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ABSTRACT: To determine the effects of continuation versus discontinuation of alendronate on BMD and markers of bone turnover, we conducted an extension trial in which 1099 older women who received alendronate in the FIT were re-randomized to alendronate or placebo. Compared with women who stopped alendronate, those continuing alendronate for 3 years maintained a higher BMD and greater reduction of bone turnover, showing benefit of continued treatment. However, among women who discontinued alendronate and took placebo in the extension, BMD remained higher, and reduction in bone turnover was greater than values at FIT baseline, showing persistence of alendronate’s effects on bone.

INTRODUCTION

ALENDRONATE SODIUM (ALENDRONATE), an oral bisphosphonate, has been shown to increase BMD and reduce the rate of fracture for up to 4 years in postmenopausal women with low BMD in the Fracture Intervention Trial (FIT)(1,2) and two other phase III clinical trials. (3) Evidence from these studies show that BMD increases rapidly early during alendronate therapy, with smaller gains continuing for up to 3–4 years. However, the optimal duration of alendronate treatment is uncertain.

Once incorporated into mineralized bone, bisphosphonates, including alendronate, have a long residence with an estimated terminal half-life of >10 years, (4) although it is unknown whether they remain biologically active. Data from open-label (5) and double-blind (6,7) extension studies of two phase III clinical trials (3) in women with low BMD suggest that women continuing alendronate therapy beyond 3 years for a total duration of up to 10 years maintain earlier gains in BMD at the hip and have persistent small increases in BMD at the lumbar spine, while women discontinuing
alendronate treatment have small decreases in BMD at the hip and maintain BMD at the lumbar spine. However, these studies did not randomly assign participants to continuation or discontinuation of alendronate treatment, and follow-up beyond 5 years is reported for only 350 women.

FIT was a randomized, placebo-controlled trial of the effect of alendronate treatment on fracture risk among 6459 postmenopausal women with low BMD with an average follow-up of 3.8 years. We sought to determine whether additional therapy with alendronate beyond this period would result in preservation or further gains in BMD relative to discontinuation of alendronate therapy and whether skeletal effects of alendronate persist after treatment is stopped. We therefore conducted a follow-up placebo-controlled extension trial to FIT (FIT long-term extension [FLEX]) in which 1099 women assigned to alendronate therapy in FIT with an average duration of use of 5 years were re-randomized for an additional 5 years to alendronate or placebo. We report herein the results of a preplanned interim analysis at 3 years.

MATERIALS AND METHODS

Participants

The design, methods,1 and main outcomes of FIT have been published.2 Participants were postmenopausal women, 55–81 years of age, with low BMD (≤0.68 g/cm² at the femoral neck [T score ≤ −1.6]) as measured by DXA (QDR 2000 densitometers; Hologic, Bedford, MA, USA). A total of 6549 women were enrolled in one of two study arms based solely on the presence or absence of an existing radiographic vertebral deformity: 2027 women with at least one deformity were enrolled in the vertebral fracture arm of FIT and followed an average of 2.9 years, whereas 4432 women with no existing deformity were enrolled in the clinical fracture arm of FIT and followed for an average of 4.2 years. Participants were randomly assigned to double-blind treatment with alendronate (5 mg/day for 2 years and 10 mg/day thereafter; n = 3236) or to identical placebo (n = 3233). At the conclusion of FIT, all participants were offered 1 year of therapy with open-label alendronate 10 mg/day at no cost, regardless of their blinded treatment assignment. At the end of this year, FIT investigators recommended that all participants make their decisions about whether or not to continue alendronate therapy with their personal physician.

Women were eligible for FLEX if they had been assigned to alendronate in FIT and had a total duration of alendronate use of at least 3 years during the blinded phase of FIT (average follow-up, 3.8 years) and the period after completion of FIT up to beginning of FLEX (average, 1.9 years between conclusion of FIT and beginning of FLEX; range, 1.0–3.3 years). A total of 10 women (0.9% of randomized participants) received waivers and were enrolled with a duration of use slightly <3 years. Women were excluded from participation in FLEX if they had a total hip BMD <0.515 g/cm² (T score < −3.5) at the FLEX screening visit and a total hip BMD less than or equal to corresponding baseline FIT total hip BMD or were currently receiving and planning to continue open-label alendronate, hormone therapy, or calcitonin. We also excluded women with documented abnormalities of the esophagus (e.g., stricture, achalasia, Barrett’s esophagus); diagnosis of dysphagia, esophagitis, gastritis, or peptic ulcer disease within the past 3 months that was not adequately controlled with medical management (e.g., H₂ antagonists or proton-pump inhibitors); upper gastrointestinal bleed or myocardial infarction during the previous 3 months; severe malabsorption syndrome; or impaired renal function (serum creatinine >2.0 mg/dl). A total of 2852 surviving participants from 10 of the 11 FIT clinical centers (participants from the Seattle FIT center were not screened for participation in FLEX because the Seattle FIT center declined to participate in the extension trial) who had been assigned to alendronate in FIT were offered an opportunity to be screened for participation in FLEX (Fig. 1). Of these, 1099 women (39%) enrolled in the study between January 1998 and September 1998. All women provided written informed consent, and the protocol was approved by the appropriate institutional review boards.

Treatment assignment

Women were randomly assigned in a double-blind manner to alendronate 10 mg/day (30%), alendronate 5 mg/day (30%), or placebo (40%) for 5 years. Each participant was assigned a unique allocation number that was obtained from a series of consecutive numbers assigned to each clinical center according to a computer-generated, randomized schedule and that did not overlap her original allocation number from FIT. Randomization was stratified by fracture risk; women with at least one radiographic morphometric vertebral deformity identified by the end of FIT and/or who experienced a clinical fracture during FIT were assigned to the high-risk stratum. Compliance to study medication was assessed at each annual follow-up visit by a tablet count of unused study drug. All participants were strongly encouraged to take a daily supplement containing calcium (500 mg) and vitamin D (250 IU). The proportion of participants receiving the supplement was 97.5%; this proportion was similar at baseline and throughout the 3 years of follow-up in the three treatment groups.

Several measures were used to ensure maintenance of the blind. All participants; investigators, including those responsible for adjudicating outcome and adverse-experience data; clinical and coordinating center support staff; and sponsor monitoring staff were unaware of treatment assignment. The treatment assignments were only available to the statistician responsible for reports to the Data Safety Monitoring Group (DSMG). Participants and clinical center investigators were not informed of results of BMD measurements during follow-up.

Assessment of outcomes

Women were contacted by telephone at 3-month intervals to encourage compliance, assess adverse experiences, verify concurrent medications, and obtain information on fractures.
and medical procedures. Participants returned to their clinical center for annual visits.

**BMD measurement**

BMD was measured at the total hip and its subregions, posterior-anterior lumbar spine, and the total body in all participants at the FLEX baseline using DXA with the same Hologic QDR 2000 densitometers that were used for FIT (Hologic). BMD at the hip was repeated annually; BMD at the spine and in the total body was repeated at the 36-month visit. In addition, forearm BMD (one-third of the way up from the wrist to the elbow) was measured in a 40% sample of participants. Quality control measures were the same as those used in FIT and have been outlined in detail elsewhere.(8) Investigators were notified without revealing treatment assignment if any participant experienced excessive bone loss (defined as a decrease of 8% or more in total hip BMD over the first year with an additional 2% decrease added for each subsequent year of follow-up) or three or more incident fractures, including incident radiographic morphometric vertebral fractures. The clinical investigator provided this information to the participant and counseled her on the risks and benefits of continued participation in the trial. In addition, if any follow-up total hip BMD in FLEX was 5% or more below the participant’s total hip BMD at the FIT baseline exam (n = 16), discontinuation of study medication was mandatory.

**Markers of bone turnover**

Measurement of biochemical markers was performed in all FLEX participants at baseline and at 12- and 36-month visits in a central laboratory. Serum was analyzed for bone-specific alkaline phosphatase (BSAP), an indicator of bone formation, using a commercially available assay (Ostase; Hybritech, La Jolla, CA, USA). This immunoradiometric assay (IRMA) uses two monoclonal antibodies directed against the human bone isoenzyme and bone alkaline phosphatase (BAP) purified from human SAOS-2 osteosarcoma cells as a standard. This assay has a 16% cross-reactivity with the circulating liver isoenzyme.(9) Urine was analyzed for a biochemical marker of bone resorption, urinary type I collagen cross-linked N-telopeptide (NTX), using a commercially available assay (Osteomark; Ostex International, Seattle, WA, USA). This ELISA uses a monoclonal antibody directed against the N-telopeptide-to-helix intermolecular cross-linking domain of type I collagen isolated from human urine.(10) Of the 1099 FLEX participants, 159 women (14%) also had NTX measured at baseline and
annual visits during FIT using the same assay used in FLEX.

**Adverse experiences**

Participants were queried at each contact regarding adverse events, defined as any untoward condition, including minor illnesses. Three general categories of adverse events were included in the analysis: serious (fatal, life-threatening, or those requiring or prolonging hospitalization); those considered by the clinical investigators as definitely, probably, or possibly related to study medication; and those resulting in discontinuation of the study medication. In addition, because of reports of upper gastrointestinal disorders in patients on bisphosphonate therapy, we analyzed upper gastrointestinal disorders by specific symptoms and diagnoses.

**Statistical analyses**

Given the enrolled sample size of 1099 women, the observed SD of ~4%, and a two-sided α level of 0.05, the trial had a 90% power to detect a difference of 0.9% in change in total hip BMD between the alendronate groups (5 and 10 mg combined) and the placebo group from FLEX baseline to 3 years.

An independent data and safety monitoring group (DSMG) examined endpoints and adverse experiences by treatment group once a year, with predefined operating guidelines. An interim analysis was planned at 3 years to publish results on changes in BMD, changes in markers of bone turnover, and incidence of adverse experiences. The interim analyses were undertaken with the explicit understanding that the trial would not be stopped for reasons of significance. BMD efficacy that might be observed. To preserve study blinding and data integrity, the DSMG did not release interim data at 3 years on clinical fractures, radiographic vertebral morphometric fractures, or stature; these results will be available at the end of the trial. The principal investigators remained blinded to individual treatment assignments for the entire 5-year duration of the trial.

Randomized participants who did not withdraw informed consent received complete follow-up, to the extent possible, for all outcomes. All analyses were performed according to the intention-to-treat principle with use of all available data from all participants who were assigned to study medication, irrespective of compliance. Missing values were not imputed or replaced.

ANOVA and \( \chi^2 \) tests of homogeneity were used to compare characteristics at the FLEX baseline examination by treatment group. Analysis of mean percentage change in BMD was performed according to the intention-to-treat approach using an ANOVA model with treatment, study center, and fracture risk stratum as factors. Findings were similar when the analyses were repeated with the last observation carried forward (data not shown). Primary analyses compared the mean percentage change in BMD from FLEX baseline to FLEX 36-month visit in alendronate groups (5 and 10 mg combined) with that in the placebo group; secondary analyses compared the mean percentage change in BMD in the alendronate 10 mg group with that in the alendronate 5 mg group. We also performed analyses comparing the mean percentage change in BMD from FIT baseline to FLEX 36-month visit in alendronate groups (5 and 10 mg combined) to that in the placebo group.

Analyses of percentage change in markers of bone turnover were performed according to an intent-to-treat approach using an ANOVA model with treatment, study center, and fracture risk stratum as factors. Results were similar when analyses were repeated using a per protocol approach. A natural log transformation was used to normalize the distribution of changes in markers (log[fraction of baseline value at month 36]); all results were back-transformed from the log scale. Primary analyses compared the mean percentage change in marker from FLEX baseline to FLEX month-36 visit in alendronate groups (5 and 10 mg combined) with that in the placebo group. In the subset of 159 participants who also had NTX measured during FIT using the same assay as that used in FLEX, we also performed a secondary analysis comparing the mean percentage change in marker from FIT baseline to FLEX 36-month visit in alendronate groups (5 and 10 mg combined) with that in the placebo group.

Adverse experiences were reported as the proportion of women with one or more events. We used Fisher’s exact test to test for differences between treatment groups.

**RESULTS**

**Study participants**

Of the 3236 women enrolled in FIT and assigned to alendronate treatment, 2852 surviving women from 10 of the 11 FIT clinical centers were contacted about the possibility of participating in FLEX (Fig. 1). Of these, a total of 1099 women (39%) were enrolled in FLEX and randomized to placebo (n = 437), alendronate 5 mg/day (n = 329), or alendronate 10 mg/day (n = 333). Among the 1753 women who were contacted and not enrolled in FLEX, the most common reasons for not participating were a desire to remain on open-label alendronate (n = 360), other bone active medications (n = 223), or a duration of alendronate use of less than 3 years (n = 325). Compared with the 1753 women who were contacted but not enrolled, the 1099 FLEX participants were slightly younger (mean age, 67.9 years) versus 68.4 years at FIT baseline, \( p = 0.058 \). In addition, despite having similar total hip BMD at FIT baseline (0.70 versus 0.69 g/cm²), FLEX participants had a higher average increase in total hip BMD during FIT (3.8% versus 2.9%, \( p < 0.001 \)) and were less likely to have a new radiographic vertebral fracture (2.2% versus 4.6%, \( p < 0.001 \)) or incident nonspine fracture during FIT (10.3% versus 13.0%, \( p = 0.013 \)).

At FLEX baseline, the average age of participants was 73 years, and 97% identified themselves as white. The mean duration of alendronate use among participants was 5 years; 80% reported current alendronate use. Mean BMD at the total hip corresponded to a T score of −1.9, mean BMD at the femoral neck corresponded to a T score of −2.2, and mean BMD at the lumbar spine corresponded to a T score of −1.3. Thirty-eight percent of participants were assigned to the high fracture risk stratum based on having at least one radiographic morphometric vertebral deformity identified.
by the end of FIT and/or having experienced a clinical fracture during FIT. Baseline characteristics of FLEX participants were equally distributed across the three treatment groups (Table 1), except that women assigned to placebo, on average, were slightly older (73.7 years) than those assigned to alendronate 5 mg/day (72.7 years) and alendronate 10 mg/day (72.9 years; \( p = 0.046 \)).

A total of 1060 women (96% of randomized participants enrolled in FLEX and 99% of survivors) completed 3 years of follow-up (average follow-up, 2.9 years; range, 0.3–3.3 years). Of these, 1008 women (95%) had a measurement of hip BMD at the 36-month visit. At the time of the 36-month visit, 85.7% of surviving randomized participants were still taking study medication, and this proportion did not vary by treatment assignment (\( p = 0.830 \)). Of those taking study medication at the time of the 36-month visit, 96% of those in each treatment group had taken at least 75% of their pills since the last clinic visit.

**BMD**

Among women enrolled in FLEX, all of whom had prior alendronate therapy in FIT, further therapy with alendronate (5 and 10 mg groups combined) for 3 years maintained BMD compared with placebo at the total hip (2.0% difference, \( p < 0.001 \); Table 2). The average BMD at the total hip in the groups receiving alendronate declined by 0.3% compared with a 2.4% decrease in the placebo group. Findings were similar at the femoral neck where BMD in the groups receiving alendronate increased 0.6% compared with a decrease of 1.1% in the placebo group (1.7% difference, \( p < 0.001 \)) and trochanter where BMD in the groups receiving alendronate increased 0.7% compared with a decrease of 1.9% in the placebo group (2.6% difference, \( p < 0.001 \); Table 2). At the lumbar spine, women receiving alendronate (5 and 10 mg groups combined) had an increase in BMD of 3.5% at 3 years compared with an increase of 1.0% in the placebo group (\( p < 0.001 \); Table 2). Smaller differences between alendronate and placebo were observed at the total body where the increase in BMD among women receiving alendronate at the 5 or 10 mg dose was 0.6% compared with a 0.3% decline in the placebo group (0.9% difference, \( p < 0.001 \)) and forearm where BMD in the groups receiving alendronate decreased by 0.9% compared with a 2.1% decrease in the placebo group (1.2% difference, \( p < 0.001 \); Table 2). The effect of alendronate treatment on change in BMD was consistent within the two fracture risk strata defined at baseline (data not shown).

Among women enrolled in FLEX who were assigned to alendronate treatment, there was some evidence that preservation or increases in BMD at 3 years was higher among women taking 10 mg/day compared with women taking 5 mg/day (Table 2). The differences were small in magnitude (<1.0%) and achieved significance at the total hip, femoral

---

**Table 1. Characteristics of the Randomized Participants at FLEX Baseline**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 437)</th>
<th>Alendronate 5 mg (n = 329)</th>
<th>Alendronate 10 mg (n = 333)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (years)</td>
<td>73.7 ± 5.9</td>
<td>72.7 ± 5.7</td>
<td>72.9 ± 5.5</td>
<td>0.046</td>
</tr>
<tr>
<td>Self-reported health status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good/excellent</td>
<td>57.9</td>
<td>62.8</td>
<td>63.3</td>
<td>0.196</td>
</tr>
<tr>
<td>Good</td>
<td>35.9</td>
<td>33.5</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td>Fair/poor</td>
<td>6.2</td>
<td>3.7</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>6.4</td>
<td>9.2</td>
<td>7.6</td>
<td>0.379</td>
</tr>
<tr>
<td>Past</td>
<td>42.4</td>
<td>38.4</td>
<td>43.2</td>
<td>0.401</td>
</tr>
<tr>
<td>Never</td>
<td>51.2</td>
<td>52.4</td>
<td>49.2</td>
<td>0.714</td>
</tr>
<tr>
<td>Mean dietary calcium intake ± SD (mg/day)</td>
<td>635 ± 390</td>
<td>655 ± 403</td>
<td>667 ± 406</td>
<td>0.532</td>
</tr>
<tr>
<td>Alendronate use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>78.0</td>
<td>83.6</td>
<td>78.7</td>
<td>0.132</td>
</tr>
<tr>
<td>Past</td>
<td>22.0</td>
<td>16.4</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>Mean duration of alendronate use ± SD (years)</td>
<td>5.0 ± 0.7</td>
<td>5.0 ± 0.7</td>
<td>4.9 ± 0.7</td>
<td>0.099</td>
</tr>
<tr>
<td>Mean body mass index ± SD (kg/m²)</td>
<td>25.8 ± 4.3</td>
<td>25.7 ± 4.2</td>
<td>26.0 ± 4.5</td>
<td>0.733</td>
</tr>
<tr>
<td>Any fracture since age 45 (%)</td>
<td>78.3</td>
<td>78.4</td>
<td>78.1</td>
<td>0.966</td>
</tr>
<tr>
<td>High fracture risk stratum (%)‡</td>
<td>37.8</td>
<td>38.0</td>
<td>39.3</td>
<td>0.899</td>
</tr>
<tr>
<td>Mean BMD ± SD (g/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td>0.72 ± 0.09</td>
<td>0.73 ± 0.09</td>
<td>0.73 ± 0.09</td>
<td>0.361</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.61 ± 0.07</td>
<td>0.62 ± 0.07</td>
<td>0.61 ± 0.07</td>
<td>0.714</td>
</tr>
<tr>
<td>Posterior-anterior spine</td>
<td>0.90 ± 0.14</td>
<td>0.90 ± 0.15</td>
<td>0.89 ± 0.13</td>
<td>0.777</td>
</tr>
<tr>
<td>Total body</td>
<td>0.97 ± 0.09</td>
<td>0.98 ± 0.10</td>
<td>0.98 ± 0.09</td>
<td>0.874</td>
</tr>
<tr>
<td>Forearm†</td>
<td>0.44 ± 0.05</td>
<td>0.45 ± 0.06</td>
<td>0.45 ± 0.06</td>
<td>0.574</td>
</tr>
<tr>
<td>Mean serum BSAP ± SD (ng/ml)</td>
<td>9.1 ± 3.4</td>
<td>8.8 ± 3.0</td>
<td>8.9 ± 3.3</td>
<td>0.430</td>
</tr>
<tr>
<td>Mean urinary N-telopeptide-creatinine ratio ± SD‡</td>
<td>19.6 ± 12.9</td>
<td>18.9 ± 12.2</td>
<td>19.4 ± 12.4</td>
<td>0.575</td>
</tr>
</tbody>
</table>

*At least one radiographic vertebral fracture at end of FIT and/or a clinical fracture during FIT.
†Measured in a 40% sample of participants.
‡N-telopeptide was measured in picomoles and creatinine in micromoles.
neck, trochanter, and total body, but not at the lumbar spine or forearm.

The cumulative increase in total hip BMD from FIT baseline (mean follow-up, 8.6 years) among FLEX participants (all of whom received alendronate during FIT) was higher for women receiving alendronate (5 and 10 mg groups combined) during FLEX (3.1%) compared with those taking placebo during FLEX (0.9%; 2.2% difference; \( p \leq 0.01 \); Fig. 2A). The rates of bone loss at the total hip were similar among women receiving placebo in FLEX and those receiving placebo in FIT (Fig. 2A). However, despite discontinuation of alendronate for at least 3 years, total hip BMD at the FLEX 36-month visit in women receiving placebo during FLEX was greater than that at their FIT baseline examination 8.6 years previously (\( p < 0.001 \)).

Similarly, although the cumulative gain in spine BMD from FIT baseline was higher for women receiving alendronate during FLEX (12.9%) compared with those taking placebo during FLEX (10.4%; 2.5% difference; \( p < 0.001 \); Fig. 2B) and the rates of gain in spine BMD were similar among women receiving placebo in FLEX and those receiving placebo in FIT (Fig. 2B), women receiving placebo for 3 years during FLEX after discontinuation of alendronate had a spine BMD greater than that 8.6 years earlier at their FIT baseline examination (\( p < 0.001 \)).

Our findings regarding the effect of continuation versus discontinuation of alendronate treatment on change in BMD at the hip and spine were similar when we excluded the 20% of FLEX participants not currently taking alendronate at FIT baseline (data not shown).

Markers of bone turnover

Further therapy with alendronate (5 and 10 mg groups combined) for 3 years during FLEX was associated with relatively stable levels of the biochemical markers of bone turnover compared with increases in women assigned to placebo (Fig. 3). The mean BSAP in the women receiving alendronate decreased by 3.0% between FIT baseline and FLEX 36-month visit compared with a 15.4% increase in the placebo group (18.4% difference; \( p < 0.001 \)), whereas there was no change in mean NTX in women assigned to alendronate at either dose between FIT baseline and FLEX 36-month visit compared with a 21.6% increase in women assigned to placebo (21.6% difference; \( p < 0.001 \)). Differences between alendronate (5 and 10 mg groups combined) and placebo groups were not altered when we excluded the 20% of participants at FLEX baseline who were not currently taking alendronate from our analyses.

Among the subset of 159 women with NTX measurements during FIT and FLEX, substantial reductions in bone turnover were observed during FIT when all were receiving

### Table 2. Mean Percentage Change in BMD from FIT Baseline to FLEX Month 36 (Mean, 2.9 Years)

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Placebo (n = 437)</th>
<th>Alendronate (5 and 10 mg groups; n = 662)</th>
<th>Alendronate (5 mg; n = 329)</th>
<th>Alendronate (10 mg; n = 333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip</td>
<td>-2.38 (-2.74, -2.03)</td>
<td>-0.34 (-0.64, -0.05)</td>
<td>-0.68 (-1.09, -0.27)</td>
<td>-0.01 (-0.41, 0.40)</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-1.10 (-1.61, -0.60)</td>
<td>0.57* (0.15, 0.99)</td>
<td>0.11* (-0.47, 0.69)</td>
<td>1.03 (0.45, 1.61)</td>
</tr>
<tr>
<td>Trochanter</td>
<td>-1.90 (-2.34, -1.46)</td>
<td>0.71* (0.35, 1.07)</td>
<td>0.27* (-0.23, 0.78)</td>
<td>1.14 (0.63, 1.64)</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.97 (0.50, 1.45)</td>
<td>3.50* (3.10, 3.89)</td>
<td>3.16 (2.61, 3.70)</td>
<td>3.83 (3.29, 4.38)</td>
</tr>
<tr>
<td>Total body</td>
<td>-0.31 (-0.64, 0.02)</td>
<td>0.62* (0.35, 0.90)</td>
<td>0.28* (-0.10, 0.66)</td>
<td>0.96 (0.58, 1.34)</td>
</tr>
<tr>
<td>Forearm(^1)</td>
<td>-2.13 (-2.62, -1.64)</td>
<td>-0.90* (-1.31, -0.49)</td>
<td>-0.879 (-1.34, -0.24)</td>
<td>-1.02 (-1.61, -0.44)</td>
</tr>
</tbody>
</table>

\* \( p < 0.001 \) for comparison between alendronate (5 and 10 mg groups pooled) and placebo.

\( ^{1} \) \( p < 0.05 \) for comparison between alendronate 5 mg group and alendronate 10 mg group.

\( ^{1} \)Forearm BMD performed on a 40% sample of participants.

---

**FIG. 2.** Mean (± SE) percentage changes in BMD from FIT baseline to FLEX month 36 (mean, 8.6 years) in women receiving alendronate or placebo during FLEX.
alendronate treatment. Between FIT baseline and an average of 3.8 years later at FIT closeout visits, NTX in these women decreased by 72.3% (p<0.001). At FLEX baseline, the level of NTX had slightly increased, but remained well below FIT baseline value (66.4%; p<0.001). The cumulative reduction in NTX from FIT baseline to FLEX 36 months (mean follow-up, 8.6 years) seemed slightly greater in women receiving alendronate during FLEX (66.6%) compared with those taking placebo during FLEX (63.2%), but the difference did not reach significance (3.4% difference; p=0.406; Fig. 4).

### Safety

Similar proportions of women assigned to alendronate (10.4% in 5 and 10 mg groups combined) and those taking placebo (11.4%) permanently discontinued study medication because of adverse experiences (p=0.621; Table 3). There were no differences in adverse experiences resulting in hospitalization or in rates of death; 35.7% of women taking placebo reported any upper gastrointestinal events compared with 29.8% of women taking alendronate (p=0.041). There were no differences between the two groups in rates of specific upper gastrointestinal tract events, including abdominal pain, acid reflux, esophagitis, esophageal ulcer, gastric ulcer, or duodenal ulcer (Table 3).

**FIG. 3.** Mean (± SE) percentage changes in markers of bone turnover from FLEX baseline to FLEX month 36 (mean, 2.9 years) in women receiving alendronate or placebo during FLEX.

**FIG. 4.** Mean (± SE) percentage changes in urinary NTX:creatinine ratio from FIT baseline to FLEX month 36 (mean, 8.6 years) in women receiving alendronate or placebo during FLEX.

### Discussion

We found that, among older women with low BMD who had taken alendronate therapy for an average of 5 years, those women continuing therapy had greater preservation of BMD and suppression of biochemical markers of bone turnover after 3 years compared with women discontinuing therapy. Among women discontinuing alendronate treatment, rates of change in hip and spine BMD resumed at background rates, but stopping therapy did not result in either accelerated bone loss or a marked increase in bone turnover showing persistence of alendronate’s effects on bone. Our results are generally consistent with those of two smaller extension studies of phase III alendronate trials(6,7) that enrolled women a decade younger than FLEX participants. The random assignment of continuation or discontinuation of alendronate therapy and the follow-up of 99% of surviving participants in FLEX avoids some of the potential biases inherent in the other studies in which entire treatment groups previously assigned to alendronate treatment were assigned to continue therapy or take placebo, and a substantial number of participants dropped out during the extension phases.

Women who discontinued alendronate treatment for 3 years after an average of 5 years of use experienced hip bone loss, albeit at a rate that did not override the effect of the earlier gain. Observational data(12,13) have suggested that women ≥65 years of age have an average rate of bone loss at the total hip of 0.6%/year (4.8% over 8 years). Given these average rates of hip bone loss typical of community-dwelling older women, hip BMD in women discontinuing alendronate was substantially higher than that anticipated with 8 years of advancing age had they never been treated. The previous course of alendronate therapy had a persistent effect in that it prevented the aging-related bone loss that would have occurred in the absence of therapy and also resulted in some gain. In comparison, continuation of alendronate therapy in women for 3 years after 5 years of use maintained, but did not further increase, the gain in hip BMD obtained with the first 5 years of use.
Spine BMD increased at 3 years in women with prior alendronate use of 5 years, whether or not they continued alendronate treatment, although the increase was greater in those continuing alendronate therapy. The rate of change in spine BMD among women discontinuing alendronate and taking placebo in FLEX was similar in magnitude to that among women taking placebo in FIT (both groups of women received supplementation with calcium and vitamin D). The increase in spine BMD in women who discontinued alendronate and took placebo may reflect a number of factors, including persistence of alendronate's effect, an effect of the calcium and vitamin D supplementation, or artifact caused by progression of spinal degenerative joint disease and/or abdominal aortic calcification. Maintenance of spine BMD after discontinuation of bisphosphonate therapy has been reported in other smaller extension studies of etidronate(14) and pamidronate(15) in osteoporotic women, although an extension of a 2-year trial(16) evaluating risedronate therapy in early postmenopausal women reported a decrease from baseline of 2.3% in spine BMD 1 year after discontinuing treatment. Given the randomized design of FLEX, the greater gain among women continuing alendronate show that ongoing therapy results in further increases in spine BMD and is consistent with results of other smaller extension studies of bisphosphonate treatment, including investigations of alendronate(6,7) and etidronate.(14) Whether or not this continued gain results in further reductions in risk for radiographic vertebral fractures is uncertain; 5-year data from FLEX will address this question.

During the first 3 years of FLEX, levels of bone turnover markers remained stable in women continuing alendronate, whereas they increased among women discontinuing alendronate. However, compared with pretreatment levels at the beginning of FIT, bone turnover as assessed by NTX remained well below baseline levels in both groups of women. These results, taken in their entirety, suggest that 5 years of alendronate therapy in older women is associated with persistent suppression of bone turnover after 3 years both in women who stop alendronate and those who continue long-term alendronate treatment. The effect of this continued suppression of bone turnover on bone strength and fracture risk is unknown. It has been proposed that prolonged reductions in turnover with long-term bisphosphonate treatment may result in reduced capacity to repair microfractures and consequently impair bone strength.(17) On the other hand, histomorphometric data from studies conducted in osteoporotic women after 2–3 years of alendronate treatment(18,19) and findings from animal studies(20–23) evaluating the effects of prolonged alendronate treatment suggest that structural and morphological properties of both cortical and trabecular bone are preserved. The effect of alendronate treatment for 8–11 years on bone quality in women with low bone mass will be evaluated in a subset of FLEX participants undergoing transiliac bone biopsy specimens at the 5-year final visit.

In the absence of a direct head-to-head comparison in FLEX, the effect of discontinuation of other therapies on BMD and bone turnover in our study population of older women is uncertain. However, in comparison with our findings, accelerated or “catch-up” bone loss and substantial increases in bone turnover after withdrawal of hormone therapy have been noted in a number of clinical investigations(24,25) including a recent extension of a trial evaluating the combination of alendronate and estrogen(26) in postmenopausal women (average age, 64 years) that found decreases in BMD of 4.5% at the spine and 1.8% at the total hip and increases in markers of bone turnover back to baseline levels in women during the 1-year period after discontinuing estrogen therapy. In contrast, no significant changes in BMD at the hip or spine were observed in this same extension trial 1 year after discontinuation of alendronate and 1 year after discontinuation of combination (alendronate and estrogen) therapy. In addition, McClung et al.(27) in their investigation of the effects of alendronate and estrogen on the rate of bone loss after discontinuation of therapy in younger postmenopausal women, noted greater rates of bone loss among women who discontinued estrogen-progestin therapy compared with those stopping alendronate treatment. Furthermore, epidemiologic studies(28–30) suggest that BMD, rates of bone loss, and risk for fracture are similar in past estrogen users compared with those women who never used estrogen. A small extension study(31) evaluating the effect of discontinuation of raloxifene therapy in postmenopausal women after 5 years of

<table>
<thead>
<tr>
<th>Type of adverse experience</th>
<th>Placebo (n = 437)</th>
<th>Alendronate (n = 662)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any leading to permanent discontinuation</td>
<td>50 (11.4)</td>
<td>69 (10.4)</td>
<td>0.621</td>
</tr>
<tr>
<td>Any resulting in hospitalization</td>
<td>125 (28.6)</td>
<td>183 (27.6)</td>
<td>0.732</td>
</tr>
<tr>
<td>Deaths</td>
<td>8 (1.8)</td>
<td>16 (2.4)</td>
<td>0.674</td>
</tr>
<tr>
<td>Upper gastrointestinal tract events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>156 (35.7)</td>
<td>197 (29.8)</td>
<td>0.041</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>25 (5.7)</td>
<td>33 (5.0)</td>
<td>0.585</td>
</tr>
<tr>
<td>Acid reflux</td>
<td>16 (3.7)</td>
<td>22 (3.3)</td>
<td>0.866</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>3 (0.7)</td>
<td>3 (0.5)</td>
<td>0.687</td>
</tr>
<tr>
<td>Esophageal ulcer</td>
<td>2 (0.5)</td>
<td>4 (0.6)</td>
<td>0.999</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>4 (0.9)</td>
<td>3 (0.5)</td>
<td>0.446</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1 (0.2)</td>
<td>3 (0.5)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

*Five and 10 mg alendronate groups combined.
treatment reported decreases of 2.4% in spine BMD and 3.0% in femoral neck BMD during the 1-year period after discontinuing therapy. To our knowledge, the effect of discontinuation of injectable parathyroid hormone on BMD and bone turnover in postmenopausal women has not been investigated.

Among women in our trial who continued alendronate therapy, we found similar effects on BMD in women taking 10 mg daily compared with those taking 5 mg daily, although at most sites, preservation or increases in BMD at 3 years was slightly higher among women taking 10 mg/day compared with women taking 5 mg/day. Because participants in FLEX had a variable experience with respect to alendronate dose and duration during FIT and between FIT and FLEX and all had taken at least 1 year of alendronate 10 mg/day, our study was not primarily designed to identify the optimal dose of alendronate therapy for long-term treatment. However, our findings indicate that, among women who have taken alendronate 10 mg daily for a few years, continued treatment with alendronate 5 mg daily may be sufficient to maintain or increase BMD. A prior extension of phase III alendronate trials showed increases at 7 years in femoral neck BMD of 4.6% with 10 mg daily and 2.6% with 5 mg daily, whereas spine BMD increased by 11.4% with 10 mg daily and 8.4% with 5 mg daily. In addition, our trial evaluated the effects of daily alendronate therapy. Previous trials have shown the equivalence of alendronate 10 mg (5 mg) daily with alendronate 70 mg (35 mg) weekly on changes in BMD and markers of bone turnover.

We observed no differences in the rates of adverse events, including upper gastrointestinal conditions, among women continuing alendronate compared with those discontinuing treatment. Although clinical use of alendronate has been occasionally associated with esophagitis and rarely with peptic ulcer disease, our findings are not unexpected because all FLEX participants previously took alendronate for an average of 5 years and therefore tolerated the drug well. In addition, women with active upper gastrointestinal disease or symptoms during the screening process were not eligible for participation in FLEX. However, because the incidence of esophageal abnormalities and peptic ulcer disease increases with advancing age, our results provide some reassurance about the upper gastrointestinal safety of long-term alendronate in elderly women.

Our study must rely on changes in BMD and bone turnover markers rather than fracture data to evaluate the effect of continuation versus discontinuation of alendronate treatment. There is disagreement regarding the extent to which the antifracture efficacy of antiresorptive drugs, including alendronate, can be attributed to the magnitude of increases in BMD or reductions in bone turnover. Some investigations have concluded that changes in BMD observed with antiresorptive agents account for most of the observed reductions in fracture risk, whereas others have suggested that changes in BMD substantially underestimate the degree to which these drugs reduce risk. It is also uncertain whether the continued maintenance or small gains in BMD and suppression of bone turnover observed with long-term alendronate treatment sustain earlier reductions in fracture risk observed with treatment for up to 4 years. In theory, if long-term alendronate treatment is able to maintain BMD, fracture risk should not increase with advancing age to the degree that it does in untreated women. Finally, although we observed a persistent effect of alendronate on BMD and bone turnover 3 years after its discontinuation, this report does not address whether antifracture efficacy is maintained, decreases, or ceases after stopping treatment. Fracture results will be included in the final analysis of our trial at 5 years and could provide information concerning these unresolved, but clinically relevant, issues.

We conclude that, while continuing alendronate treatment is best for long-term preservation of BMD and reduction of bone turnover in postmenopausal women, the effects of alendronate on BMD and bone turnover persist to varying degrees for up to 3 years after stopping treatment. Studies that evaluate the effect of continuation versus discontinuation on fracture risk are warranted before making definitive recommendations regarding the optimal length of alendronate treatment.

ACKNOWLEDGMENTS

Members of the FLEX Research Group are as follows. Clinical Centers—Wake Forest University Winston-Salem/ Greensboro: SA Quandt (co-principal investigator), CD Furberg (principal investigator), J Spangler (medical director), and S Marion (project director/clinic coordinator); Kaiser Permanente Center for Health Research, Portland: A Feldstein (co-investigator), E Harris (co-investigator/project director), and M Rix (clinic coordinator); Stanford Medical Center, Palo Alto: WL Haskell (principal investigator), A Laws (co-investigator), and J Fair (project director/clinic coordinator); University of California, San Diego: E Barrett-Connor (principal investigator), ML Carrion-Petersen (project director), N Kamantique (clinical coordinator), and K Kadlec (clinic coordinator); University of Iowa, Iowa City/Davenport: J Torner (co-principal investigator), RB Wallace (principal investigator), D Staub (sub-investigator), D Meyerholtz (project director/clinic coordinator), and K Canady (project director/clinic coordinator); University of Maryland, Baltimore: MC Hochberg (principal investigator), R Flores (co-investigator), and K Roney (project director); University of Miami: S Levis (principal investigator) and A Herrin (clinic coordinator); University of Minnesota, Minneapolis: KE Ensrud (principal investigator), S Diem (co-investigator), and C Quinton (clinical coordinator); University of Pittsburgh: J Cauley (principal investigator), R McDonald (principal investigator), L Harper (project director), M Nasim (clinical coordinator), and L Prebehalla (clinic coordinator); and University of Tennessee, Memphis: S Satterfield (principal investigator), K Johnson (co-investigator), and LD Burch (project director). Coordinating Center and Radiology Group—University of California, San Francisco: D Black (principal investigator), SR Cummings (co-principal investigator, SC Chair), MC Nevitt (co-investigator, director morphometry and BMD QC), D Bauer (co-investigator, endpoint coordinator), A Schwartz (project director), L Palermo (senior statistical programmer), C Fox (senior programmer), R Scott (radiology group), C Yeung (radiology group/X-rays), L Nusgar-
ten (fracture coordinator), and L. Denton (project assistant). Sponsor—Merck Research Laboratories: A Lombardi (medical monitor), A Rybak-Feiglin (medical program coordinator), D Cohn (associate medical program coordinator), S Holk (associate medical program coordinator), C Dave (assistant medical program coordinator), J DiBona (assistant medical program coordinator), and S Suryawanshi (statistician). Data and Safety Monitoring Board—C Rosen (chair), D DeMets, A Santora, and S Suryawanshi. This study was supported by funding from Merck Research Laboratories, Rahway, NJ.

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Received in original form January 28, 2004; in revised form February 27, 2004; accepted March 29, 2004.