FOSAMAX® & FOSAMAX® PLUS D

Joint Meeting of
The Advisory Committee for Reproductive Health Drugs
and
The Drug Safety and Risk Management Advisory Committee

Briefing Document

Available for Public Disclosure Without Redaction

TABLE OF CONTENTS

PAGE

List of Tables --
List of Figures --
Request 1: *Provide an opinion and discussion of whether your efficacy and safety data support a long-term duration use (i.e., > 3 years) for FOSAMAX® (alendronate sodium) tablets and oral solution and FOSAMAX® Plus D (alendronate sodium/cholecalciferol) tablets* 1
1. Response to Request 1 1
1.1 Overview 1
1.2 Pharmacokinetics of Alendronate 3
1.3 Summary of Efficacy Data 4
1.3.1 Treatment of Osteoporosis 4
1.3.1.1 Primary US/International Phase III Studies 4
1.3.1.2 Fracture Intervention Trial (FIT) 5
1.3.1.3 10-Year Extension Studies of Alendronate 8
1.3.1.3.1 Phase III 10-Year Extension Studies 8
1.3.1.3.2 FIT Long-Term Extension Study (FLEX) 9
1.3.2 Prevention of Osteoporosis 10
1.3.2.1 Early Postmenopausal Cohort Study (EPIC) 10
1.3.2.2 EPIC Extension Study 13
1.4 Safety Data 14
1.4.1 General Safety 14
1.4.2 Long-Term Data 14
1.4.2.1 Osteonecrosis of the Jaw 15
1.4.2.2 Esophageal Cancer 15
1.4.2.3 Subtrochanteric and Femoral Shaft Fractures 15
1.4.2.3.1 Epidemiology of Subtrochanteric and other Femoral fractures 15
Request 2: *Provide an opinion and discussion of whether either restricting the duration of use or implementing a drug holiday may be beneficial for patients requiring long-term treatment.* 20
2. Response to Request 2 20
2.1 Treatment of Osteoporosis 20
2.1.1 ≤ 5 years 20
2.1.2 5 to 10 years 21
2.1.3 > 10 years 22
2.2 Prevention of Osteoporosis in Postmenopausal Women 22
2.2.1 ≤ 6 years 22
2.2.2 > 6 years 22
3. List of References 23

List of Tables

		PAGE
Table 1	Controlled Alendronate Studies > 3 Years in Duration	2
Table 2	Incidence Rates for Femoral Fractures from 1996-2009 [22]	18

List of Figures

		PAGE
Figure 1	Three-Year Increase in BMD vs. Placebo Alendronate 10 mg/day	5
Figure 2	Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT	6
Figure 3	Cumulative Incidence of First† Clinical Fracture During FIT Combined Osteoporotic Cohort	8
Figure 4	Treatment in the Early Postmenopausal Cohort Study	11
Figure 5	Change in Spine and Total Hip BMD in EPIC	12
Figure 6	Change in BMD During and Following Treatment with Alendronate or Hormone Therapy Early Postmenopausal Cohort Study	13
Figure 7	Annual Incidence‡ of Hip and Subtrochanteric/Femoral Shaft Fractures: 1996 – 2009	17

Request 1: ***Provide an opinion and discussion of whether your efficacy and safety data support a long-term duration use (i.e., > 3 years) for FOSAMAX® (alendronate sodium) tablets and oral solution and FOSAMAX® Plus D (alendronate sodium/cholecalciferol) tablets***

1. Response to Request 1

1.1 Overview

The available data support a favorable benefit to risk profile during long-term (10-year) treatment with alendronate in osteoporotic patients who remain at risk of osteoporotic fracture and who have not experienced adverse reactions that required discontinuation of therapy.

FOSAMAX® was approved by FDA in 1995. As described in the current US Physicians Circular (USPC) [1], treatment of osteoporosis with alendronate increases bone mass and reduces the incidence of fractures, including those of the hip and spine, based on data from clinical trials of 3 to 4 years' duration. The clinical trial data supporting the safety and efficacy of treatment with alendronate beyond 3 years are substantial. The safety and efficacy of long-term (up to 10 years) use of alendronate in the treatment and prevention of osteoporosis was demonstrated in a series of controlled clinical trials, each of which extended the findings of prior studies.

Two long-term studies in the FOSAMAX development program directly compared the effects of continuing alendronate for 10 years vs. discontinuing treatment after 5 years of use. Together these studies enrolled 1449 patients, of whom 897 received alendronate (5 or 10 mg daily) for up to 10 years, with 587 of these completing 10 years [2; 3]. There are no similar controlled studies of this duration for other bisphosphonates, and few if any similar long-term placebo-controlled studies of other drugs that are used to treat chronic disease. Key findings from these studies include the following:

- Continued treatment for 5 additional years was associated with a 55% reduced risk of clinical vertebral fractures and a 50% reduced risk of non-vertebral fractures in patients whose hip neck bone mineral density (BMD) remained low (T-score ≤ -2.5) after 5 years of prior treatment.

- Continued treatment with alendronate resulted in maintenance of hip BMD, small increases in spine BMD, and stable biochemical markers of bone turnover.

- Discontinuation of treatment resulted in gradual loss of hip BMD with no change in spine BMD and increase in biochemical markers of bone turnover toward pre-treatment levels. Resolution of effects was consistent with the pharmacokinetics of alendronate, with small residual effects observed > 1 year post-treatment.

- Safety of alendronate during long-term treatment up to 10 years was consistent with the safety profile previously established in placebo-controlled studies up to 4 years in duration. No reports of osteonecrosis of the jaw have been reported in clinical studies of alendronate conducted by Merck. Subtrochanteric and diaphyseal femur fractures were infrequent vs. hip fractures, with no difference in the risk of subtrochanteric and diaphyseal femur fractures observed between drug and placebo treatment groups.

These long-term data are derived primarily from extensions of shorter placebo-controlled trials. A list of these studies, which include the Primary Phase III studies, the Fracture Intervention Trial (FIT), and the study evaluating prevention of osteoporosis in postmenopausal women (EPIC), and their extensions are provided in Table 1. An understanding of the efficacy and safety findings during initial placebo-controlled treatment periods of these studies as well as the pharmacokinetics of alendronate is critical to the interpretation of the results of the extension studies.

Table 1
Controlled Alendronate Studies > 3 Years in Duration

Study Name (Protocol No.)	Study Duration† (Months)	ALN Daily Doses (mg)	Patients Enrolled			References for Responses
			ALN	PBO/ Comparator	Total	
Studies 3 or 4 Years in Duration						
Treatment of Osteoporosis in Postmenopausal Women						
Phase III U.S. Osteoporosis (035)	36	5, 10, 20	286	192	478	• [7] (Tucci)
Phase III Multinational Osteoporosis (037)	36	5, 10, 20	311	205	516	• [8] (Devogelaer) • [12] (Liberman)
FIT- Fracture Intervention Trial (051) Vertebral Fracture Study	36	5 for 24 months; 10 for remainder of study	1022	1005	2027	• [14] (Black)
FIT - Fracture Intervention Trial (051) Clinical Fracture Study	54	5 for 24 months; 10 for remainder of study	2214	2218	4432	• [11] (Cummings)
Studies > 5 Years in Duration						
Treatment of Osteoporosis in Postmenopausal Women						
10-year Primary Phase III Study Extensions						
Phase III U.S. Osteoporosis (035) Phase III Multinational Osteoporosis (037)	36+24 +24+ 36	5, 10, 20	235	115	350‡	• [2] (Bone) Combined report of both studies
FLEX (FIT extension) (051-22)	60+60	5, 10	662	437	1099	• [19] (Black 2010) • [3] (Black) • [17] (Schwartz)
Prevention of Osteoporosis in Postmenopausal Women						
EPIC - Early Postmenopausal Interventional Cohort (055)	72 + 36	2.5 and 5	997	502 PBO 110 EP	1609	• [10] (Wasnich) • [18] (McClung)

ALN: Alendronate.
PBO: Placebo.
EP: Estrogen and progestin.
† Duration of the original study followed by the duration of the extension study (where applicable), including off-drug periods.
‡ Reported numbers are for patients entering year 6.

1.2 Pharmacokinetics of Alendronate

Absorption

Like all bisphosphonates, the bioavailability of oral alendronate is low (0.64% in postmenopausal women when administered fasting at least two hours before a meal). Dosing 0.5 or 1 hour before a meal reduces bioavailability further, by about 40%. As dosing instructions indicate that the drug must be administered fasting at least 30 minutes before food, the typical bioavailability is 0.4% (with food 30 min post dose) to 0.65% (with food > 2 hours post dose) , and absorbed alendronate is estimated to be 40 to 65 micrograms per day following an oral 10-mg daily dose [1]. These data should be considered when comparing doses of oral and intravenous bisphosphonates.

Distribution

Bisphosphonates are potent and selective inhibitors of osteoclasts for two reasons related to their distribution. Absorbed bisphosphonates such as alendronate distribute either to bone or are excreted by the kidney, with about 50% of an absorbed dose found in bone and 50% recovered in urine a day after dosing. Alendronate in bone is initially concentrated on bone surfaces under osteoclasts. Osteoclasts have the unique ability to release bisphosphonates from bone through acidification and absorb them by endocytosis. These unique distribution characteristics are the reason for alendronate's selective inhibition of osteoclast-mediated bone resorption. Alendronate has no direct action on osteoblasts that form bone.

The duration of action of a bisphosphonate in bone is also linked to its distribution. Inhibition of bone resorption by osteoclasts decreases as alendronate is lost from the surface of bone, either by release back into the circulation or by incorporation into new bone. The half-life of drug on the surface of bone is multi-phasic, estimated to be between 2 to 5 weeks [4]. Within several months after a single dose, the great majority of alendronate is found within newly formed bone where it would not be expected to inhibit osteoclasts, with very little alendronate remaining on bone surfaces. While alendronate within bone has no effect on osteoclasts on the surface of bone, it would inhibit the activity of osteoclasts that may subsequently release trapped alendronate as they resorb bone formed during prior alendronate treatment. The 2 to 5 week half-life of alendronate on the surface of bone is the reason that a 70 mg weekly dose and a 10 mg daily dose of alendronate have equivalent effects on bone resorption and bone formation during long-term treatment. The therapeutic equivalence of their effects on lumbar spine BMD was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. Additional details of the pharmacokinetics of alendronate are described in the FOSAMAX® US Physicians Circular [1] and reviews [5].

Elimination

Pharmacokinetic studies of alendronate have characterized its elimination via renal excretion over 18 months in postmenopausal osteoporotic women [6]. About 50% of an IV dose is initially retained in bone. One-third of the drug initially retained is excreted in urine over the following 2 months. The remaining alendronate is incorporated into new bone. Alendronate within bone may be resorbed, released back into the circulation, and excreted by the kidney.

Alendronate is the only bisphosphonate for which the terminal-elimination half-life has been calculated in humans. Analysis of excretion 12 to 18 months after dosing alendronate yields an

average terminal elimination half-life of 10.5 years. Terminal elimination half-life is determined by both the half-life of alendronate in bone and the fractional excretion of alendronate released from bone during bone resorption. The fractional renal excretion of alendronate released from bone is estimated to be 50%, the same as the fractional excretion after an IV dose.

Alendronate accumulation in bone during long-term treatment and the rate of its subsequent release may be estimated based on data from pharmacokinetic studies. It is estimated that after 10 years of oral treatment with alendronate 10 mg daily the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed daily from the gastrointestinal tract [1].

The time course of alendronate's effect on bone turnover in clinical studies is predicted by the pharmacokinetic studies of the drug's distribution and elimination. The effects of a low daily dose of alendronate (10 mg) on bone resorption gradually increase, reaching steady-state after 2 to 3 months. Bone resorption is coupled with subsequent bone formation during remodeling; thus decreases in bone formation are delayed, reaching steady state after 6 to 9 months of treatment [7; 8]. When dosing with a daily dose was discontinued, the effects of prior therapy on bone resorption greatly diminished over about 3 months. Bone formation increased, trailing the increase in bone resorption by about 3 months [9].

The magnitude of persistent effects on bone turnover and BMD loss are related to dose and duration of prior treatment [9; 10]. No persistent long-term effect on bone resorption was found after short-term (1- to 2-year) treatment with alendronate was discontinued [9; 10]. When treatment for 5 years was discontinued, markers of bone turnover increased and only small long-term reductions in bone turnover remained. Five years of treatment with alendronate 10 mg was shown to be sufficient to slow, but insufficient to prevent, bone loss following discontinuation of treatment [2; 11].

1.3 Summary of Efficacy Data

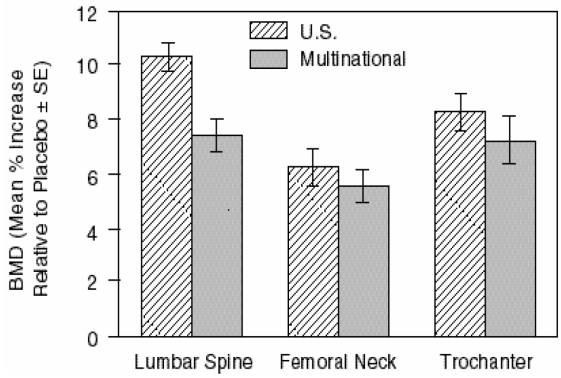
1.3.1 Treatment of Osteoporosis

1.3.1.1 Primary US/International Phase III Studies

The Primary Phase III studies of alendronate were two replicate, 3-year, placebo-controlled trials that demonstrated the effects of alendronate on BMD and bone turnover and a reduction in the proportion of patients with spine fracture. Each study had the same design (one in the US and one multinational, with 478 and 516 patients, respectively), with a pooled evaluation for spine and non-vertebral fracture risk [7; 8; 12]. Patients were postmenopausal women with a spine BMD T-score $\leq$ -2.5 with or without a prior vertebral fracture. Safety was monitored using periodic clinical and laboratory evaluations for adverse events. An extensive bone biopsy program documented both a dose-related reduction in bone turnover and no qualitative abnormalities of bone [13].

At 3 years, significant increases in BMD, relative to both baseline and placebo, were seen at each measurement site in each study with alendronate 10 mg/day [Figure 1]. Total body BMD also increased significantly in each study. There was a reduction in the proportion of patients experiencing one or more new vertebral fractures with alendronate vs. placebo (3.2% vs. 6.2%; a 48% relative risk reduction; $p<0.05$).

Figure 1
Three-Year Increase in BMD vs. Placebo
Alendronate 10 mg/day



1.3.1.2 Fracture Intervention Trial (FIT)

FIT consisted of two independent, randomized, placebo-controlled studies with common recruitment: the Vertebral Fracture Study (referred to as the "Three-Year Study") and the Clinical Fracture Study (referred to as the "Four-Year Study"). Patients in the Vertebral Fracture Study were treated up to 3 years while patients in the Clinical Fracture Study were treated up to 4.5 years. FIT demonstrated that treatment of osteoporosis with alendronate led to fewer spine and hip fractures [14; 15].

Patients who met the femoral neck BMD entry criterion (≤0.68 g/cm2, by Hologic QDR-2000 densitometry) were eligible for either the Vertebral or Clinical Fracture Study depending on the presence or absence, respectively, of a prevalent vertebral fracture as determined by morphometric assessment of baseline spine radiographs. The Vertebral Fracture Study recruited 2027 patients with low BMD and at least one prevalent vertebral fracture at baseline; the primary endpoint was the incidence of new vertebral fractures based on morphometric assessment of radiographs. The Clinical Fracture Study recruited 4432 postmenopausal women with low bone mass but without a prevalent vertebral fracture; the primary endpoint was the cumulative incidence of all clinical fractures.

In FIT, the initial dosage of alendronate was 5 mg/day, based upon preliminary 12-month results of a Phase II dose-ranging study with alendronate. However, 24-month BMD data from the Primary Phase III studies of alendronate indicated that alendronate 10 mg daily was associated with significantly greater efficacy to increase BMD at all measured sites than alendronate 5 mg/day with a similar safety profile. Therefore, in FIT, the dose of alendronate was increased to 10 mg daily at the 24-month visit.

Results of the Vertebral Fracture Study of FIT ("Three-Year Study") for the major fracture risk effects of treatment with alendronate are described in the FOSAMAX USPC [1]:

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

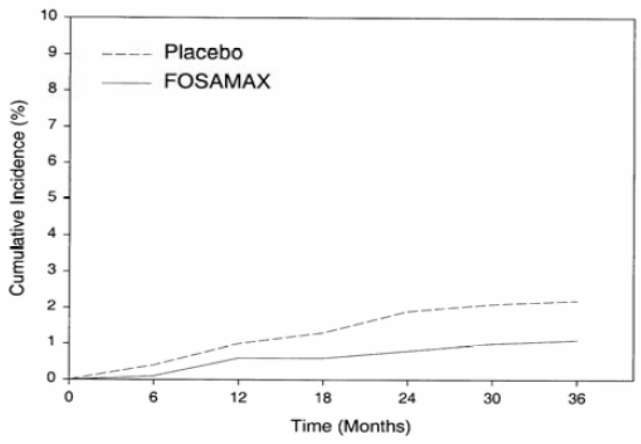
Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT (patients with vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)[†]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26[‡]
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

[†]Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
*p<0.05, **p<0.01, ***p<0.001, [‡]p=0.007

Fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX (p=0.047, for between-group difference) in the Vertebral Fracture Study. Figure 2 below displays the cumulative incidence of hip fractures.

Figure 2
Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT



Treatment with FOSAMAX also significantly reduced the incidence of hospitalizations over 3 years (25.0% vs. 30.7%) in the Vertebral Fracture Study.

Unlike in the Vertebral Fracture Study in which the presence of vertebral fracture at baseline identified women as osteoporotic, in the Clinical Fracture Study of patients without prevalent vertebral fracture the diagnosis of osteoporosis was based on BMD. The study protocol specified a "femoral neck bone mineral density (Hologic, QDR-2000) at least 2 SD below the mean, female, peak bone density (i.e., ≤0.68 g/cm2)." However, Hologic revised its hip reference values in 1997 after the US National Health and Nutritional Examination Survey (NHANES III) to reflect that the value of 0.68 g/cm2 was found to be ~1.6 SD below the young adult mean. Thus, the statistical analysis plan was changed to describe results for all patients enrolled and for the "osteoporotic cohort," i.e., those with baseline femoral neck BMD (revised) T-scores ≤ -2.0.

Results of the Clinical Fracture Study ("Four-Year Study") for the major fracture risk effects are described in the FOSAMAX USPC [16]:

Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of FOSAMAX on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)††				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48***
≥ 2 new vertebral fractures	0.1	0.6	0.5	78*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)†††
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

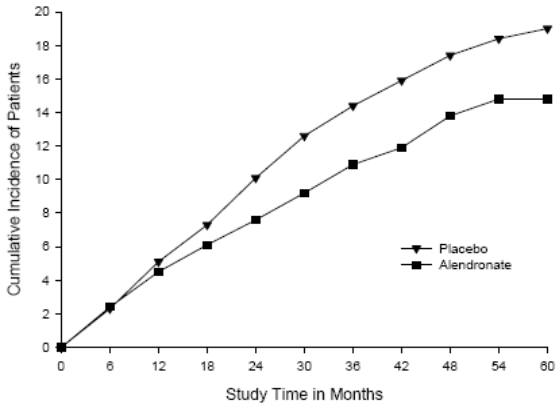
†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
††Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
†††Not significant. This study was not powered to detect differences at these sites.
*p=0.035, ** p=0.01, ***p<0.001

Although the absolute risk of fracture observed in the 4-year Clinical Fracture Study was lower than that observed in the 3-year Vertebral Fracture Study, *relative* reductions in fracture risk were consistent across studies. In the 3-year Vertebral Fracture Study, treatment with alendronate reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the 3-year Primary Phase III studies (US/Multinational combined), the risk was reduced from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

The incidence of fractures over time was also analyzed based on a combined osteoporotic cohort analysis that included all patients in the Vertebral Fracture Study and patients in the "osteoporotic

cohort" of the Clinical Fracture Study. The cumulative incidences gradually diverge after approximately 12 months [Figure 3].

Figure 3
Cumulative Incidence of First† Clinical Fracture During FIT
Combined Osteoporotic Cohort



† Excludes fractures present at baseline.

1.3.1.3 10-Year Extension Studies of Alendronate

Two controlled clinical trials of alendronate compared the effects of continuing alendronate for 10 years vs. discontinuing treatment with alendronate after 5 years of use in postmenopausal women with osteoporosis and low BMD. These 10-year trials enrolled patients who had received alendronate in either the Primary Phase III studies or FIT, and are referred to as the Phase III 10-Year Extension studies [2] or the FIT Long-Term Extension study (FLEX) [3], as noted in Table 1.

1.3.1.3.1 Phase III 10-Year Extension Studies

The 3-year double-blind treatment period of the US and Multinational Phase III osteoporosis treatment studies of alendronate was followed by treatment with alendronate (either 5 or 10 mg daily) during a 2-year extension study. Patients completing 5 years of treatment were recruited into an extension study that ultimately provided an additional 5 years of controlled treatment experience (Years 6 through 10 relative to the first treatment with alendronate). In the 5-year extension period, patients previously treated with either alendronate 5 mg daily or 10 mg daily were continued on the same doses throughout the extension. Patients who had received 20 mg daily for Years 1 and 2, then 5 mg daily for Years 3 through 5 (average exposure, 11 mg per day) were switched to placebo for the next 5 years. Of the 482 patients originally assigned to alendronate at the study sites that participated in the extension, 350 entered Year 6 and 247 (51.0 percent) participated in all extensions of the study.

Bone et al. provided an overview of all 10 years of the Phase III studies and their extensions [2]. Treatment with alendronate 10 mg daily for 10 years produced mean increases in BMD of 13.7% at the lumbar spine (95% CI, 12.0-15.5%), 10.3% at the trochanter (95% CI, 8.1-12.4), 5.4% at

the femoral neck (95% CI, 3.5-7.4 %), and 6.7% at the total proximal femur (95% CI, 4.4-9.1%). Continued treatment beyond 5 years produced small annual increases in spine BMD and maintenance of prior BMD gains at the femur and forearm. After 5 years of prior therapy, discontinuation of alendronate resulted in a gradual loss of effect with decreases in BMD and increases in biochemical markers of bone remodeling. The limited number of fracture events did not allow precise estimates of fracture risk reduction. However, available fracture and stature data did not suggest that prolonged treatment resulted in any loss of benefit.

1.3.1.3.2 FIT Long-Term Extension Study (FLEX)

After patients in the FIT Vertebral and Clinical Fracture Studies completed 3 and 4.5 years, respectively, of placebo-controlled treatment, most received open-label alendronate 10 mg daily for at least 1 year (for a total exposure of ~ 5 years in the alendronate group). Ten of the 11 FIT study sites participated in a follow-on study in which patients in the alendronate treatment group of FIT were asked to enroll in a new long-term extension study (FLEX) in which they were randomly assigned to receive alendronate 5 mg/day (N=329), 10 mg/day (N=333), or placebo (N=437) for 5 years. The primary outcome was total hip BMD, with fractures assessed and adjudicated as in FIT and analyzed as an exploratory endpoint.

Black et al. provides a concise summary of FLEX [3]. Switching to placebo for 5 years resulted in declines in BMD at the total hip (-3.4%), femoral neck (-1.5%) and forearm (-3.2%), while BMD did not decrease at the spine (+1.5%). Final BMD remained above pretreatment levels obtained 10 years earlier at most measured sites, but returned to pretreatment levels in the forearm and total hip. Conversely, continued treatment with alendronate (pooled results for the 5- and 10-mg groups) was associated with an increase in spine BMD (+5.3%), a small decrease in total hip (-1.0%) and forearm (-1.2%) BMD, and no change in femoral neck (+0.5%) or trochanter (0.0%) BMD. Evaluation of data for the 5 and 10 mg groups showed a significant difference for changes in total body BMD (alendronate 5 mg, +0.6%; alendronate 10 mg, +1.5%; $p<0.01$), but not at other measured sites.

Biochemical markers of bone turnover were stable in patients treated with alendronate, with no statistical difference between the 5- and 10-mg doses, but increased to new plateaus when patients were switched to placebo (resorption: serum C-telopeptides of type 1 collagen, +55.6%; formation: serum N-propeptide of type 1 collagen, +59.5%; serum bone-specific alkaline phosphatase, +28.1%).

Fractures were an important safety endpoint and carefully evaluated, with comparisons of risk in patients treated with alendronate (pooled 5- and 10-mg groups) and those treated with placebo. Despite the reduced size of FLEX relative to FIT, continued treatment was associated with lower risk of new clinical vertebral fractures (i.e., symptomatic vertebral fractures with acute onset of pain and radiographic confirmation of new vertebral compression fracture) by 55% in those who continued alendronate (2.4% with alendronate vs. 5.3% with placebo; RR, 0.45; 95% CI, 0.24-0.85). The risk of most other categories of fractures was similar in patients treated with alendronate and those treated with placebo. An additional *post hoc* evaluation of fracture risk in FLEX [17] demonstrated that the risk of non-vertebral fractures in patients without prior vertebral fracture but with a femoral neck BMD T-score of ≤ -2.5 when they entered FLEX was lower in patients treated with alendronate. The relative risk was 0.79 (95% CI 0.37–1.66) in those with T-scores between -2.0 and -2.5) and 0.50 (95% CI 0.26–0.96) in those with T-scores ≤ -2.5. An

additional observation was that in patients without prior vertebral fracture who were switched to placebo, 5-year non-vertebral fracture risk was related to baseline femoral neck BMD: 10.8% in patients with a BMD T-score > -2.0, 15.9% for BMD between -2.0 and -2.5, and 28% for BMD ≤ -2.5 [17].

Bone biopsies were obtained in 31 consenting FLEX patients during the 5th year of the extended treatment. Bone histomorphometry was fully evaluable in 18 specimens and differed only by a non-significant trend toward lower mineralizing surface (as a percentage of total bone surface) in patients who continued treatment with alendronate vs. those switched to placebo. Dual tetracycline labeling was present in all specimens and no qualitative abnormalities of bone were found in any specimen.

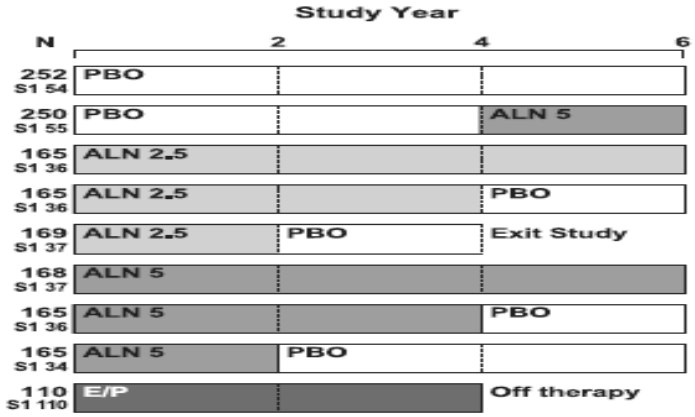
1.3.2 Prevention of Osteoporosis

1.3.2.1 Early Postmenopausal Cohort Study (EPIC)

The estrogen deficiency associated with menopause results in bone loss that is most rapid in the peri-menopausal period but persists throughout life. Whether an individual woman becomes osteoporotic depends on the peak bone mass achieved prior to menopause, her rate of menopausal bone loss, and how long she lives. Concurrent disease, nutrition, some drugs (e.g., glucocorticoids) and exercise may modify that risk. Alendronate was shown in osteoporotic postmenopausal women to reduce hip and spine fracture risk while increasing BMD and reducing accelerated bone turnover; use of alendronate was hypothesized to prevent (or at least reduce) the increase in fracture risk that normally accompanies bone loss in postmenopausal women at risk of developing osteoporosis. Therefore, the appropriate clinical efficacy endpoint in recently postmenopausal women is prevention of BMD loss.

EPIC enrolled 1609 postmenopausal women under 60 years of age (mean 53, range 45-59) who were not on treatment for osteoporosis. Patients were enrolled into 2 strata, based on their candidacy for hormone therapy (absence of contraindications) and willingness to receive hormone therapy. Stratum 1 received daily alendronate 2.5 mg, 5 mg, or placebo for alendronate, or estrogen/progestin; Stratum 2 received alendronate 2.5 mg, 5 mg or placebo (but not estrogen/progestin). Hormone therapy was conjugated equine estrogens plus medroxyprogesterone acetate or a cyclic regimen of 17β-estradiol and norethisterone acetate. Concise published reports of EPIC that focus on the effect of continued treatment [18] and post-treatment resolution of effect [10] are available. The treatment allocation and sample size are summarized below (from Figure 1, McClung et al.[18]).

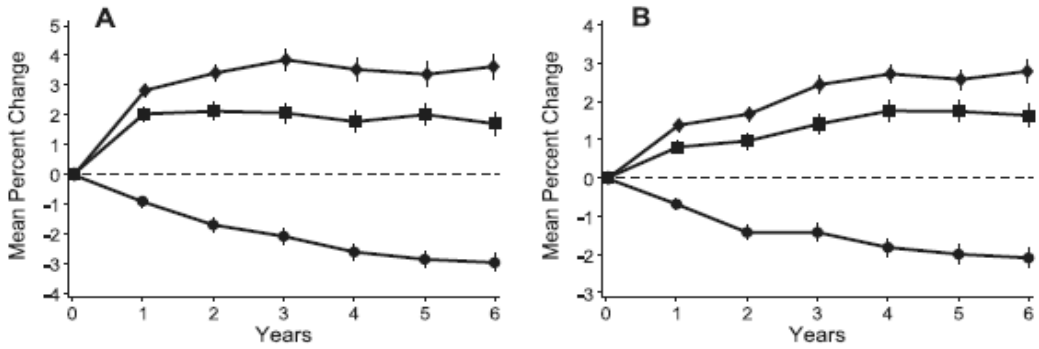
Figure 4
Treatment in the Early Postmenopausal Cohort Study



Treatment allocation and sample sizes, by stratum and year of study.
Stratum 1 (S1): women were randomized to receive placebo, alendronate 2.5 or 5 mg) daily, or open-label estrogen-/ progestin.
PBO, placebo; ALN, alendronate; E/P, estrogen-progestin.

Treatment with alendronate at both 2.5-mg and 5-mg doses prevented decreases in BMD at all measured sites except the forearm, where BMD decreased over the first four years before reaching a new plateau with no further decreases during years 5 and 6. Lumbar spine BMD increased by 3.4% and 1.5%, and total hip increased by 2.6 and 1.5%, over 6 years of treatment with alendronate 5 and 2.5 mg daily, respectively. BMD increases at the femoral neck were 1.0% and 0.5% for alendronate 5 mg and 2.5 mg daily, respectively. The pattern of response showed that most of the BMD increase occurred in the first year, with maintenance of BMD thereafter. For total Body BMD, which reflects total calcium balance, treatment with alendronate was associated with small decreases from baseline of -0.5% (with 5 mg; p=NS) and -1.3% (with 2.5 mg, $p<0.001$). In contrast, treatment with placebo was associated with progressive decreases from baseline at all measured sites over 6 years: lumbar spine -3.2%; total hip -2.3%; femoral neck -3.5%; trochanter -2.1%; and total body -3.5%. Decreases in BMD observed with placebo were all significant versus baseline and both the 2.5 and 5 mg doses of alendronate reduced the BMD losses versus placebo ($p<0.001$). Increases in BMD were significantly larger for the 5-mg alendronate group compared with the 2.5-mg group at all measured sites except for the femoral neck. Figure 5 (that is Figure 2 from the publication by McClung et al. [18]) is provided to illustrate the change in lumbar spine (Panel A) and total hip (Panel B) BMD.

Figure 5
Change in Spine and Total Hip BMD in EPIC

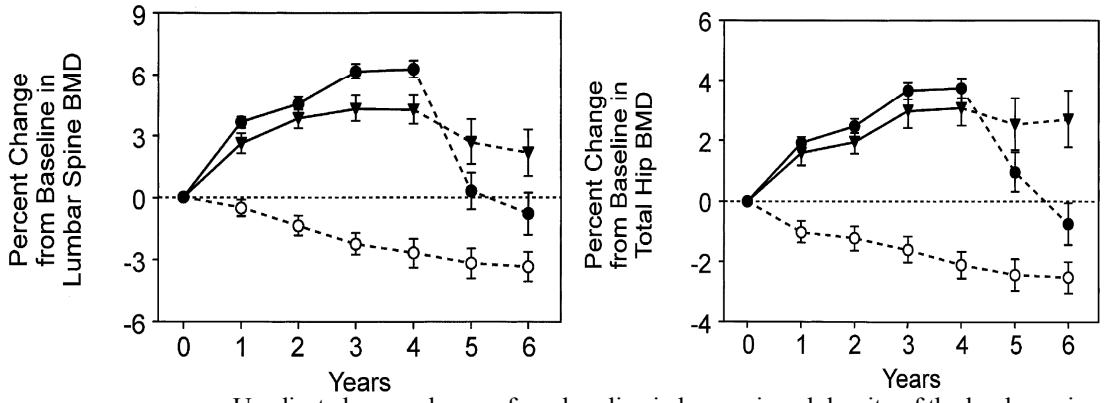


Panel A - Spine BMD, Panel B - Total Hip BMD
Means and bars representing 1 SE are shown.
Symbols represent treatment groups: closed diamonds for alendronate 5 mg, closed boxes for alendronate 2.5 mg and closed circles for placebo
From McClung et al. [18]

Biochemical markers of bone resorption (urine N-telopeptides of type 1 collagen to creatinine ratio; NTx) decreased in all treatment groups, including the placebo group, possibly reflecting the effect of calcium and vitamin D supplements administered as part of the protocol and time since menopause. Changes from baseline at Year 6 were -37% with placebo, -63.9% with alendronate 2.5 mg and -68.0% with alendronate 5 mg daily. The cumulative incidences of fractures over 6 years were similar (no statistically significant differences) in the placebo (11.5%), alendronate 2.5 mg (10.3%) and alendronate 5 mg (8.9%) treatment groups.

Resolution of effect was observed following discontinuation of alendronate after both 2 and 4 years of treatment. The rate of loss was similar to that observed in the placebo group during the first 2 to 4 years of the study. However, much of the BMD increases is retained for several years, with no evidence for accelerated loss back to the level observed in people who were never treated with alendronate. Wasnich et al. [10]addressed resolution of effect and Figure 3 from that publication illustrates the different patterns of bone loss following discontinuation of alendronate and estrogen/progestin.

Figure 6
Change in BMD During and Following Treatment with Alendronate or Hormone Therapy
Early Postmenopausal Cohort Study



Unadjusted mean changes from baseline in bone mineral density of the lumbar spine and total hip in the placebo (○), alendronate (ALN) 5 mg for 4 years (▼) and estrogen/progestin for 4 years (●) (stratum 1 only). Off therapy, (- - -). Bars represent standard errors. BMD = bone mineral density.

When treatment with alendronate was discontinued, biochemical markers of bone turnover returned toward the levels seen in patients treated with placebo. In patients treated with alendronate 5 mg daily for two years, no residual reduction in N-telopeptides of type 1 collagen to creatinine ratio (NTx) vs. placebo was observed two years following discontinuation. Among the groups that stopped taking alendronate, the difference compared with placebo was statistically significant only in the group treated with alendronate 5 mg for 4 years followed for 2 years after discontinuation (−12.7% vs. placebo, $P < 0.001$).

1.3.2.2 EPIC Extension Study

Patients in two treatment groups in EPIC were recruited into a 3-year extension in which all patients were continued on either alendronate 5 mg daily or placebo, based on the dose they received in Years 5 and 6 of EPIC. Both treatment groups had received alendronate 5 mg daily for the first 4 years of EPIC. In the group that continued treatment with alendronate 5 mg daily for the final 2 years of EPIC plus 3 more years of the extension, BMD at all skeletal sites was maintained at approximately the same levels as in EPIC. In the group that switched to placebo after 4 years of alendronate 5 mg, BMD gradually decreased over 5 years.

In summary, EPIC and its Extension study provide data to support the use of alendronate for the prevention of osteoporosis in postmenopausal women over 9 years. Alendronate at a 5 mg daily dose prevented bone loss or produces small increases in BMD at clinically relevant sites in recently postmenopausal women with normal or low-normal BMD. Prevention of loss occurred quickly at all measured sites except the forearm where BMD decreased by approximately 2% over 4 years prior to stabilizing at a new level. Biochemical markers of bone formation decreased within several months to a new lower level that was stable up to 9 years of continued treatment.

The 5 mg daily dose of alendronate appeared to prevent BMD loss in a greater proportion of postmenopausal women than did treatment with 2.5 mg daily for 6 years, and continuation of alendronate 5 mg daily prevented bone loss for 9 years. However, the ability of doses lower than 5 mg daily to maintain the BMD changes produced by alendronate 5 mg daily for 6 years has not been evaluated. BMD is lost more slowly following discontinuation of alendronate than following discontinuation of estrogen/progestin.

1.4 Safety Data

1.4.1 General Safety

The safety profile of alendronate in the 4-year Clinical Fracture Study of FIT was similar to that observed in the 3-year Vertebral Fracture Study of FIT, the 3-year Primary Phase III osteoporosis treatment studies, and other shorter studies of alendronate. The best summary of these data may be found in the presentation of adverse event data from controlled clinical trials in the Adverse Reactions, Warnings and Precautions sections of FOSAMAX US Physicians Circular [1]. The FOSAMAX USPC also summarizes other less common adverse reactions that have not been observed in clinical trials.

In EPIC, there were no increases in adverse experiences that appeared more frequent with either the 2.5 or 5 mg daily dose of alendronate compared to placebo. Gastrointestinal symptoms such as abdominal pain that were more frequent with alendronate 10 mg daily in earlier studies in an osteoporosis treatment population were not increased relative to placebo in EPIC.

1.4.2 Long-Term Data

In the 2 Primary Phase III Study extensions, adverse event data, including gastrointestinal events, were consistent with previous periods of study (i.e., the first three years of double-blind treatment). (It should be noted that patients treated with placebo over 5 years of the extension studies had previously received alendronate for approximately 5 years, and thus represent a bisphosphonate-tolerant population.) No significant between-group differences were found for any adverse experiences or groups of adverse experiences in FLEX out to 10 years. No new, previously unrecognized adverse effects were identified during these long-term extensions. In both EPIC (through 6 years) and the EPIC extension study, the safety profile of alendronate 5 mg daily was similar to that observed in previous studies of alendronate, with no adverse drug effects associated with long-term use up to 9 years found that were not previously recognized in prior studies up to 3 years' duration.

In announcing the Sep 9, 2011 Meeting of the Advisory Committees, FDA stated that, "*the committees will discuss the benefits and risks of long-term bisphosphonate use for the treatment and prevention of osteoporosis in light of the emergence of the safety concerns of osteonecrosis of the jaw and atypical femur fractures that may be associated with the long-term use of bisphosphonates.*". Moreover in July 2011 the FDA issued a Drug Safety Communication regarding its ongoing safety review of oral bisphosphonate drugs and potential increased risk of esophageal cancer. A brief summary of the incidence of these events in clinical trials follows.

1.4.2.1 Osteonecrosis of the Jaw

There were no reports of osteonecrosis of the jaw in any study of alendronate sponsored by Merck.

1.4.2.2 Esophageal Cancer

As noted in a July 2011 FDA Drug Safety Communication, the Agency is continuing to review data from published studies to evaluate whether use of oral bisphosphonate drugs is associated with an increased risk of cancer of the esophagus. The announcement noted that there have been conflicting findings from studies evaluating this risk, and the Agency has not concluded that patients taking oral bisphosphonates have an increased risk of esophageal cancer.

There has been only one report of esophageal cancer in a clinical trial of oral alendronate conducted by Merck. A patient in a study of Paget's disease of bone developed symptoms of esophagitis after 10 days of treatment with alendronate 40 mg daily. Difficulty swallowing persisted following discontinuation of treatment. Further evaluation revealed adenocarcinoma of the esophagus with metastases. No other cases of esophageal cancer were reported in other studies of alendronate, including the long-term studies listed in Table 1.

1.4.2.3 Subtrochanteric and Femoral Shaft Fractures

As described in the FOSAMAX US Physicians Circular in Precautions, "*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 transverse 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.*"

A recent re-analysis of femur fracture location in several studies of bisphosphonates (including FIT and FLEX) was conducted to detect and report the occurrence of subtrochanteric and femoral shaft fractures. While original radiographs from FIT were not available to determine whether any of these fractures had "atypical" features, the total number of fractures in this region of the femur was low—one in a patient treated with alendronate for approximately 4.6 years and one in a patient treated with placebo for 2.6 years [19]. In contrast, there were approximately 20-times as many fractures of the hip (i.e., in either the femoral neck or intertrochanteric femur), than subtrochanteric/femoral shaft fractures. Evaluation of the location of all femur fractures in FLEX [19] showed that fractures of the subtrochanteric or diaphyseal femur were observed in 2/662 patients receiving alendronate and 1/437 patients on placebo (relative hazard, 1.33; 95% CI, 0.12-14.67). Radiographs were not available to determine whether these fractures had atypical features.

1.4.2.3.1 Epidemiology of Subtrochanteric and other Femoral fractures

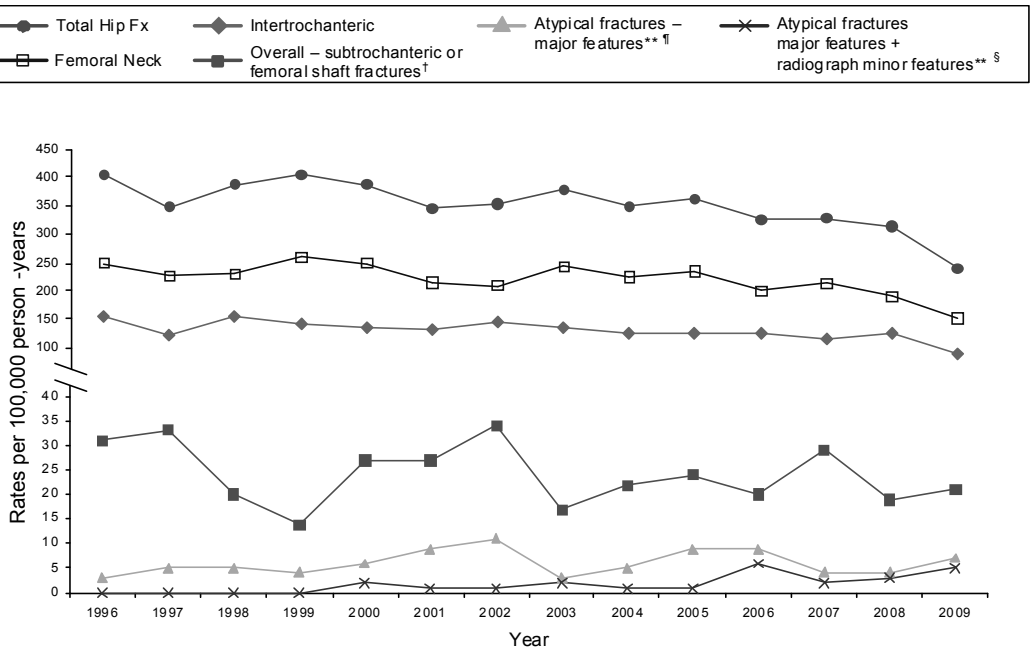
Nieves et al., recently reported a study of the epidemiology of femoral fractures from 1996 through 2009 in the US [20], using International Classification of Diseases (ICD-9-CM) codes from US national discharge and medical claims data. Secular trends in incidence rates were

evaluated for hip, subtrochanteric, femoral shaft and distal femur fractures in men and women 50 years and older. Incidence rates at the four fracture locations increased exponentially with age in both women and men. In women, hospital discharge rates for hip fracture decreased from 1996 to 2006, from about 600 to 400 per 100,000 person-years, while the subtrochanteric, femoral shaft and distal femur fracture discharge rate remained stable, each at about 20 per 100,000 person-years. Similar trends were noted in men though corresponding rates were lower.

In the Study of Osteoporotic Fractures, a large multicenter prospective cohort study of risk factors for fracture in 9704 women aged 65 and older enrolled between 1986 and 1988, hip (femoral neck and intertrochanteric) and subtrochanteric fracture incidence rates were estimated based on confirmation by radiographic report. The expected exponential increase in fracture incidence by age across all fracture types was observed. Corresponding incidence rates for femoral neck, intertrochanteric and subtrochanteric/diaphyseal fractures were 581, 491 and 31 per 100,000 person-years respectively [21].

Atypical subtrochanteric and diaphyseal fractures can not be identified on the basis of ICD-9 or ICD-10 codes or radiographic reports alone. Radiographic review is required to identify the subset of subtrochanteric and diaphyseal femur fractures that have atypical features. Feldstein completed a study at Kaiser Permanente Northwest to evaluate temporal trends in femur fractures from 1996 through 2009, using radiographic review [22]. Radiographs of subtrochanteric and diaphyseal femur fractures were reviewed and categorized based on the presence or absence of atypical features, according to the ASBMR criteria [23]. The incidence of femur fractures from 1996 to 2009 is shown in Figure 7. Consistent with prior reports, results showed a declining incidence of hip (femoral neck and intertrochanteric) fractures. The incidence of femoral neck fractures ranged from a high of 261.3/100,000 person-years in 1999 to a low of 152/100,000 person-years in 2009. The incidence rate for intertrochanteric fractures followed a similar pattern, from a high of 156.1/100,000 in 1996 to a low of 89.1/100,000 person-years in 2009. The incidence rates of both all subtrochanteric and diaphyseal femur fractures and those with ASBMR major criteria for atypia were much lower than the rate of hip fractures. The incidence rate for atypical subtrochanteric fractures was low and relatively flat over the 13.5-year period. Overall incidence rates over the 13.5-year period for each fracture type are shown in the table below.

Figure 7
Annual Incidence‡ of Hip and Subtrochanteric/Femoral Shaft Fractures:
1996 – 2009



† Rates are graphed on a different scale than the hip fractures.

** Incidence rates based on radiograph reviewed fractures only.

‡ Incidence rates based on best available evidence for fracture site.

¶ ASBMR Atypical fractures-major features – femur fracture from just distal to lesser trochanter to just proximal to the supracondylar flare, associated with no or minimal trauma, transverse or short oblique morphology, non-comminuted.

§ Adds minor radiograph features of localized periosteal reaction of the lateral cortex (beaking), increase in cortical thickness of the diaphysis or signs of stress fracture.

Table 2
Incidence Rates for Femoral Fractures from 1996-2009 [22]

Type of femoral fracture	Overall Incidence /100,000 person-years 1996-2009	95% Confidence Interval
Hip	353.0	342.8, 363.5
o Femoral neck	222.1	214, 230.4
o Intertrochanteric	130.9	124.7, 137.4
Subtrochanteric/femoral shaft fractures (typical and atypical)	24.1	21.5, 27.0
o Subtrochanteric/femoral shaft fracture (typical – no ASBMR features of atypia)	18.2	16, 20.7
o Subtrochanteric/femoral shaft fracture (atypical-meets ASBMR major criteria for atypia)	5.9	4.6, 7.4
o Subtrochanteric/femoral shaft fracture (atypical-meets ASBMR major and minor criteria for atypia)*	1.7	1.1, 2.6
* Subtrochanteric fractures meeting ASBMR major and minor criteria are a subset of the subtrochanteric fracture category meeting major criteria		

Guisti also used radiographic review to identify atypical subtrochanteric fractures in a hospital cohort over a 10-year period (1997-2007) [18]. The atypical subtrochanteric fractures accounted for 1.1% of all femoral fractures that occurred during this period. Incidence increased with age and there was no significant difference in the distribution of patients according to fracture site during 1997-2002 compared to 2003-2007.

A number of large database studies evaluating risk factors for subtrochanteric/diaphyseal fractures have been published since 2009 [1; 19; 3; 17; 2; 18; 10; 22]. Studies vary in their case definition, design, and completeness of medical history and medication exposure. In some studies, cases were identified on the basis of diagnostic codes (ICD9 or ICD10) alone, while in others radiographic review allowed for identification of subtrochanteric fractures with specific atypical features. ICD9 or ICD10 codes cannot be used to identify atypical features; expert review of each radiograph and case history is required to separate atypical from typical fractures of this region of the femur. Questions have been raised about a possible association between atypical subtrochanteric/diaphyseal fractures with long-term use of alendronate but findings of an elevated risk have been inconsistent [1; 19; 3; 17; 2; 18; 10]. Consistent findings among the studies include the following:

- The incidence of low energy subtrochanteric/diaphyseal fractures of the femur increases with age, in parallel with other much more common osteoporotic fractures of the proximal femur [10].
- Subtrochanteric/diaphyseal fractures as defined by ICD9 or ICD10 codes are rare relative to hip fracture [1; 19; 3; 17; 2; 18; 10; 22].
- Subtrochanteric/diaphyseal fractures with atypical radiographic features represent a small subset of the subtrochanteric/diaphyseal fractures [1; 18; 22].
- Subtrochanteric/diaphyseal fractures have had a steady incidence rate since 1996, compared to a declining hip incidence rate [10; 22].

- Subtrochanteric/diaphyseal fractures with or without atypical features occur in both bisphosphonate users and non-users [1; 19; 3; 17; 2; 18; 10; 22].
- Bisphosphonate use appears to be more common in patients with subtrochanteric/diaphyseal fractures with atypical features than in those with subtrochanteric/diaphyseal fractures without atypical features [1; 18; 22].

Although the size of some retrospective databases with available radiographs such as Kaiser Permanente offers the opportunity to identify rare atypical subtrochanteric fracture cases, limitations of the databases make it difficult to fully evaluate potential predisposing factors, including physical activity, structural features of the femur (e.g. bowing), ethnicity, BMD, detailed medication use and family history. Furthermore, potential confounding by indication when evaluating association with bisphosphonate use makes interpretation difficult because the outcome of interest (osteoporotic fracture) is the primary indication for treatment.

Request 2: ***Provide an opinion and discussion of whether either restricting the duration of use or implementing a drug holiday may be beneficial for patients requiring long-term treatment.***

2. Response to Request 2

In this reply we use the term "drug holiday" to mean a period of time during which alendronate is not administered. The perceived benefit of the drug holiday is that the patient avoids the cost and inconvenience of the medicine, as well as lowers the risk of potential adverse effects (e.g., esophagitis). A drug holiday may be considered for patients who have previously received long-term treatment and are no longer considered to have a sufficiently high fracture risk.

The decision to continue long-term treatment with alendronate must be based on an individual patient's characteristics. Moreover, this decision must also take into consideration a patient's preference among the available treatment options.

As long-term clinical trial data (>3 years) are available only for the treatment and prevention of osteoporosis in postmenopausal women, there are insufficient data to address this request within the context of either glucocorticoid-induced osteoporosis or the treatment of osteoporosis in men. However, the data available for postmenopausal women are very likely to apply to men of a similar age with hypogonadism who have similar reductions in bone mineral density.

2.1 Treatment of Osteoporosis

2.1.1 ≤ 5 years

For patients on alendronate, the controlled clinical trial data do not suggest a benefit of a "drug holiday" before 5 years in postmenopausal osteoporotic women, unless the patient has had an adverse drug reaction to alendronate or the patient has developed a concurrent medical condition that is a contraindication to the use of the drug. The treating physician should also take Warnings and Precautions into consideration, as well as other Prescribing Information. Moreover, short-term treatment is not likely to result in sufficient skeletal alendronate content to prevent rapid bone loss if treatment is stopped.

Clinical trial data provide evidence of a benefit to reduce the risk of spine, hip and other non-vertebral fractures during treatment for up to 4.5 years. The average duration of treatment of patients in the Clinical Fracture Study of the Fracture Intervention Trial was 4.25 years and many patients were treated for 4.5 years. Clinical fracture risk reduction was similar during each year of study, consistent with continued benefit over time. Moreover, the risk of adverse experiences did not appear to increase over this time frame. Gastrointestinal adverse reactions appeared less frequently over time as sensitive individuals discontinued oral alendronate—typically in the first weeks to months of treatment—and patients without symptoms were adherent to treatment. Based on a modest (1/2 year) extrapolation beyond the placebo-controlled data, we conclude that there is no benefit to restricting treatment with alendronate to less than 5 years in osteoporotic women who have had no adverse reactions to the product

2.1.2 5 to 10 years

Interruption of treatment (a "drug holiday") may reasonably be considered on a case-by-case basis in an osteoporotic postmenopausal woman treated with alendronate for 5 to 10 years, based on her response to therapy and a comprehensive assessment of her fracture risk and overall medical condition. Some patients respond well to drug, nutrient (i.e., calcium, vitamin D), exercise or other interventions and may have a current fracture risk that allows a physician to consider whether to discontinue the medicine. For patients requiring continued treatment, the dose selected should be based on the goal of treatment, using 70 mg once weekly to treat osteoporosis and 35 mg once weekly to prevent osteoporosis.

As described in the Response to Request 1, the clinical trial data provide several key points of information concerning treatment for 5 to 10 years.

- After 5 years of treatment, the rate of bone loss returns to pre-treatment rates within 1 to 2 years after treatment is discontinued. "Catch-up" bone loss that follows discontinuation of hormone therapy is not observed following discontinuation of alendronate.

- Continued treatment with alendronate > 5 years maintains the BMD increases that were accrued during the first 5 years of treatment, but produces additional gain in BMD only at the spine.

- Biochemical markers of bone turnover return toward pre-treatment levels over 3 to 6 months following treatment discontinuation. A residual reduction of bone turnover persists up to 5 years post-treatment and is most likely due to "recycling" of alendronate that is released from bone during new bone remodeling. Continued post-treatment reduction of bone turnover prevents accelerated "catch-up" loss like that observed following discontinuation of hormone therapy, but is insufficient to fully prevent bone loss.

- The FLEX study suggested that the clinical vertebral fracture risk was lower for those who remained on alendronate for 10 years compared to those who discontinued, and that the non-vertebral fracture risk is lower in some populations of patients who remain on treatment compared to those who discontinue treatment. The BMD of a previously treated patient identifies those who are at highest risk of fracture as well as those who will experience the greatest fracture risk reduction with continued treatment [17].

The decision to continue treatment with alendronate beyond 5 years must be based on both individual patient characteristics and clinical trial data. Clinical trial data demonstrate average efficacy and safety. The decision in clinical practice is for each patient, one at a time. While this decision process is often referred to as "medical judgment," there are many pieces of information that can aid the physician responsible for the decision.

The current standard of care in the US is to re-evaluate postmenopausal osteoporotic patients currently on drug treatment on an annual basis. Physicians gather several key pieces of information by answering the following questions:

- What are the patient's other current active medical problems and how are they being treated? Would any of these affect the patient's bone mass/strength, risk of falling or interact with an osteoporosis therapy?

- Has the patient had any new fractures and/or change in BMD (measured by serial DXA)?
- Has the patient been compliant with the osteoporosis drug regimen and have there been any problems that might represent adverse drug reactions?
- Are there other drug treatment options that might produce superior fracture risk reduction than that produced by a bisphosphonate?
- What are the patient's expectations (both benefits and risks) if she receives, or does not receive, a drug treatment for her osteoporosis?

2.1.3 > 10 years

There are no clinical trial data that describe the results of treatment of postmenopausal osteoporosis for more than 10 years. Therefore, precise characterization of benefit to risk profile is not possible. However, there is no reason to expect the clinical profile of alendronate to change substantially after 10 years. Each patient must be evaluated on a case-by-case basis and no "blanket" recommendation would be appropriate for all women.

2.2 Prevention of Osteoporosis in Postmenopausal Women

2.2.1 ≤ 6 years

Clinical trial data do not suggest a benefit of discontinuing treatment with alendronate before 6 years in postmenopausal women using the medicine for prevention of osteoporosis, unless the patient has had an adverse drug reaction to alendronate or developed a concurrent medical condition that is a contraindication to the use of the drug. The treating physician should also take Precautions and Warnings into consideration, as well as other Prescribing Information.

The Phase III study of alendronate in the prevention of osteoporosis in postmenopausal women (EPIC) [18; 10]was a 6-year study with observations on both continuous treatment and the effects of treatment discontinuation after both 2 and 4 years. A 5 mg daily dose of alendronate (equivalent to 35 mg once weekly) prevented bone loss in the great majority of women at spine and hip DXA BMD sites. Only forearm BMD declined slightly and that decline stopped after 4 years. There was little residual inhibition of bone turnover after treatment for 2 or 4 years was discontinued, and BMD declined post-treatment at approximately the same rate as in subjects treated with placebo. Because the BMD decrease post treatment is relatively large, a "drug holiday" after only 2 to 4 years of alendronate 5 mg daily is likely to result in incomplete prevention of all BMD loss.

2.2.2 > 6 years

In the 3-year extension study of EPIC, continued treatment with alendronate 5 mg/day prevented bone loss at almost all BMD sites through 9 years of treatment. The loss of bone density following discontinuation of treatment with alendronate 5 mg daily for 6 years has not been studied.

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