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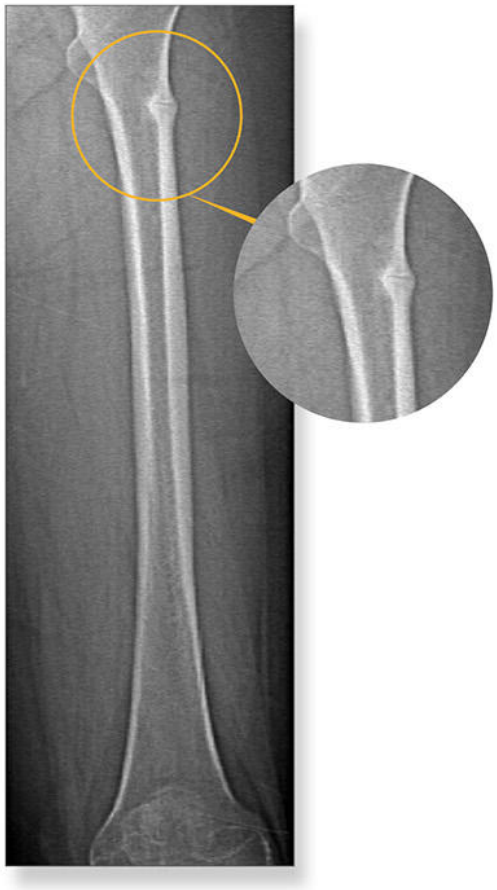

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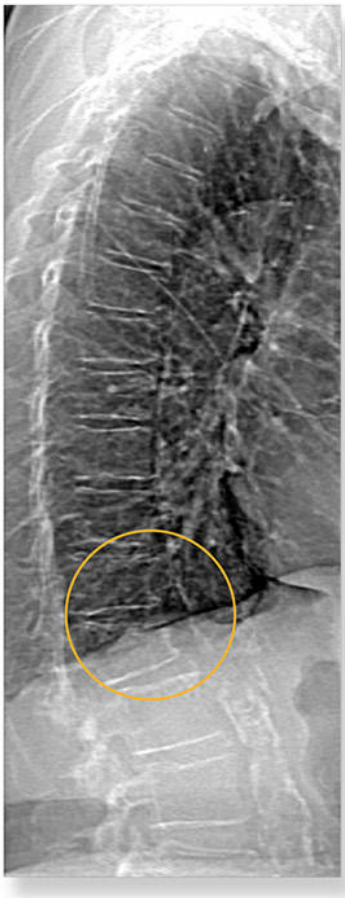

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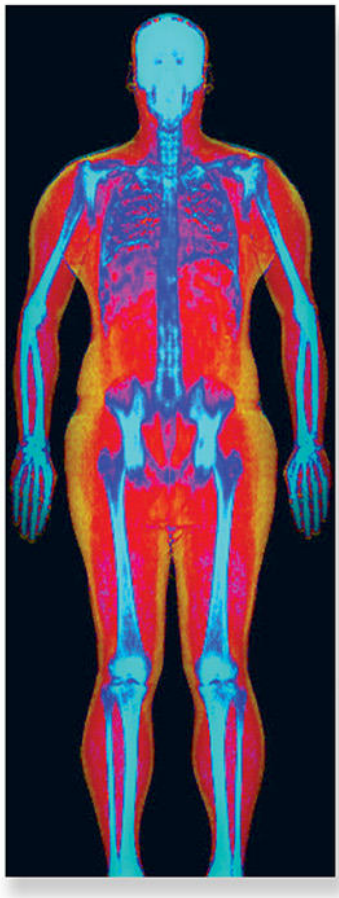

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Original Article

Comparison of BMD Changes and Bone Formation Marker Levels 3 Years After Bisphosphonate Discontinuation: FLEX and HORIZON-PFT Extension I Trials†

Tiffany Y. Kim, MD;[1,3] Douglas C. Bauer, MD;[1,2] Brian L. McNabb, MD; [1] Anne L. Schafer, MD;[1,2,3] Felicia Cosman, MD;[4,5] Dennis M. Black, PhD;[2] Richard Eastell, MD[6]

Departments of [1]Medicine, and [2]Epidemiology and Biostatistics, University of California, San Francisco, CA, USA; [3]Medical Service, San Francisco Veterans Affairs Health Care System, San Francisco, CA, USA; [4]Department of Clinical Medicine, Columbia University, New York, NY, USA; [5]Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA; [6]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

Corresponding author:
Tiffany Y. Kim, MD
University of California, San Francisco and the San Francisco Veterans Affairs Health Care System
1700 Owens St, Room 349
San Francisco, CA 94158
Phone: (415) 575-0549
Fax: (415) 575-0593
tiffany.kim@ucsf.edu

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ABSTRACT

An ASBMR task force recommends a drug holiday for certain women treated for ≥5 years with oral alendronate or ≥3 years with intravenous zoledronic acid, with reassessment 2-3 years later. It is not known whether changes in BMD or bone turnover markers differ after oral or intravenous therapy. Our goal was to compare changes in BMD and procollagen type I N propeptide, PINP, after oral or intravenous bisphosphonate use. In the Fracture Intervention Trial Long-term Extension (FLEX), women who received a mean 5 years of alendronate were randomized to placebo or continued treatment. In the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial Extension I (HORIZON-PFT E1), women who received 3 years of zoledronic acid were randomized to placebo or continued treatment. We examined the proportion of participants with BMD loss or PINP gain ≥least significant change (LSC), and those whose values exceeded a threshold (T score ≤-2.5 or PINP ≥36.0 ng/mL, a premenopausal median value). After 3 years of placebo, the FLEX group had greater mean total hip BMD decreases (-2.3% versus -1.2% in the HORIZON-PFT E1 group, $p<0.01$), and greater rises in PINP (+11.6 ng/mL versus +6.7 ng/mL, $p<0.01$). There was a greater proportion of individuals in FLEX with total hip BMD loss and PINP increases that exceeded LSC, and PINP values ≥36.0 ng/mL. In contrast, there were small changes in the proportion of women with femoral neck T scores ≤-2.5 in both groups. In conclusion, 3 years after bisphosphonate discontinuation, a considerable proportion of former alendronate and zoledronic acid users had meaningful declines in total hip BMD and elevations in PINP. Despite a longer treatment course, alendronate may have a more rapid offset of drug effect than zoledronic acid. This article is protected by copyright. All rights reserved

Keywords: OSTEOPOROSIS; ANTIRESORPTIVES; DXA; BIOCHEMICAL MARKERS OF BONE TURNOVER

INTRODUCTION

The optimal management of osteoporosis for those on long-term bisphosphonate therapy is unclear because of limited fracture-based evidence. The ASBMR Task Force has published recommendations that are largely based on two long-term bisphosphonate trials: those of oral alendronate (Fracture Intervention Trial and Long-term Extension, FLEX) and IV zoledronic acid (Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial Extension I, HORIZON-PFT E1). The Task Force Report recommends that women at high fracture risk consider continued treatment, while women not at high fracture risk after 5 years of oral or 3 years of IV bisphosphonate treatment could consider a drug holiday. Both fracture occurrence on initial treatment and hip BMD achieved after a course of treatment have been proposed as criteria to estimate risk in these patients.[1-3] It has also been proposed that patients be reassessed after 2-3 years of a medication holiday.[1] Only one study has examined fracture outcomes after bisphosphonate use and did not find a relationship between 1-year changes in BMD or bone turnover markers with fracture risk.[4] Given that there are few studies with fracture outcomes, a better understanding of biomarkers throughout the drug holiday period could inform management.

Even though bisphosphonates have long-term retention in bone,[5] offset of drug effect is likely occurring during a drug holiday, with BMD loss and elevated bone turnover markers. In both the FLEX and HORIZON-PFT E1 extension studies, those who stopped bisphosphonate treatment had an increased risk of vertebral fracture, although there was no difference in nonvertebral fracture.[6, 7] It is unknown whether offset of drug effect differs after oral compared to IV bisphosphonates, as there are no head-to-head comparison trials off therapy. Although

zoledronic acid has higher skeletal binding affinity than alendronate,[8] the usual initial treatment duration with alendronate is longer (5 years compared to 3 years with zoledronic acid).

In this post hoc analysis, we examined the placebo extension arms of the largest bisphosphonate randomized trials, the FLEX trial and the HORIZON-PFT E1 trial. These are the only large fracture trials in which patients were randomized to receive continued treatment or placebo during the study extension. As there are no formal definitions for the offset of drug effect, we examined 3-year changes in BMD and bone formation marker levels that exceed least significant change or threshold values.

MATERIALS AND METHODS

We examined the group of women who were randomized to receive a bisphosphonate during the core trial and then randomized to placebo during the extension trial (Figure 1). Calcium and vitamin D were provided to every participant throughout all of the trials. All participants provided written informed consent and the protocols were approved by the institutional review boards at each participating center. Both trials were registered at www.clinicaltrials.gov (FLEX: NCT00398931; HORIZON-PFT E1: NCT00145327).

The Fracture Intervention Trials (FIT) and Long-term Extension (FLEX)

For the two multicenter US FIT studies, 6459 postmenopausal women with low femoral neck BMD (<0.68 gm/cm^2, equivalent to a T score of <-1.6) were randomized to daily alendronate (5 mg/day for 2 years and then 10 mg/day afterwards) or placebo. One trial enrolled

women with existing spine fractures and the other enrolled women without existing vertebral fracture.[9, 10] They were followed for 3-4 years and were then offered open-label alendronate for up to 1 year at no cost. Subsequently in the FLEX trial, women originally assigned to the alendronate arm who received at least 3 years of treatment were eligible for the randomized extension trial of continued alendronate or placebo. Women were excluded if total hip BMD T score was <-3.5 or lower than FIT baseline. In this trial, 1099 women were randomized, with 437 assigned to receive placebo, for a total of 5 years.[6]

The Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) and Extension I

For the international HORIZON-PFT study, 7765 postmenopausal women with either femoral neck T score <-2.5 or <-1.5 with a vertebral fracture were randomized to receive an annual infusion of zoledronic acid 5 mg or placebo, and followed for 3 years.[11] In the E1 extension trial, women who received 3 zoledronic acid or placebo infusions in the core study were eligible to enroll. Exclusion criteria included age >93 years, and specific bone-active medication use. For the extension trial, 1233 women originally assigned to the zoledronic acid arm were randomized, with 617 assigned to receive placebo, for a total of 3 years.[7]

BMD measurements

In FLEX, all participants had hip BMD measured annually, and spine BMD measured at 3 and 5 years with Hologic QDR 2000 densitometers (Hologic Inc, Bedford, Massachusetts). In HORIZON-PFT E1, BMD was measured at 1.5 and 3 years at the total hip and femoral neck for all participants, and at the lumbar spine in a subset. Local densitometers were used, and quality

control and BMD scan analyses were performed centrally (Synarc, Portland). For both studies, we calculated BMD change from year 0 to year 3 of the extension. Given precision errors with BMD measurements, we categorized these changes by least significant change. The International Osteoporosis Foundation defines the least significant change for BMD as ≥4% loss at the total hip and femoral neck, and ≥5% loss at the lumbar spine.[12] Since a femoral neck T score ≤-2.5 is an important clinical threshold that the ASBMR task force considers for retreatment, we categorized the proportion of participants with femoral neck T scores ≤-2.5. FLEX utilized different normal reference values for T score calculations, and T scores were recalculated using NHANES reference data to be comparable to HORIZON-PFT E1.[13, 14]

Bone formation marker measurements

PINP was measured in both trials. The International Osteoporosis Foundation recommends using PINP as the serum bone formation marker and the bone resorption marker, CTX, as reference markers.[15] CTX data for both studies were limited and therefore not included in these analyses. Of the 1099 FLEX participants, PINP measurements were performed in a subset of 239 participants who had a complete set of samples (core trial; extension baseline, year 3 and 5) and were adherent throughout the study. In HORIZON-PFT E1, all participants had PINP measured at year 1.5 and 3 of the extension. The same assay was used in both trials (Roche Diagnostics, Penzburg, Germany) and analyzed at a central laboratory (Synarc, Lyon, France). Intra-assay and interassay coefficients of variation for PINP were 1.2-4.9% and 4.3-6.5%, respectively. At baseline and year 3 of the extension trials, we dichotomized PINP values using a threshold of the median value for premenopausal women (36.0 ng/mL).[16] There is not a standardized bone formation marker threshold value, but lower levels may indicate relatively low

vertebral fracture risk in bisphosphonate trials.[17] The International Osteoporosis Foundation defines the least significant change for PINP as 25% change.[12]

Statistical Analyses

The primary outcome was total hip BMD change from the beginning of the extension trial to year 3, as the total hip is the preferred site for monitoring.[18] Secondary outcomes included BMD change at the femoral neck and lumbar spine, 3-year T scores at the femoral neck, 3-year changes in PINP, and PINP values at year 3. PINP values were not normally distributed therefore geometric means were calculated. Differences in extension baseline characteristics and outcomes were assessed using chi-squared, Mann-Whitney, Student's *t*-test, and McNemar's test. Outcomes were also estimated using linear regression models, adjusting for differences in baseline characteristics, which included age, prevalent vertebral fracture at extension baseline, and T score or PINP value at the beginning of the extension; normalizing log transformations were used if needed. Although FLEX was performed in the United States and HORIZON-PFT E1 was international, geographic location was not adjusted due to lack of covariate overlap. We performed sensitivity analyses excluding individuals in FLEX who stopped therapy during the open-label extension, since these individuals may bias results. We also conducted a sensitivity analysis excluding those who would be less likely to be on a drug holiday based on the ASBMR recommendation (femoral neck T score $\leq$-2.5 at extension baseline or occurrence of a clinical fracture during initial treatment course).[19] Data were analyzed using Stata 14 software (StataCorp, College Station, Texas).

RESULTS

Study participants in the placebo extension arms

Participant characteristics at extension baseline are shown in Table 1. On average, HORIZON-PFT E1 participants were older (75.5 years compared to 73.7 years, $p<0.01$) and had a higher prevalence of vertebral fracture (63.2% compared to 34.3%, $p<0.01$) than FLEX participants, respectively. While eligibility criteria for FLEX required ≥3 years of alendronate treatment, women on average received alendronate for 5.0 years during the core trial and the open-label extension. After the open-label extension period, 78.0% of the FLEX placebo arm remained on active therapy. In contrast, 99.8% of the participants in the HORIZON-PFT E1 placebo arm had received active therapy ($p<0.01$), with an average of 394.2 days since the last zoledronic acid infusion. The mean total hip T score was higher in FLEX (-1.8 versus -2.0 in HORIZON-PFT E1, $p<0.01$) and there was a trend for the median PINP level to be higher in FLEX (22.6 ng/mL versus 20.8 ng/mL in HORIZON-PFT E1, $p=0.08$).

In both trials, there were similar proportions of participants who received placebo until the end of the study (n=299, 68.4% in FLEX; n=430, 69.7% in HORIZON-PFT E1, $p=0.71$; Figure 2). A higher percentage of participants in FLEX (n=401, 91.8%) had values for the primary outcome compared to HORIZON-PFT E1 (n=467, 75.7%, $p<0.01$).

BMD values in the placebo extension arms

During the placebo extension, total hip BMD in the HORIZON-PFT E1 group was initially stable at 1.5 years and then changed by -1.2% (95% confidence interval, CI, -1.5% to -0.8%) after 3 years of placebo (Figure 3). In contrast, BMD in FLEX had progressive decline in

the first year, and by year 3 had changed by -2.3% (95% CI -2.6% to -1.9%), which was a greater decrease compared to HORIZON-PFT E1 ($p<0.01$). At the femoral neck, there was a significant decline in BMD for both groups after 3 years of placebo (-1.1% in FLEX, -0.5% in HORIZON-PFT E1), with a trend toward greater femoral neck BMD loss in the FLEX ($p=0.07$). At the spine, the differences in BMD changes were not statistically significant (+0.8% in FLEX, +1.6% in HORIZON-PFT E1, $p=0.12$). Adjustments for differences in baseline characteristics between the two trials (age, history of vertebral fracture, and T score at extension baseline) yielded similar results at the 3 anatomic sites: total hip, -2.4% in FLEX versus -1.1% in HORIZON-PFT E1; femoral neck, -1.2% in FLEX versus -0.5% in HORIZON-PFT E1; lumbar spine, +0.9% in FLEX versus +1.5% in HORIZON-PFT E1.

When 3-year BMD change was categorized by BMD loss greater than least significant change, 25.2% of the FLEX placebo group met that criterion, compared to 18.7% of the HORIZON-PFT E1 placebo group ($p=0.02$, Figure 4). There were similar trends with femoral neck BMD loss: 28.4% in FLEX versus 19.8% in HORIZON-PFT E1, $p<0.01$. In contrast, few participants had spine BMD loss, 7.9% in FLEX and 4.8% in HORIZON-PFT E1, $p=0.25$. Adjustments for differences in baseline characteristics produced similar results (data not shown).

At the beginning of FLEX, 126 of 437 participants (28.8%) had femoral neck T score values $\leq$-2.5. After 3 years, this slightly increased to 135 of 401 participants (33.7%, $p<0.01$ for the difference from year 0 to 3). In HORIZON-PFT E1, there were more participants at the placebo extension baseline with femoral neck T score values $\leq$-2.5: 325 of 615 (52.9%). This proportion also slightly increased after 3 years to 261 of 471 participants (55.4%, $p=0.03$ for the difference).

PINP values in the placebo extension arms

Compared to pre-treatment baseline values, mean PINP levels at the beginning of the placebo extension trial were relatively suppressed and in the lower range for premenopausal women (Figure 5). Over 3 years of placebo treatment, PINP increases were higher in FLEX (+11.6 ng/mL) compared to HORIZON-PFT E1 (+6.7 ng/mL, $p<0.01$). In both trials, the majority of women had changes in PINP that exceeded least significant change (66.0% in FLEX, 56.5% in HORIZON-PFT E1, $p=0.08$ for difference between groups). Adjustments for age, prevalent vertebral fracture, and PINP value at extension baseline yielded similar results; mean PINP change was +12.9 ng/mL in FLEX versus +6.3 ng/mL in HORIZON-PFT E1, and 77.0% of FLEX participants and 51.4% of HORIZON-PFT E1 participants had PINP changes that exceeded least significant change. Mean values remained in the lower range for premenopausal women and did not return to pre-treatment levels.

After three years of placebo, the proportion of individuals with PINP levels above the median for premenopausal women (36.0 ng/mL) was 42.0% in FLEX versus 24.6% in HORIZON-PFT E1 ($p<0.01$). In the adjusted analyses, there were similar proportions of individuals with PINP levels about the premenopausal median, 37.0% in the FLEX and 19.8% in HORIZON-PFT E1. There were some individuals with values ≥36.0 ng/mL at the beginning of the placebo extension trial, and if those individuals were excluded, the proportion of individuals above the PINP threshold changed to 31.3% in FLEX compared to 20.1% in HORIZON-PFT E1 ($p=0.03$).

Sensitivity analyses

Since there was an open label extension period between the alendronate core and extension trial, we performed sensitivity analyses only including the 78% of participants who were taking alendronate at the start of the placebo extension. This analysis resulted in similar trends for mean BMD loss, with greatest declines in the first year (Supplemental Figure 1A). Mean PINP changes during the placebo extension were also similar (Supplemental Figure 1B). The ASBMR recommends that high-risk women should consider continuing bisphosphonate therapy, therefore we excluded women who sustained a fracture during the initial treatment course and those with a femoral neck T score ≤-2.5 at the beginning of the extension trial (37% of FLEX and 56% of HORIZON-PFT E1). BMD changes and PINP levels were similar in this subgroup of women, compared to the overall cohort. There was a mean total hip BMD change of -2.3% in FLEX and -1.1% in HORIZON-PFT E1 with 24.3% of FLEX participants and 15.1% of HORIZON-PFT E1 participants with total hip BMD loss greater than least significant change. Mean PINP increased by 11.7 ng/mL in FLEX and 7.6 ng/mL in HORIZON-PFT E1, with 64.6% of FLEX and 56.2% of HORIZON-PFT E1 with changes in PINP levels that exceeded least significant change. Three-year PINP values were greater than the premenopausal median value in 40% of FLEX and 25.5% of HORIZON-PFT E1.

DISCUSSION

In the FLEX and HORIZON-PFT E1 randomized extension trials, we analyzed the arms that initially received a bisphosphonate treatment course and were then randomized to placebo.

After three years of placebo, there was a significant percentage of participants with BMD loss and PINP elevation that exceeded least significant change. These proportions were generally greater in the FLEX group than in the HORIZON-PFT E1 group, although there were only small changes in the proportion of women with femoral neck T scores ≤-2.5.

We suspect that offset of drug effect may present as BMD loss or increases in bone turnover markers. This is interesting to consider given that pharmacokinetic studies have demonstrated bisphosphonates are detectable in urine months or years after administration, with estimated half-lives of several years or more than 10 years for alendronate.[20, 21] It is unknown if there is a threshold where offset of drug effect can be detected by increased bone turnover and loss of bone mass, or if such an effect is attenuated by retained bisphosphonates in the skeleton. Offset of drug effect could be a useful factor to help individualize therapy and weigh the risks and benefits of a drug holiday, especially given that the long-term side effects such as atypical fractures are very rare.[22] It is important to note that offset of drug effect as assessed by BMD or bone turnover markers has not been associated with fracture. An analysis of the FLEX data did not find any significant associations between 1- or 2-year changes in BMD or bone turnover markers with subsequent clinical fracture, with the exception of 2-year changes of total hip BMD that were weakly associated with clinical fracture.[4] There are also concerns that BMD and bone turnover markers have shortcomings as surrogates for treatment-induced fracture reduction.[23] In sum, detecting the offset of drug effect provides valuable information that could influence clinical management, but the value of such information is theoretical while the connection to fracture risk remains unknown.

The ASBMR task force on Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment recommends considering reassessment 2-3 years after bisphosphonate

discontinuation,[1] and many clinicians are measuring BMD or bone turnover markers in this time-frame. Our results provide context for clinicians to interpret such results. It's important to note that despite small mean changes in BMD and PINP, there were considerable proportions of individuals with hip BMD loss and PINP increases that exceeded least significant change. Of note, predicting which women would have higher rates of BMD loss was not possible in a previously published analysis of the FLEX placebo arm.[24] While T scores at the beginning and end of bisphosphonate treatment courses have been examined, T scores off therapy have not been described or compared, and we demonstrated that there were small changes in the proportion of women with femoral neck T scores ≤-2.5 for both drugs. The ASBMR task force report notes that it is reasonable to consider withholding therapy as long as BMD is stable and to restart therapy if the T score is ≤-2.5. However, it is unknown whether this threshold or the trajectory of BMD change is the more important factor to consider when evaluating women on bisphosphonate drug holidays for retreatment. At a minimum, offset of drug effect may prompt a clinician to monitor more closely or optimize supportive measures such as calcium and vitamin D intake or weight-bearing exercise.

Differences in offset of drug effect may influence a clinician's treatment decision. The delay in detectable offset of drug effect for zoledronic acid may indicate that the time to retreatment can be longer relative to alendronate. This is despite the longer initial treatment course with alendronate given in the FIT trial. This likely reflects differences in pharmacodynamics and patient compliance during the initial treatment course, as oral bisphosphonate therapy has more potential for medication nonadherence than IV administration. Other studies support the prolonged effect of zoledronic acid. In a subgroup analysis of the HORIZON trials, women who received a single infusion of zoledronic acid had a 32% reduction

in clinical fracture risk over 3 years of follow-up compared to women who received placebo.[25] In a smaller randomized trial of postmenopausal women with osteopenia, anti-resorptive effects on BMD and bone turnover markers persisted 5 years after a single dose of zoledronic acid.[26] The gradual offset of zoledronic acid and higher rates of compliance may be a factor in the initial treatment decisions for osteoporosis pharmacotherapy.

A limitation of this analysis is that despite adjustments for differences between the two trials, not all factors could be accounted for and confounding factors may have persisted after adjustment. For example, we could not adjust for regional differences between the two trials, given lack of covariate overlap as FLEX was only performed in the United States. This may have resulted in bias due to regional differences in osteoporosis management or race. While a direct head-to-head trial would ideally compare offset of drug effect, it is unlikely that there will be a large randomized trial of sufficient duration to address this question. Our results may be generalizable to other community-dwelling postmenopausal women who have recently completed a course of alendronate or zoledronic acid, although the initial eligibility criteria and treatment regimen for the alendronate trials are different than current practices. We chose BMD and PINP as surrogates for offset of drug effect, which have not been validated with fracture outcomes. Another limitation of this study is that we were underpowered to examine the relationship to fracture, as there were too few participants with data on PINP and on fracture. Finally, we did not analyze changes in the resorption marker, CTX, as insufficient data were available to perform such an analysis. Given the coupling of bone turnover, increases in PINP reflect increases in bone resorption in this population. A major strength is that this is the largest longitudinal study of this length that compares the offset of bisphosphonate effect.

In summary, we found that 3 years after cessation of alendronate or zoledronic acid, there were small changes in mean BMD and PINP, although a considerable proportion of individuals had hip BMD loss or increases in PINP that exceeded least significant change. Alendronate had more rapid detectable offset of drug effect compared to zoledronic acid after drug discontinuation. The gradual offset of zoledronic acid and higher rates of compliance may be factors in the initial treatment decisions for osteoporosis pharmacotherapy.

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FIGURE LEGENDS

Fig. 1. Schema of study populations included in this analysis. A, Fracture Intervention Trial (FIT) and FIT Long-Term Extension (FLEX) randomized control trials of alendronate (ALN). B, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) and Extension I (E1) randomized control trials of zoledronic acid (ZOL). *, BMD and PINP outcomes used in post-hoc analyses.

Fig. 2. Flow diagrams of FLEX and HORIZON-PFT E1 trials.

Fig. 3. Mean unadjusted changes in BMD over 3 years in the placebo extension group. Error bars represent 95% confidence interval.

Fig. 4. Proportion of participants with unadjusted BMD loss greater than least significant change from extension baseline to year 3. Least significant change at the hip is 4% and 5% at the spine. * $p<0.01$ for the difference between alendronate and zoledronic acid.

Fig. 5. Mean unadjusted serum PINP levels in the placebo extension group. Geometric means, error bars represent 95% confidence interval. Dashed line represents median value for premenopausal women (36.0 ng/mL). Gray area represents 95% reference interval for premenopausal women (16.3 ng/mL to 78.2 ng/mL).[16]

Supplemental Figure 1. BMD and PINP changes in the FLEX subgroup that continued alendronate during the open-label extension compared to all FLEX participants in the placebo extension arm. A, Mean changes in unadjusted total hip BMD over 3 years in the placebo extension group. B, Mean serum PINP levels in the placebo extension group. Dashed line represents median value for premenopausal women (36.0 ng/mL). Gray area represents 95% reference interval for premenopausal women (16.3 ng/mL to 78.2 ng/mL).

TABLES

Table 1. Characteristics of the study participants at extension baseline

	FLEX placebo (n=437)	HORIZON-PFT E1 placebo (n=617)	P value
Age, years	73.7 ± 5.9	75.5 ± 4.9	<0.01
Body mass index, kg/m^2	25.8 ± 4.3	25.6 ± 4.5	0.46
Region			
North America/Oceania	437 (100)	112 (18.2)	<0.01
Western Europe		226 (36.6)	
Eastern Europe		137 (22.2)	
Latin America		115 (18.6)	
Asia		27 (4.4)	
Prevalent vertebral fracture	150 (34.3)	390 (63.2)	<0.01
Total hip T score	-1.8 ± 0.7	-2.0 ± 0.7	<0.01
≤ -2.5	76 (17.4)	152 (24.6)	<0.01
> -2.5 to ≤-1.5	207 (47.4)	316 (51.2)	
> -1.5	154 (35.2)	147 (23.8)	
Missing	0 (0)	2 (0.3)	
BMD, g/cm^3			
Total hip	0.72 ± 0.09	0.69 ± 0.09	<0.01
Femoral neck	0.61 ± 0.07	0.57 ± 0.06	<0.01
Lumbar spine	0.90 ± 0.14	0.82 ± 0.16	<0.01
Serum PINP, ng/mL	22.6 (16.9-31.0)	20.8 (16.2-27.5)	0.08
Years of alendronate use in core study	5.0 ± 0.7	NA	--
Current alendronate use	341 (78.0)	NA	--
Days since last zoledronic acid infusion	NA	394.2 (50.8)	--

Data are expressed as means ± standard deviations, counts (percentages) or median (interquartile range)

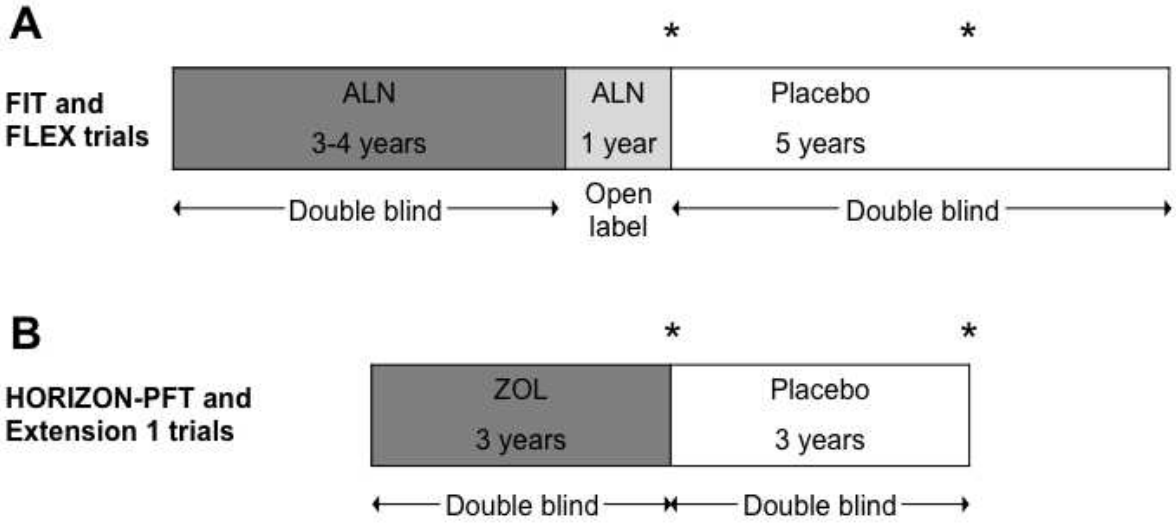


Figure 1

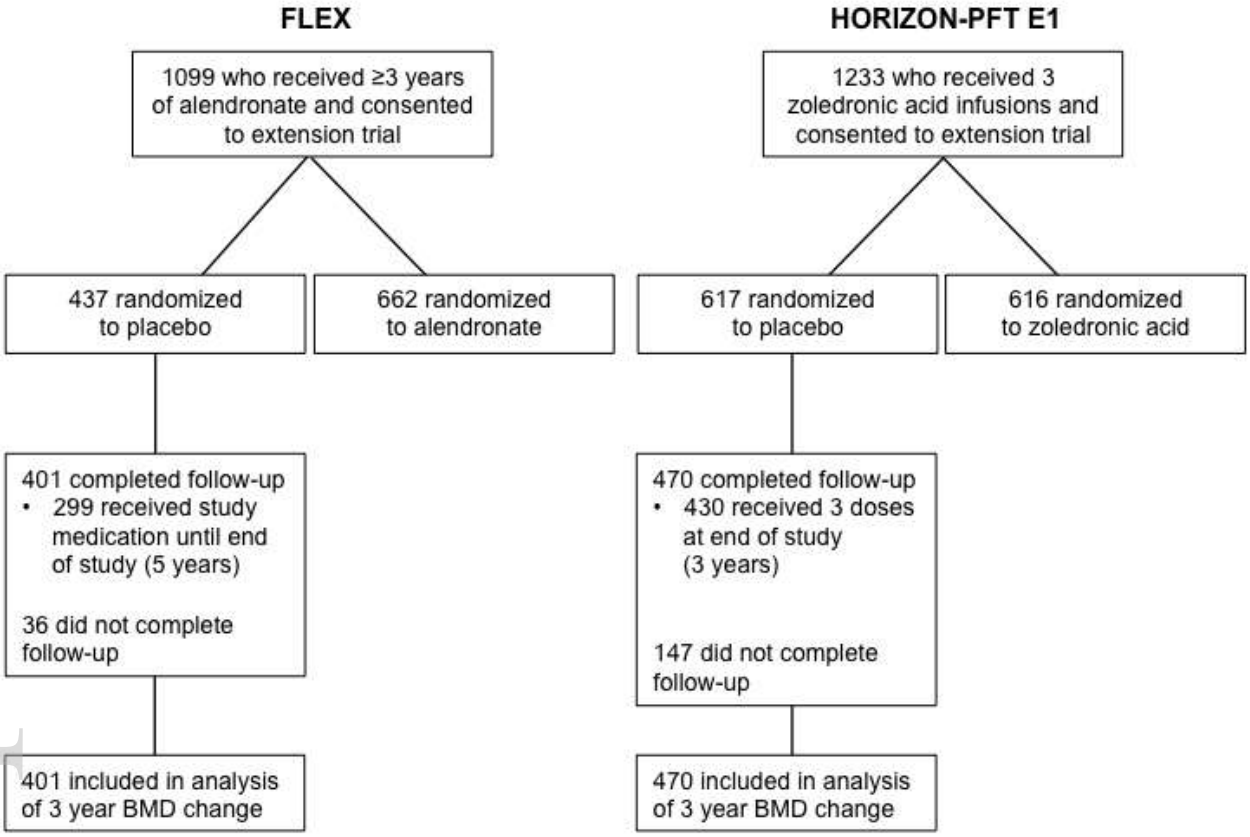


Figure 2

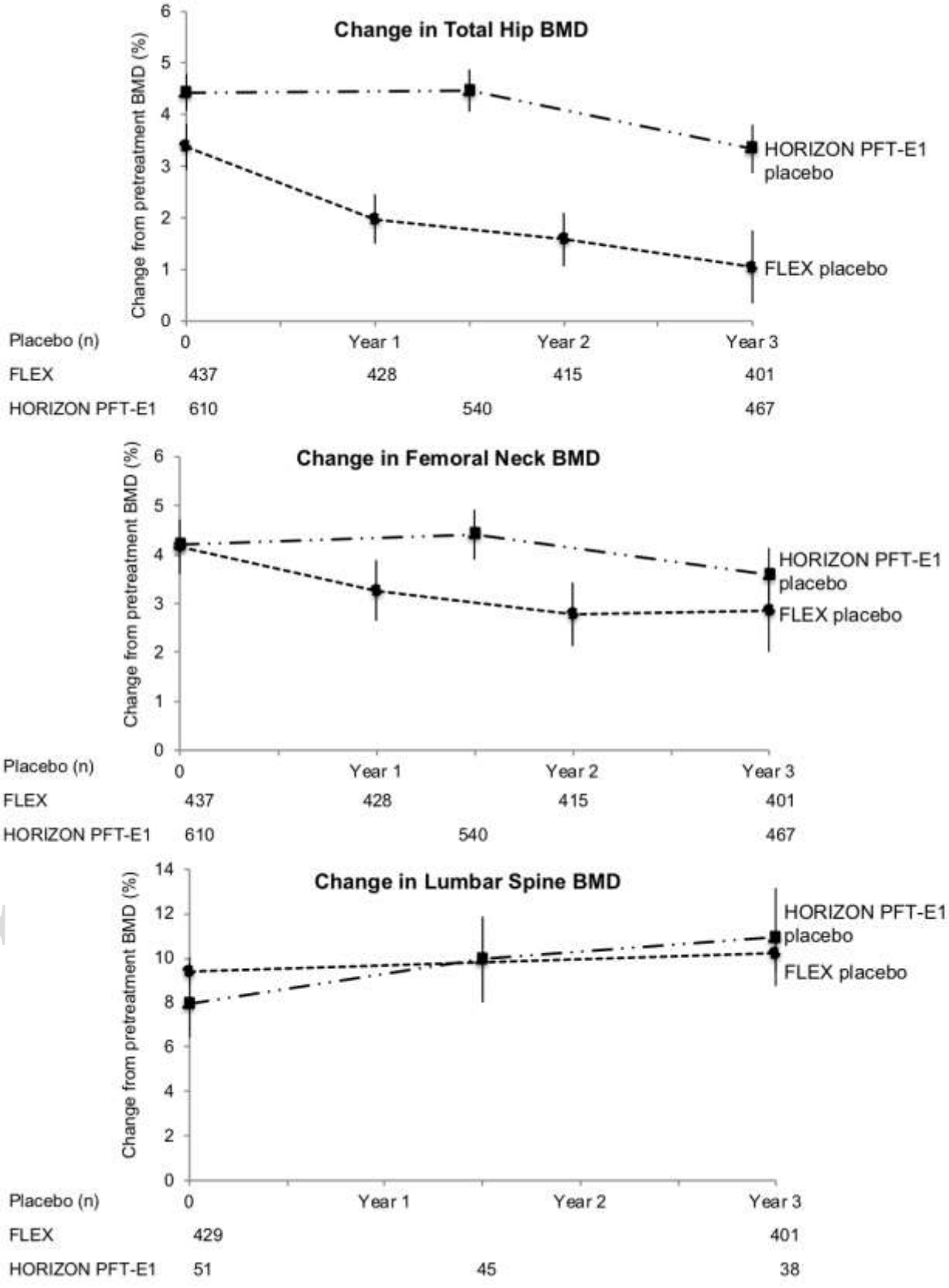


Figure 3

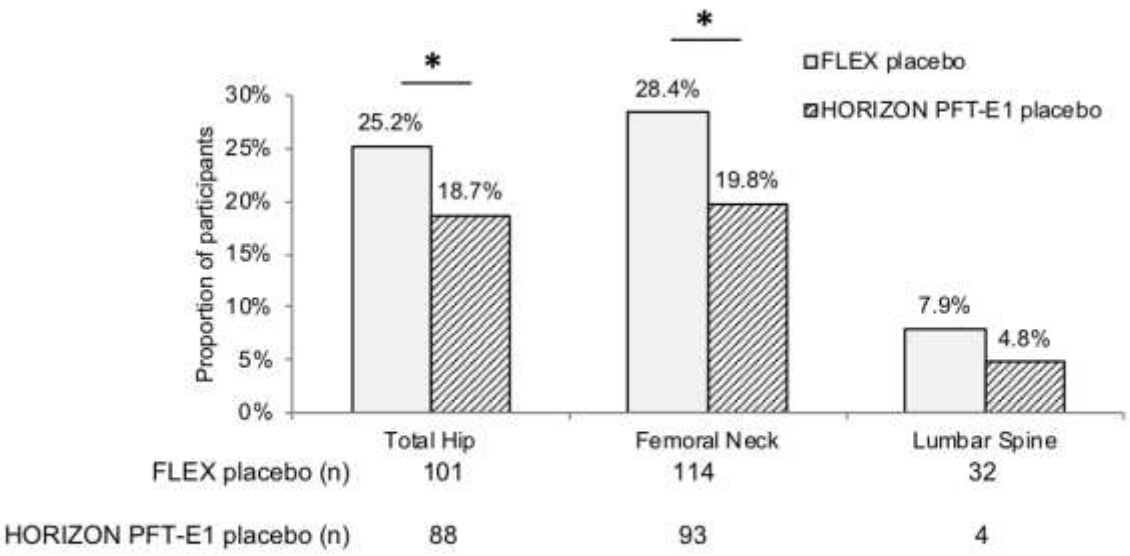
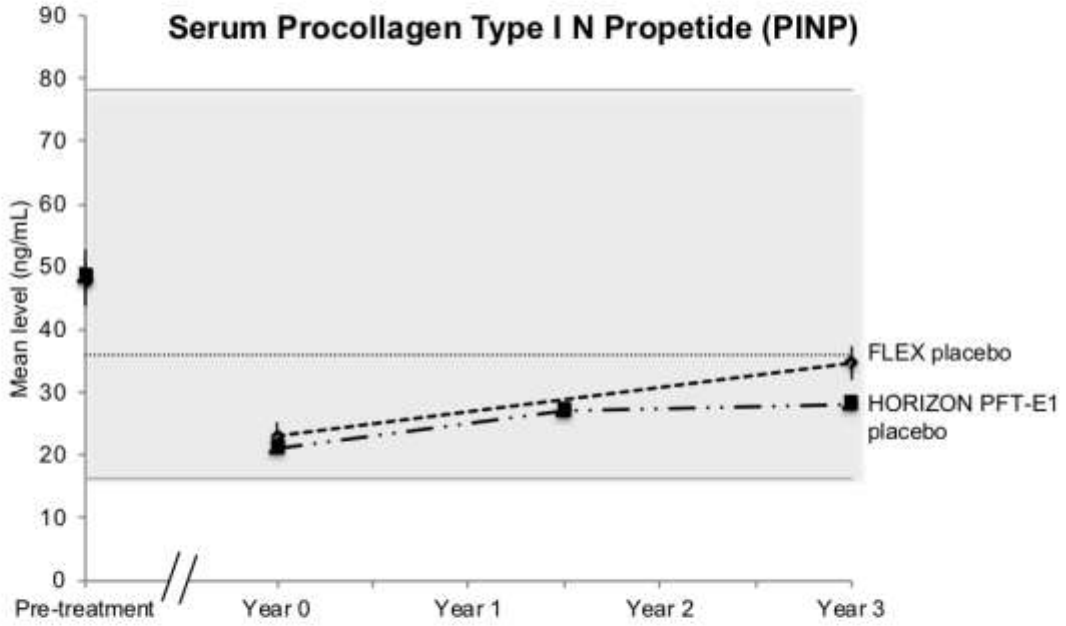


Figure 4



Placebo (n)				
FLEX	98	100		100
HORIZON PFT-E1	134	574	460	414

Figure 5