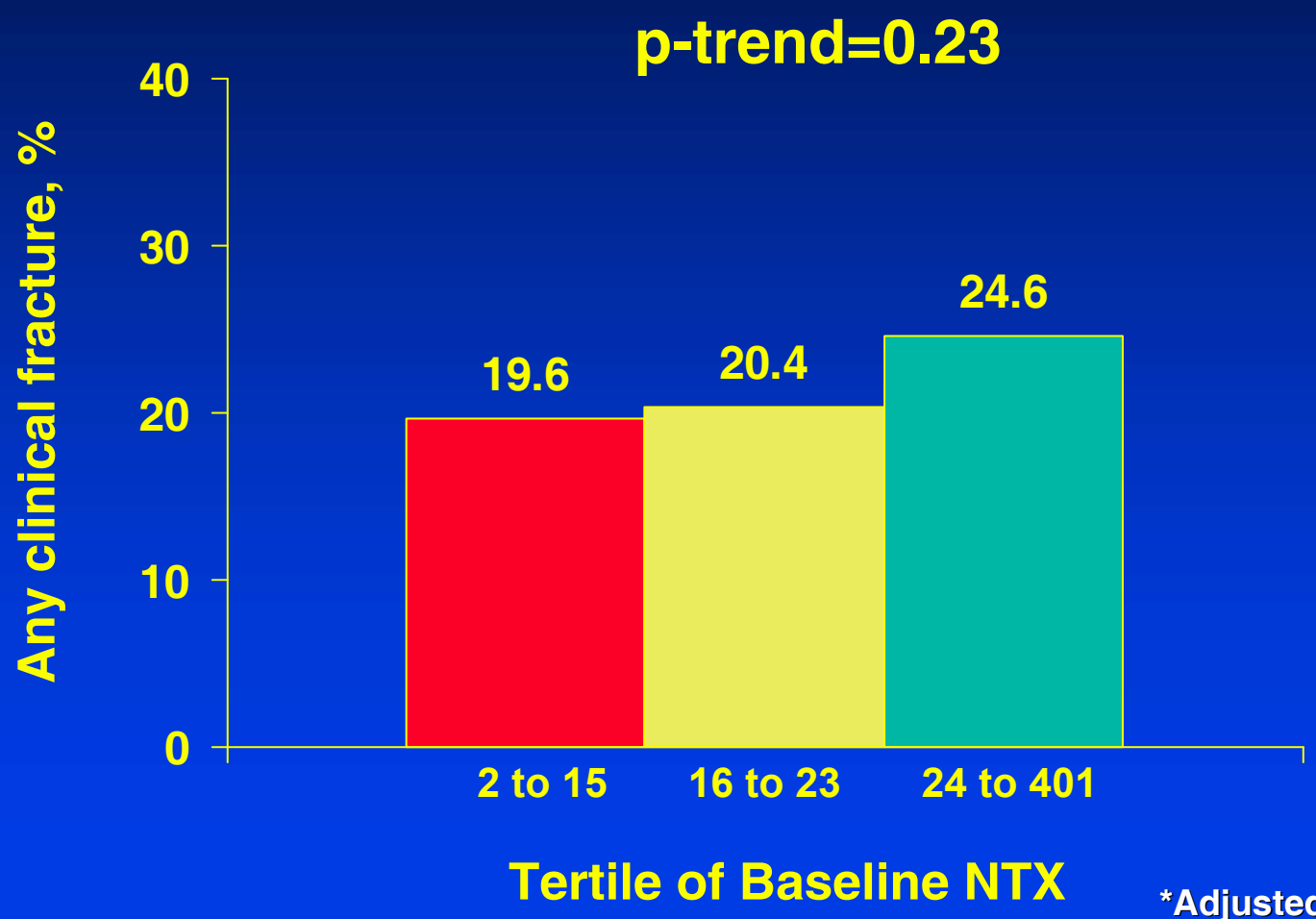
Do BMD or BTM measurements at the time of discontinuation predict fracture outcomes over the next 5 years?

Any Clinical Fracture by Tertile of FLEX Baseline Hip BMD in Placebo Group*



*Adjusted for age and existing vertebral fracture

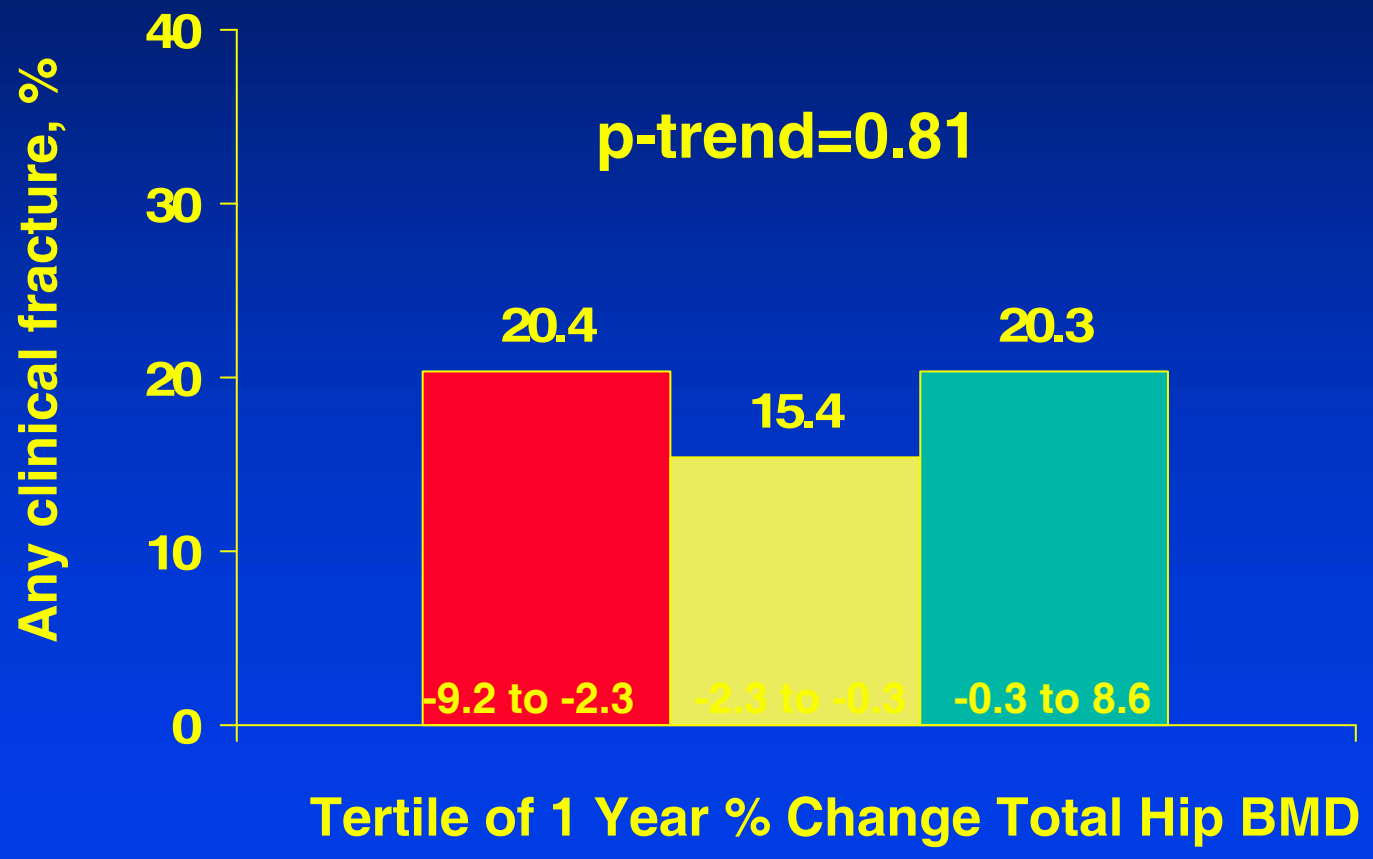
Any Clinical Fracture by Tertile of FLEX Baseline NTX in Placebo Group*



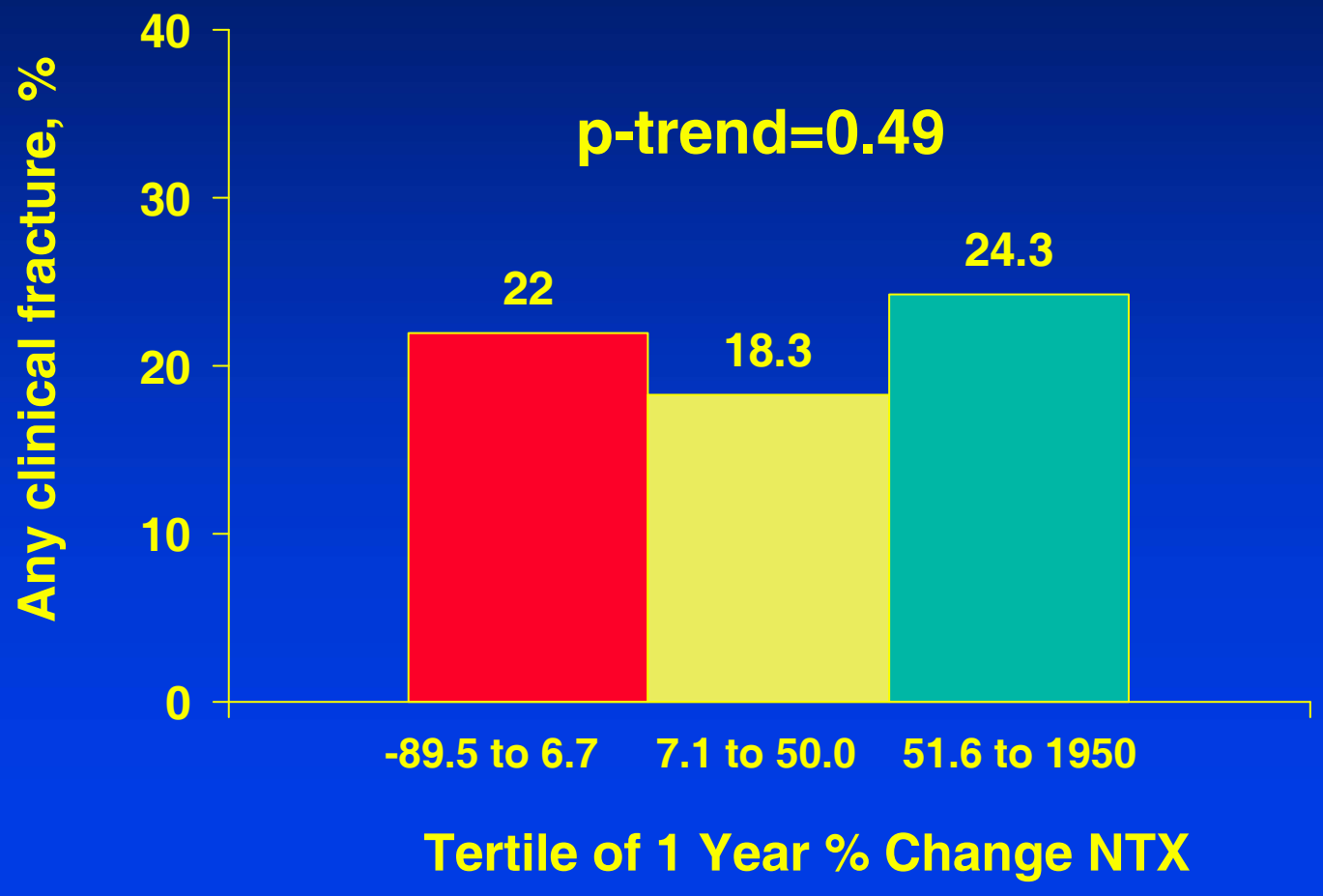
*Adjusted for age, existing vertebral fracture and BMD

Do 1-2 year changes in BMD or BTM after discontinuation predict fracture outcomes?

Any Clinical Fracture by Tertile of FLEX Baseline-1 Yr. ΔBMD in Placebo Group



Any Clinical Fracture by Tertile of FLEX Baseline-1 Yr. ΔNTX in Placebo Group



Strengths of FLEX

- FLEX is the only study published to date with
  - Randomization to continuation vs. discontinuation of bisphosphonate
  - Prolonged blinded follow-up after discontinuation
  - Objectively documented fracture outcomes

Limitations of FLEX

- Low power, particularly subgroups with substantial bone loss or markedly increased turnover
- Newer BTMs (PINP, CTX) not available
- Results apply to older women treated with daily alendronate for approximately 5 years
  - Likely generalizable to weekly dosing
  - Other bisphosphonates?

Discontinuation of Other Bisphosphonates?

- HORIZON Extension among women who received 3 yr. vs. 6 yr. of yearly zoledronic acid
  - Non-vertebral fracture RH= 1.0, CI: 0.7, 1.5
  - Morphometric vert. fx RH= 0.5, CI: 0.3, 0.9
- No randomized continuation vs. discontinuation data for other bisphosphonates
- Uncertainty given pharmacokinetic differences

Black et al, ASBMR, 2010

Summary 1: Discontinuation of Alendronate

- Compared to alendronate therapy for 10 yr, discontinuation after 5 yr. is associated with
  - Modest reduction in hip BMD
  - Modest increases in bone turnover
  - Increased risk of clinical vert. fracture
  - No increased risk of non-spine fracture
- Qualitatively similar non-spine fracture results for 3 vs. 6 yr. of zoledronic acid

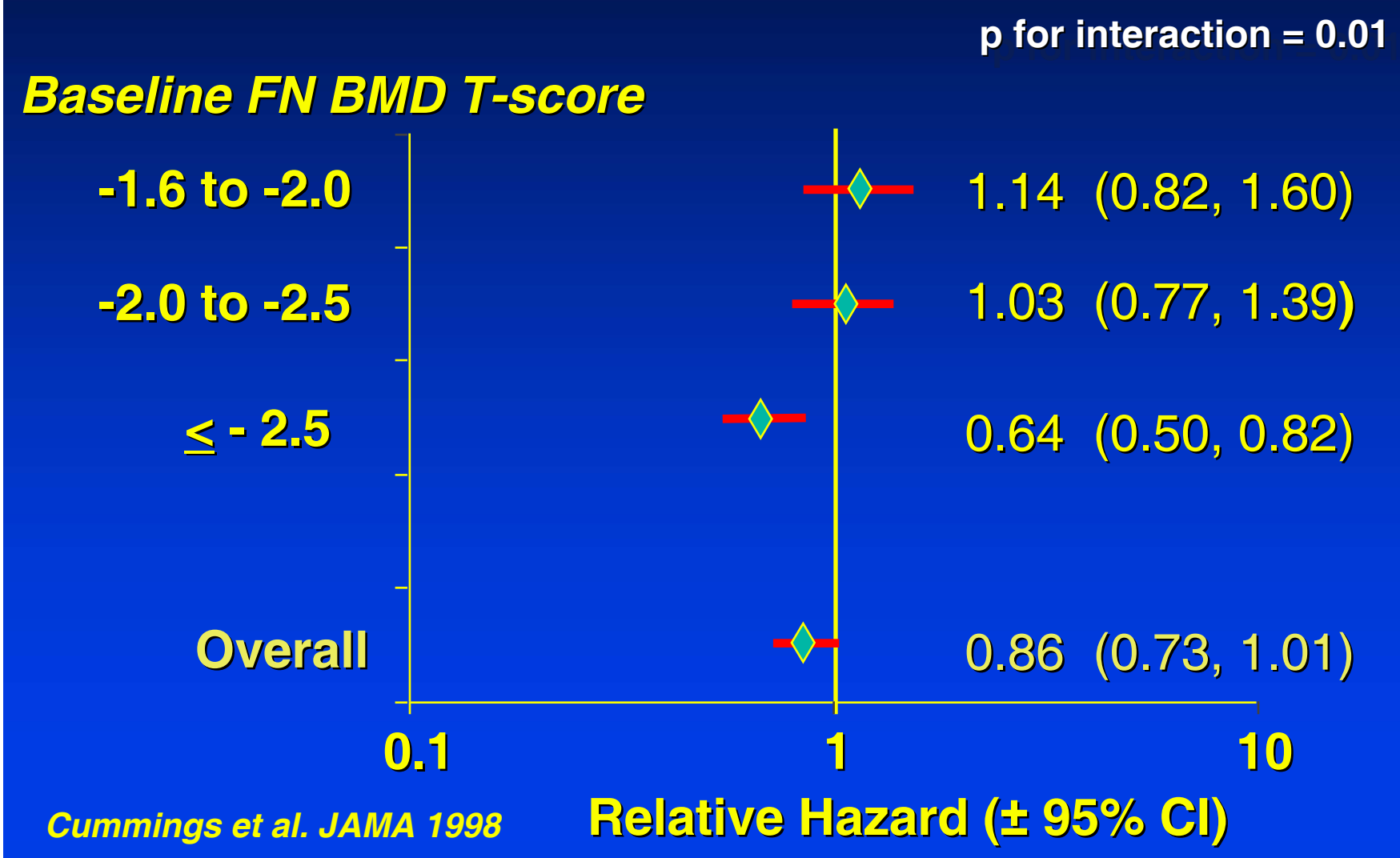
Summary 2
Discontinuation of Alendronate

- In addition to age and existing vertebral fracture, risk after discontinuation is strongly related to hip BMD at the time of discontinuation
  - Not related to bone turnover
- 1 or 2 year change in BMD or BTM after discontinuation not associated with subsequent fracture risk
  - Suggests limited role for monitoring
- Continued therapy >5 yr. may be prudent among women at high risk of fracture
  - History of hip or vertebral fracture
  - Hip BMD T-score remains <-2.5

Acknowledgements

- FIT/FLEX Research Group
- Dennis Black, Ann Schwartz and Steve Cummings at UCSF
- NIAMS K24 funding

FIT II: Women without Prevalent Vertebral Fracture
Any Clinical Fracture Risk



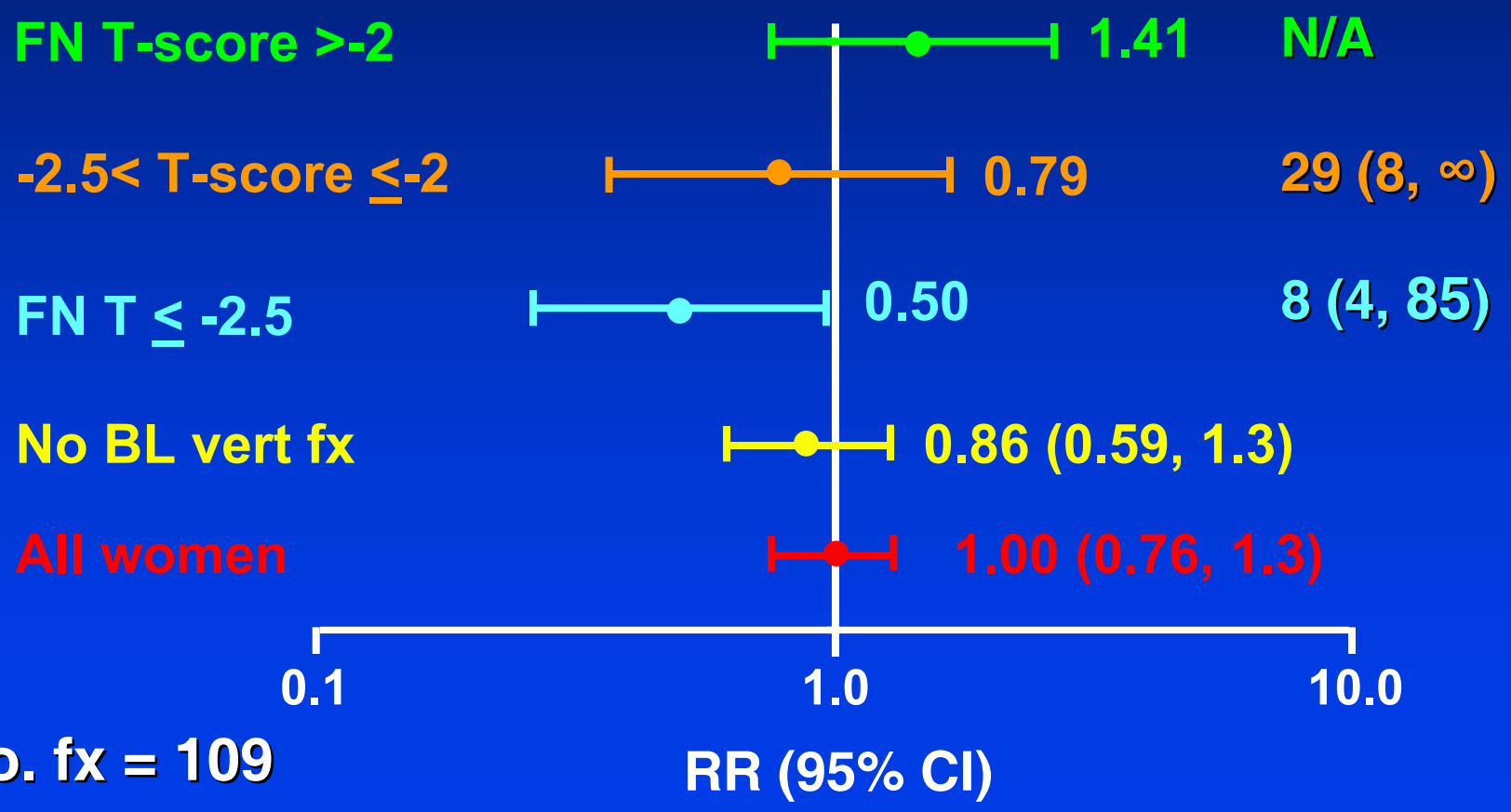
Cummings et al. JAMA 1998

Women without Baseline Vertebral Fracture

Relative Risk of Fracture by FLEX Baseline Femoral Neck T-score

Non-spine Fractures

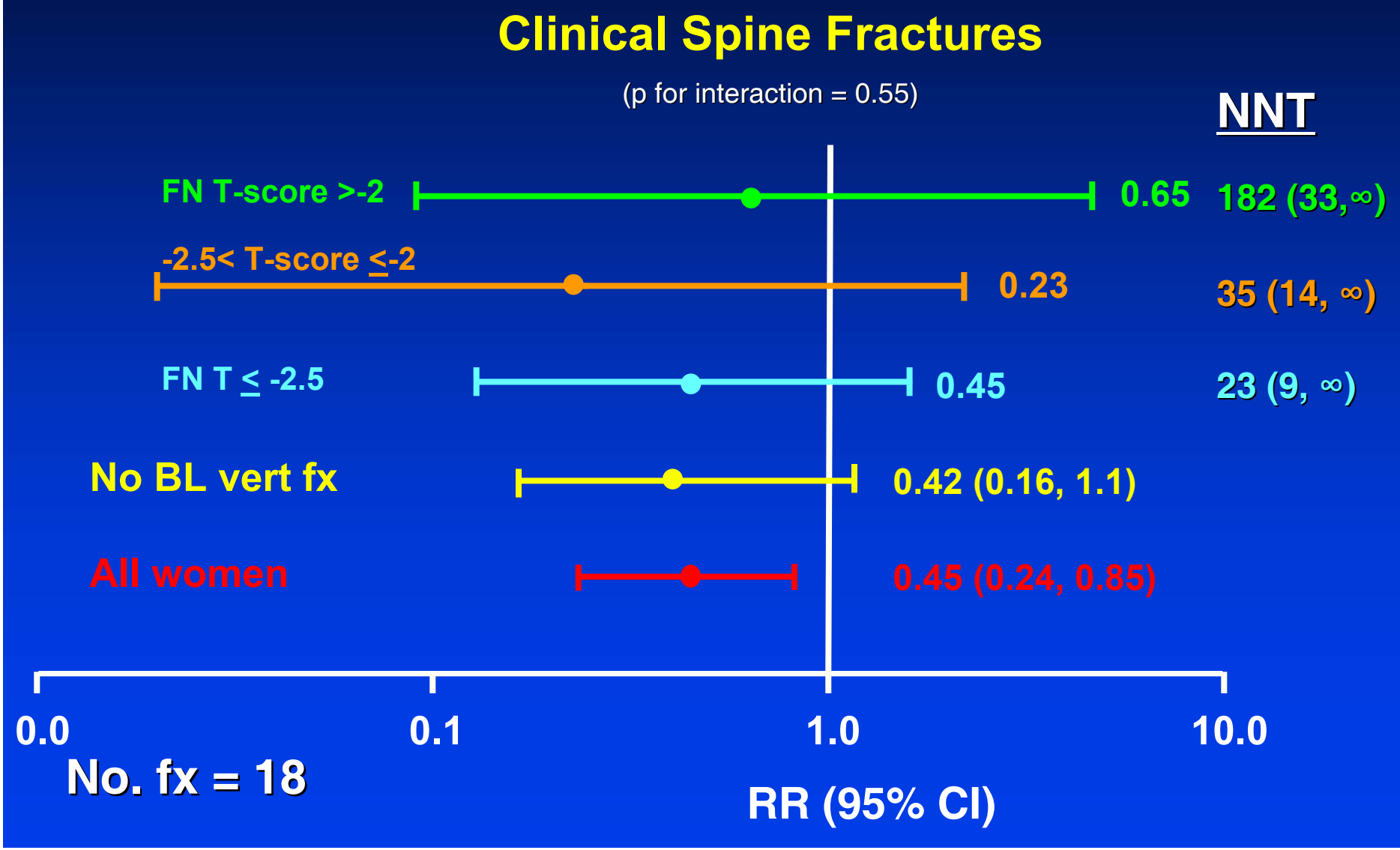
p for interaction = 0.019



No. fx = 109

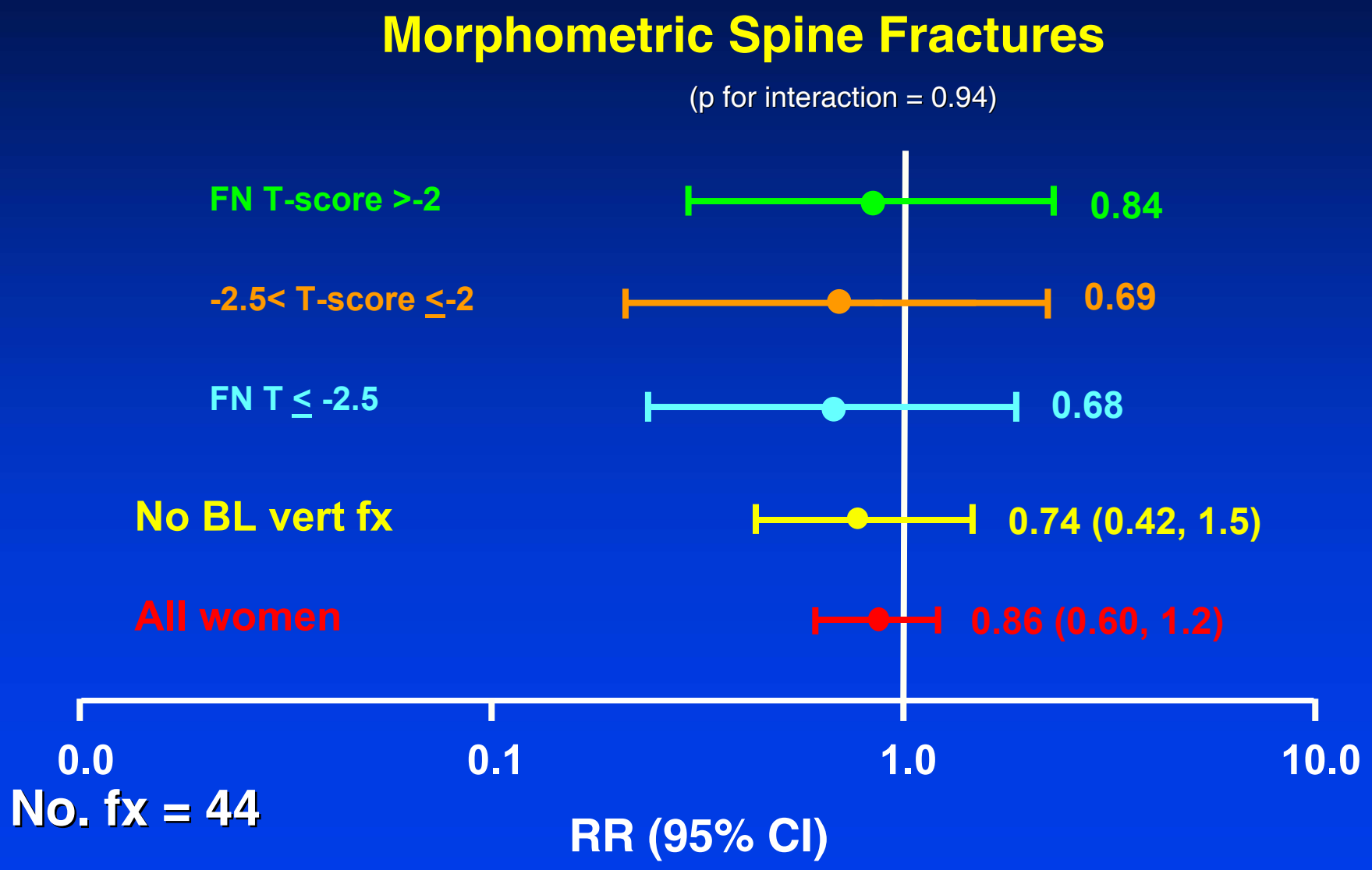
Women without Baseline Vertebral Fracture

Relative Risk of Fracture by FLEX Baseline Femoral Neck T-score



Women without Baseline Vertebral Fracture

Relative Risk of Fracture by FLEX Baseline Femoral Neck T-score



Bisphosphonate Long Term Use

Summary

Theresa Kehoe, M.D.
Medical Officer, Team Leader
Division of Reproductive and Urologic Products
Office of New Drugs, CDER, FDA

Bisphosphonate Long-term Use

- Bisphosphonates are highly efficacious in reducing the risk for fracture
- They are widely prescribed for the prevention and/or treatment of osteoporosis
- Although widely prescribed, drug use data suggest that only a minority of patients continue therapy for a prolonged duration of time

Bisphosphonate Long-term Use

- Recent events have raised questions regarding the safety of bisphosphonates when used for years, most notably
  - Atypical subtrochanteric fractures
  - Osteonecrosis of the jaw
  - Esophageal cancer
- AERS data are not helpful for assessing these safety issues

Atypical Subtrochanteric Fractures

- There may be an association between bisphosphonate use and atypical subtrochanteric and femoral diaphyseal fractures
- Relationship between atypical fracture and duration of bisphosphonate use remains unclear

Osteonecrosis of the Jaw

- Based on the limited number of cases in the PROBE study, it appears that the prevalence of ONJ may increase with increased duration of exposure to oral bisphosphonate
- Highest prevalence at 4 or more years of use

Esophageal Cancer

- Available evidence is inconclusive concerning esophageal cancer and bisphosphonate use

Bisphosphonate Long-term Use

- Placebo-controlled clinical trial data out to a minimum of three and maximum of 5 years is available.
- Clinical trial data on bisphosphonate extended use are available out to 10 years
  - Various trial designs, including randomized withdrawal designs
  - There are limitations

Bone Mineral Density

- Continued drug therapy to 5 years
  - Similar BMD Response for all bisphosphonate products
- Continued drug therapy beyond 5 years
  - Maintenance at Femoral Neck
  - Increases at Lumbar Spine
- Cessation of therapy after 3 – 5 years
  - Decrease, then plateau above baseline at Femoral Neck
  - Continued small increases at Lumbar Spine

Fracture

- Continued drug therapy to 5 years
  - Robust fracture efficacy
- Continued drug therapy beyond 5 years
  - No clear benefit or evidence of harm for overall osteoporotic fractures
  - No subset with clear and consistent fracture benefit
- Cessation of therapy after 3 – 5 years
  - No difference in rates compared to active therapy
  - Possible maintenance of benefit after 3 – 5 years of exposure

Drug Holiday

- Data are sparse
- Unanswered Questions
  - Who is a candidate?
  - What factors should be considered?
  - Who should resume therapy?
  - When should therapy be resumed?

Issues for Consideration

- FDA has presented all of the data that we have available pertaining to the duration of use for bisphosphonates in the prevention and treatment of osteoporosis
- When the risks and benefits are evaluated together, can further recommendations be made regarding the optimal bisphosphonate duration of use?
- What other data are needed?