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## Prevention of Bone Loss with Risedronate in Breast Cancer Survivors: A Randomized, Controlled Clinical Trial

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### Abstract

**Purpose**—Aromatase inhibitors (AIs), adjuvant endocrine therapy for postmenopausal women with hormone receptor positive breast cancer, are associated with bone loss and fractures. Our objectives were to determine if 1) oral bisphosphonate therapy can prevent bone loss in women on an AI and, 2) early changes in bone turnover markers (BTM) can predict later changes in bone mineral density (BMD).

**Methods**—We conducted a 2 year double-blind, placebo-controlled, randomized trial in 109 postmenopausal women with low bone mass on an aromatase inhibitor (AI-anastrozole, letrozole, or exemestane) for hormone receptor positive breast cancer. Participants were randomized to once weekly risedronate 35 mg or placebo and all received calcium plus vitamin D. The main outcome measures included BMD, BTM [carboxy-terminal collagen crosslinks (CTX) and N-terminal propeptide of type 1 procollagen (P1NP)] and safety.

**Results**—Eighty-seven percent completed 24 months. BMD increased more in the active treatment group compared to placebo with an adjusted difference at 24 months of  $3.9 \pm 0.7$  percentage points at the spine and  $3.2 \pm 0.5$  percentage points at the hip (both  $p < 0.05$ ). The adjusted difference between the active treatment and placebo groups were  $0.09 \pm 0.04$  nmol/LBCE for CTX and  $23.3 \pm 4.8$   $\mu\text{g/mL}$  for P1NP (both  $p < 0.05$ ). Women with greater 12-month decreases in CTX and P1NP in the active treatment group had a greater 24-month increase in spinal BMD ( $p < 0.05$ ). The oral therapy was safe and well tolerated.

**Conclusion**—In postmenopausal women with low bone mass and breast cancer on an AI, the oral bisphosphonate risedronate maintained skeletal health.

### Keywords

Clinical trials; antiresorptives; DXA; Biochemical markers of bone turnover

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## Introduction

Aromatase inhibitors (AIs) have become standard adjuvant endocrine therapy for postmenopausal women with hormone receptor positive breast cancer.<sup>(1-3)</sup> AIs inhibit peripheral conversion of androgens to estrogens resulting in lower levels of estrogen. Because estrogen inhibits bone resorption, AIs contribute to bone loss and osteoporosis.<sup>(1-3)</sup>

We have previously demonstrated that the oral bisphosphonate risedronate can prevent bone loss in newly postmenopausal women with breast cancer.<sup>(4)</sup> In that study women were included with or without tamoxifen, an antiestrogen or on AI concomitant therapy. Due to a switch in the standard of care during the 24 months of the trial, a portion of women were switched from tamoxifen to an AI or started on an AI by their private physician. Despite this challenge, we found that women with breast cancer with or without AI therapy received skeletal benefit from an oral bisphosphonate. Furthermore, women on a bisphosphonate and not on an AI obtained the greatest improvement in bone density.

There have been several pivotal studies that demonstrate that intravenous (IV) bisphosphonates improve bone density with women with breast cancer on a specific aromatase inhibitor (AI). The Z-FAST and ZO-FAST trials included postmenopausal women with early breast cancer receiving adjuvant letrozole and found significant increases in spine bone mineral density (BMD) between upfront or delayed zoledronic acid.<sup>(5, 6)</sup> The ABCSG-12 study included premenopausal women with hormone receptor positive early breast cancer on tamoxifen or anastrozole (both with goserelin) and reported favorable spine BMD responses in those randomized to IV zoledronic acid compared to placebo.<sup>(7)</sup>

Studies that have included oral bisphosphonates have also demonstrated favorable outcomes in maintaining bone mass in women on a specified AI.<sup>(8-11)</sup> The Sabre study examined postmenopausal women with hormone receptor positive breast cancer on the AI anastrozole, and were classified as low, moderate or high risk for an osteoporotic fracture as assessed by BMD T-scores and clinical risk factors.<sup>(8)</sup> The moderate fracture risk group of women on anastrozole, with T-scores from -1.0 to -2.0, was randomized to risedronate or placebo for 2 years. They reported that women receiving adjuvant anastrozole for breast cancer at moderate risk for fracture had favorable effects in BMD with risedronate compared with placebo. Similar favorable BMD outcomes were reported in the IBIS-II trial.<sup>(12)</sup> This study followed postmenopausal women with osteoporosis on anastrozole for 3 years but 36% dropped out and patients with significant bone loss were excluded from the per protocol analysis. Subsequently the ARBI trial, centered in Athens, Greece found that once weekly risedronate did not improve BMD at 12 months, but did at 24 months.<sup>(11)</sup>

Little data are available on postmenopausal women with hormone receptor positive breast cancer and low bone mass on other AIs *besides* anastrozole.<sup>(8, 9, 11-14)</sup> Because women often have side effects from the initial AI and are switched to an alternative AI,<sup>(15, 16)</sup> it is important to determine the impact of bone loss on available AI preparations. The **R**isedronate **E**ffect on **B**one in women with **B**reast **C**ancer 2 (REBBeca2) was designed to examine the preservation of bone mass with an oral bisphosphonate, in women with osteopenia or low bone mass on a non-specified AI for adjuvant therapy and allowed

participants to switch AI preparations during the trial to mimic conventional clinical care thus providing greater generalizability. Furthermore, our second goal was to determine if early changes in biochemical markers of bone turnover were predictive of longer term changes in BMD in this cohort.

### Study Design

The study was a 24 month double-blind, placebo-controlled, randomized clinical trial. Patients were randomly assigned to receive oral risedronate 35 mg once weekly or placebo. Compliance was assessed by pill count. Dietary calcium intake was assessed with a validated questionnaire<sup>(17)</sup> and all women received daily calcium up to 1200 mg daily by diet and/or supplement.<sup>(18, 19)</sup> The calcium supplement contained calcium carbonate 500 mg plus vitamin D 200 IU. Participants from the greater Pittsburgh, Pennsylvania area were enrolled and treated between January 2008 and March 2013 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00485953) Identifier: NCT00485953).

## Materials and Methods

### Participants

We enrolled postmenopausal women with hormone receptor positive breast cancer over age 55 years, currently receiving an AI including anastrozole, letrozole, or exemestane. Participants were permitted to switch their AI. Postmenopausal status was determined by history. Participants were included if they had low bone mass as classified by the World Health Organization (T-score between  $-1.0$  and  $-2.5$  at the spine or hip<sup>(20)</sup>), were not treated with a bisphosphonate in the previous year, and had no illnesses or were on no other medications known to affect bone and mineral metabolism such as glucocorticoids or certain antiepileptic medications. If the patient had an initial BMD T-score in the osteoporotic range (T-score  $\leq -2.5$ ) or an adult fragility fracture they were counseled about options for therapy versus participation in the trial. They were allowed to participate in the trial after discussion and approval from their health care professional and/or oncologist. The protocol was approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent before participation.

### Randomization and Blinding

The study biostatistician randomized participants in a 1:1 ratio using random block sizes of 2 and 4. The independent research pharmacist provided identically-appearing active drug or placebo. Investigators, study personnel, providers, and participants were blind to treatment assignment.

### Clinical Protocol

Study visits occurred at baseline, 6, 12, 18, and 24 months.

### Outcome Variables

The primary outcome variables were the changes in spine and hip BMD at 24 months. Additional outcomes included BMD changes at 12 months and changes in dual-energy x-ray

absorptiometry (DXA) was performed using a Discovery densitometer (Hologic Inc., Bedford, MA). Our precision ranged from 1.2 to 1.9% at these skeletal sites.<sup>(21)</sup> Measured skeletal sites included the hip (total hip, femoral neck), spine (posterior-anterior), and total body. The markers of bone turnover markers (BTMs) included a marker for bone resorption assessed by serum C-telopeptide crosslinks type I collagen (CTX, Crosslaps, Osteometer Biotech, Herlev, Denmark). Bone formation was assessed by serum intact N-terminal propeptide type I procollagen (PINP, Orion Diagnostica, Espoo, Finland). Serum 25-hydroxy vitamin D was assessed by liquid chromatography/mass spectrometry.

### Sample Size

Standard deviations of BMD improvement is approximately 4%.<sup>(22–24)</sup> We conservatively assumed a one-year dropout rate of 20%, and zero BMD change in dropouts. Under this assumption, we conservatively sought to detect 75% of effect actually attained by others<sup>(25)</sup> or 2.76%. With 55 participants per arm, we estimated to have 89% power to detect statistical significance of such an effect in a two-tailed test at  $\alpha=0.05$ .

### Statistical Analysis

Analyses were performed on an intention-to-treat basis. To compare baseline characteristics between subjects in the active and placebo arms, we used independent sample *t*-, chi square and Fisher's exact tests. For the main analysis, we fitted a series of linear mixed models, using raw and percent change between baseline and follow-up assessment in each of the BMD and biomarker measures as the dependent variable; treatment arm (active/placebo), follow-up assessment (6,12,18,24 months) and their interaction as fixed effects of interest; baseline value of the measure as a fixed effect covariate; and a subject random effect to account for multiple measurements from the same participant over time and the resulting non-independence of observations. We used appropriately constructed contrasts to compare treatment arms at each of the 6-, 12-, 18-, and 24-month assessments. We assessed sensitivity of the results to both last-value-carried-forward and multiple imputation<sup>(26)</sup> approaches to missing data. To examine association between early changes in markers of bone turnover with more distal changes in BMD, we computed correlation coefficients between 12-month change in markers and 24-month changes in BMD; and additionally compared 24-month BMD changes across tertiles of 12-month marker changes using analysis of variance. SAS<sup>®</sup> version 9.3 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

### Results

During the recruitment period 280 women were screened via a phone interview, 110 were evaluated for inclusion by the study staff with coordination from their primary care physician and/or oncologist, and 109 were randomized (Figure 1). At randomization, 77% were currently taking anastrozole, 15% letrozole, and 8% exemestane. Twelve (11%) women reported use of more than one AI prior to randomization and 9 (8%) reported changing AI preparations at some point during the study. At baseline the mean age was 70.5 years and there were no baseline differences between the groups in age, BMI, calcium/vitamin D intake or BMD (Table 1). Eighty-seven percent completed 24 months of the

study. Compliance by pill count was assessed every 6 months and considered compliant if women took at least 80% of the pills in the previous 6-month period. During the four 6-month periods of the 24 month study, compliance ranged from 90–98% in the risedronate group and 89–96% in the placebo group.

### Bone Mineral Density

Spine BMD increased in the active treatment group and decreased in the placebo over 12 months ( $2.0 \pm 0.5$  vs.  $-1.2 \pm 0.5\%$ , mean  $\pm$  SE,  $p < 0.0001$ ) and over 24 months ( $2.3 \pm 0.6$  vs.  $-1.7 \pm 0.6$ ,  $p < 0.0001$ ); the adjusted difference was  $3.9 \pm 0.7$  percentage points in favor of the active group at 24 months ( $p < 0.0001$ , Figure 2). Total hip BMD increased more in the active treatment group than placebo, both at 12 months ( $0.5 \pm 0.4$  vs.  $-1.6 \pm 0.4$ ;  $p < 0.0001$ ) and 24 months ( $0.6 \pm 0.4$  vs.  $-2.7 \pm 0.5$ ,  $p < 0.0001$ ); the adjusted difference at 24 months was  $3.2 \pm 0.5$  percentage points,  $p < 0.0001$ .

Similar differences were observed in the femoral neck with an adjusted difference of  $2.6 \pm 0.8$  percentage points at 24 months ( $p = 0.0009$ ). We also observed significant differences in total body ( $2.4$  percentage point adjusted difference at 24 months,  $p < 0.0001$ ). Results were descriptively similar among those on different AIs.

### Biochemical Markers of Bone Turnover

As assessed by the marker of bone resorption, CTX decreased in the active treatment group at 12 and 24 months ( $p < 0.01$ , Figure 2) and did not significantly change in the placebo group, with an adjusted difference of  $0.09 \pm 0.04$  nmol/LBCE at 24 months ( $p = 0.0157$ ). As expected, the marker of bone formation, P1NP, decreased in the active treatment group at 12 and 24 months ( $p < 0.0001$ ), with an adjusted difference of  $27.1 \pm 4.7$   $\mu\text{g/mL}$  at 12 months ( $p < 0.0001$ ) and  $23.3 \pm 4.8$  at 24 months ( $p < 0.0001$ , Figure 2). There were no significant correlations between the baseline BTMs and subsequent changes in BMD.

In the risedronate group, the 12-month changes in markers were associated with the 1- and 2-year percent changes in BMD (Table 2). Women in the highest (43%) 12-month CTX decrease tertile had a 3.3 to 3.4 percentage point greater 24-month spine BMD improvement compared to those in other tertiles (Figure 3;  $p < 0.05$ ). Similarly women in the highest two (37–50% and 50%) 12-month P1NP decrease tertiles had a 2.7 to 4.9 percentage point greater 24-month spine BMD improvement compared to those in the lowest tertile ( $p < 0.05$ ). Similar trends were observed for P1NP change and total hip BMD change (data not shown).

### Adverse Events

Twenty-four percent of participants had a serious adverse event and 94% had a nonserious adverse event. There were no differences between the groups (Table 3).

### Discussion

We found that once weekly oral risedronate improved bone density and decreased bone turnover in postmenopausal women with hormone receptor positive breast cancer on an AI over 2 years. Furthermore, the early decrease in BTMs predicted the increase in vertebral

BMD. In comparison to previous studies that used IV bisphosphonates and only allowed one AI, this study allowed use of 3 different AIs during the study and used an oral once weekly bisphosphonate.

Studies in postmenopausal women on AIs for breast cancer with lower bone mineral density or osteoporosis using IV bisphosphonates have also demonstrated improvement in BMD with antiresorptive medication. Two large trials using IV zoledronic acid every 4 months in women on letrozole adjuvant therapy compared immediate to delayed therapy and reported skeletal benefits from therapy<sup>(7, 27)</sup> but neither trial was designed to demonstrate fracture reduction. A meta-analysis with 15 trials demonstrated a 22% fracture reduction with IV zoledronic acid therapy<sup>(28)</sup> and other reviews support use of bisphosphonates in women with breast cancer on an AI.<sup>(29, 30)</sup> Parental therapy with denosumab subcutaneously every 6 months for 2 year also found improvements in BMD with therapy, but no difference in fractures.<sup>(31, 32)</sup> These studies with a parental antiresorptive therapy and previous trials with oral risedronate, have only allowed a single AI preparation. This is the first trial to allow the spectrum of available AIs and to allow women to change preparations which is the standard of care and provides greater generalizability. Roughly 75% were on anastrozole, and 25% were on the other available AIs. Furthermore, roughly 11% had changed AIs before the trial and 8% switched during the study.

Previous studies on the prevention of bone loss with antiresorptive therapy in women with breast cancer on an AI have not explored the relationship between early decreases in BTMs and longer term changes in bone density. We found that the decreases in BTMs at 1 year predict the improvements in BMD at 2 years. We have previously demonstrated this in postmenopausal women on alendronate therapy.<sup>(33, 34)</sup> Assessment of a blood test halfway through the course of therapy may be clinically useful to reassure patients and physicians that the BMD trajectory is in the right direction, but larger studies are needed to validate this.

### **Our study had several limitations**

The duration of the study was only 2 years. We only included women with low bone mass who were unlikely to fracture and we were not powered for fracture efficacy. However our study had several strengths. We performed the study at a single center on a single machine, thereby reducing extraneous variability due to site and equipment. Our compliance (defined as using 80% of the pills) was at least 90% during each of the 6-month periods between assessments. Eighty-seven percent completed the 2 year study. Furthermore, we had performed analyses based on intention-to-treat; results were similar when multiple approaches for accounting for missing data were employed. Finally the reduction in biochemical markers of bone turnover, provide an extra level of support for the validity of increases we observed in BMD.

In summary, we found that an oral once weekly bisphosphonate, risedronate improved bone density and decreased bone turnover in postmenopausal with hormone receptor positive breast cancer on an AI preparation. The bisphosphonate was well tolerated and provides a therapeutic option to maintain skeletal integrity in this cohort.

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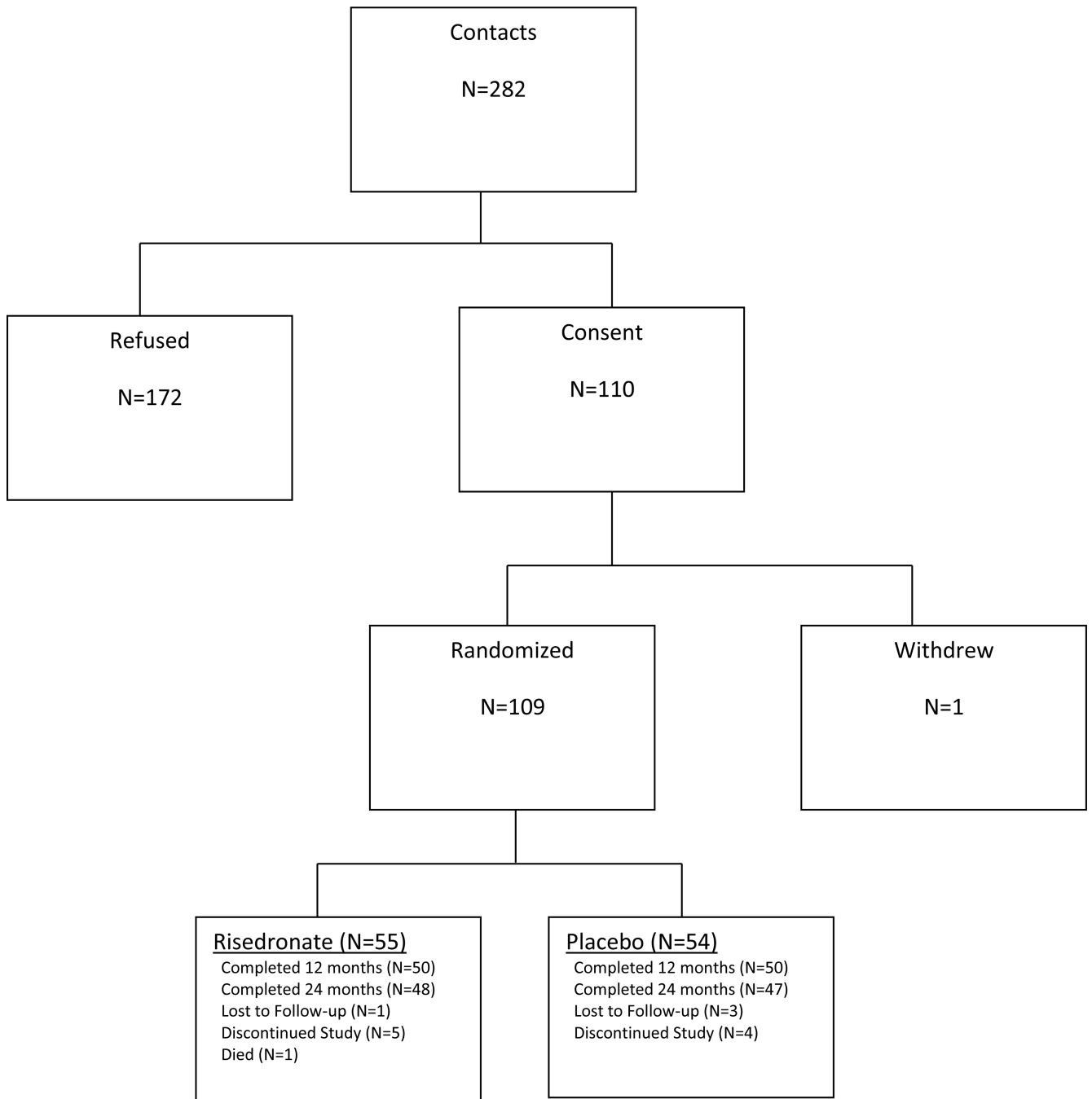
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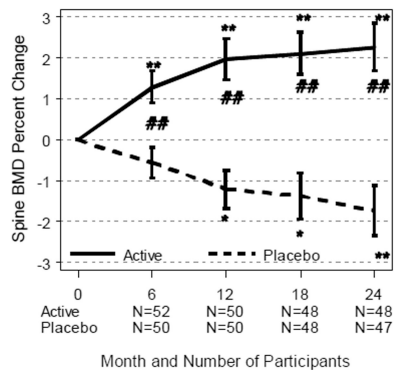


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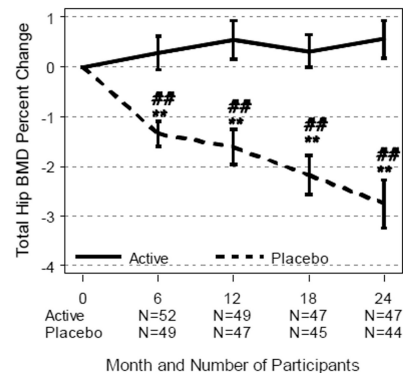


**Figure 1.**  
Enrollment and Study Design Flow Chart- CONSORT Diagram

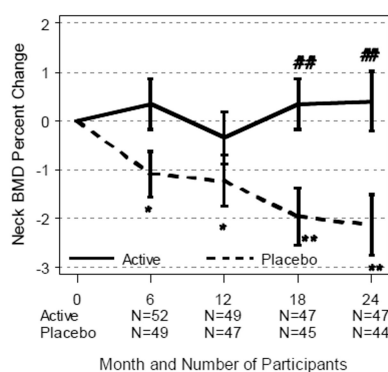
A: Spine



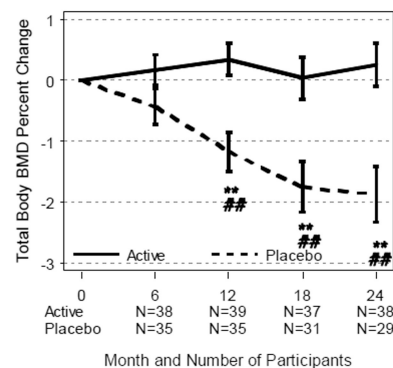
B: Total Hip



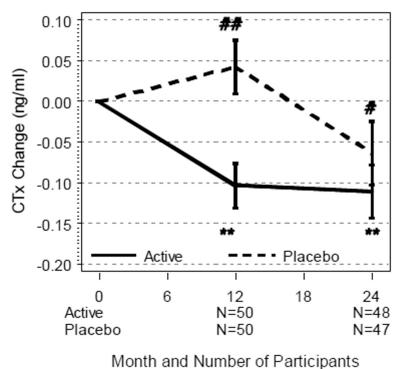
C: Femoral Neck



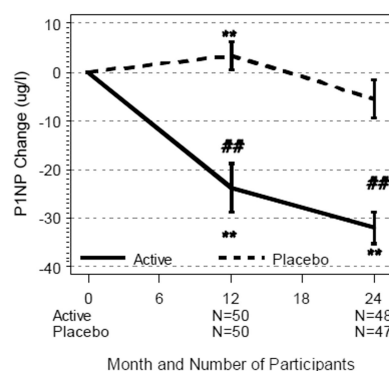
D: Total Body



E: CTX

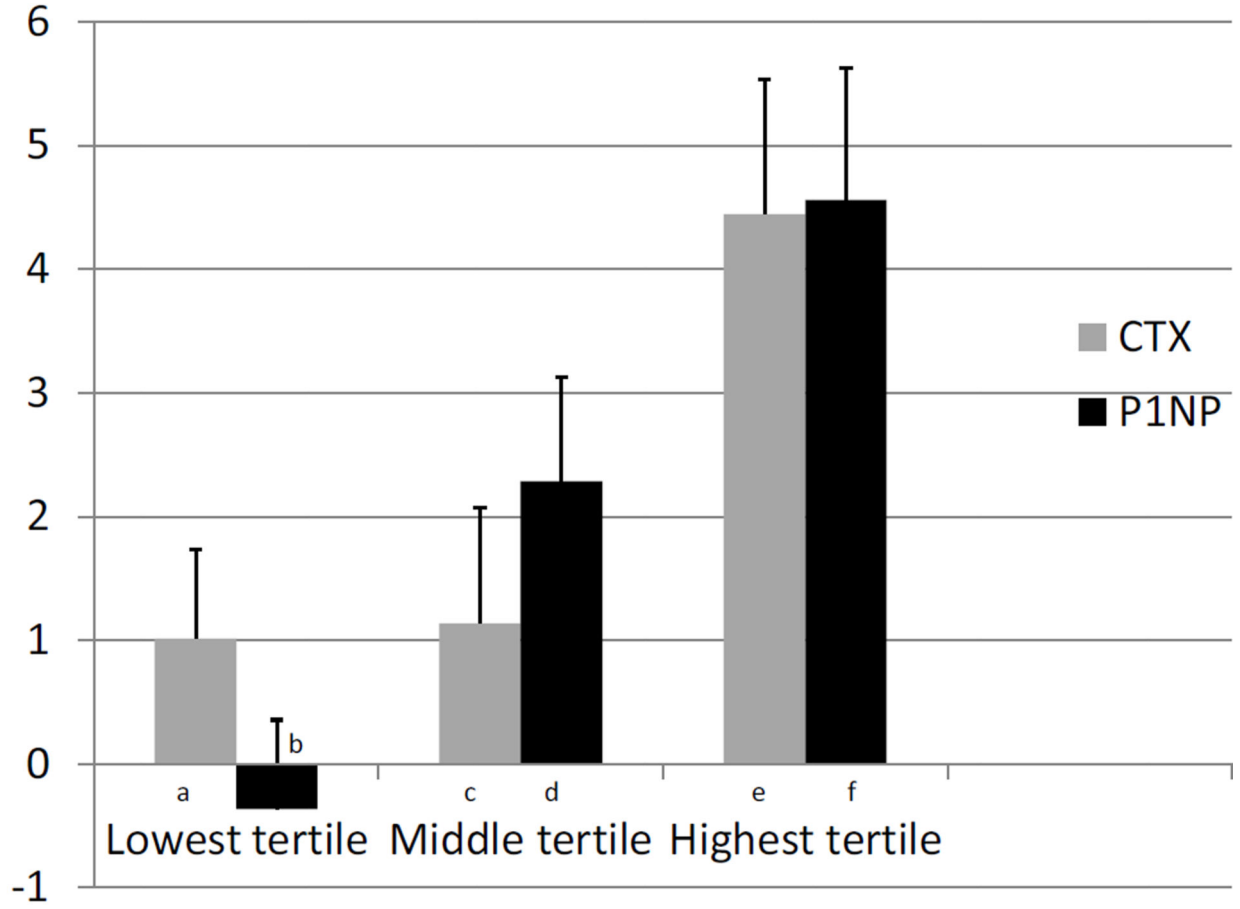


F: P1NP

**Figure 2.**

Mean  $\pm$  SE percent change in bone mineral density in spine (A), total hip (B), femoral neck (C), total body (D) and the absolute change in biochemical markers of bone turnover including CTX [(E), nmol/L BCE] and P1NP [(F),  $\mu$ g/mL] from baseline to 24 months (unadjusted). \*  $p < 0.05$ , \*\*  $p < 0.01$  change from baseline using paired t-test. # $p < 0.05$ , ## $p < 0.01$  for comparison between risedronate (solid line) and placebo (dashed line) groups using linear mixed models.

Percentage change in Spine BMD at 24 months



**Figure 3.** Percent change in spine bone mineral density (BMD) after 24 months of risedronate grouped by percentage decrease in bone turnover markers (in tertiles) at 12 months. Results as mean  $\pm$  SEM. For CTX (overall ANOVA pairwise comparison  $p < 0.05$ ), group a) lowest tertile ( $< 13\%$ ), b) middle tertile ( $13 - < 43\%$ ) and c) highest tertile ( $> 43\%$  decrease). For P1NP (overall ANOVA pairwise comparison  $p < 0.01$ ), group d) lowest tertile ( $< 37\%$ ), e) middle tertile ( $37 - 50\%$ ), and f) highest tertile ( $> 50\%$  decrease). Significance between tertiles: a vs. c ( $p < 0.01$ ), b vs. c ( $p < 0.05$ ), d vs. e ( $p < 0.05$ ), d vs. f ( $p < 0.01$ ), and e vs. f ( $p = 0.07$ ).

**Table 1**

Baseline Characteristics, Bone Mineral Density and Bone Turnover

Variable	Risedronate (N=55)	Placebo (N=54)	P-value
Age (years)	65 ± 1	64 ± 1	0.58
Menopausal age (years)	50 ± 1	51 ± 1	0.65
AI use prior to study (days)	747 ± 101	684 ± 87	0.64
Body mass index (kg/m <sup>2</sup> )	31 ± 3	31 ± 3	0.905
Daily calcium (mg/d)	743 ± 48	827 ± 54	0.25
<b>Breast cancer treatment</b>			
Lumpectomy, N (%)	43 (81)	43(79)	0.84
Mastectomy, N (%)	19 (35)	17(32)	0.73
Axillary node removal	39(75)	48(89)	0.06
Radiation therapy, N (%)	42 (76)	49 (91)	0.09
Chemotherapy, N (%)	17 (32)	27 (50)	0.077
<b>Aromatase inhibitor</b>			
Anastrozole, N (%)	45 (82)	39 (72)	0.261
Letrozole, N (%)	4 (7)	12 (22)	0.033
Exemestane, N (%)	6 (11)	3 (6)	0.489
<b>Bone metabolism</b>			
Calcium (mg/dl)	9.8 ± 0.1	9.7 ± 0.1	0.22
25 hydroxyvitamin D (ng/mL)	36 ± 2	36 ± 2	1.00
<b>Bone Mineral Density (g/cm<sup>2</sup>)</b>			
Spine	0.980 ± 0.019	0.994 ± 0.017	0.60
Total hip	0.866 ± 0.014	0.874 ± 0.014	0.69
Femoral neck	0.744 ± 0.013	0.744 ± 0.013	1.00
<b>T-score (SD)</b>			
PA Spine	-0.64 ± 0.16	-0.45 ± 0.15	0.39
Total hip	-0.67 ± 0.12	-0.58 ± 0.11	0.60
Femoral neck	-1.01 ± 0.11	-0.95 ± 0.16	0.75
<b>Bone turnover markers</b>			
CTX (nmol/LBCE)	0.38 ± 0.02	0.46 ± 0.03	0.04
PINP (µg/mL)	62.05 ± 3.04	62.61 ± 3.51	0.9055

**Table 2**

Correlations Between 12-month Change in Markers of Bone Turnover and 12–24-Month Percent Changes in Bone Mineral Density Among the Women Receiving Active Treatment

BMD Site	12-Month CTX Change		12-Month P1NP Change	
	12-Month BMD Percent Change	24-Month BMD Percent Change	12-Month BMD Percent Change	24-Month BMD Percent Change
PA Spine	-0.38**	-0.32*	-0.30*	-0.43**
Total Hip	-0.22	-0.17	-0.37**	-0.20
Femoral Neck	-0.04	-0.26	0.09	-0.12
Total Body	-0.37*	-0.42**	-0.20	-0.31

\* P<0.05,

\*\* p<0.01

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**Table 3**

## Adverse Events

Adverse Event	Risedronate N (%)	Placebo N (%)	P-value
Breast related	5 (9)	4 (7)	1.00
Gastrointestinal	4 (7)	13 (24)	0.019
Cardiovascular	8 (14)	11 (20)	0.459
Respiratory	4(7)	10(18)	0.093
Musculoskeletal	27 (49)	33 (61)	0.250
Serious	10 (18)	16 (30)	0.183
Nonserious	52(95)	50(93)	0.716

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