

The effect of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial: a meta-analysis of the US, German, Netherlands, and Belgium sub-studies

Peyman Hadji · Lina Asmar · Johanna G. H. van Nes · Thomas Menschik · Annette Hasenburg · Joachim Kuck · Johan W. R. Nortier · Cornelis J. H. van de Velde · Stephen E. Jones · May Ziller

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Abstract

Purpose We performed a meta-analysis of three sub-studies of the randomized Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial to determine the effects of exemestane and tamoxifen on bone health.

Methods Patients received exemestane or tamoxifen as adjuvant therapy for hormone receptor-positive breast cancer. Bone mineral density (BMD) was assessed at baseline and after 12 and 24 months of treatment. Bone turnover markers were also measured.

Results Patients receiving tamoxifen showed a mean increase from baseline in lumbar spine BMD of 1.2% at month 12 and 0.2% at month 24. Patients receiving exemestane showed a mean decrease from baseline of 2.6% after 12 months and 3.5% after 24 months. There were significant differences in the changes in lumbar spine BMD between treatment groups ($P < 0.0001$ at both time points).

Changes in BMD from baseline at the total hip were also significantly different between exemestane and tamoxifen ($P < 0.05$ at both time points). Bone turnover markers decreased from baseline with tamoxifen and increased with exemestane.

Conclusions Exemestane resulted in decreases in BMD and increases in bone turnover markers. BMD increased and bone turnover markers decreased with tamoxifen.

Keywords Aromatase inhibitor · Early breast cancer · Exemestane · Tamoxifen · Bone mineral density

Introduction

Tamoxifen is an established adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive breast cancer. The third-generation aromatase inhibitors (AIs), anastrozole, exemestane, and letrozole, have demonstrated superior efficacy as adjuvant therapy compared with tamoxifen in several clinical trials (Coates et al. 2007; Coombes et al. 2007; Forbes et al. 2008) and are now recognized options in this setting (Goldhirsch et al. 2009; National Comprehensive Cancer Network 2009).

The AIs exhibit a tolerability profile distinct from that of tamoxifen, with a lower incidence of gynecological adverse events, thromboembolic events, and endometrial cancer (Coates et al. 2007; Coombes et al. 2007; Forbes et al. 2008; Hadji 2008b). However, while tamoxifen has demonstrated a positive effect on the bone health of postmenopausal women (Love et al. 1992), AI treatment has been associated with a decrease in bone mineral density (BMD) and an increased risk of fracture and osteoporosis (Coates et al. 2007; Coombes et al. 2007; Forbes et al. 2008; Hadji 2007; Hadji and Bundred 2007). This impact on bone is

P. Hadji (✉) · M. Ziller
Department of Gynaecological Endocrinology, Reproductive
Medicine and Osteoporosis, Philipps-University of Marburg,
Baldingerstrasse, 35033 Marburg, Germany
e-mail: hadji@med.uni-marburg.de

L. Asmar · S. E. Jones
US Oncology Research Inc, Houston, TX, USA

J. G. H. van Nes · J. W. R. Nortier · C. J. H. van de Velde
Leiden University Medical Centre, Leiden, The Netherlands

T. Menschik
Pfizer Oncology Europe, Paris, France

A. Hasenburg
University of Freiburg, Freiburg, Germany

J. Kuck
Independent Clinical Research Consulting, Berlin, Germany

likely to be an indirect consequence of the estrogen-depriving mechanism of action of AIs: estrogen withdrawal favors increased osteoclastic activity and bone resorption (Frenkel et al. 2010).

The efficacy and safety of exemestane for the adjuvant treatment of postmenopausal hormone receptor–positive breast cancer was investigated in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial (Jones et al. 2008b). In this large, multinational, phase III, open-label trial, 9,775 postmenopausal patients with hormone receptor–positive breast cancer were randomized to receive 5 years' exemestane or 2.5–3 years' tamoxifen followed by 2–2.5 years' exemestane (Jones et al. 2008b). TEAM was originally designed to investigate 5 years' exemestane versus 5 years' tamoxifen. However, the study design was amended following the interim results of the Intergroup Exemestane Study (IES), which showed that switching to exemestane after 2–3 years of tamoxifen improved disease-free survival (DFS) versus continuing tamoxifen (Coombes et al. 2004); subsequent follow-up analyses confirmed that the benefits of exemestane versus tamoxifen are maintained up to more than 5 years post-treatment (Coombes et al. 2009).

In the first analysis of TEAM, a head-to-head comparison of exemestane and tamoxifen after 2.75 years, exemestane was associated with an improvement in DFS compared with tamoxifen (HR 0.89; $P = 0.12$) and significant improvements in relapse-free survival (HR 0.85; $P = 0.02$) and time to distant metastases (HR 0.81; $P < 0.02$) (Jones et al. 2008b). Exemestane was associated with a significant increase in the incidence of osteoporosis, but not fractures, versus tamoxifen (Jones et al. 2008b). At a median follow-up of 5.1 years, TEAM showed no significant differences in efficacy between 5 years' exemestane and the sequence of tamoxifen followed by exemestane (Rea et al. 2009). Upfront exemestane was associated with a significant increase in osteoporosis, arthralgia, and fractures versus sequential treatment (Rea et al. 2009). Sub-studies of TEAM were conducted to determine the effects of exemestane and tamoxifen on bone health in the United States (Jones et al. 2008a), Germany (Hadji et al. 2009a, b), and the Netherlands/Belgium (van Nes et al. 2008). To increase sample size and power, we performed a meta-analysis of these three sub-studies to determine the effects of exemestane and tamoxifen on BMD and markers of bone turnover after 12 and 24 months of treatment in the TEAM trial.

Methods

The TEAM trial was conducted in compliance with the Declaration of Helsinki and was approved by local ethics committees. All patients provided informed consent.

Study design

These were sub-studies of the randomized, open-label, multicenter TEAM trial, designed to assess the effects of exemestane and tamoxifen on BMD, with or without markers of bone turnover, in postmenopausal women with hormone receptor–positive breast cancer. Methodologies for each sub-study have been reported previously (Hadji et al. 2009a; Jones et al. 2008a; van Nes et al. 2008).

Patients received exemestane for 5 years or tamoxifen for 2.5–3 years followed by 2–2.5 years of exemestane, for a total of 5 years' endocrine therapy. Patients were assessed for the first 2 years in these bone sub-studies.

Patients

Postmenopausal women with stages I, IIA, IIB, and IIIA T_{1–3}, N_{0–2}, M₀, estrogen receptor (ER)-positive and/or progesterone (PR)-positive breast cancer who were candidates for adjuvant endocrine therapy were eligible. All patients were required to have completed primary surgery and/or radiotherapy and/or chemotherapy, if indicated, in accordance with local guidelines. Patients were also required to have adequate renal, hepatic, and hematological function and an Eastern Cooperative Oncology Group performance status 0–2 (van Nes et al. 2010).

Exclusion criteria included one of the following: inflammatory breast cancer, histologically positive supraclavicular nodes, local skin ulceration/infiltration, neoadjuvant chemotherapy, ER- and PR-negative primary tumor or ER/PR-unknown status, or evidence of distant metastasis. Patients were ineligible if they were receiving hormonal adjuvant therapy for prior breast cancer. Patients with uncontrolled cardiac disease, other significant malignancies within the past 3 years, or other serious illnesses were excluded. Patients with diseases requiring chronic intake of drugs that interfere with bone metabolism (e.g., glucocorticosteroids, antiepileptics, bisphosphonates, calcitonin, fluoride, vitamin K antagonists) or metabolic diseases affecting bone metabolism and/or requiring treatment (e.g., primary hyperparathyroidism) were also excluded.

Treatment

Patients received oral treatment with exemestane 25 mg/day or tamoxifen 20 mg/day. Dose modification, escalation, or reduction was not permitted. Treatment was discontinued if the patient withdrew consent, if the investigator considered it was medically necessary, or if there was unacceptable toxicity or relapse of disease. Patients were withdrawn from the bone sub-study if they had a fracture or developed osteoporosis (T-score less than

–2.5). All patients were followed up for survival regardless of whether they discontinued treatment prematurely. To document treatment compliance in the US and German sub-studies, patients completed a ‘Drug Administration Record’ at home, which was brought to each clinic visit.

Assessments

Bone mineral density

BMD was measured by dual-energy X-ray absorptiometry (DXA) imaging at the lumbar spine (L1–L4) and total hip (g/cm^2 and standardized as T- and Z-scores; Z-scores were not available from the US sub-study) in accordance with the standard operating procedure of the manufacturer. BMD measurements were recorded at baseline. Subsequent measurements were taken 12 and 24 months after treatment initiation with exemestane or tamoxifen.

Markers of bone turnover

Bone turnover markers were assessed in the sub-studies performed in Germany and the Netherlands/Belgium and included the bone formation marker amino terminal propeptide of type I procollagen (PINP) and the bone resorption markers.

C-telopeptide (CTX; the Netherlands/Belgium) and ICTP (carboxyterminal crosslinked telopeptide of type I collagen; Germany). Blood samples (20 mL) were taken at baseline and after 3, 6, 12, and 24 months of treatment. Details of assessments of bone turnover markers have been reported previously (Hadji et al. 2009b).

Primary objective

The primary objective was to compare exemestane and tamoxifen with regard to changes from baseline to months 12 and 24 in BMD (g/cm^2) in lumbar spine (integral of L1–L4).

Secondary objectives

Secondary objectives included the comparison of exemestane and tamoxifen with regard to changes from baseline to months 12 and 24 in standardized BMD (T- and Z-scores) in lumbar spine (integral L1–L4) and BMD (g/cm^2 and standardized as T- and Z-scores) in total hip. Mean changes from baseline to months 3, 6, 12, and 24 in the markers of bone turnover were also assessed.

Statistical analysis

As this was an analysis of pooled data, a sample size calculation was not indicated. The pooled analysis was performed on patients from the US, German, and Netherlands/Belgium sub-studies. In the US sub-study, only patients who were fully compliant with adjuvant endocrine therapy and had BMD measurements at all time points were included in the analysis. The German and Netherlands/Belgium sub-studies included all patients who had a baseline assessment and at least one post-baseline measurement of BMD or bone turnover (Fig. 1). Patients were analyzed as randomized, irrespective of the treatment actually received.

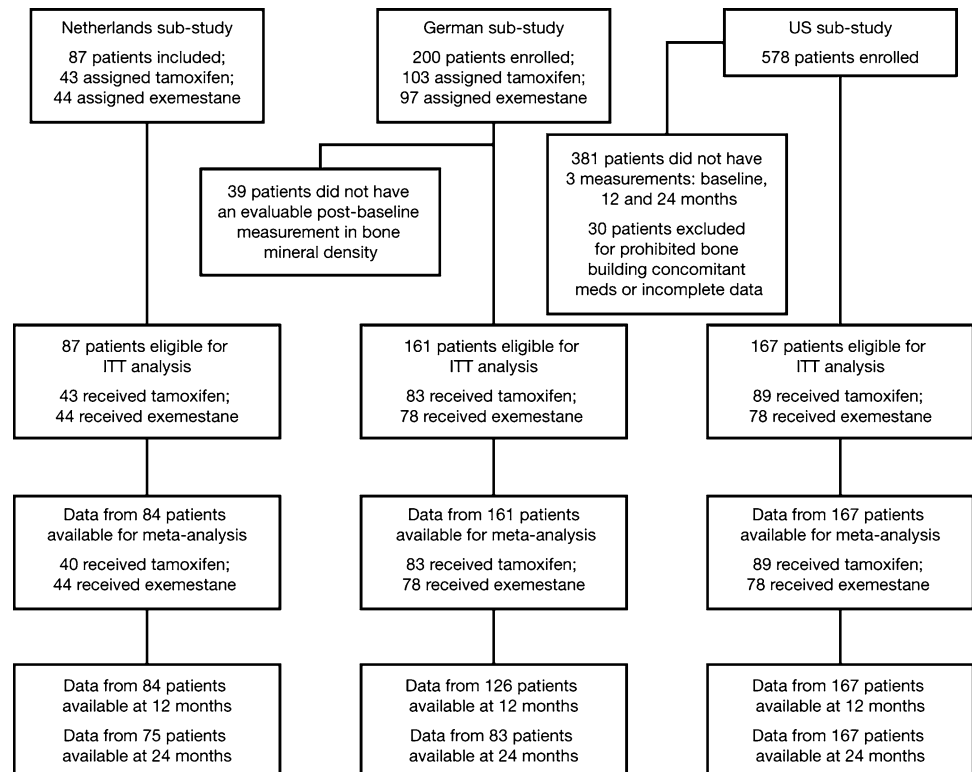
The analysis was based on observed cases (missing values were not imputed) and covered the period until the visit at month 24 (i.e., before the patients receiving tamoxifen switched to exemestane). All statistical modeling of treatment effects and other possible effects on the target variables was considered exploratory. Consequently, *P*-values associated with the respective models were not adjusted for multiple testing. All tests were performed two-sided at a significance level of 0.05. Baseline comparability in terms of BMD and bone turnover variables was assessed by analysis of variance (ANOVA) using the baseline value as a dependent variable, and treatment, sub-study and the interaction between treatment and sub-study as model terms. Baseline comparability in terms of demographic variables was also assessed by ANOVA. Baseline comparability in terms of clinical baseline characteristics was assessed by the Cochran–Mantel–Haenszel test. Differences in changes from baseline to the specific time point between exemestane and tamoxifen were assessed by analysis of covariance using the absolute values of the parameter, with treatment, sub-study, and the interaction between treatment and sub-study as model terms and the baseline value as a covariate. All data were analyzed using the Statistical Analysis System, version 9.1.3.

Results

Patient characteristics

In total, data from 412 patients were available for this analysis: 212 patients in the tamoxifen group and 200 in the exemestane group (Fig. 1; Table 1).

In general, the treatment groups were balanced with respect to demographics and baseline characteristics in all three sub-studies (except for weight in the Netherlands/Belgium sub-study; *P* = 0.0299; Table 1). Chemotherapy rates varied across sub-studies; however, there was no difference in chemotherapy rates between treatment groups in the pooled data. Furthermore, there were no significant

Fig. 1 Study profile

differences in the baseline values of BMD (Table 2) or bone turnover markers (Table 3) between treatment groups.

Between sub-studies, significant differences in age ($P = 0.0059$), tumor stage ($P = 0.0002$), and the number of positive lymph nodes ($P < 0.0001$) were observed. There were also significant between-study differences in the baseline values of BMD (Table 2), except for L1–L4 [Z-score].

Primary objective

Across all sub-studies, patients in the tamoxifen group experienced a mean increase in the lumbar spine BMD of 1.2% from baseline to month 12 and 0.2% to month 24. Patients in the exemestane group showed a decrease from baseline of 2.6% after 12 months and 3.5% after 24 months (absolute values are shown in Table 2; mean changes from baseline are illustrated in Fig. 2a). The differences in the changes from baseline to months 12 and 24 between treatment groups were statistically significant (each treatment comparison $P < 0.0001$). Similar results were obtained in the analyses of individual sub-studies (all treatment comparisons $P < 0.01$).

Secondary objectives

Standardized BMD measurements in lumbar spine

Changes from baseline in standardized BMD measurements in lumbar spine revealed a similar pattern. Patients

receiving tamoxifen had an increase in mean lumbar spine T-score from -0.34 to -0.21 after 12 months and to -0.24 after 24 months. In contrast, patients receiving exemestane showed a decrease from -0.59 to -0.79 after 12 months, remaining at -0.79 after 24 months (each treatment comparison $P < 0.0001$; Table 2 and Fig. 2b). Patients in the tamoxifen group showed an increase in mean lumbar spine Z-score from 0.59 to 0.76 after 12 months and to 0.81 after 24 months, whereas patients receiving exemestane showed a decrease from 0.53 to 0.34 after 12 months and to 0.28 after 24 months (each treatment comparison $P \leq 0.0001$; Table 2 and Fig. 2c).

Changes in BMD in total hip

Significant differences between treatment groups were also found in changes in total hip BMD values. In the tamoxifen group, a mean increase from baseline of 0.8% after 12 months and a mean decrease from baseline of 0.4% after 24 months were observed, when compared with a mean decrease of 1.3% after 12 months and 3.3% after 24 months in the exemestane group (each treatment comparison $P < 0.05$; Table 2 and Fig. 3a). Mean total hip T-scores remained at -0.41 after 12 months and increased to -0.39 after 24 months in the tamoxifen group. In the exemestane group, a decrease in mean total hip T-scores from -0.43 to -0.60 and to -0.72 after 12 and 24 months, respectively, was observed (each treatment comparison

Table 1 Demographics and clinical baseline characteristics

Variable	Netherlands/Belgium sub-study			German sub-study			US sub-study			Pooled data		
	Tam. n = 40	Exe. n = 44	Overall N = 84	Tam. n = 83	Exe. n = 78	Overall N = 161	Tam. n = 89	Exe. n = 78	Overall N = 167	Tam. n = 212	Exe. n = 200	Overall N = 412
<i>Demographic characteristic, mean</i>												
Age, years*	62.6	61.3	61.9	61.1	61.0	61.1	65.1	62.7	64.0	63.0	61.8	62.4
Height, cm	164.0	163.6	163.8	164.3	163.1	163.7	NA	NA	NA	164.2	163.3	163.7
Weight, kg	78.1 [†]	72.1 [†]	74.9	73.9	70.5	72.2	NA	NA	NA	75.3	71.1	73.2
<i>Baseline characteristics, n (%)</i>												
Tumor stage*												
0 or I	2 (5.0)	7 (15.9)	9 (10.7)	58 (69.9)	54 (69.2)	112 (69.6)	NA	NA	NA	60 (48.8)	61 (50.0)	121 (49.4)
II	28 (70.0)	34 (77.3)	62 (73.8)	1 (1.2)	1 (1.3)	2 (1.2)	NA	NA	NA	29 (23.6)	35 (28.7)	64 (26.1)
III	10 (25.0)	3 (6.8)	13 (15.5)	22 (26.5)	23 (29.5)	45 (28.0)	NA	NA	NA	32 (26.0)	26 (21.3)	58 (23.7)
NA	0 (0)	0 (0)	0 (0)	2 (2.4)	0 (0)	2 (1.2)	NA	NA	NA	2 (1.6)	0 (0)	2 (0.8)
Tumor grade												
G1	7 (17.9)	6 (13.6)	13 (15.7)	2 (2.4)	3 (3.8)	5 (3.1)	NA	NA	NA	9 (7.4)	9 (7.4)	18 (7.4)
G2	15 (38.5)	18 (40.9)	33 (39.8)	62 (74.7)	61 (78.2)	123 (76.4)	NA	NA	NA	77 (63.1)	79 (64.8)	156 (63.9)
G3	17 (43.6)	20 (45.5)	37 (44.6)	19 (22.9)	13 (16.7)	32 (19.9)	NA	NA	NA	36 (29.5)	33 (27.0)	69 (28.3)
GX	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)	1 (0.6)	NA	NA	NA	0 (0)	1 (0.8)	1 (0.4)
Lymph nodes*												
Negative	4 (10.0)	5 (11.4)	9 (10.7)	58 (69.9)	54 (69.2)	112 (69.6)	67 (75.3)	60 (76.9)	127 (76.0)	129 (60.8)	119 (59.5)	248 (60.2)
1–3 positive	22 (55.0)	29 (65.9)	51 (60.7)	21 (25.3)	19 (24.4)	40 (24.8)	16 (18.0)	13 (16.7)	29 (17.4)	59 (27.8)	61 (30.5)	120 (29.1)
≥4 positive	10 (25.0)	3 (6.8)	13 (15.5)	3 (3.6)	5 (6.4)	8 (5.0)	6 (6.7)	5 (6.4)	11 (6.6)	19 (9.0)	13 (6.5)	32 (7.8)
Missing value	4 (10.0)	7 (15.9)	11 (13.1)	1 (1.2)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	5 (2.4)	7 (3.5)	12 (2.9)
Prior therapy												
Chemotherapy	25 (62.5)	19 (43.2)	44 (52.4)	32 (38.6)	31 (39.7)	63 (39.1)	26 (29.2)	24 (30.8)	50 (29.9)	83 (39.2)	74 (37.0)	157 (38.1)
Radiotherapy	30 (75.0)	28 (63.6)	58 (69.0)	70 (84.3)	69 (88.5)	139 (86.3)	50 (56.2)	41 (52.6)	91 (54.5)	150 (70.8)	138 (69.0)	288 (69.9)

NA not available

* Significant difference between sub-studies (age: $P = 0.0059$; tumor stage: $P = 0.0002$; number of positive lymph nodes: $P < 0.0001$; ANOVA using pooled data)

[†] Significant difference between treatment groups ($P = 0.0299$; ANOVA using the Netherlands/Belgium sub-study data)

$P < 0.01$; Table 2 and Fig. 3b). A slight increase was also found in mean total hip Z-scores in the tamoxifen group from 0.54 to 0.63 at month 12 and to 0.62 at month 24 versus a decrease from 0.60 to 0.55 after 12 months and to 0.46 after 24 months in the exemestane group (each treatment comparison $P < 0.01$; Table 2 and Fig. 3c).

Bone turnover markers

PINP levels (the Netherlands/Belgium and German sub-studies only) decreased from baseline in the tamoxifen group and increased in the exemestane group (Table 3 and Fig. 4a). Differences between treatment groups in changes from baseline to month 6 ($P < 0.0001$) and month 12 ($P < 0.0001$) were statistically significant (other time points were not tested). Differences between treatment groups in changes from baseline to month 12 were also significantly different between the German and Netherlands/Belgium sub-studies for PINP levels ($P = 0.0237$).

The trends over the study period for the differences between treatment groups in CTx (the Netherlands/

Belgium sub-study only) and ICTP (German sub-study only) followed a similar pattern as observed with PINP levels (Table 3; Fig. 4b, c).

Additional analysis

Shift in BMD status

Among patients with a normal BMD value at baseline, a higher proportion of those in the exemestane group developed osteopenia at months 12 and 24 (Fig. 5). Only one patient in the exemestane group with a normal BMD value at baseline developed osteoporosis at 12 months.

Discussion

Our results show that tamoxifen and exemestane were significantly different with regard to change from baseline to months 12 and 24 in lumbar spine BMD. The observed changes in lumbar spine BMD corresponded to an average

Table 2 Measured bone mineral density values at screening and at months 12 and 24

Variable	Netherlands/Belgium sub-study			German sub-study			US sub-study			Pooled data		
	<i>n</i>	Tam. mean (SD)	Exe. mean (SD)	<i>n</i>	Tam. mean (SD)	Exe. mean (SD)	<i>n</i>	Tam. mean (SD)	Exe. mean (SD)	<i>n</i>	Tam. mean (SD)	Exe. mean (SD)
L1-L4 (g/cm²)												
Screening	43	1.02 (0.17)	1.00 (0.20)	61	1.14 (0.17)	1.10 (0.15)	89	1.10 (0.17)	1.09 (0.16)	193	1.09 (0.17)	1.07 (0.17)
Month 12	40	1.06 (0.17)	0.99 (0.70)	57	1.16 (0.18)	1.08 (0.15)	89	1.11 (0.17)	1.06 (0.16)	186	1.11 (0.18)	1.05 (0.17)
Month 24	32	1.07 (0.16)	0.99 (0.18)	34	1.15 (0.17)	1.06 (0.15)	89	1.09 (0.17)	1.05 (0.15)	155	1.10 (0.17)	1.04 (0.16)
L1-L4 (T-score)												
Screening	43	-0.68 (1.37)	-0.89 (1.68)	61	-0.37 (1.41)	-0.66 (1.23)	89	-0.14 (1.22)	-0.36 (1.27)	193	-0.34 (1.33)	-0.59 (1.38)
Month 12	41	-0.60 (1.33)	-1.08 (1.50)	57	-0.21 (1.51)	-0.82 (1.21)	89	-0.03 (1.29)	-0.62 (1.17)	187	-0.21 (1.38)	-0.79 (1.28)
Month 24	35	-0.41 (1.23)	-1.01 (1.54)	35	-0.26 (1.42)	-0.93 (1.20)	89	-0.17 (1.21)	-0.59 (1.11)	159	-0.24 (1.26)	-0.79 (1.26)
L1-L4 (Z-score)												
Screening	38	0.53 (1.32)	0.58 (1.71)	59	0.63 (1.34)	0.50 (1.33)	NA	NA	NA	97	0.59 (1.33)	0.53 (1.48)
Month 12	40	0.75 (1.27)	0.26 (1.56)	55	0.77 (1.44)	0.41 (1.33)	NA	NA	NA	95	0.76 (1.37)	0.34 (1.43)
Month 24	32	0.84 (1.26)	0.33 (1.54)	36	0.77 (1.28)	0.23 (1.23)	NA	NA	NA	68	0.81 (1.26)	0.28 (1.37)
Total hip (g/cm²)												
Screening	42	0.80 (0.14)	0.82 (0.15)	50	0.96 (0.14)	0.99 (0.13)	89	0.93 (0.16)	0.91 (0.16)	181	0.91 (0.16)	0.91 (0.16)
Month 12	40	0.83 (0.14)	0.83 (0.13)	50	0.97 (0.14)	0.98 (0.13)	89	0.93 (0.14)	0.90 (0.16)	179	0.92 (0.15)	0.90 (0.15)
Month 24	32	0.85 (0.10)	0.82 (0.13)	29	0.97 (0.12)	0.95 (0.12)	89	0.91 (0.16)	0.88 (0.13)	150	0.91 (0.14)	0.88 (0.14)
Total hip (T-score)												
Screening	42	-0.95 (1.29)	-0.88 (1.18)	50	-0.12 (1.09)	0.08 (1.02)	89	-0.32 (1.12)	-0.48 (1.20)	181	-0.41 (1.19)	-0.43 (1.19)
Month 12	41	-0.95 (1.17)	-0.90 (1.00)	50	-0.13 (1.14)	0.01 (1.08)	89	-0.31 (1.08)	-0.74 (1.21)	180	-0.41 (1.15)	-0.60 (1.18)
Month 24	35	-0.55 (1.22)	-0.90 (1.05)	29	-0.17 (0.95)	-0.36 (1.03)	89	-0.40 (1.19)	-0.79 (1.05)	153	-0.39 (1.16)	-0.72 (1.06)
Total hip (Z-score)												
Screening	38	0.19 (1.23)	0.29 (1.07)	44	0.83 (0.95)	0.86 (1.05)	89	NA	NA	82	0.54 (1.13)	0.60 (1.09)
Month 12	40	0.41 (1.06)	0.35 (0.92)	42	0.84 (1.03)	0.78 (1.03)	89	NA	NA	82	0.63 (1.06)	0.55 (0.99)
Month 24	34	0.46 (1.06)	0.43 (0.92)	26	0.83 (0.84)	0.49 (0.98)	89	NA	NA	60	0.62 (0.98)	0.46 (0.94)

NA not available

Table 3 Measured bone turnover values at screening and at months 3, 6, 12, and 24

Variable	Netherlands/Belgium sub-study				German sub-study				Pooled data			
	<i>n</i>	Tam. mean (SD)	<i>n</i>	Exe. mean (SD)	<i>n</i>	Tam. mean (SD)	<i>n</i>	Exe. mean (SD)	<i>n</i>	Tam. mean (SD)	<i>n</i>	Exe. mean (SD)
PINP (µg/L)*												
Screening	36	59.42 (24.77)	40	58.15 (22.07)	63	54.15 (30.92)	68	57.75 (39.84)	99	56.06 (28.82)	108	57.90 (34.23)
Month 3	38	42.82 (17.57)	38	61.97 (26.60)	51	43.90 (18.33)	61	79.82 (57.24)	89	43.44 (17.91)	99	72.97 (48.47)
Month 6	35	37.43 (18.72)	37	63.70 (27.88)	52	39.51 (19.32)	60	81.20 (56.83)	87	38.67 (19.00)	97	74.53 (48.47)
Month 12	34	30.41 (11.60)	37	64.62 (27.60)	60	33.20 (15.67)	66	84.61 (49.05)	94	32.19 (14.33)	103	77.43 (43.53)
Month 24	32	32.24 (19.12)	35	59.00 (17.55)	15	30.11 (11.66)	17	66.01 (31.48)	47	31.63 (17.00)	52	61.29 (28.78)
CTx (µg/L)												
Screening	36	0.31 (0.12)	40	0.35 (0.16)								
Month 3	38	0.22 (0.10)	38	0.38 (0.20)								
Month 6	35	0.20 (0.10)	37	0.40 (0.19)								
Month 12	34	0.20 (0.10)	37	0.46 (0.20)								
Month 24	32	0.21 (0.12)	35	0.45 (0.23)								
ICTP (µg/L)												
Screening		NA		NA	63	5.20 (1.80)	68	5.24 (1.79)		NA		NA
Month 3		NA		NA	51	4.56 (2.79)	61	5.97 (2.16)		NA		NA
Month 6		NA		NA	52	4.24 (1.72)	60	5.89 (3.09)		NA		NA
Month 12		NA		NA	60	3.88 (1.45)	66	5.41 (1.72)		NA		NA
Month 24		NA		NA	15	3.61 (0.95)	17	3.95 (1.36)		NA		NA

NA not available

* Differences between treatment groups in changes from baseline to month 12 were significantly different between the German and Netherlands/Belgium sub-studies ($P = 0.0237$)

bone gain of 1.2% after 12 months and 0.2% after 24 months in the tamoxifen group, compared with an average bone loss of 2.6% after 12 months and 3.5% after 24 months in the exemestane group. Although the differences between the treatment groups remained statistically significant, the BMD changes appeared to stabilize over time. Observed changes in the other BMD variables followed a similar pattern. Markers of bone turnover were increased with exemestane and decreased with tamoxifen, and there was a statistically significant difference between the treatment groups at months 6 and 12. These changes, which are indicative of bone loss with exemestane, also appeared to stabilize after initial treatment.

In the first analysis of the overall TEAM trial at 2.75 years, exemestane was associated with a significant increase compared with tamoxifen in the incidence of osteoporosis (4.7% vs. 2.1%, respectively; $P \leq 0.001$), but no significant increase in the incidence of fractures (2.7% vs. 2.3%, respectively) (Jones et al. 2008b). At a median of 5.1 years of follow-up, compared with the sequence of tamoxifen followed by exemestane, upfront exemestane was associated with a significant increase in osteoporosis (5.4% vs. 9.9%, respectively; $P < 0.001$), arthralgia (20.0% vs. 23.5%, respectively; $P < 0.001$), and fractures (3.5% vs. 5.1%, respectively; $P < 0.001$) (Rea et al. 2009).

Results from other studies evaluating the effects of exemestane on bone health are generally consistent with our findings. A randomized, double-blind study comparing exemestane and placebo showed that exemestane modestly enhanced BMD loss from the femoral neck, but had no significant influence on lumbar bone loss after 2 years of treatment. There was a significant increase in the markers of both bone resorption and formation in the exemestane group (Lønning et al. 2005). The fracture rate was similar in the exemestane and placebo groups (Lønning et al. 2005).

In the IES, patients who were disease-free after 2–3 years of tamoxifen were randomized to switch to exemestane or continue treatment with tamoxifen, for a total of 5 years' endocrine therapy. In this study, patients who switched to exemestane had significantly longer OS when patients with ER-negative disease were excluded from the analysis. The effects of tamoxifen and exemestane on bone health were assessed in a sub-group of 206 patients (Coleman et al. 2007). Within 6 months, patients who switched to exemestane experienced a significant decrease in BMD from baseline at both the total hip and lumbar spine. In year 2, the rate of bone loss had slowed (Coleman et al. 2007). There was also an increase in bone resorption and bone formation markers in patients receiving exemestane (Coleman et al. 2007).

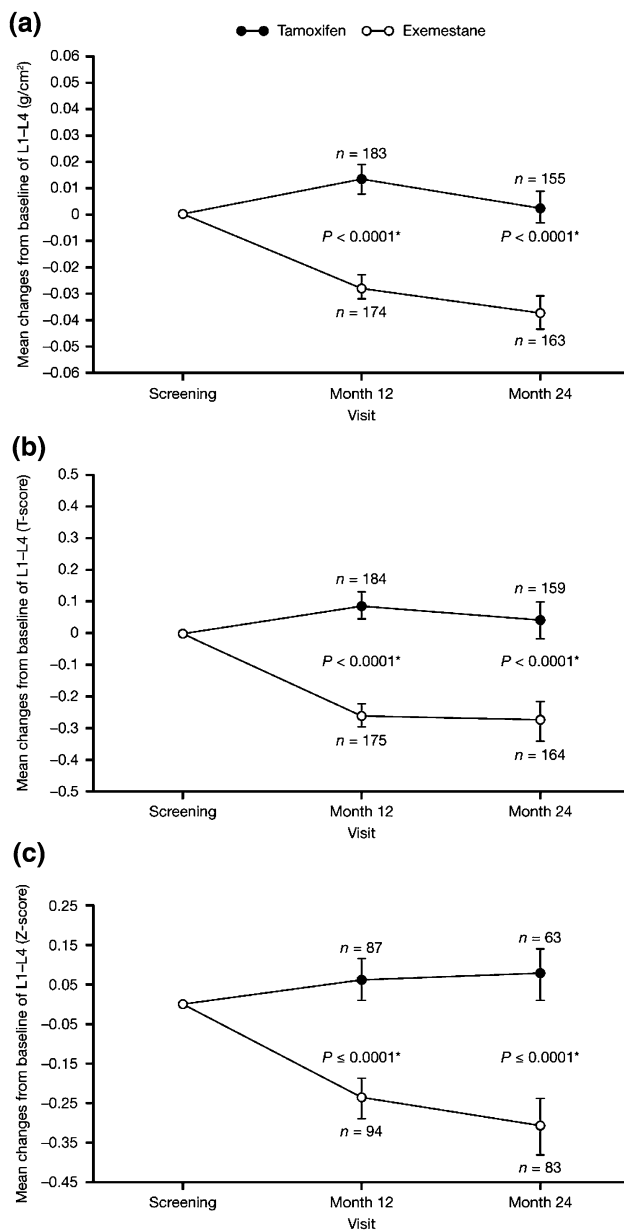


Fig. 2 Mean changes from baseline (\pm SEM) in BMD values over time for lumbar spine **a** g/cm², **b** T-score and **c** Z-score (pooled data). **P* value of differences between treatment groups

Other AIs have been shown to decrease BMD when used as adjuvant treatment. In the Anastrozole, Tamoxifen Alone or in Combination (ATAC) bone sub-study, BMD at the lumbar spine and total hip was significantly decreased by 6–7% in the anastrozole group and increased in the tamoxifen group after 5 years' treatment (Eastell et al. 2008). In the overall ATAC study, there was a significantly increased rate of fractures ($P < 0.0001$) in patients treated with anastrozole compared with those receiving tamoxifen (Howell et al. 2005). Similarly, in the Breast International Group (BIG) 1-98 trial of adjuvant therapy with letrozole

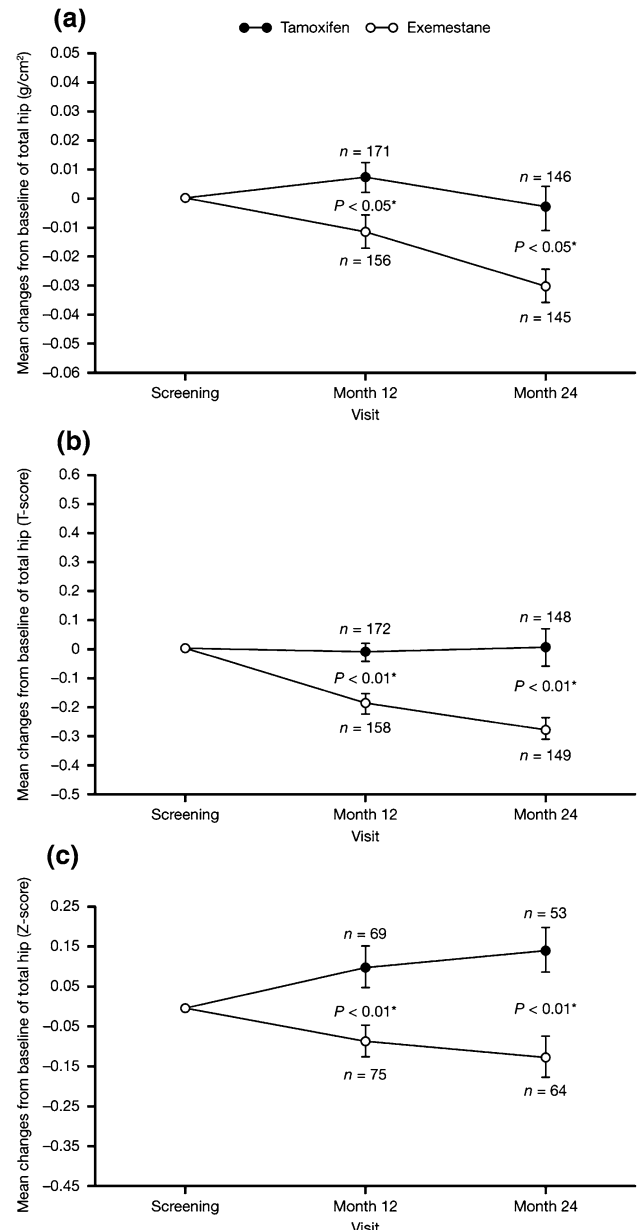


Fig. 3 Mean changes from baseline (\pm SEM) in BMD values over time for total hip **a** g/cm², **b** T-score and **c** Z-score (pooled data). **P* value of differences between treatment groups

or tamoxifen in postmenopausal patients with endocrine-responsive early breast cancer, after 5 years of treatment, the incidence of fractures was higher among patients treated with letrozole (9.3%) than among patients treated with tamoxifen (6.5%) (Rabaglio et al. 2009).

Long-term data suggest the effect of AIs on bone health may be reversed after treatment completion. At a median follow-up of 100 months in the overall ATAC study, patients treated with anastrozole had experienced a significantly higher incidence of fractures during active treatment compared with patients receiving tamoxifen;

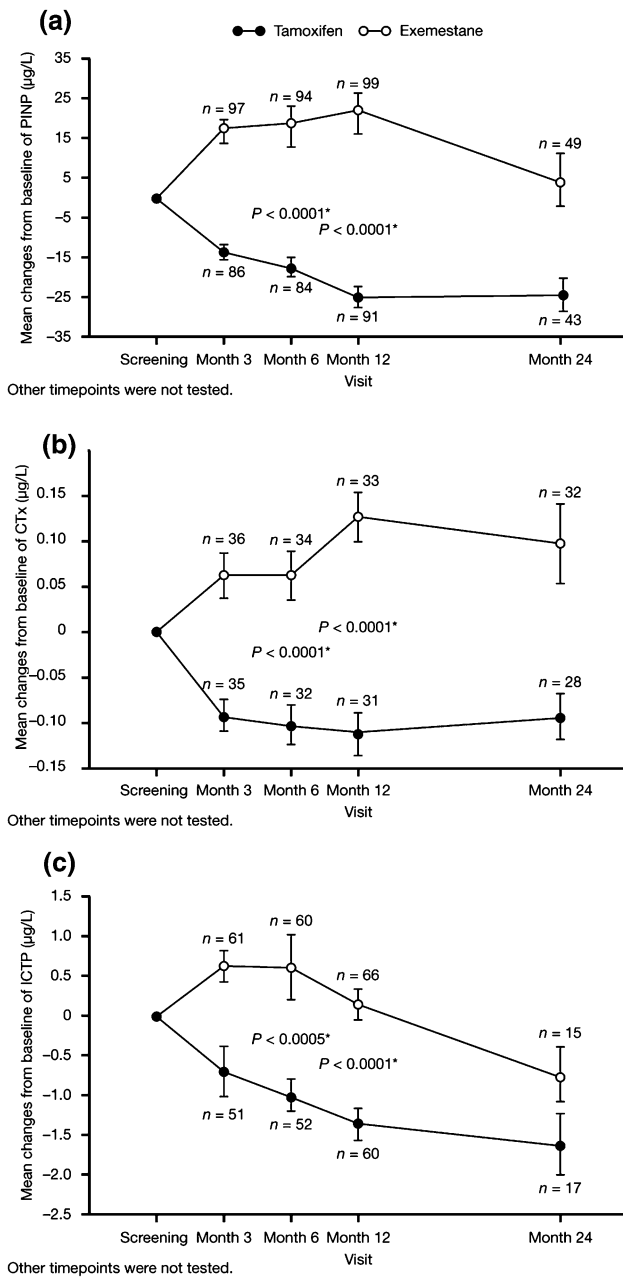


Fig. 4 Mean changes from baseline (±SEM) in bone turnover values over time for **a** PINP (µg/L; pooled data), **b** CTx (µg/L; Netherlands/Belgium sub-study only) and **c** ICTP (µg/L; German sub-study only). *P value of differences between treatment groups

however, there was no difference in the incidence of fractures after completion of treatment (Forbes et al. 2008). It remains unclear whether these results were due to selection bias, since women with a high risk of fracture or who sustained a fracture during the trial were excluded or dropped out. Additionally, it is unknown to what extent anti-fracture medications (such as bisphosphonates) were used. Data from the IES (at a median follow-up of 91 months) suggested that the differences between

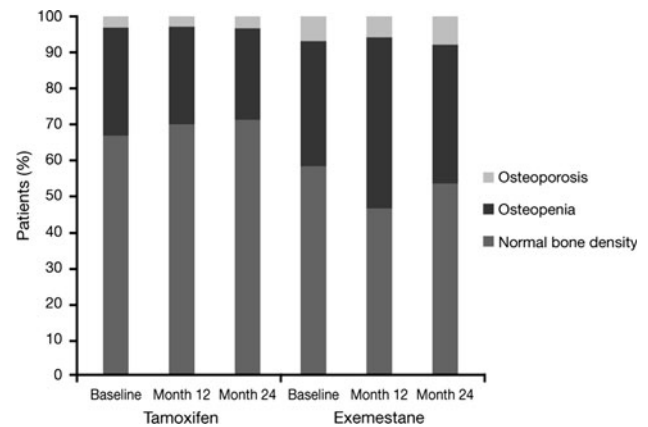


Fig. 5 Proportion of patients with normal BMD, osteopenia, or osteoporosis at baseline, month 12, and month 24

tamoxifen- and exemestane-treated patients with regard to incidence of osteoporosis or fracture decreased after treatment completion (Coleman et al. 2008a; Coombes et al. 2009).

It has been proposed that the steroidal AI exemestane may have different effects on bone metabolism compared with the non-steroidal AIs letrozole and anastrozole. A recent study in postmenopausal patients with breast cancer showed that although there were no significant differences in bone turnover marker levels between exemestane and anastrozole, there was a significant difference in BMD levels in favor of exemestane, after 3 years of treatment (Hozumi et al. 2010). However, results to date have been conflicting, and further studies are required to fully determine any differential effects of AIs on bone health (Goss et al. 2004, 2007; Hadji 2008a; Hadji and Bundred 2007; McCloskey et al. 2007; Miller et al. 2008).

The effects of AIs on bone health should be considered in the context of their superior efficacy and other tolerability benefits relative to tamoxifen. Furthermore, AI-associated bone loss is not life threatening and can be managed (Coleman et al. 2008b; Hadji et al. 2008).

In conclusion, exemestane treatment resulted in decreases in BMD and increases in the markers of bone formation and resorption. In contrast, BMD was increased and markers of bone turnover were decreased with tamoxifen. However, BMD and bone turnover changes appeared to stabilize after initial treatment.

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