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Comparison of Weekly Treatment of Postmenopausal Osteoporosis with Alendronate versus Risedronate Over Two Years

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ABSTRACT

Objective: A 1-year extension of the FOSAMAX® ACTONEL® Comparison Trial (FACT) was completed to compare changes in bone mineral density (BMD), bone turnover, and upper gastrointestinal tolerability over 2 years of treatment.

Design: Randomized, double-blind extension conducted at 72 US sites.

Patients and Methods: Of the 1053 women who completed Year 1, 833 postmenopausal women with low BMD entered the extension, continuing their same treatment allocation (once-weekly (OW) alendronate 70 mg or OW risedronate 35 mg). Changes in BMD at the hip trochanter, total hip, femoral neck, and lumbar spine and in markers of bone turnover were compared at 24 months. Tolerability was assessed by adverse experience reporting.

Results: Alendronate produced greater increases from baseline in BMD at 24 months than did risedronate at the trochanter (ALN, 4.6%; RIS, 2.5%, $p<0.001$), as well as at all other BMD sites. Significantly more alendronate than risedronate patients had measured BMD increases of ≥0% and ≥3% at all BMD sites ($p<0.001$), and fewer alendronate patients had measured decreases of ≥3% at all BMD sites. Significantly greater reductions in all biochemical markers of bone turnover occurred with alendronate compared with risedronate. No differences were seen in occurrence or discontinuations due to upper gastrointestinal adverse experiences.

Conclusions: Patients receiving OW alendronate 70 mg had greater gains in BMD, were more likely to maintain or gain BMD, and had greater reductions in bone turnover markers than patients receiving OW risedronate 35 mg after 24 months, with no differences in upper gastrointestinal tolerability.

NCT00092014: http://www.clinicaltrials.gov/ct/show/NCT00092014?order=25

INTRODUCTION

Nitrogen-containing bisphosphonates are the most commonly prescribed drugs for the prevention and treatment of postmenopausal osteoporosis. Alendronate and risedronate have been shown to reduce the risk of both spine and non-spine fractures in postmenopausal women with osteoporosis (1-5). The FOSAMAX® ACTONEL® Comparison Trial (FACT) was a 1-year, double-blind, active comparator trial of 1053 postmenopausal women with osteoporosis (6). FACT compared the changes from baseline to 1 year in the surrogate endpoints of bone mineral density (BMD) and biochemical markers of bone turnover using the FDA-approved doses of once-weekly (OW) alendronate and risedronate (alendronate 70 mg OW and risedronate 35 mg OW) for the treatment of osteoporosis. The trial also compared, in a head-to-head fashion, overall and upper gastrointestinal (UGI) tolerability of these two agents. Both agents produced significant increases in BMD from baseline at 6 and 12 months at the hip trochanter, postero-anterior (PA) lumbar spine, total hip, and femoral neck, but the increases were significantly greater with alendronate than with risedronate at all skeletal sites at all time points. Both agents also produced statistically significant reductions in markers of bone turnover from baseline at 3, 6, and 12 months; again, the reduction of bone turnover was greater at all time points with alendronate compared with risedronate. Overall and UGI tolerability were similar for the two agents.

A 1-year extension of FACT was completed to determine if the differences in BMD and bone turnover persisted over 2 years and if tolerability remained similar. This report provides the results from this extension of the original study, encompassing 2 years of treatment.

METHODS

Patient Enrollment

Participants in FACT were community-dwelling, ambulatory, postmenopausal (at least 6 months) women ≥ 40 years of age (≥ 25 years if surgically menopausal) with a BMD ≥ 2.0 standard deviations below young normal mean bone density in at least one of four sites [total hip, hip trochanter, femoral neck, or PA lumbar spine (L1 to L4)]. Women were required to be in good general health, with hip and spinal anatomy suitable for dual-energy x-ray absorptiometry (DXA). In accordance with alendronate prescribing information, individuals with a history of abnormalities of the esophagus that delay esophageal emptying, such as stricture or achalasia, were excluded, as were those unable to remain upright for 30 minutes after dosing. The specific exclusion criteria have been published previously (6). Women with hypocalcemia, hypovitaminosis D [serum 25(OH)D < 10 ng/ml], or metabolic bone diseases other than postmenopausal osteoporosis were excluded.

Study Design

The extension (Protocol 211-10) was a double-blind, active-controlled, multicenter study during which all eligible women maintained their original randomized, blinded treatment allocation (oral alendronate 70 mg OW or oral risedronate 35 mg OW) from Year 1 for an additional 12 months. Seventy-two of the original 78 sites within the United States chose to participate in the extension

study. The study was conducted in accordance with consideration for the protection of patients, as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All participants gave written, informed consent before entering the study extension.

Women were eligible to enter the extension study if they completed the original 12-month study, described by Rosen et al. (6). They were to begin treatment within 7 days after their final Year 1 study visit and to take their dose on the same day each week. In addition to study medication, all patients were instructed to consume 1000 mg of elemental calcium and 400 international units (IU) of vitamin D daily, from either their preexisting diet or a supplement provided by the sponsor (Os-cal 500+D®, SmithKline Beecham, Pittsburgh, PA) with their noon or evening meals. Women recorded medication use during the 24 months of treatment.

Assessment of Outcomes

Bone mineral density was measured by DXA using Hologic or Lunar densitometers on the same machine during baseline and all follow-up visits to the investigational site through Month 24. Instrument quality control and all BMD analyses were performed by a central analysis facility (Bio-Imaging Technologies, Inc., Newtown, PA) blinded to treatment allocation. No significant machine drifts or shifts occurred during the 2-year study based on phantom BMD measurements on each dual-energy X-ray absorptiometer.

Two markers each of bone resorption and bone formation were used to evaluate changes in bone turnover. Bone resorption was measured by urinary N-telopeptide of type I human collagen (NTX) corrected for creatinine (Ortho Vitros, Ortho Clinical Diagnostics, Amersham, United Kingdom) and serum C-telopeptide (CTX; Roche Elecsys, measured on the Elecsys 2010 automated analyzer, Manheim, Germany). Bone formation was measured by bone-specific alkaline phosphatase (BSAP; Access OSTASE Assay, Beckman-Coulter, Fullerton, CA) and serum N-terminal propeptide of type 1 procollagen (P1NP; INTACT P1NP, Orion Diagnostic, P1NP RIA, Espoo, Finland). Samples for serum biochemical markers and a fasting second morning-void for urinary N-telopeptide were obtained at 24 months. Stored samples were analyzed in batches by time point at the end of the study. The intra-assay and inter-assay coefficient of variation ranged from 1.9 – 2.4% for BSAP, 3.4 – 9.6% for P1NP, 1.6 – 5.0% for NTX, and <8% for CTX.

Efficacy and Safety Evaluations

The primary efficacy endpoint was the comparison of the mean percentage change from baseline in trochanteric BMD at 24 months between the two treatment groups. As noted in the report of the Year 1 results, this site was chosen as the primary endpoint because of both the precision at measuring BMD at this site and the rapid and large gains in BMD seen at this site in response to bisphosphonate therapy (6). Secondary BMD endpoints included a comparison of the mean percentage change from baseline in total hip, femoral neck, and

lumbar spine BMD at 24 months between the two treatment groups and the proportion of patients with pre-defined increases of trochanteric and lumbar spine BMD ≥ 0% and ≥ 3% from baseline at 24 months. Additional secondary endpoints were a comparison of the mean percentage change from baseline in biochemical markers of bone turnover (NTX, CTX, BSAP, and P1NP) at 24 months between the two treatment groups. Other prespecified analyses included determination of the proportion of women with BMD increases ≥ 0, 1, 2, 3, 4, and 5% from baseline at each BMD site at 24 months and an analysis of the proportion of women with BMD losses ≥ 3% at each BMD site.

Safety was monitored by investigators, who recorded clinical and laboratory adverse experiences (AEs) during study visits. Patients could report AEs in person or by phone at any time during the study.

Statistical Methods

The hypothesis of the extension study stated that, in postmenopausal women with osteoporosis, treatment with oral alendronate 70 mg OW will produce a mean percent increase from baseline in hip trochanter BMD at 24 months that is greater than that observed with oral risedronate 35 mg OW. All statistical analyses were conducted by Merck & Co., Inc. Treatment effect at 6, 12, and 24 months on BMD for all women entering the extension study was assessed by an analysis of variance (ANOVA) on percentage change from baseline using a linear model that included terms for treatment and study center. Treatment differences were estimated by differences in least squares means (LS

means) from the ANOVA model, and the 95% confidence intervals (CIs) were calculated. All patients who were enrolled in the 12-month extension who had a baseline BMD, a BMD measurement in the extension, and took at least one dose of study drug in the extension were included in the modified intention-to-treat (mITT) analysis. Patients were analyzed according to the group to which they were randomized. Missing values were imputed by carrying the last post-baseline value forward to the 24-month time point.

The log-transformed fraction of baseline value (calculated by dividing the on-treatment value by the baseline value and then applying the natural log) was applied to normalize the distribution of changes in biochemical markers before comparisons of alendronate and risedronate were assessed using the same model as in the BMD analyses. The Delta method was used to estimate a 95% CI of the treatment difference in percentage change from baseline from the above ANOVA model. For the biochemical marker data at 24 months, the primary analysis was based on a per-protocol (PP) approach, with no data being carried forward. All patients or time points with important protocol violations were excluded from the PP analyses. The same cohort of patients included in the 24-month analyses were used for analyses at 3, 6, and 12 months if they were not protocol violators at the specific time point.

Because the primary analysis of treatment effect on BMD was performed only on data from the women who continued into the extension at the completion of Year 1 (extension cohort, N=833), which is a subset of all randomized patients,

a post-hoc supportive analysis was performed for all randomized patients (original cohort, N=1053) during the entire 2-year treatment period. If patients discontinued during the first 12 months or completed the first 12 months but did not enter the extension, the last on-treatment measurements were carried forward to 24 months. Treatment effect in the original cohort was analyzed in the same manner as described above for the extension cohort.

The safety analysis included all patients who received at least one dose of study medication in the extension in either treatment group. Differences in proportions of patients with any AEs, serious AEs, and discontinuations due to AEs were analyzed using Fisher's Exact test. The treatment groups were also compared for the proportion of patients with UGI AEs using Fisher's Exact test.

RESULTS

Patient Disposition

Of the 892 eligible women who completed the baseline study, 833 (79.1%) enrolled in the 1-year extension (**Figure 1**). The completion rates for the extension were similar in the two treatment groups (alendronate 92.3%; risedronate 91.6%).

A similar proportion of alendronate-treated and risedronate-treated women were included in the mITT and biomarker PP analyses (90.6% vs 89.5% and 81.4% vs 79.5%, respectively). All 825 women who received at least one dose of study medication in the extension were included in the safety analysis.

Demographics and Baseline Characteristics

There were no meaningful differences in baseline characteristics between the alendronate and risedronate treatment groups in the extension (**Table 1**). The demographics of the extension cohort were similar to those of the 1053 women in the Year 1 study cohort and to the 220 women who were not eligible or chose not to enroll in the extension.

Primary and Secondary Endpoints

Increases from baseline in BMD at Month 24 were significantly ($p < 0.001$) greater in alendronate patients than in risedronate patients at all sites measured: the trochanter, total hip, femoral neck, and lumbar spine (**Figure 2**). At Month 24,

the treatment differences were 2.1% (95% CI: 1.4% to 2.8%) at the trochanter, 1.7% (95% CI: 1.3% to 2.2%) at the total hip, 1.9% (95% CI: 1.2% to 2.5%) at the femoral neck, and 1.8% (95% CI: 1.2% to 2.5%) at the lumbar spine. The differences increased with time at all sites (**Figure 2**). The increases in BMD from baseline at all time points were significant for both treatment groups.

Significantly more women treated with alendronate maintained or gained BMD at each of the four sites than those treated with risedronate (**Figure 3, Table 2**). Regardless of the level used to categorize gains in BMD, the differences in the proportions between the two treatment groups achieving the respective levels consistently favored alendronate. Alendronate-treated patients were 1.4 to 1.7 times more likely than risedronate-treated patients to show a gain of 3% or more in BMD. In general, the higher the cutpoint, the greater the relative BMD response favoring alendronate (e.g., for trochanter, 86%/75% = 1.15 for ≥0%, 67%/45% = 1.49 for ≥3%, 49%/30% = 1.63 for ≥5%).

Fewer alendronate-treated patients showed a measured decrease in BMD than those treated with risedronate. This was true regardless of the level used to categorize the decrease or the site of BMD measurement. For example, risedronate-treated patients were two-to-four times more likely than alendronate-treated patients to show a decrease of 3% or more depending on the skeletal site (**Figure 3, Table 2**).

Biochemical Markers of Bone Turnover

Both treatments significantly reduced bone resorption, as measured by percent reduction from baseline in urine NTX (**Figure 4**) and serum CTX. After 24 months of therapy, alendronate reduced NTX and CTX by 56.6% and 73.4%, respectively, whereas the corresponding reductions for risedronate were 43.9% and 53.1%. The differences between the two treatment groups were significant by as early as 3 months and were maintained at 24 months ($p < 0.001$).

Both treatments also reduced serum levels of the bone formation markers BSAP (**Figure 4**) and P1NP (–62% alendronate, –46% risedronate, $p<0.001$) after 24 months. The differences between the two treatment groups favoring alendronate were significant at 24 months ($p < 0.001$) and at all earlier time points.

Comparison of Original and Extension Cohorts

The 12-month treatment differences for the extension cohort (n= 833) differed slightly from those reported at the end of Year 1 for the original cohort (n= 1053). At the end of Year 1 in the extension cohort, the treatment differences were 1.6% (95% CI: 1.0% to 2.2%) at the trochanter, 1.3% (95% CI: 0.8% to 1.8%) at the lumbar spine, 1.2% (95% CI: 0.8% to 1.7%) at the total hip, and 0.8% (95% CI: 0.3% to 1.4%) at the femoral neck. In comparison, the treatment differences reported at the end of Year 1 in the original cohort were 1.4%, 1.2%, 1.0%, and 0.7%, respectively (6). These differences were all within the respective

95% CIs for the extension cohort. An analysis of the original cohort was also performed, carrying all data forward to 24 months. The treatment differences at 24 months were also within the 95% CIs for the treatment differences of the extension cohort at 24 months (data not shown).

Safety

There were no significant differences between treatment groups in the overall rate of clinical AEs at 24 months: 87.1% alendronate-treated and 86.5% risedronate-treated women reported one or more clinical AEs. There were no significant differences between the treatment groups in the incidence of serious AEs (12.4% alendronate, 13.5% risedronate) or discontinuations due to AEs (2.2% in each group). Similarly, over 24 months, there were no significant differences in UGI AEs between the two treatment groups (24.8% alendronate, 22.9% risedronate) or in the proportion of women discontinuing due to an UGI AE (1.7% alendronate, 1.2% risedronate; **Table 3**). The most common UGI AEs reported overall were dyspepsia (7.0%), nausea (6.7%), and reflux disease (4.0%). The differences between the treatment groups were not significant. There was a single death due to a serious UGI AE (hemorrhagic duodenal ulcer) that occurred in the risedronate treatment group during the extension study.

Clinical fractures that occurred during the trial, regardless of association with trauma or skeletal site, were reported by investigators as clinical AEs. There was no requirement for radiographic confirmation or adjudication because fractures were not an efficacy endpoint. Over the 24-month treatment period, 37

fractures were reported in 34 alendronate-treated patients (19 in months 0-12 and 18 in months 12-24), and 42 fractures were reported in 34 risedronate-treated patients (14 in months 0-12 and 28 in months 12-24). There was no significant difference in the proportion of patients reporting fractures as AEs between treatment groups (8.3% alendronate versus 8.2% risedronate). When those women who either were not eligible for or who chose not to enroll in the extension were also considered with the 2-year extension cohort, there were a total of 45 known fractures in the alendronate-treated women and 47 known fractures in the risedronate-treated women during the 2 years of the study. Women who discontinued from the study were not monitored for further fracture events.

DISCUSSION

In this 1-year, double-blind extension of the 12-month FOSAMAX® ACTONEL® Comparison Trial, greater gains in BMD at all sites measured and greater reductions in all markers of bone turnover were seen with alendronate 70 mg OW compared to risedronate 35 mg OW. The upper gastrointestinal tolerability of the two OW bisphosphonates was similar over 24 months. The analysis presented here extends and confirms the findings reported by Rosen et al. (6). The BMD treatment differences appeared to diverge over time, whereas differences in bone turnover were consistent over time, with no evidence of a further reduction in bone turnover markers.

There has been much debate about the clinical utility of changes in BMD and biochemical markers observed during clinical trials (7-10). Multiple analyses using individual patient data from clinical trials have shown that gains in BMD and reductions in bone turnover markers are associated with decreases in both vertebral and nonvertebral fractures (11-14). It is well known, however, that changes in BMD during anti-resorptive therapy do not account for all of the observed reduction in fracture risk, with the proportion varying depending on the analysis design and the statistical methodology used (9, 15, 16). Similarly, changes in bone turnover markers in response to antiresorptive therapy have been shown to predict fracture reduction (7, 11, 12). Although the complete nature of this relationship is unknown, there is no evidence for a threshold effect for non-vertebral fractures for either agent (11, 12). Because head-to-head trials

of anti-osteoporosis drugs from the same class are not likely to include fracture endpoints, for reasons previously discussed, (6, 17) surrogate or intermediate endpoints are the best tools currently available to compare the relative effects of two agents with similar mechanisms of action (18).

Bone mineral density nonresponse to therapy is of potential concern to clinicians and patients alike (19). The analysis presented here focuses on comparing BMD response to therapy between the two bisphosphonates. Not only were there greater increases seen in BMD overall with alendronate, but there were also greater responses at all the pre-specified levels of BMD at each site of interest. Importantly, there was a significant difference between the two agents in preventing a decrease in BMD, regardless of the BMD site measured. Women treated with risedronate were 1.2 to 1.3 times more likely to show a measured decrease in BMD than those treated with alendronate. This ratio became more pronounced when the proportion of women losing 3% or more were compared between the two treatment groups.

An analysis by Watts et al. (20) using data from the two Vertebral Efficacy with Risedronate Therapy (VERT) trials (3,4) and the Hip Intervention Program (HIP) (5) showed that, among patients treated with 2.5 mg or 5 mg of risedronate daily, those who had measured increases in BMD at the spine were less likely to suffer vertebral fracture than patients who had a measured loss of BMD. Similar findings have been reported from studies with alendronate (21). Both Hochberg et al. (21) and Bauer et al. (12) have shown that greater increases in BMD at the

lumbar spine or hip among alendronate-treated patients resulted in a lower risk of vertebral fractures. These studies demonstrate that there is clinical benefit in terms of fracture risk reduction in having patients experience measured increases in BMD, rather than measured decreases. In another analysis, Chapurlat et al. (22) suggested that women losing up to 4% of BMD at the lumbar spine or total hip during treatment with alendronate still had a significantly decreased risk of vertebral fracture compared to women in the placebo group who had a similar decrease in BMD. The authors noted that this magnitude of change was likely to be less than the least significant change needed to conclude that the BMD had actually changed (22). Declines in BMD greater than 4% in the alendronate-treated women in this study were not associated with significant reductions in spine fracture risk vs. the placebo-treated women with similar declines. This suggests that stability of the bone mass on anti-resorptive therapy results in spine fracture risk reduction compared to similar stability in BMD in placebo-treated women. Consequently, the findings from Chapurlat et al. (22) do not negate the greater benefit of gaining bone density on therapy compared to losing it. Thus, reducing BMD loss should be seen as advantageous to patients.

In the present study, the effectiveness of alendronate and risedronate on maintaining or increasing BMD and decreasing bone turnover marker levels were compared. Previous placebo-controlled studies have shown that these two agents are effective in reducing the risk of vertebral and non-vertebral fractures (1, 3). As has been previously reported, the sample size required to make meaningful comparisons in fracture risk reduction is not consistent with the size

of this study (6). The results presented here do not address the question of whether the differences observed here in BMD and bone turnover markers translate into more effective protection from fracture with alendronate. Although claims have been made from non-fracture studies regarding fracture risk reductions, most, if not all, of these studies compared an active agent versus a placebo (23, 24). Whether the differences in anti-resorptive efficacy observed in the current trial are due to differences in dose or reflect true differences in the in vivo potency of the two agents also cannot be answered from this study. Although other noninvasive techniques may become available to identify and quantify factors other than BMD and bone turnover that contribute to fracture risk, at present, changes in BMD and bone turnover are used to explain, in part, the decreased fracture risk achieved with anti-resorptive agents (14, 16).

In clinical trials, neither OW alendronate nor OW risedronate has been documented to induce more UGI side effects than seen in placebo groups. This is the first study to assess the UGI tolerability of the two once-weekly bisphosphonates in a direct comparator fashion over 24 months using doses approved for the treatment of postmenopausal osteoporosis. The UGI intolerance was low and similar in both treatment groups.

CONCLUSION

In this cohort of postmenopausal women with osteoporosis followed for 2 years in the 1-year FACT and 1-year extension, alendronate 70 mg once weekly produced significantly greater gains in BMD at all skeletal sites and significantly

greater reduction of all bone turnover markers compared to risedronate 35 mg once weekly, with equal tolerability. Alendronate was more effective than risedronate in reducing the risk of bone loss. These findings may be useful to clinicians in making prescribing and management decisions for their patients.

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Table 1. Patient Demographics and Baseline BMD Measurements

Baseline Characteristics	Two-Year Cohort N = 833	One-Year Cohort N = 1053	Year 1 Pts Who Did Not Enter Extension N = 220
Age [years, mean (SD)]	64.4 (9.5)	64.5 (9.8)	64.7 (10.7)
Years Since Menopause [mean (SD)]	18.1 (11.6)	18.5 (11.9)	20.1 (12.8)
Race (% Caucasian)	95.3	95.3	95.0
T-score [mean (SD)]			
Hip Trochanter	-1.6 (0.7)	-1.6 (0.8)	-1.7 (0.8)
Femoral Neck	-2.1 (0.6)	-2.1 (0.7)	-2.2 (0.7)
Total Hip	-1.8 (0.7)	-1.8 (0.7)	-1.8 (0.7)
PA Lumbar Spine	-2.3 (0.9)	-2.2 (0.9)	-2.2 (1.0)

Table 2. Secondary Endpoints

	Alendronate **%**	**Risedronate** **%**
BMD Gains/Losses	N=375	N=375
Total Hip		
≤–3%	2	8
<0%	14	33
≥0%	86	67
≥3%	49	28
≥5%	25	12
Femoral Neck		
≤–3%	6	17
<0%	24	41
≥0%	76	59
≥3%	48	29
≥5%	26	16
P<0.001 for all comparisons except total hip ≤–3%, P=0.002		

Table 3. Upper Gastrointestinal Adverse Events

	Alendronate 70 mg OW (N=411) n (%)	**Risedronate 35 mg OW (N=414) n (%)**
With One or More UGI AE	102 (24.8)	95 (22.9)
Discontinued due to UGI AE	7 (1.7)	5 (1.2)
Discontinued due to serious UGI AE	1* (0.2)	2** (0.5)
UGI: upper gastrointestinal ***duodenal ulcer; **GERD, hemorrhagic duodenal ulcer**		

Figure Legends

Figure 1. Patient Accounting.

Figure 2. Mean Percentage Changes in Bone Mineral Density (BMD) from Baseline. Mean percent change from baseline to month 24 ± standard error (modified intention-to-treat approach) a. Hip trochanter BMD; b. Total hip BMD; c. Femoral neck BMD; d. Lumbar spine BMD.

Figure 3. Proportion of Patients with Losses and Gains in BMD at 24 Months. Percent of patients with ≤3%, <0%, ≥0%, ≥3%, or ≥5% gains in BMD from baseline to 24 months a. Hip trochanter; b. Lumbar spine. $P<0.05$ for all between-group comparisons.

Figure 4. Changes in Biochemical Markers Expressed as Mean Percentage Change from Baseline ± SE at 6, 12, and 24 Months (Per-Protocol Approach). a. Urine N-telopeptide of type 1 human collagen (NTX) corrected for creatinine; b. Serum bone-specific alkaline phosphatase (BSAP). $P<0.001$ for all time points.

Figure 1

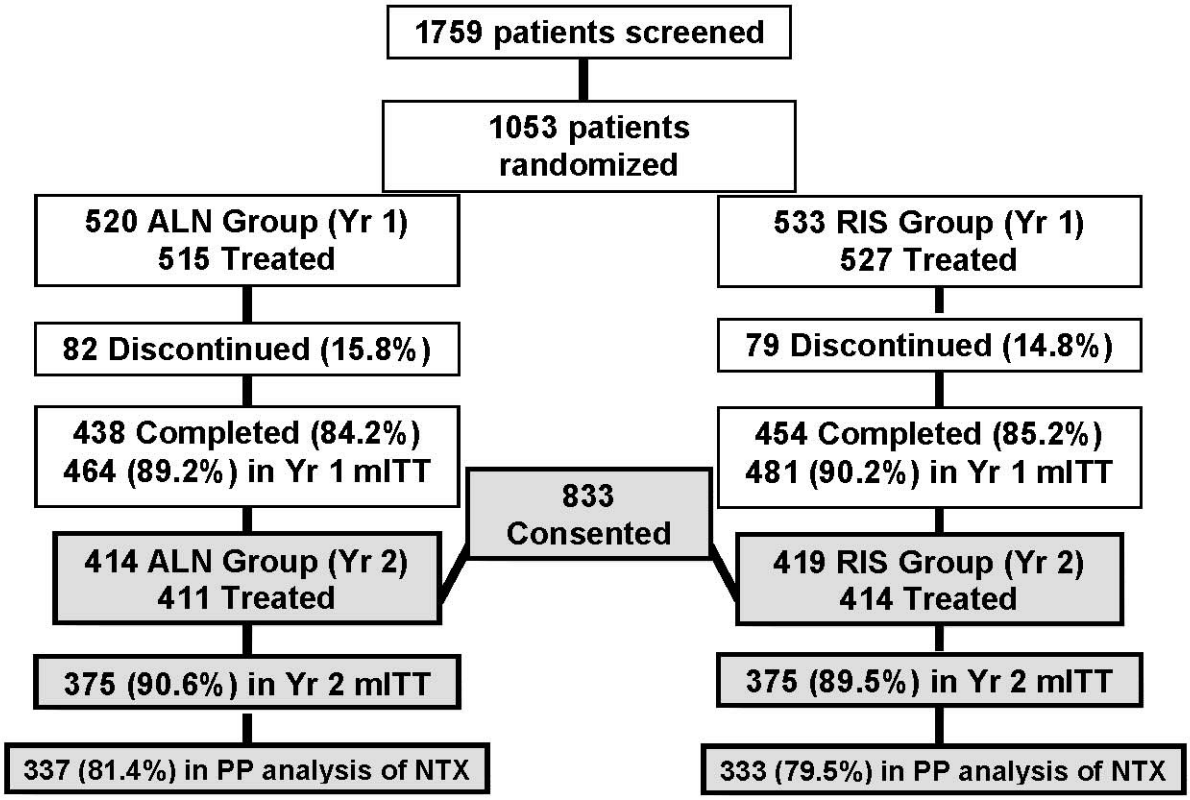
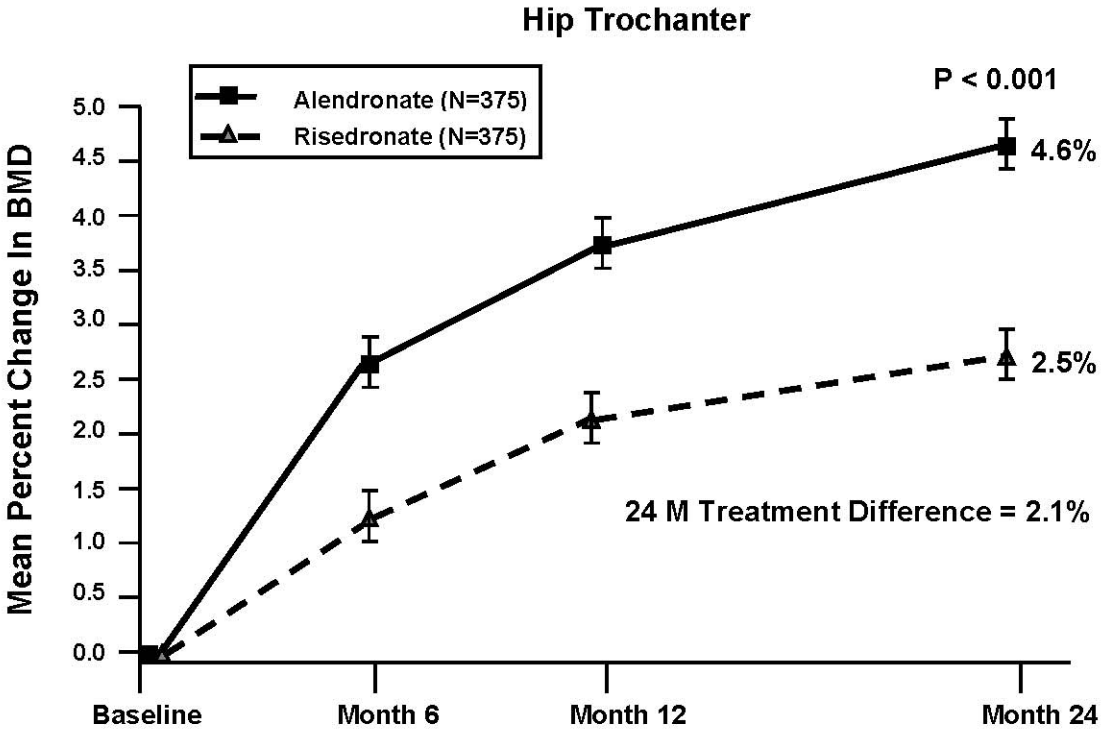
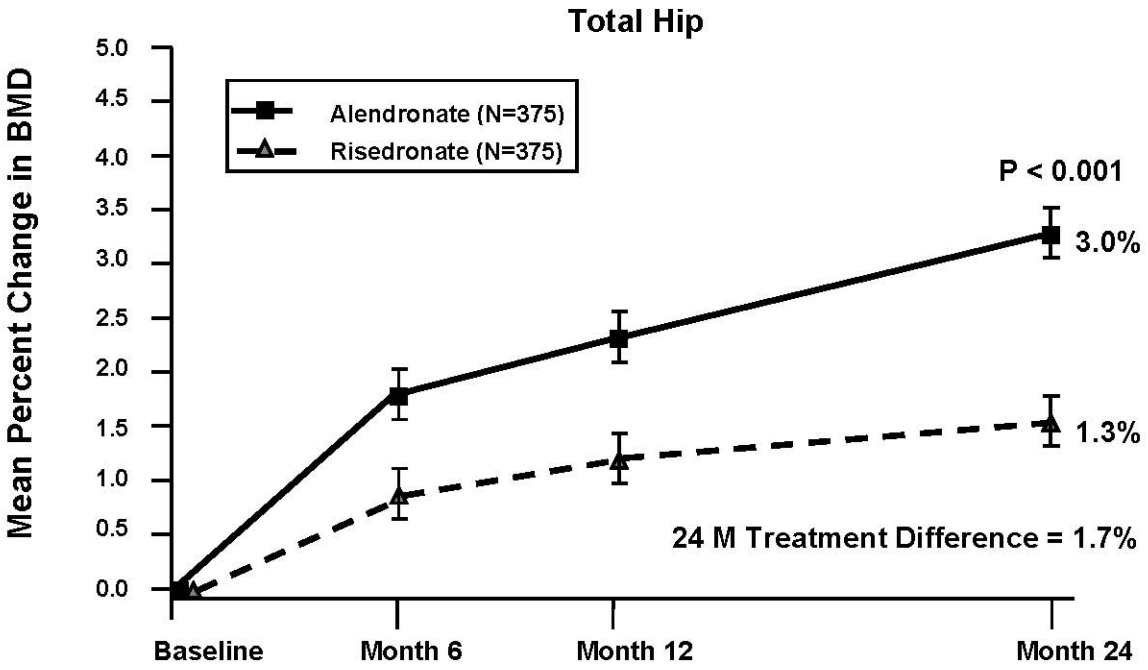

1759 patients screened
1053 patients randomized
520 ALN Group (Yr 1) 515 Treated
533 RIS Group (Yr 1) 527 Treated
82 Discontinued (15.8%)
79 Discontinued (14.8%)
438 Completed (84.2%) 464 (89.2%) in Yr 1 mITT
454 Completed (85.2%) 481 (90.2%) in Yr 1 mITT
833 Consented
414 ALN Group (Yr 2) 411 Treated
419 RIS Group (Yr 2) 414 Treated
375 (90.6%) in Yr 2 mITT
375 (89.5%) in Yr 2 mITT
337 (81.4%) in PP analysis of NTX
333 (79.5%) in PP analysis of NTX

Figure 2a.



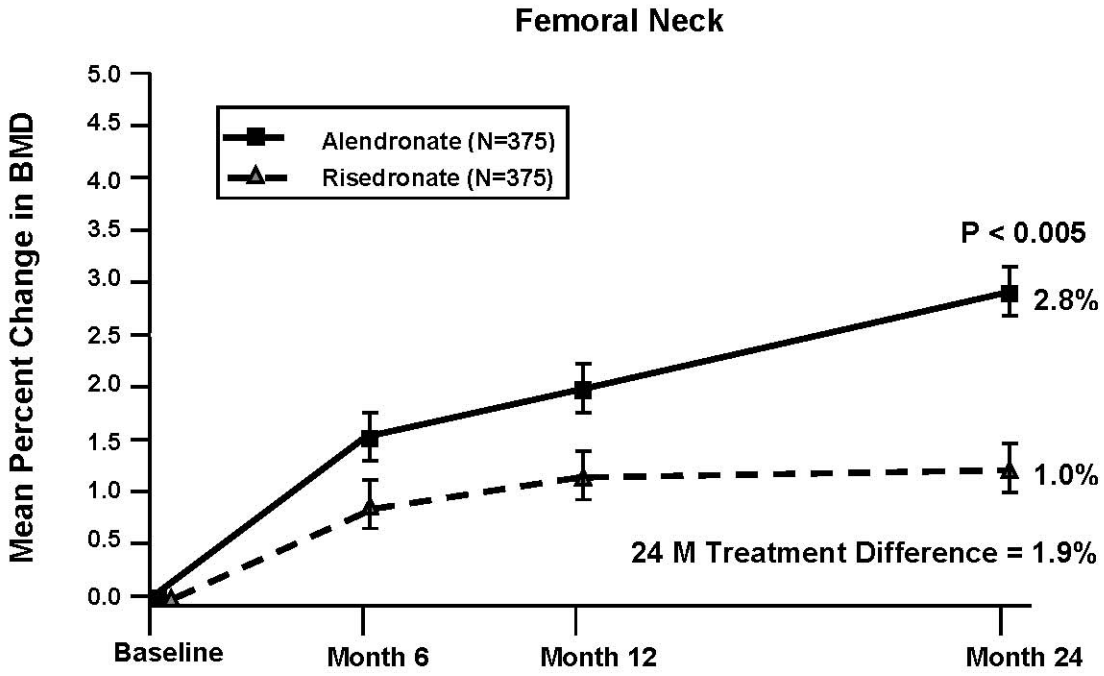
Based on patients enrolled in Extension.

Figure 2b.



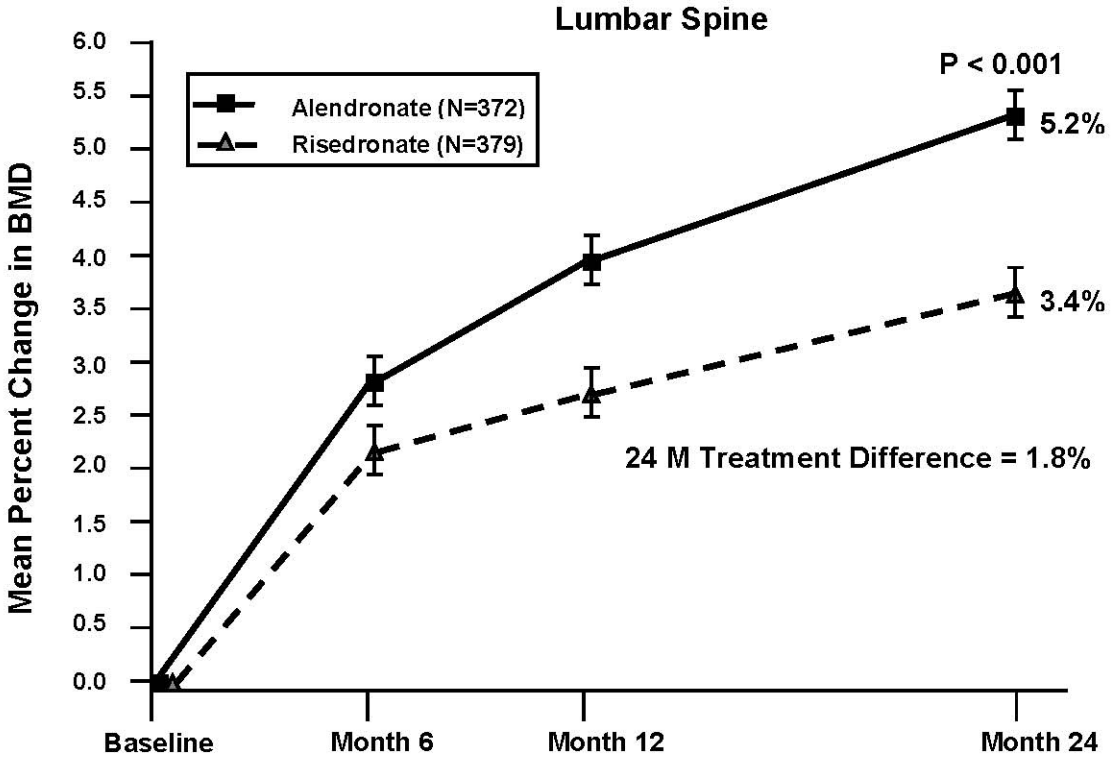
Based on patients enrolled in Extension.

Figure 2c.



Based on patients enrolled in Extension.

Figure 2d.



Based on patients enrolled in Extension.

Figure 3a.

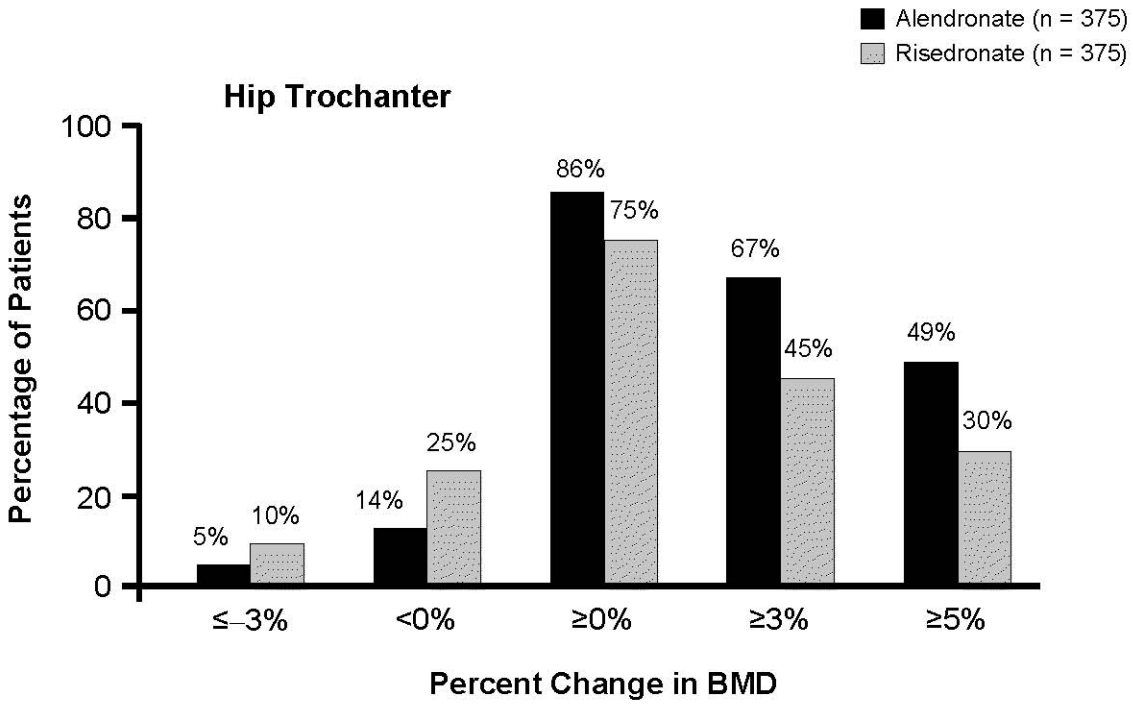

Alendronate (n = 375)
Risedronate (n = 375)
Hip Trochanter
Percentage of Patients
100
80
60
40
20
0
5%
10%
14%
25%
86%
75%
67%
45%
49%
30%
≤–3%
<0%
≥0%
≥3%
≥5%
Percent Change in BMD

Figure 3b.

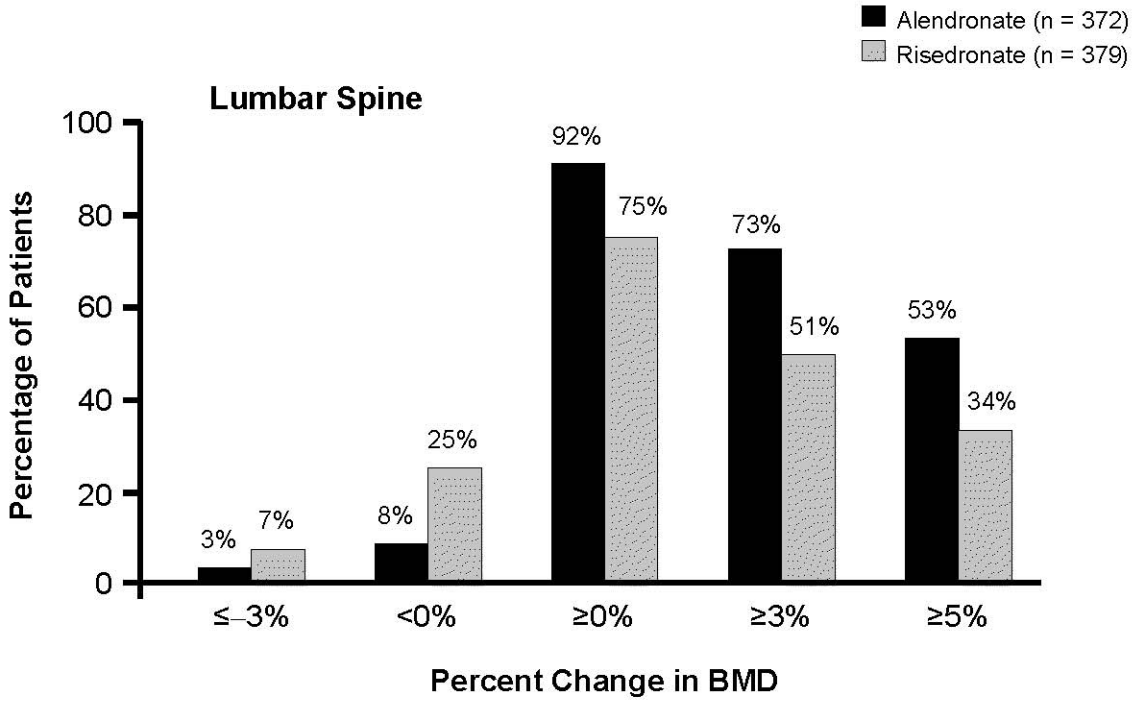
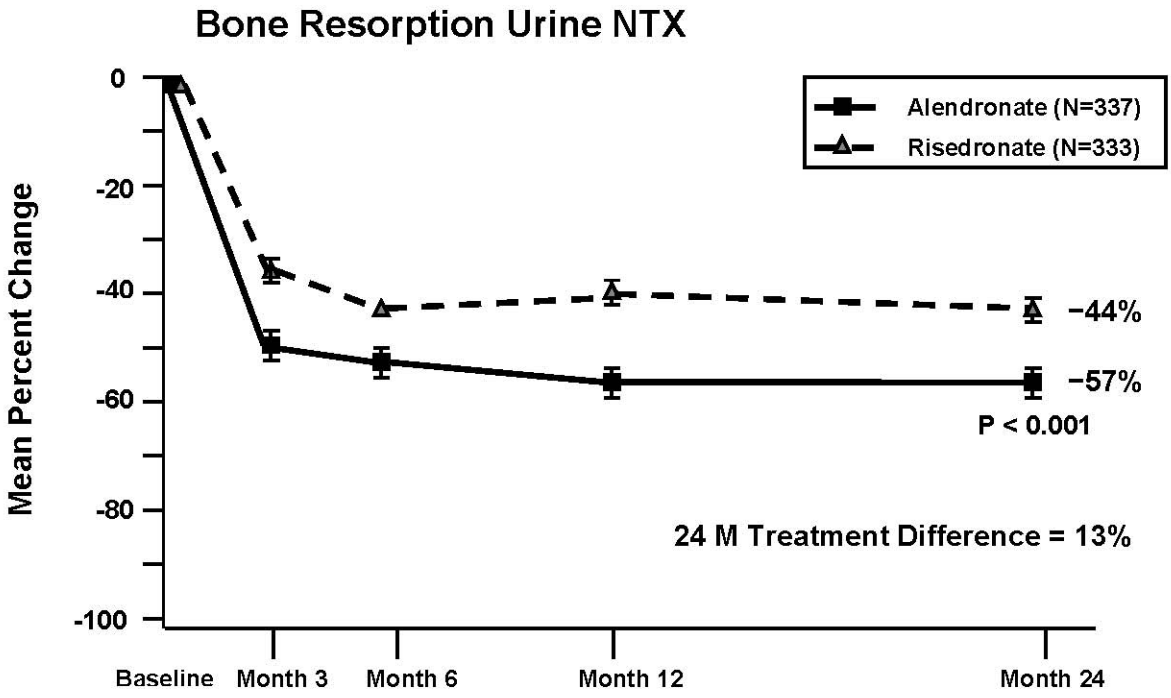
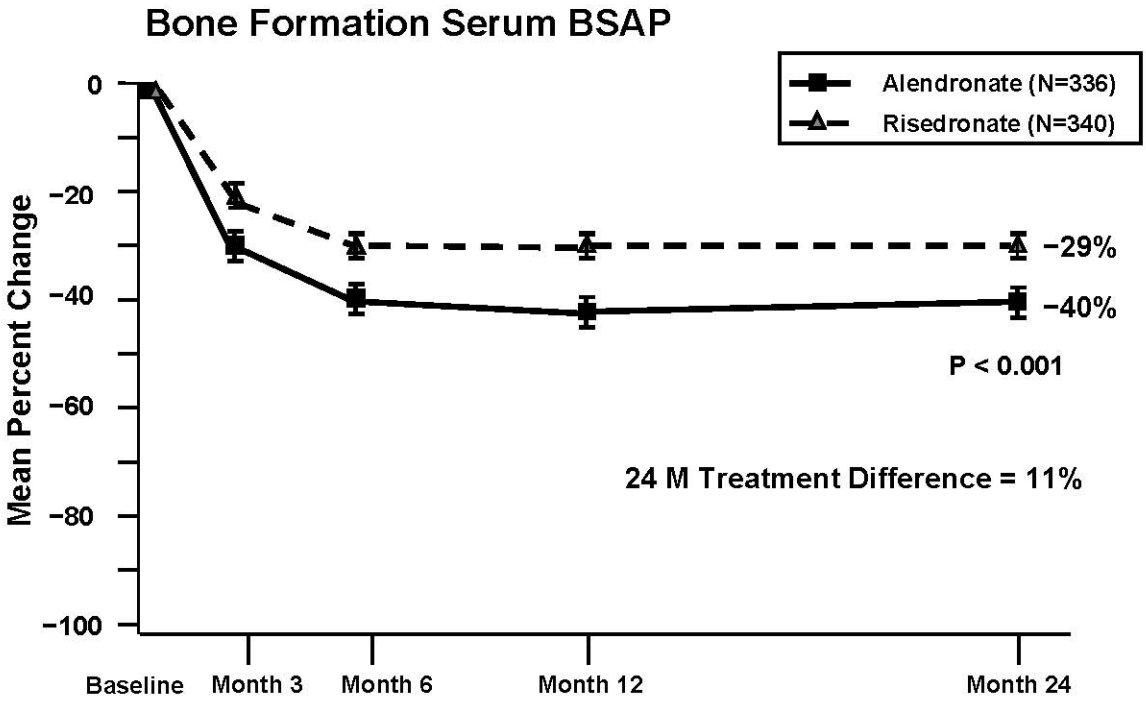

Alendronate (n = 372)
Risedronate (n = 379)
Lumbar Spine
Percentage of Patients
100
80
60
40
20
0
3%
7%
8%
25%
92%
75%
73%
51%
53%
34%
≤–3%
<0%
≥0%
≥3%
≥5%
Percent Change in BMD

Figure 4a.



* The displayed values are back-transformed from [ln(Fraction of Baseline) − 1] x 100%.
Based on patients enrolled in Extension.

Figure 4b.



* The displayed values are back-transformed from [ln(Fraction of Baseline) − 1] x 100%.
Based on patients enrolled in Extension.