UCSF

UC San Francisco Previously Published Works

Title

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

Permalink

https://escholarship.org/uc/item/47w4v1v8

Journal

Journal of Bone and Mineral Research, 34(5)

ISSN

0884-0431

Authors

Kim, Tiffany Y
Bauer, Douglas C
McNabb, Brian L
et al.

Publication Date

2019-05-01

DOI

10.1002/jbmr.3654

Peer reviewed

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

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

[1]Department of Medicine, University of California, San Francisco, CA, USA

[2]Medical Service, San Francisco Veterans Affairs Health Care System, San Francisco, CA, USA

[3]Department of Epidemiology and Biostatistics, University of California, 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

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 to 3 years later. It is not known whether changes in bone mineral density (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

Address correspondence to: Tiffany Y Kim, MD, University of California, San Francisco and the San Francisco Veterans Affairs Health Care System, 1700 Owens Street, Room 349, San Francisco, CA 94158, USA. tiffany.kim@ucsf.edu.

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. © 2018 American Society for Bone and Mineral Research.

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 i.v. 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, whereas women not at high fracture risk after 5 years of oral or 3 years of i.v. bisphosphonate treatment could consider a drug holiday. Both fracture occurrence on initial treatment and hip bone mineral density (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 to 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 with i.v. bisphosphonates because 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 with 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. Because 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 (Fig. 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/d for 2 years and then 10 mg/d 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 to 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, MA, USA). 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, OR, USA). 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] Because 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% to 4.9% and 4.3% to 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-square, 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 because of 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 −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, TX, USA).

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 with 73.7 years, *p* < 0.01)

and had a higher prevalence of vertebral fracture (63.2% compared with 34.3%, $p < 0.01$) than FLEX participants, respectively. Although 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, $p = 0.71$; Fig. 2). A higher percentage of participants in FLEX (n 401, 91.8%) had values for the primary outcome compared with 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 (Fig. 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 with 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 with 18.7% of the HORIZON-PFT E1 placebo group ($p = 0.02$, Fig. 4). There were similar results 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 -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 -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 with pretreatment baseline values, mean PINP levels at the beginning of the placebo extension trial were relatively suppressed and in the lower range for premenopausal women (Fig. 5). Over 3 years of placebo treatment, PINP increases were higher in FLEX (+11.6 ng/mL) compared with 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 pretreatment 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 with 20.1% in HORIZON-PFT E1 ($p = 0.03$).

Sensitivity analyses

Because 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 Fig. S1A). Mean PINP changes during the placebo extension were also similar (Supplemental Fig. S1B).

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 with 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 3 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 $\leq$ −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 to 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] Although 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 $\leq$ −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 $\leq$ −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 i.v. 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 with women who received placebo.[25] In a smaller randomized trial of postmenopausal women with osteopenia, antiresorptive 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 attributable to regional differences in osteoporosis management or race. Although 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 because there were too few participants with data on PINP and on fracture. Finally, we did not analyze changes in the resorption marker, CTX, because 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 with 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Authors' roles:

Study concept: RE, DMB, and TK. Data collection: DMB, DCB, and RE. Data analysis: TK. Data interpretation: all authors. Drafting manuscript: TK. Revising manuscript content: all authors. Approving final version of manuscript: all authors. TK takes responsibility for the integrity of the data analysis.

References

1. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31(1):16–35. [PubMed: 26350171]

2. Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res. 2010;25(5): 976–82. [PubMed: 20200926]

3. Cosman F, Cauley JA, Eastell R, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? J Clin Endocrinol Metab. 2014;99(12):4546–54. [PubMed: 25215556]

4. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. JAMA Intern Med. 2014;174(7):1126–34. [PubMed: 24798675]

5. Cremers S, Papapoulos S. Pharmacology of bisphosphonates. Bone. 2011;49(1):42–9. [PubMed: 21281748]

6. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296(24):2927–38. [PubMed: 17190893]

7. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27(2):243–54. [PubMed: 22161728]

8. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone. 2006;38(5):617–27. [PubMed: 16046206]

9. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996; 348(9041):1535–41. [PubMed: 8950879]

10. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280(24):2077–82. [PubMed: 9875874]

11. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007; 356(18):1809–22. [PubMed: 17476007]

12. Diez-Perez A, Adachi JD, Agnusdei D, et al. Treatment failure in osteoporosis. Osteoporos Int. 2012;23(12):2769–74. [PubMed: 22836278]

13. Lu Y, Genant HK, Shepherd J, et al. Classification of osteoporosis based on bone mineral densities. J Bone Miner Res. 2001;16(5): 901–10. [PubMed: 11341335]

14. Boonen S, Kaufman JM, Reginster JY, Devogelaer JP. Patient assessment using standardized bone mineral density values and a national reference database: implementing uniform thresholds for the reimbursement of osteoporosis treatments in Belgium. Osteoporos Int. 2003;14(2):110–5. [PubMed: 12730782]

15. Vasikaran S, Eastell R, Bruyere O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int. 2011;22(2):391–420. [PubMed: 21184054]

16. Glover SJ, Gall M, Schoenborn-Kellenberger O, et al. Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States. J Bone Miner Res. 2009;24(3):389–97. [PubMed: 18665786]

17. Eastell R, Hannon RA, Garnero P, Campbell MJ, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate: review of statistical analysis. J Bone Miner Res. 2007;22(11):1656–60. [PubMed: 17931100]

18. Baim S, Binkley N, Bilezikian JP, et al. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD position development conference. J Clin Densitom. 2008;11(1):75–91. [PubMed: 18442754]

19. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. Am J Epidemiol. 2005;162(3):267–78. [PubMed: 15987729]

20. Khan SA, Kanis JA, Vasikaran S, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res. 1997;12(10):1700–7. [PubMed: 9333131]

21. Weiss HM, Pfaar U, Schweitzer A, Wiegand H, Skerjanec A, Schran H. Biodistribution and plasma protein binding of zoledronic acid. Drug Metab Dispos. 2008;36(10):2043–9. [PubMed: 18625688]

22. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med. 2010; 362(19):1761–71. [PubMed: 20335571]

23. Boonen S, Ferrari S, Miller PD, et al. Postmenopausal osteoporosis treatment with antiresorptives: effects of discontinuation or long-term continuation on bone turnover and fracture risk—a perspective. J Bone Miner Res. 2012:27(5):963–74. [PubMed: 22467094]

24. McNabb BL, Vittinghoff E, Schwartz AV, et al. BMD changes and predictors of increased bone loss in postmenopausal women after a 5-year course of alendronate. J Bone Miner Res. 2013:28(6):1319–27. [PubMed: 23408577]

25. Reid IR, Black DM, Eastell R, et al. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. J Clin Endocrinol Metab. 2013;98(2):557–63. [PubMed: 23293335]

26. Grey A, Bolland MJ, Horne A, et al. Five years of anti-resorptive activity after a single dose of zoledronate—results from a randomized double-blind placebo-controlled trial. Bone. 2012:50(6):1389–93. [PubMed: 22465268]
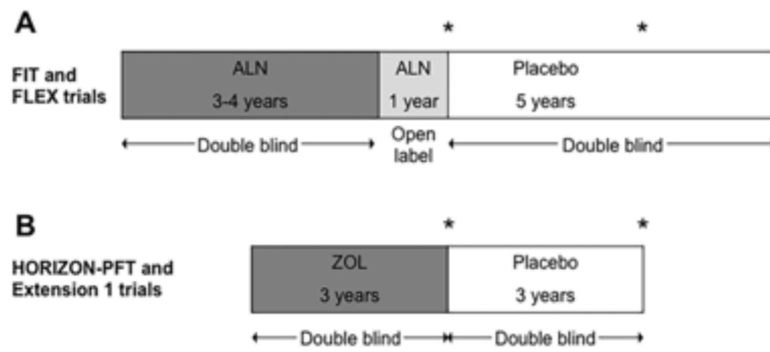
Fig. 1.
Schema of study populations included in this analysis. (*A*) Fracture Intervention Trial
(FIT) and FIT Long-Term Extension (FLEX) randomized control trials of alendronate
(ALN). (*B*) Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-
Pivotal Fracture Trial (HORIZON-PFT) and Extension I (E1) randomized control trials of
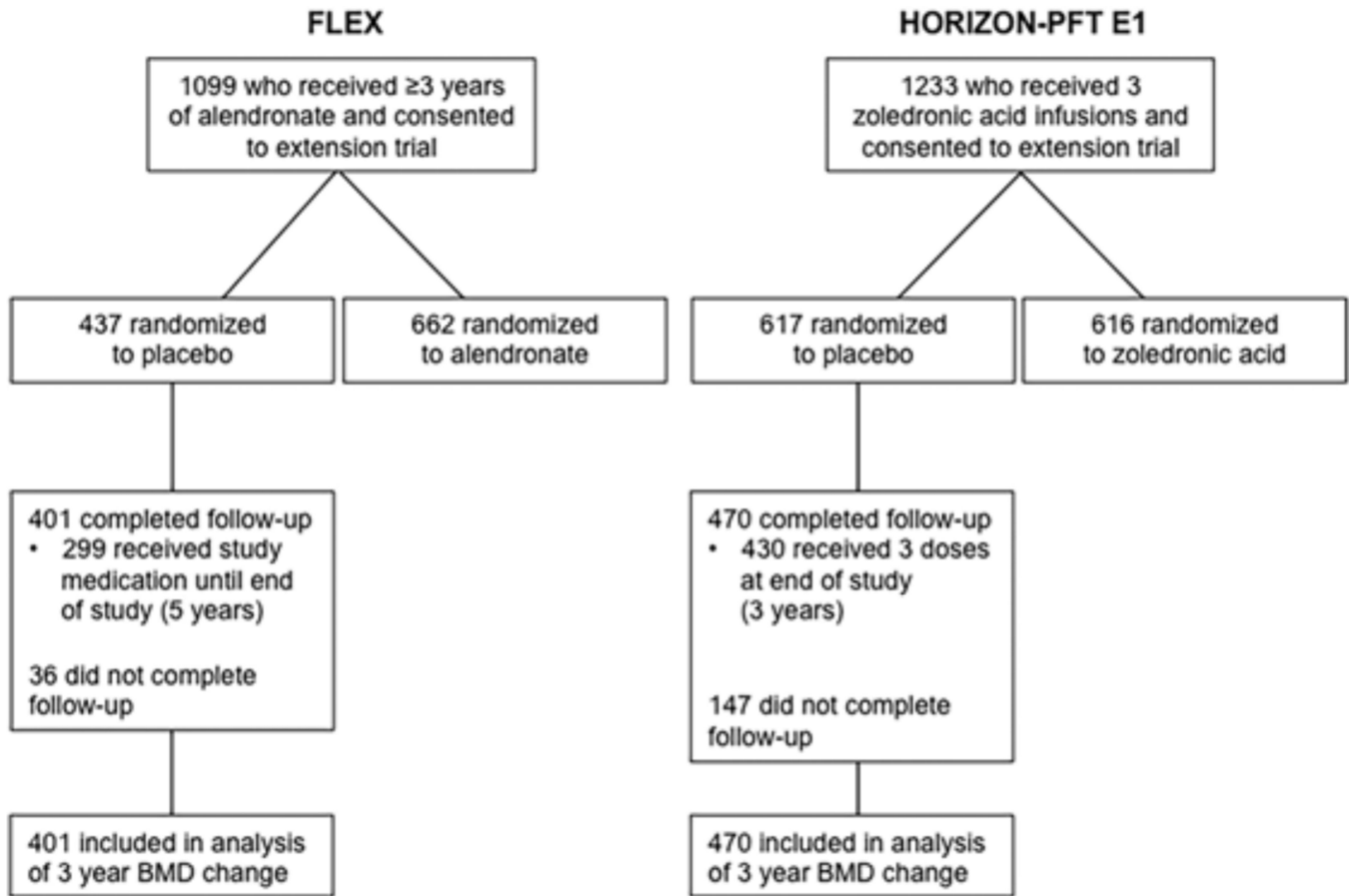zoledronic acid (ZOL). *BMD and PINP outcomes used in post hoc analyses.

FLEX

1099 who received ≥3 years of alendronate and consented to extension trial

437 randomized to placebo

662 randomized to alendronate

401 completed follow-up
- 299 received study medication until end of study (5 years)

36 did not complete follow-up

401 included in analysis of 3 year BMD change

HORIZON-PFT E1

1233 who received 3 zoledronic acid infusions and consented to extension trial

617 randomized to placebo

616 randomized to zoledronic acid

470 completed follow-up
- 430 received 3 doses at end of study (3 years)

147 did not complete follow-up

470 included in analysis of 3 year BMD change

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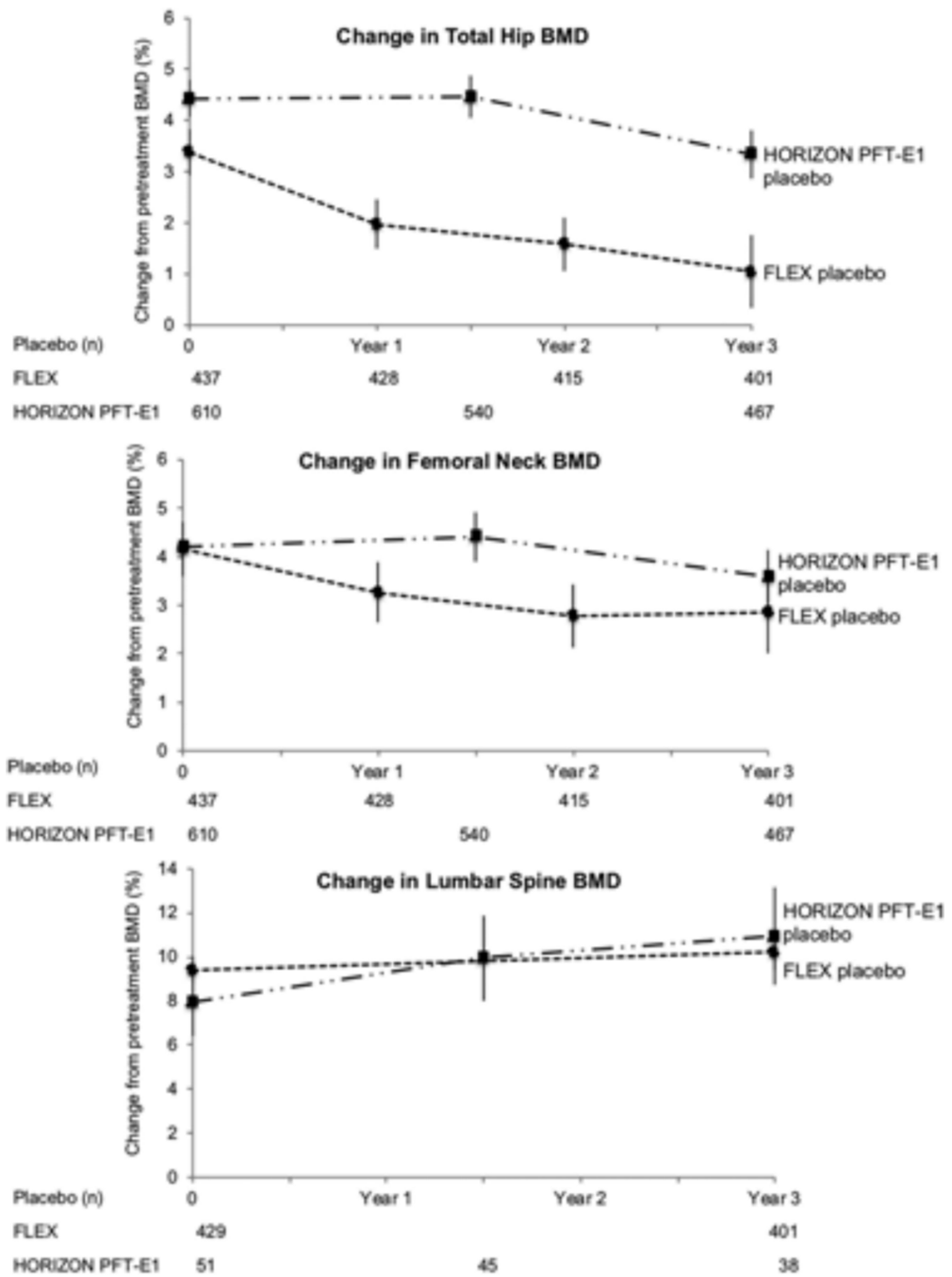Flow diagrams of FLEX and HORIZON-PFT E1 trials.

Fig. 3.
Mean unadjusted changes in BMD over 3 years in the placebo extension group. Error bars represent 95% confidence interval.
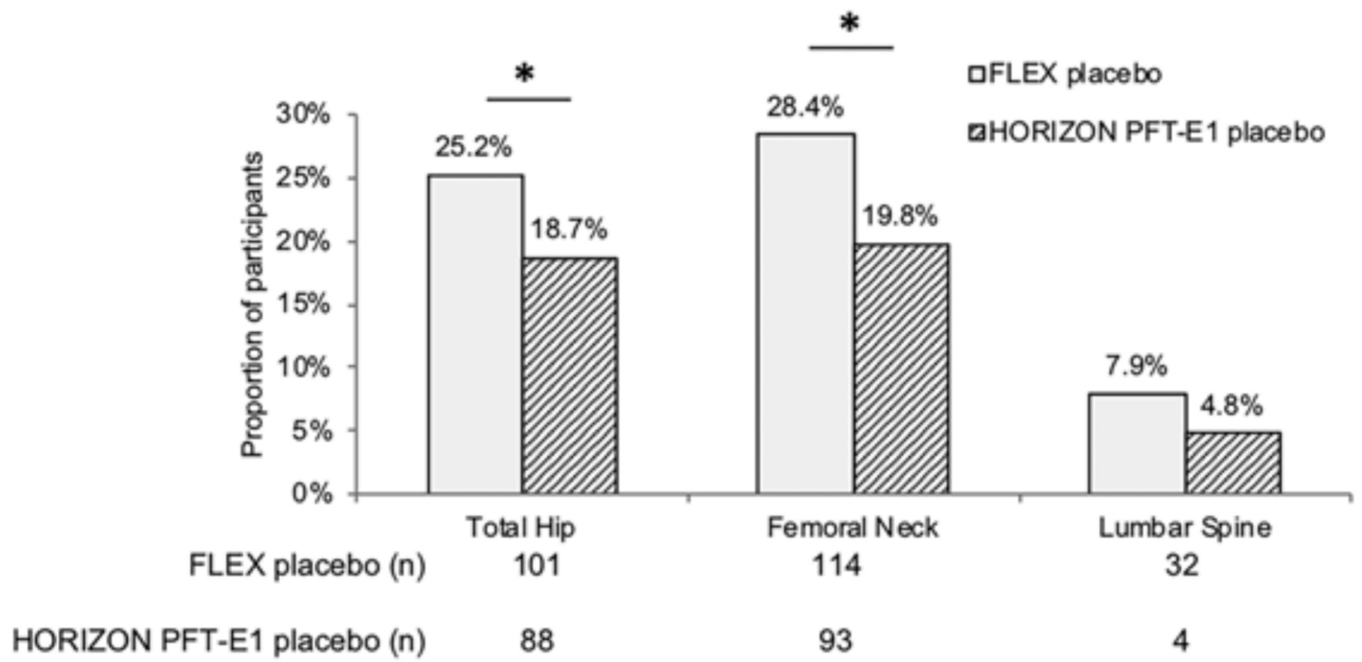
Fig. 4.
Proportion of participants with unadjusted BMD loss greater than least significant change from extension baseline to year 3. Least significant change at the hip is 4% and 5% at the spine. *$p < 0.01$ for the difference between alendronate and zoledronic acid.
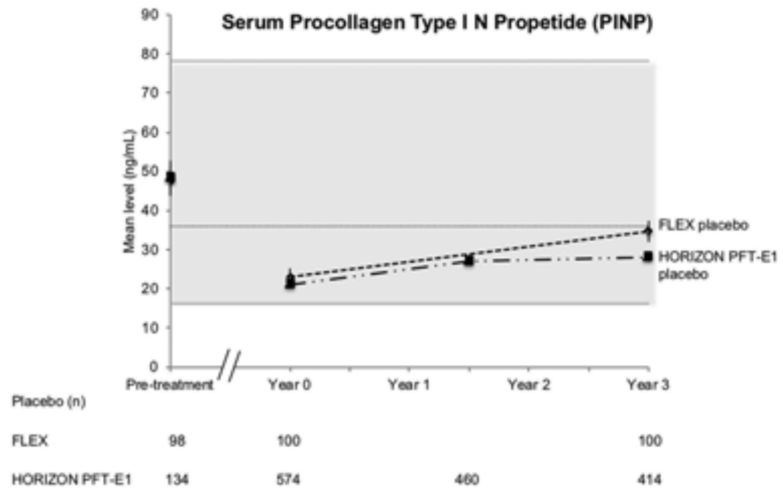
Fig. 5.
Mean unadjusted serum PINP levels in the placebo extension group. Geometric means, error bars represent 95% confidence interval. Dashed line represents median value for premenopausal women (36.0 ng/mL). Gray area represents 95% reference interval for premenopausal women (16.3 ng/mL to 78.2 ng/mL).[16]

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			<0.01
North America/Oceania	437 (100)	112 (18.2)	
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)	
Bone mineral density (g/cm^2)			
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).