

## Zoledronic Acid Inhibits Adjuvant Letrozole–Induced Bone Loss in Postmenopausal Women With Early Breast Cancer

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### A B S T R A C T

#### Purpose

Treatment with aromatase inhibitors decreases bone mineral density (BMD) and may increase the risk of fractures in postmenopausal women with early-stage breast cancer. The addition of zoledronic acid to adjuvant letrozole therapy may protect against bone loss.

#### Patients and Methods

Patients receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (LS) or total hip (TH) T score decreased to less than  $-2.0$  or when a nontraumatic fracture occurred. The primary end point of this study was to compare the change in LS BMD at month 12 between the groups. Secondary end points included change in TH BMD and changes in serum bone turnover markers at month 12.

#### Results

The upfront and delayed groups each included 301 patients. At month 12, LS BMD was 4.4% higher in the upfront group than in the delayed group (95% CI, 3.7% to 5.0%;  $P < .0001$ ), and TH BMD was 3.3% higher (95% CI, 2.8% to 3.8%;  $P < .0001$ ). In the upfront group, mean serum N-telopeptide and bone-specific alkaline phosphatase concentrations decreased by 15.1% ( $P < .0001$ ) and 8.8% ( $P = .0006$ ), respectively, at month 12, whereas concentrations increased significantly in the delayed group by 19.9% ( $P = .013$ ) and 24.3% ( $P < .0001$ ), respectively.

#### Conclusion

With 1 year of follow-up, results of the primary end point of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) indicate that upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer.

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### INTRODUCTION

The third-generation aromatase inhibitors (AIs; letrozole, anastrozole, and exemestane), administered either alone or sequentially after tamoxifen, are currently the preferred adjuvant treatment of postmenopausal women with hormone receptor–positive breast cancer.<sup>1-6</sup> Compared with tamoxifen, the third-generation AIs are not associated with an increased risk for endometrial cancer, thromboembolic events, ischemic cerebrovascular events, deep venous thrombosis, hot flashes, or vaginal bleeding<sup>4</sup>; however, AIs have been shown to accelerate bone loss and increase fracture risk.<sup>2-8</sup>

Estrogen plays an essential role in the maintenance of bone mass in adult women.<sup>9</sup> In postmenopausal women with breast cancer, the third-generation AIs result in nearly complete suppression of aromatase activity and significant decreases in circulat-

ing estrogen concentrations, thereby accelerating the rate of bone loss.<sup>10,11</sup> Treatment with AIs is associated with increased concentrations of bone resorption markers and an increased incidence of osteoporosis.<sup>6,8,12</sup> Therefore, effective therapy to prevent bone loss associated with AIs is needed.

Zoledronic acid, a potent nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption, is approved by the US Food and Drug Administration for the treatment of hypercalcemia of malignancy, multiple myeloma, and bone metastases from solid tumors.<sup>13</sup> Recent clinical trials have demonstrated that zoledronic acid maintains or increases bone mineral density (BMD) in a variety of hypogonadal states.<sup>14-16</sup>

We report the results of the primary and secondary end points of the first 12 months of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST), which evaluates the effect of upfront and delayed-start

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zoledronic acid for prevention of bone loss in postmenopausal women with early-stage breast cancer receiving adjuvant letrozole for 5 years.

## PATENTS AND METHODS

### Study Patients

The study included postmenopausal women from 94 US and Canadian community-based centers who had a history of surgically resectable stage I, II, or IIIA, estrogen receptor–positive and/or progesterone receptor–positive breast cancer; a baseline Eastern Cooperative Oncology Group performance status of  $\leq 2$ ; and baseline lumbar spine (LS) and total hip (TH) T scores  $\geq -2.0$ . All patients underwent tumor resection, completed chemotherapy and/or radiation therapy within 12 weeks of study entry, and had no evidence of residual disease. Before random assignment, a complete medical history and physical examination were performed; patients were excluded if they had clinical or radiologic evidence of distant metastases, an existing LS or TH fracture, or a history of low-intensity fractures. Patients were also excluded if they had received: letrozole or other adjuvant hormone therapy; endocrine therapy; intravenous (IV) bisphosphonates or prolonged systemic corticosteroids within the previous 12 months; growth hormone, anabolic steroids, or tibolone within the previous 6 months; or teriparatide or systemic sodium fluoride. The use of any other drug known to affect the skeleton was prohibited 2 weeks before and throughout the study. Patients who reported receiving oral bisphosphonates or hormone replacement therapy discontinued use before study entry. Patients with renal dysfunction, other malignancies, and diseases known to influence bone metabolism were excluded.

### Study Design

In this open-label, multicenter, randomized study, patients received letrozole 2.5 mg orally daily for 5 years or until disease progression and were randomly assigned to upfront or delayed zoledronic acid 4 mg IV over 15 minutes every 6 months for 5 years. The upfront group received zoledronic acid after random assignment, whereas the delayed group received zoledronic acid when either postbaseline LS or TH T score decreased to less than  $-2.0$  or a nontraumatic clinical fracture occurred. Patients were instructed to take an oral calcium supplement (1,000 to 1,200 mg) and a multivitamin tablet containing vitamin D (400 to 800 U) once daily during the study. Patients were stratified according to adjuvant chemotherapy (yes *v* no) and baseline T score (normal [T score  $> -1.0$ ] *v* mild to moderate osteopenia [T score between  $-1.0$  and  $-2.0$ ]). The definitions for normal BMD, osteopenia, and osteoporosis were modeled after the WHO osteoporosis guidelines.<sup>17</sup>

The primary end point of this study was the percent change in LS BMD (L1 to L4) at 12 months in patients receiving upfront compared with delayed-start zoledronic acid. The secondary end points were the percent change in TH BMD and changes in serum N-telopeptide (NTx) and bone-specific alkaline phosphatase (BSAP) concentrations at 12 months. Additional secondary end points, including percent change in LS and TH BMD at 2, 3, and 5 years; incidence of any clinical fracture at 3 years; time to disease progression; and rate of decrease in LS and TH BMD from baseline to 5 years, will be reported as these results become available.

BMDs of the LS and TH were evaluated at baseline and at 6 and 12 months and will be evaluated at 24, 36, and 48 months and at the

final visit using either Hologic (Hologic, Bedford, MA) or Lunar (GE Medical Systems Lunar Corporation, Madison, WI) dual-energy x-ray absorptiometry (DEXA) devices. T scores were calculated using manufacturer-specific T score databases. All DEXA devices were standardized and cross-calibrated using four Bio-Imaging Bona Fide Phantoms (CIRS Tissue Simulation & Phantom Technology, Norfolk, VA). Enrollment eligibility and timing for initiation of zoledronic acid in the delayed group were based on local DEXA readings; however, a central reader (BioImaging Technologies Inc, Newtown, PA) analyzed all DEXA scans for the efficacy analysis. Patients with baseline and month 12 LS BMD measurements (month 6 BMD measurements were carried forward for women with no 12-month measurements) were included in the primary efficacy analysis. The baseline BMD measurements for 48 women were not received by the central reader; baseline BMD measurements were considered missing for these women, and they were excluded from the efficacy analysis. However, these women were included in the safety analysis.

Serum NTx concentrations, measured using the Osteomark NTx assay (Wampole Laboratories, Princeton, NJ), and BSAP concentrations, measured using the Metra immunoassay (Quidel Corporation, San Diego, CA), were evaluated in a subset of patients by a central laboratory (Clinical Reference Laboratory Inc, Lenexa, KS) at baseline and every 3 months during the first year; these concentrations will also be measured every 6 months during years 2 to 3, once at 48 months, and at the final visit. Nonfasting blood samples were drawn randomly throughout the day for serum bone marker determinations.

Adverse events (AEs) and disease progression were evaluated every 6 months. AEs were graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.<sup>18</sup> Serum creatinine levels were measured at baseline, before each infusion, and at the final visit.

The institutional review boards of the participating institutions approved the study. Informed consent was obtained from each patient before enrollment. The study was funded by Novartis Oncology (East Hanover, NJ). The study design was based on recommendations from several multidisciplinary medical consultants in the areas of breast oncology and endocrinology. The principal investigator directed the 12-month data review and analysis; all data analyses were performed by PRA International (Reston, VA).

### Statistical Analysis

This study was designed using a two-sample *t* test, with a power of 90% and a significance level of  $P = .05$  to detect a 3% difference in percent change in LS BMD with a standard deviation of 9% from baseline to 12 months between the groups. A sample size of 191 patients per treatment arm was required. To allow for a 25% dropout rate, at least 250 patients in each treatment arm were required; 301 patients per arm were enrolled.

Unless otherwise specified, all statistical tests were performed using a significance level of  $P = .05$  against a two-sided alternative hypothesis. An intent-to-treat population, which was defined as all randomly assigned patients who received at least one dose of study drug (letrozole or zoledronic acid) and underwent at least one post-baseline assessment, was included in the efficacy analysis. The safety analysis included all patients who received at least one dose of zoledronic acid or letrozole. A two-sample *t* test and Pearson  $\chi^2$  test were used to compare continuous and discrete variables, respectively. Patients who discontinued the study early were instructed to return

for a final assessment of BMD, serum NTx and BSAP concentrations, and AEs 4 weeks after treatment cessation.

The primary efficacy analysis was performed after all patients had passed the 12-month visit. An analysis of covariance model was used to compare differences between groups; paired *t* tests were used to compare differences within treatment groups in LS and TH BMD and serum NTx and BSAP concentrations from baseline to month 12.

The study was not powered to detect a difference in the incidence of clinical fractures or breast cancer relapse. The frequency of AEs was reported for both groups.

**RESULTS**

**Study Population**

Between September 28, 2002, and December 5, 2003, 602 patients were randomly assigned to receive either upfront or delayed zoledronic acid (Fig 1). Women in the upfront and delayed groups had similar baseline characteristics (Table 1). Only one patient in the upfront group received prior oral bisphosphonate therapy.

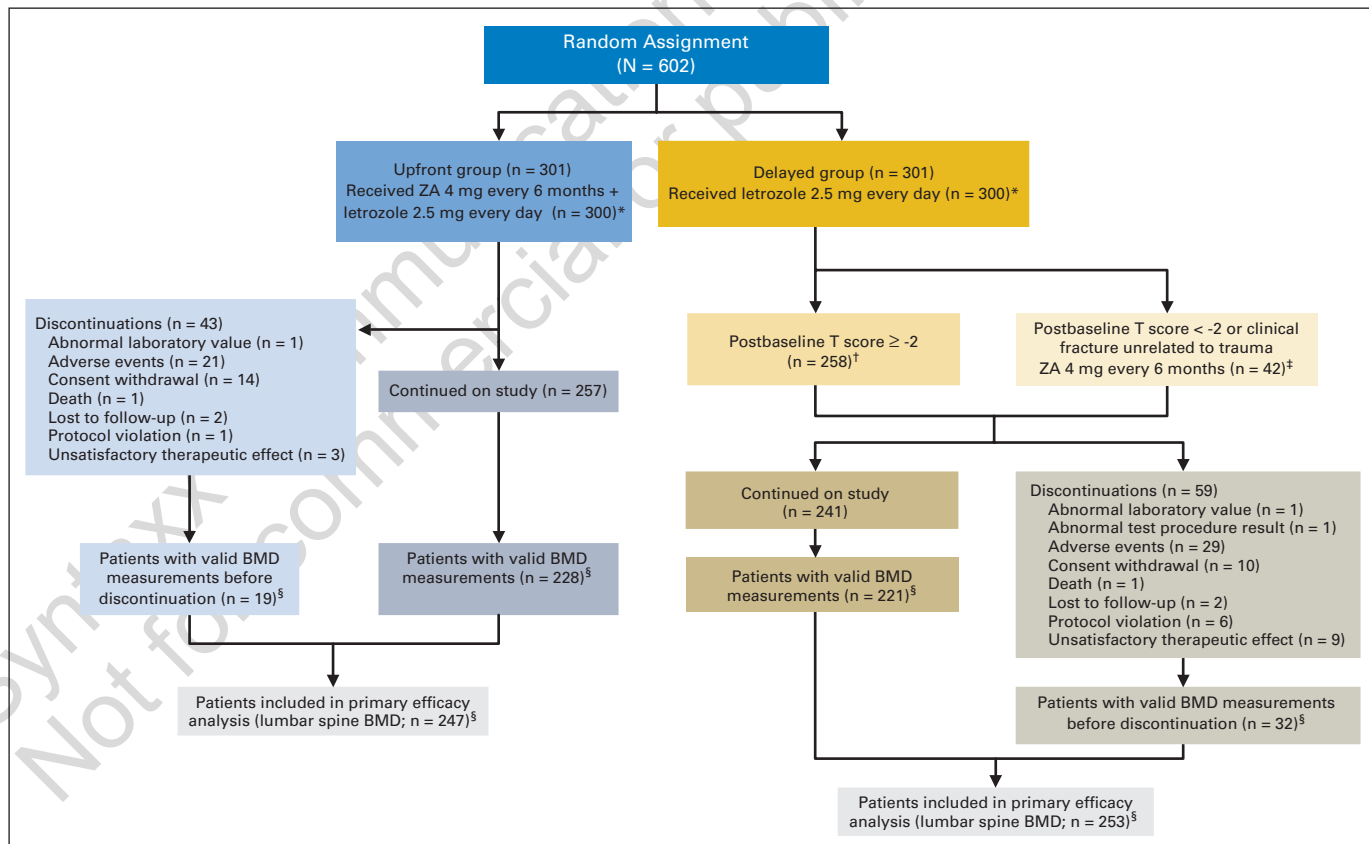
Twenty nine (9.7%) and 42 (14%) patients in the delayed group received zoledronic acid therapy by month 6 and 12, respectively. For these patients, the mean time to initiation of zoledronic acid was 8.8 months (range, 0.03 to 24.15 months). After closer evaluation, only 13 (4.3%) and 25 (8.3%) patients by 6 and 12 months, respectively, were administered zoledronic acid per protocol (ie, T score < -2.0 and/or

a clinical fracture). The remaining delayed-group patients did not meet protocol-defined criteria for zoledronic acid therapy.

**BMD**

At month 12, the mean percent difference in BMD between the groups was 4.4% for LS (95% CI, 3.7% to 5.0%; *P* < .0001) and 3.3% for TH (95% CI, 2.8% to 3.8%; *P* < .0001; Fig 2). Six-month rather than 12-month BMD measurements were used for 25 and 38 women in the upfront and delayed groups, respectively, for the LS analysis and 25 and 39 patients in the upfront and delayed groups, respectively, for the TH analysis.

At baseline, 433 patients (72%) had normal BMD of the LS and/or TH (217 patients [72.1%] in the upfront group; 216 patients [71.8%] in the delayed group; Table 1). After 12 months, a higher percentage of patients in the delayed group with normal baseline BMD developed mild to moderate osteopenia compared with patients in the upfront group (12.6% v 3.4%, respectively; Table 2). At baseline, 84 patients (27.9%) in the upfront group and 85 patients (28.2%) in the delayed group already had mild to moderate osteopenia of the LS and/or TH, placing them at a higher risk for progressing to severe osteopenia (T score between -2.0 and -2.5) or osteoporosis (T score < -2.5) with letrozole therapy (Table 1). In the delayed group, more patients progressed from mild or moderate to severe osteopenia compared with the upfront group (12 patients [14.8%] v one patient [1.4%], respectively; Table 2). Interestingly, eight patients in the delayed group with osteopenia at baseline improved to a normal BMD of



**Fig 1.** Enrollment and outcomes. (\*) One patient was erroneously randomly assigned in each group. (†) One patient met protocol-defined criteria but did not receive zoledronic acid (ZA). (‡) Twenty-five patients received ZA per protocol. (§) Per study design, 6-month bone mineral density (BMD) data were used if 12-month BMD data were unavailable or invalid (eg, illegible BMD scan).

**Table 1.** Patient Characteristics

| Characteristic  | Upfront Group |             | Delayed Group |             |
|---|---------------|-------------|---------------|-------------|
|   | No.           | %           | No.           | %           |
| Patients in safety population*                            | 301           |             | 301           |             |
| Patients in intent-to-treat population†                   | 300           |             | 300           |             |
| Age, years  |               |             |               |             |
| Median  |               | 60          |               | 60          |
| Range   |               | 35-83       |               | 41-89       |
| Age at onset of menopause, years                          |               |             |               |             |
| Median  |               | 49          |               | 49          |
| Range   |               | 21-61       |               | 23-59       |
| Race‡   |               |             |               |             |
| White   | 280           | 93.0        | 269           | 89.4        |
| Black   | 9             | 3.0         | 14            | 4.7         |
| Other   | 12            | 4.0         | 18            | 6.0         |
| ECOG performance status‡                                  |               |             |               |             |
| 0   | 253           | 84.1        | 248           | 82.4        |
| 1   | 44            | 14.6        | 46            | 15.3        |
| 2   | 1             | 0.3         | 1             | 0.3         |
| Unknown   | 3             | 1.0         | 6             | 2.0         |
| Bone mineral density, g/cm <sup>2</sup>                   |               |             |               |             |
| Lumbar spine  |               |             |               |             |
| Mean  |               | 1.110       |               | 1.106       |
| SD  |               | 0.1652      |               | 0.1663      |
| Median  |               | 1.088       |               | 1.082       |
| Range   |               | 0.818-1.649 |               | 0.807-1.642 |
| Total hip   |               |             |               |             |
| Mean  |               | 0.958       |               | 0.955       |
| SD  |               | 0.1259      |               | 0.1322      |
| Median  |               | 0.954       |               | 0.943       |
| Range   |               | 0.676-1.310 |               | 0.700-1.475 |
| Stratification factors‡                                   |               |             |               |             |
| Prior adjuvant chemotherapy                               | 137           | 45.7*       | 143           | 47.7*       |
| No prior adjuvant chemotherapy                            | 163           | 54.3*       | 157           | 52.3*       |
| T score ≤ -1 to ≥ -2§                                     | 84            | 27.9        | 85            | 28.2        |
| T score > -1§   | 217           | 72.1        | 216           | 71.8        |
| Osteoporotic risk factors                                 |               |             |               |             |
| Postmenopausal status                                     | 281           | 99.6        | 284           | 99.6        |
| Lack of adequate vitamin/dairy intake as a child          | 102           | 36.2        | 111           | 38.9        |
| Age ≥ 65 years  | 93            | 33.0        | 95            | 33.3        |
| Age at onset of menopause ≤ 45 years                      | 78            | 27.7        | 75            | 26.3        |
| Adult fracture  | 71            | 25.2        | 67            | 23.5        |
| Family history of osteoporosis                            | 63            | 22.3        | 62            | 21.8        |
| Current smoker or smoking cessation within past 10 years¶ | 60            | 21.3        | 52            | 18.2        |
| Lack of mobility or exercise                              | 51            | 18.1        | 48            | 16.8        |
| Treatment of one or more comorbidities#                   | 49            | 17.4        | 49            | 17.2        |
| Lack of adequate vitamin/dairy intake as an adult         | 47            | 16.7        | 61            | 21.4        |
| Irregular menstrual cycles                                | 44            | 15.6        | 48            | 16.8        |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

\*Includes all enrolled patients.

†One patient each in the upfront and delayed groups was erroneously randomly assigned.

‡Based on all randomly assigned patients (upfront, n = 301; delayed, n = 301).

§Based on local dual-energy x-ray absorptiometry scan results.

||Based on all randomly assigned patients who completed an osteoporotic risk assessment at baseline (upfront, n = 282; delayed, n = 285).

¶Includes cigarette and other smokers.

#Comorbid conditions include hyperthyroidism, rheumatoid arthritis, endocrine disorder, seizure disorder, dementia, anorexia nervosa, and bulimia.

the LS by month 12. Of these eight patients, two patients received zoledronic acid at month 6, and four patients had borderline osteopenia at baseline.

### Fractures

At month 12, no- or low-trauma fractures occurred in 1% of patients in the upfront group and 0.7% of patients in the delayed group. Traumatic fractures occurred in 2.3% and 2% of patients in the upfront and delayed groups, respectively.

### Markers of Bone Turnover

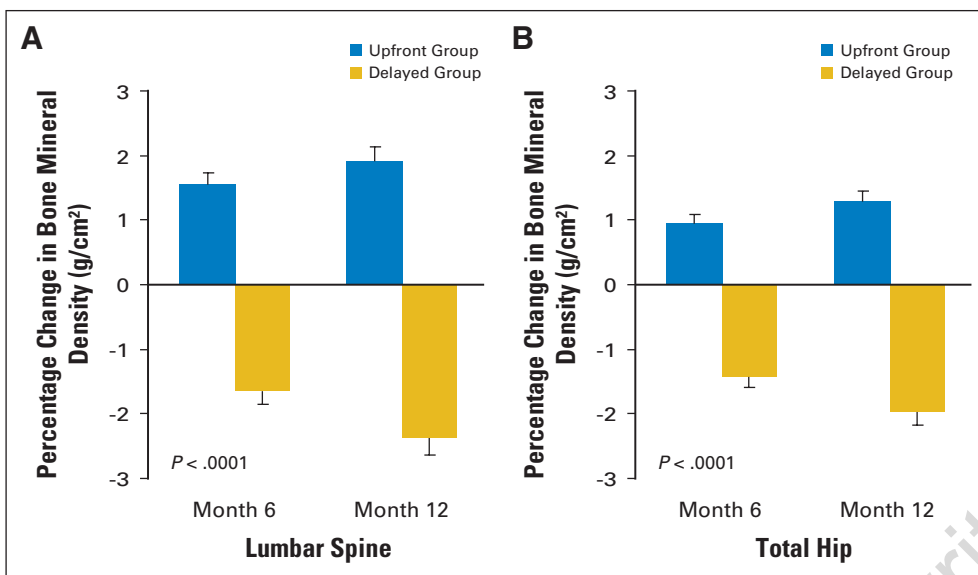
Serum NTx and BSAP concentrations were measured in a subset of 212 patients with baseline characteristics similar to the entire study population (Figs 3 and 4). Both serum NTx and BSAP concentrations significantly decreased in the upfront group and significantly increased in the delayed group by month 12. Upfront treatment with zoledronic acid induced relatively rapid decreases in the rate of bone turnover. The difference in mean percent change of bone turnover markers at month 12 between the upfront and delayed groups was -35% for serum NTx and -33% for serum BSAP (Figs 3 and 4).

### Safety

The safety analysis consisted of 300 patients in both groups (Table 3). The occurrence of AEs was similar between the groups with the exception of bone pain, which was higher in the upfront zoledronic acid group compared with the delayed group (11.3% v 4%, respectively), as expected. Neither group experienced grade 3 or 4 renal dysfunction; one patient in the upfront group experienced a grade 1 increase in serum creatinine level. Osteonecrosis of the jaw (ONJ) was not reported in either group. Serious AEs occurred in 16.7% and 18.7% of patients in the upfront and delayed groups, respectively. Seven percent of patients in the upfront group and 9.7% of patients in the delayed group withdrew from the study as a result of AEs; 1.3% and 1% of patients in the upfront and delayed groups, respectively, discontinued therapy because of serious AEs.

## DISCUSSION

Several large, prospective, randomized, controlled trials demonstrate that adjuvant AI therapy alone or sequentially after tamoxifen increases disease-free survival in postmenopausal women with localized endocrine-responsive breast cancer compared with standard tamoxifen therapy.<sup>2-6</sup> AIs are associated with accelerated bone loss and an increased fracture risk.<sup>2-8,12,16,19,20</sup> This is the first study to evaluate the efficacy and safety of zoledronic acid for the prevention of bone loss in postmenopausal women with early-stage breast cancer receiving adjuvant AI therapy. Our data show that patients who receive upfront zoledronic acid 4 mg IV every 6 months are less likely to develop bone loss at 1 year than women who receive delayed-start zoledronic acid. Women who received upfront zoledronic acid experienced increases in BMD from baseline to month 12 in both the LS (+1.9%) and TH (+1.3%), whereas patients receiving no zoledronic acid (86%) or delayed zoledronic acid (14%) experienced decreases in BMD of the LS (2.4%) and TH (1.98%) from baseline to month 12 ( $P < .0001$  for both). These results are consistent with previously reported rates of bone loss over 12 months in postmenopausal women receiving an AI in the absence of antiresorptive therapy (LS, -2.6% to -3.2%; TH, -1.7% to -2.2%; femoral neck, -2.72%).<sup>8,19,21</sup>



**Fig 2.** Mean (SEM) percent change in bone mineral density of the lumbar spine and the total hip at months 6 and 12 in women with early-stage breast cancer administered upfront or delayed zoledronic acid. *P* values correspond to intragroup comparisons from baseline to month 12. SEM, standard error of the mean.

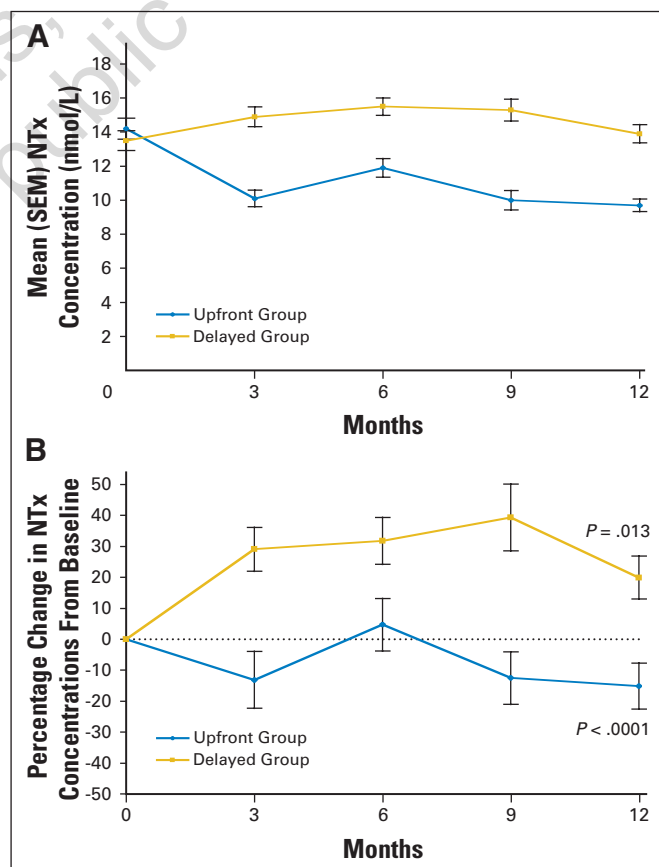
Our study results indicate that the risk of developing severe osteopenia within the first year of AI therapy may be significant in a small percentage of postmenopausal women. In the delayed group, 12.6% of patients with normal baseline BMD developed mild to moderate osteopenia by month 12, and 14.8% of patients with baseline mild to moderate osteopenia progressed to severe osteopenia. However, in the upfront group, only 3.4% of patients with normal baseline BMD developed osteopenia by month 12, and 1.4% of patients with baseline mild to moderate osteopenia progressed to severe osteopenia.

By month 12, 8.3% of patients in the delayed group required zoledronic acid because of either a T score less than  $-2.0$  or the occurrence of a nontraumatic clinical fracture. An additional 5.7% of

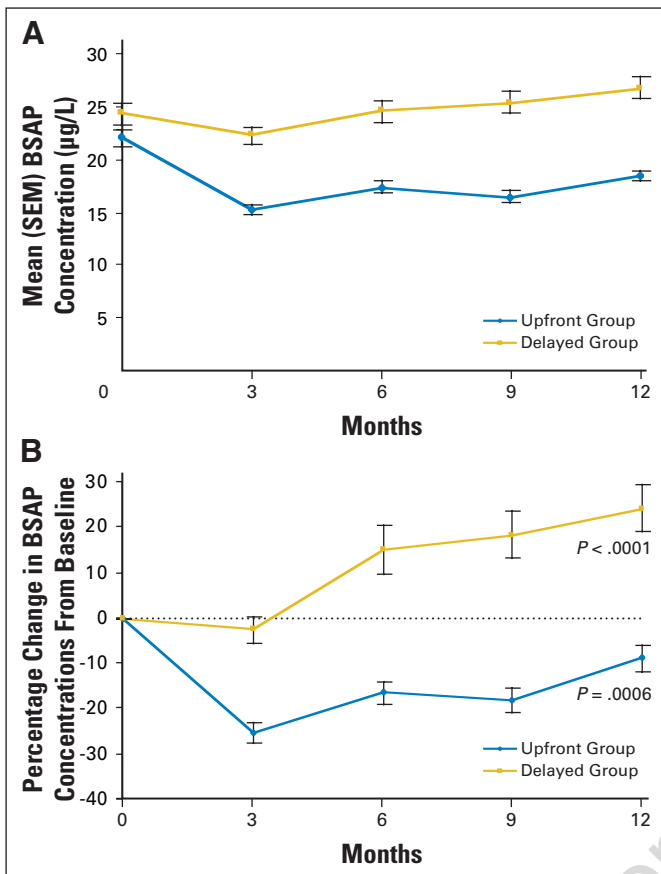
patients in the delayed group received zoledronic acid but did not meet the protocol-defined criteria for therapy initiation. At study initiation, a few study sites misinterpreted the protocol and started all

|   | Upfront Group |      | Delayed Group |      |
|---|---------------|------|---------------|------|
|   | No.           | %    | No.           | %    |
| Baseline† and Month 12 BMD                                  |               |      |               |      |
| Normal baseline BMD   | 203           |      | 198           |      |
| Month 12 BMD  |               |      |               |      |
| Normal  | 175           | 86.2 | 152           | 76.8 |
| Mild to moderate osteopenia, T score $\leq -1$ to $\geq -2$ | 7             | 3.4  | 25            | 12.6 |
| Severe osteopenia, T score $< -2$                           | 0             | 0    | 0             | 0    |
| Invalid data  | 21            | 10.3 | 21            | 10.6 |
| Osteopenia at baseline                                      | 70            |      | 81            |      |
| Month 12 BMD  |               |      |               |      |
| Normal  | 18            | 25.7 | 8             | 9.9  |
| Mild to moderate osteopenia, T score $\leq -1$ to $\geq -2$ | 44            | 62.9 | 54            | 66.7 |
| Severe osteopenia, T score $< -2$                           | 1             | 1.4  | 12            | 14.8 |
| Invalid data  | 7             | 10   | 7             | 8.6  |

Abbreviation: BMD, bone mineral density.  
 \*Based on central reading of dual-energy x-ray absorptiometry scan results.  
 †Baseline BMD data for 27 patients in upfront group and 21 patients in delayed group were not transferred to central reader from study sites and therefore not included in analysis.



**Fig 3.** (A) Mean (SEM) N-telopeptide (NTx) concentrations and (B) mean percent change (SEM) in serum NTx concentrations from baseline in women with early-stage breast cancer administered upfront or delayed zoledronic acid. *P* values correspond to intragroup comparisons from baseline to month 12. SEM, standard error of the mean.



**Fig 4.** (A) Mean (SEM) bone-specific alkaline phosphatase (BSAP) concentrations and (B) mean percent change (SEM) in BSAP concentrations from baseline in women with early-stage breast cancer administered upfront or delayed zoledronic acid. *P* values correspond to intragroup comparisons from baseline to month 12. SEM, standard error of the mean.

patients randomly assigned to the delayed group on zoledronic acid at month 6. After re-educating the study sites, the number of administration error protocol violations diminished significantly.

In the delayed group, 6-month BMD measurements were carried forward for the 12-month LS and TH analyses in approximately 8% and 13% of patients in the upfront and delayed groups, respectively.

**Table 3. Adverse Events Occurring in More Than 5% of Patients**

| Adverse Event     | Upfront Group<br>(n = 300) |      | Delayed Group<br>(n = 300) |      |
|-------------------|----------------------------|------|----------------------------|------|
|                   | No.                        | %    | No.                        | %    |
| Arthralgia        | 90                         | 30.0 | 87                         | 29.0 |
| Hot flashes       | 76                         | 25.3 | 77                         | 25.7 |
| Fatigue           | 52                         | 17.3 | 46                         | 15.3 |
| Myalgia           | 38                         | 12.7 | 29                         | 9.7  |
| Bone pain         | 34                         | 11.3 | 12                         | 4.0  |
| Headache          | 27                         | 9.0  | 22                         | 7.3  |
| Nausea            | 24                         | 8.0  | 17                         | 5.7  |
| Pain in extremity | 24                         | 8.0  | 13                         | 4.3  |
| Insomnia          | 21                         | 7.0  | 16                         | 5.3  |
| Depression        | 17                         | 5.7  | 27                         | 9.0  |
| Back pain         | 18                         | 6.0  | 17                         | 5.7  |

The use of 6-month rather than 12-month BMD measurements for these analyses may possibly lead to a smaller percentage of difference in 12-month BMD between the groups.

Several studies have shown BMD to be a robust surrogate marker for fracture risk in postmenopausal women.<sup>22-25</sup> A meta-analysis of approximately 39,000 men and women participating in 12 osteoporosis trials reported a 1.6- to 2.2-fold increase in fracture risk for each standard deviation decrease in BMD for women.<sup>24</sup> Correlation between BMD and fracture risk varies widely and is influenced by many factors other than AI use, such as site of BMD measurement, age, prior fracture history, low body weight, and inactive lifestyle.<sup>24-27</sup> The American Society of Clinical Oncology recommends that all women at high risk of osteoporosis, including women receiving AI therapy, receive baseline and annual DEXA scans.<sup>27</sup>

Only 1% of patients in the upfront and 0.7% of patients in the delayed group developed no- or low-trauma fractures by month 12. A meaningful statistical comparison of 12-month fracture rates was not possible because of the low number of fractures occurring in each group. Although the study was not designed to detect a difference in fracture rate between treatment groups, a statistical analysis of fracture incidence is planned after 36 months of therapy.

The changes in bone marker measurements observed in a subset of patients receiving upfront versus delayed zoledronic acid suggest that zoledronic acid's effect on bone remodeling is both rapid and sustained over at least 1 year. In our study, the mean differences in NTx and BSAP concentrations between the upfront and delayed groups were 35% and 33% at month 12; the differences between the treatment and placebo groups in a study of women with postmenopausal osteoporosis were approximately 60% and 50%, respectively.<sup>15</sup> The difference in bone marker measurements observed in our study compared with the postmenopausal osteoporosis study may be explained by differences in pretreatment values, assays used to measure BSAP concentrations, body fluids used to measure NTx concentrations (serum v urine), and timing of NTx collection (random v second-morning void).<sup>15,28,29</sup>

Zoledronic acid was generally well tolerated, with few discontinuations in either group. Bone pain was more common in the upfront than the delayed group but was only mildly to moderately severe.<sup>13</sup> Only one patient experienced grade 1 renal impairment, and severe renal dysfunction was not reported. The reported frequency of ONJ in women with breast cancer receiving IV bisphosphonates ranges from 0.6% to 1.2%.<sup>30,31</sup> To date, no cases of ONJ have been reported in our study.

Currently, the American Society of Clinical Oncology recommends initiation of an IV or oral bisphosphonate only after a patient's T score declines to less than -2.5 (ie, osteoporosis).<sup>27</sup> The preliminary results of this ongoing clinical trial suggest that initiation of zoledronic acid 4 mg IV every 6 months in postmenopausal breast cancer patients receiving adjuvant AI therapy may prevent or delay bone loss at 1 year of follow-up. A longer follow-up is needed to determine whether the bone loss observed in the delayed group can be stabilized or restored to baseline values with the administration of zoledronic acid. The 3- and 5-year results of this trial and other ongoing clinical trials are necessary to confirm the optimal timing for bisphosphonate initiation and its impact on fracture rates in early-stage breast cancer patients receiving adjuvant AIs.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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### Appendix

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