

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/29317> holds various files of this Leiden University dissertation.

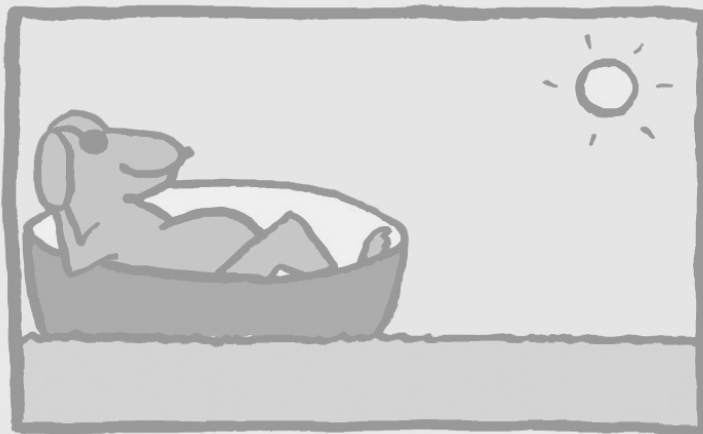
Author: Nes, Johanna Gerarda Hendrica van

Title: Clinical aspects of endocrine therapy of early breast cancer in postmenopausal women

Issue Date: 2014-10-21

5

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



P. Hadji¹, L. Asmar², J.G.H. van Nes³, T. Menschik⁴, A. Hasenburger⁵, J. Kuck⁶, J.W.R. Nortier³,
C.J.H. van de Velde³, S.E. Jones², M. Ziller¹

¹Philipps-University of Marburg, Marburg, Germany;

²US Oncology Research Inc, Houston, TX, USA;

³Leiden University Medical Centre, The Netherlands;

⁴Pfizer Oncology Europe, Paris, France;

⁵University of Freiburg, Freiburg, Germany;

⁶Independent Clinical Research Consulting, Berlin, Germany

Abstract

Background We performed a meta-analysis of three substudies 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.

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

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 and are now recognized options in this setting.¹⁻⁵

The AIs exhibit a tolerability profile distinct from that of tamoxifen, with a lower incidence of gynecological adverse events, thromboembolic events, and endometrial cancer.^{1-3,6} However, while tamoxifen has demonstrated a positive effect on the bone health of postmenopausal women, AI treatment has been associated with a decrease in bone mineral density (BMD) and an increased risk of fracture and osteoporosis.^{1-3,7-9} This impact on bone is likely to be an indirect consequence of the estrogen-depriving mechanism of action of AIs: estrogen withdrawal favors increased osteoclastic activity and bone resorption.¹⁰

The efficacy and safety of exemestane for the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer was investigated in the Tamoxifen Exemestane Adjuvant Multina-

tional (TEAM) trial.¹¹ 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.¹¹ 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; subsequent follow-up analyses confirmed that the benefits of exemestane versus tamoxifen are maintained up to more than 5 years post-treatment.^{12,13}

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; $p < 0.02$).¹¹ Exemestane was associated with a significant increase in the incidence of osteoporosis, but not fractures, versus tamoxifen.¹¹ At a median follow-up of 5.1 years, TEAM showed no significant differences in efficacy between 5 years' exemes-

tane and the sequence of tamoxifen followed by exemestane.¹⁴ Upfront exemestane was associated with a significant increase in osteoporosis, arthralgia, and fractures versus sequential treatment.¹⁴ Sub-studies of TEAM were conducted to determine the effects of exemestane and tamoxifen on bone health in the United States, Germany, and the Netherlands/Belgium.¹⁵⁻¹⁸ 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.

Patients and 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.^{15,16,18}

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

Postmenopausal women with stages I, IIA, IIB, and IIIA T1–3, N0–2, 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 0–2.¹⁹

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, calcitonin, fluoride) 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/cm² 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) 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.¹⁷

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/cm²) 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/cm² 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 substudies included all patients who had a baseline assessment and at least one post-baseline measurement of BMD or bone turnover (Figure 1). Patients were analyzed as randomized, irrespective of the treatment actually received.

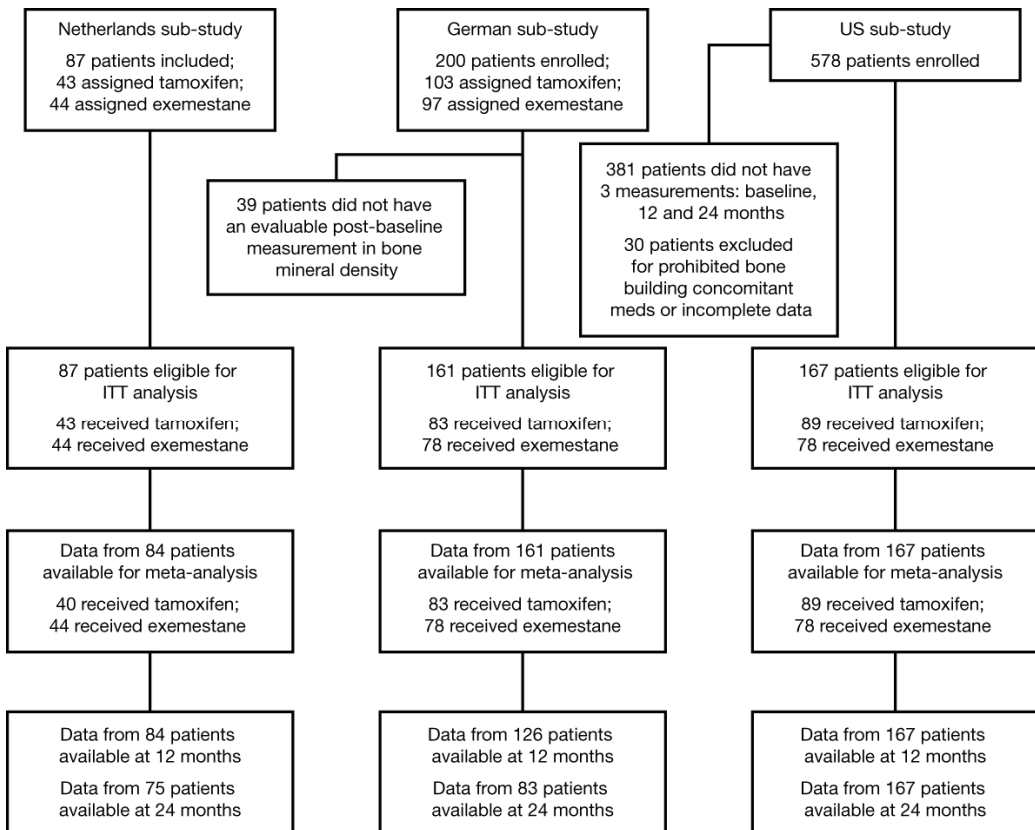


Figure 1 Study profile.

Table 1 Demographics and clinical baseline characteristics.

Variable	Netherlands/Belgium sub-study		German sub-study		US sub-study		Pooled data				
	Tamoxifen n=40	Exemestane n=44	Tamoxifen n=83	Exemestane n=78	Tamoxifen n=89	Exemestane n=78	Tamoxifen n=212	Exemestane n=200	Overall n=412		
Demographic characteristic, mean											
Age, years*	62.6	61.3	61.9	61.0	65.1	62.7	63.0	61.8	62.4		
Height, cm	164.0	163.6	163.8	163.1	NA	NA	164.2	163.3	163.7		
Weight, kg	78.1 [†]	72.1 [†]	74.9	70.5	73.9	72.2	75.3	71.1	73.2		
Baseline characteristics, n (%)											
Tumor stage*											
0 or I	2 (5.0)	7 (15.9)	9 (10.7)	58 (69.9)	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	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	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	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	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	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	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	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)	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)	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)	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)	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)	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)	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)

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 (Figure 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 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 Figure 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 Figure 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 Figure 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 Figure 3a). Mean total hip T-scores remained at -0.41 after 12

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						
	n	Tamoxifen Mean (SD)	Exemestane n Mean (SD)	n	Tamoxifen Mean (SD)	Exemestane n Mean (SD)	n	Tamoxifen Mean (SD)	Exemestane n Mean (SD)	n	Tamoxifen Mean (SD)	Exemestane n Mean (SD)				
L1-L4 (g/cm²)																
Screening	43	1.02 (0.17)	43	1.00 (0.20)	61	1.14 (0.17)	63	1.10 (0.15)	89	1.10 (0.17)	78	1.09 (0.16)	193	1.09 (0.17)	184	1.07 (0.17)
Month 12	40	1.06 (0.17)	43	0.99 (0.70)	57	1.16 (0.18)	55	1.08 (0.15)	89	1.11 (0.17)	78	1.06 (0.16)	186	1.11 (0.18)	176	1.05 (0.17)
Month 24	32	1.07 (0.16)	40	0.99 (0.18)	34	1.15 (0.17)	47	1.06 (0.15)	89	1.09 (0.17)	78	1.05 (0.15)	155	1.10 (0.17)	165	1.04 (0.16)
L1-L4 (T-score)																
Screening	43	-0.68 (1.37)	44	-0.89 (1.68)	61	-0.37 (1.41)	63	-0.66 (1.23)	89	-0.14 (1.22)	78	-0.36 (1.27)	193	-0.34 (1.33)	185	-0.59 (1.38)
Month 12	41	-0.60 (1.33)	43	-1.08 (1.50)	57	-0.21 (1.51)	55	-0.82 (1.21)	89	-0.03 (1.29)	78	-0.62 (1.17)	187	-0.21 (1.38)	176	-0.79 (1.28)
Month 24	35	-0.41 (1.23)	40	-1.01 (1.54)	35	-0.26 (1.42)	47	-0.93 (1.20)	89	-0.17 (1.21)	78	-0.59 (1.11)	159	-0.24 (1.26)	165	-0.79 (1.26)
L1-L4 (Z-score)																
Screening	38	0.53 (1.32)	40	0.58 (1.71)	59	0.63 (1.34)	64	0.50 (1.33)	NA	NA	NA	NA	97	0.59 (1.33)	104	0.53 (1.48)
Month 12	40	0.75 (1.27)	43	0.26 (1.56)	55	0.77 (1.44)	55	0.41 (1.33)	NA	NA	NA	NA	95	0.76 (1.37)	98	0.34 (1.43)
Month 24	32	0.84 (1.26)	40	0.33 (1.54)	36	0.77 (1.28)	47	0.23 (1.23)	NA	NA	NA	NA	68	0.81 (1.26)	87	0.28 (1.37)
Total hip (g/cm²)																
Screening	42	0.80 (0.14)	40	0.82 (0.15)	50	0.96 (0.14)	47	0.99 (0.13)	89	0.93 (0.16)	78	0.91 (0.16)	181	0.91 (0.16)	165	0.91 (0.16)
Month 12	40	0.83 (0.14)	42	0.83 (0.13)	50	0.97 (0.14)	40	0.98 (0.13)	89	0.93 (0.14)	78	0.90 (0.16)	179	0.92 (0.15)	160	0.90 (0.15)
Month 24	32	0.85 (0.10)	38	0.82 (0.13)	29	0.97 (0.12)	36	0.95 (0.12)	89	0.91 (0.16)	78	0.88 (0.13)	150	0.91 (0.14)	152	0.88 (0.14)
Total hip (T-score)																
Screening	42	-0.95 (1.29)	43	-0.88 (1.18)	50	-0.12 (1.09)	47	0.08 (1.02)	89	-0.32 (1.12)	78	-0.48 (1.20)	181	-0.41 (1.19)	168	-0.43 (1.19)
Month 12	41	-0.95 (1.17)	43	-0.90 (1.00)	50	-0.13 (1.14)	39	0.01 (1.08)	89	-0.31 (1.08)	78	-0.74 (1.21)	180	-0.41 (1.15)	160	-0.60 (1.18)
Month 24	35	-0.55 (1.22)	40	-0.90 (1.05)	29	-0.17 (0.95)	36	-0.36 (1.03)	89	-0.40 (1.19)	78	-0.79 (1.05)	153	-0.39 (1.16)	154	-0.72 (1.06)
Total hip (Z-score)																
Screening	38	0.19 (1.23)	39	0.29 (1.07)	44	0.83 (0.95)	44	0.86 (1.05)	89	NA	78	NA	82	0.54 (1.13)	83	0.60 (1.09)
Month 12	40	0.41 (1.06)	43	0.35 (0.92)	42	0.84 (1.03)	38	0.78 (1.03)	89	NA	78	NA	82	0.63 (1.06)	81	0.55 (0.99)
Month 24	34	0.46 (1.06)	40	0.43 (0.92)	26	0.83 (0.84)	33	0.49 (0.98)	89	NA	78	NA	60	0.62 (0.98)	73	0.46 (0.94)

N/A 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			
	n	Tamoxifen Mean (SD)	n	Exemestane Mean (SD)	n	Tamoxifen Mean (SD)	n	Exemestane Mean (SD)	n	Tamoxifen Mean (SD)	n	Exemestane 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)		NA		NA		NA		NA
Month 3	38	0.22 (0.10)	38	0.38 (0.20)		NA		NA		NA		NA
Month 6	35	0.20 (0.10)	37	0.40 (0.19)		NA		NA		NA		NA
Month 12	34	0.20 (0.10)	37	0.46 (0.20)		NA		NA		NA		NA
Month 24	32	0.21 (0.12)	35	0.45 (0.23)		NA		NA		NA		NA
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

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

NA not available.

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 $p < 0.01$; Table 2 and Figure 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 Figure 3c).

Bone turnover markers

PINP levels (the Netherlands/Belgium and German substudies only) decreased from baseline in the tamoxifen group and increased in the exemestane group (Table 3 and Figure 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; Figure 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 (Figure 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 bone

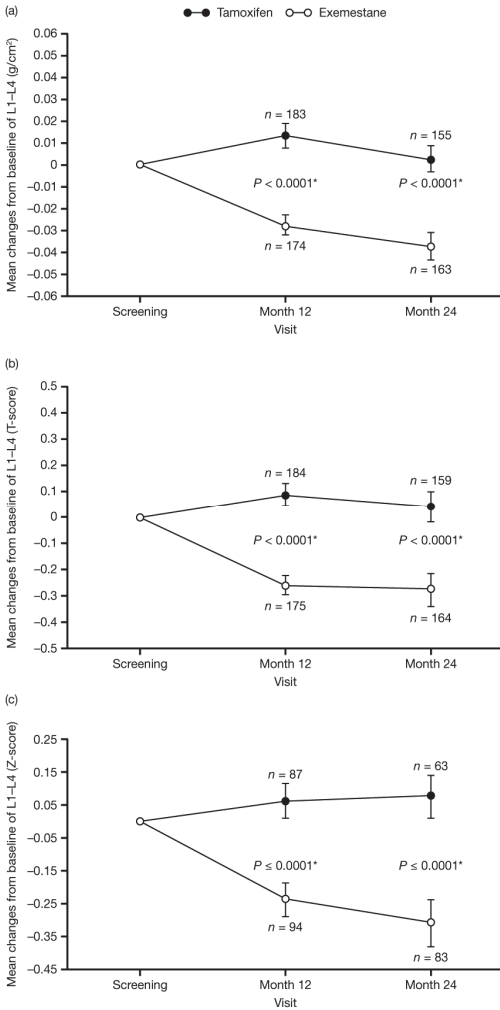


Figure 2 Mean changes from baseline (\pm SEM) in BMD values over time for lumbar spine **a** g/cm^2 , **b** T-score and **c** Z-score (pooled data).
**p* value of differences between treatment groups.

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 signifi-

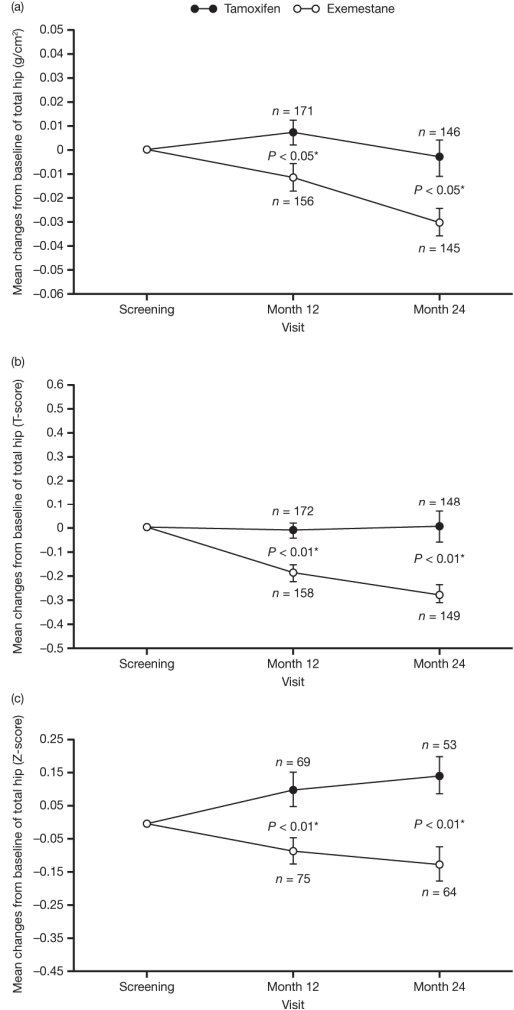


Figure 3 Mean changes from baseline (\pm SEM) in BMD values over time for total hip **a** g/cm^2 , **b** T-score and **c** Z-score (pooled data).
**p* value of differences between treatment groups.

cant 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%, respective-

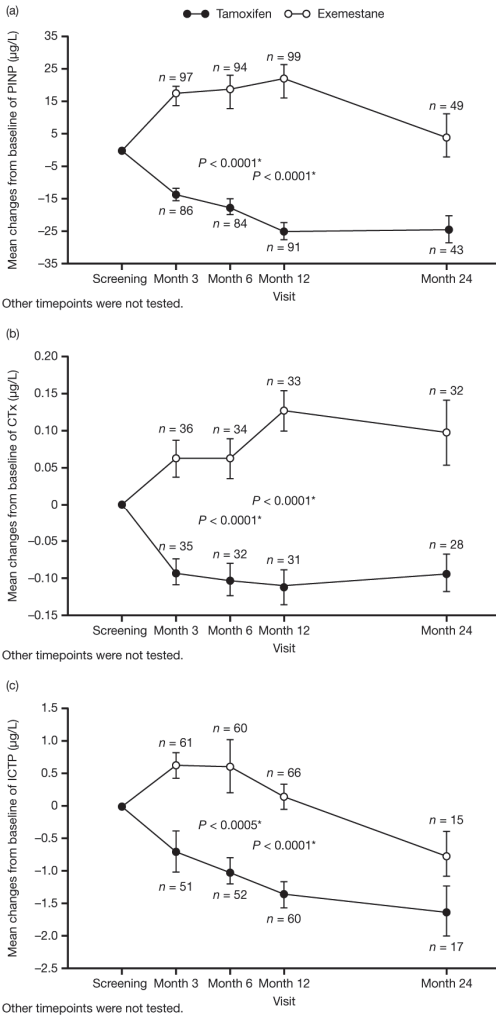


Figure 4 Mean changes from baseline (±SEM) in bone turnover values over time for **a** PINP (µg/L; pooled data), **b** CTx (µg/L; Netherlands/Belgium sub-study only) and **c** ICTP (µg/L; German sub-study only). *p value of differences between treatment groups.

ly).¹¹ 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; $p < 0.001$).¹⁴

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.²⁰ The fracture rate was similar in the exemestane and placebo groups.²⁰

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.²¹ 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.²¹ There was also an increase in bone resorption and bone formation markers in patients receiving exemestane.²¹

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.²² 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.²³ Similarly, in the Breast International Group (BIG) 1-98 trial of adjuvant therapy with letrozole 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%).²⁴

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 inci-

dence of fractures during active treatment compared with patients receiving tamoxifen; however, there was no difference in the incidence of fractures after completion of treatment.³ 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 tamoxifen- and exemestane-treated patients with regard to incidence of osteoporosis or fracture decreased after treatment completion.^{13,25}

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.²⁶ However, results to date have been conflicting, and further studies are required to fully determine any differential effects of AIs on bone health.^{9,27-31}

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.^{32,33}

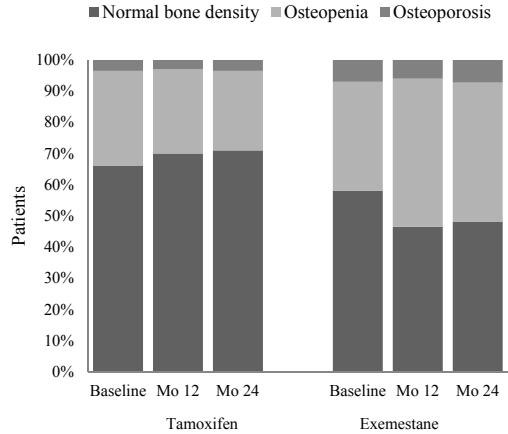


Figure 5 Proportion of patients with normal BMD, osteopenia, or osteoporosis at baseline, month 12, and month 24.

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.

Acknowledgements

The authors would like to acknowledge Dr Luc Dirix for his help with the Belgian data. Editorial assistance for this paper was provided by Caroline Masterman at ACUMED (Iytherington, UK) and was funded by Pfizer, Inc. This work was supported by a scientific research grant from Pfizer, Inc [grant number EXEAPO-0028-119].

References

- Coates AS, Keshaviah A, Thurlimann B et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol* 2007;25:486-92.
- Coombs RC, Kilburn IS, Snowdon CF et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007;369:559-70.
- Forbes JE, Cuzick J, Buzdar A et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9:45-53.
- Goldhirsch A, Ingle JN, Gelber RD et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009;20:1319-29.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer V.1.2009. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.
- Hadji P. Menopausal symptoms and adjuvant therapy-associated adverse events. *Endocrine-Related Cancer* 2008;15:73-90.
- Love RR, Mazess RB, Barden HS et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; 326:852-6.
- Hadji P. Aromatase inhibitor-associated bone loss in breast cancer. *US Oncological Disease* 2007;1:18-21.
- Hadji P, Bundred N. Reducing the risk of cancer treatment-associated bone loss in patients with breast cancer. *Semin Oncol* 2007;34:S4-10.

10. Frenkel B, Hong A, Baniwal SK et al. Regulation of adult bone turnover by sex steroids. *J Cell Physiol* 2010;224:305–10.
11. Jones SE, Seynaeve C, Hasenburg A et al. Results of the first planned analysis of the TEAM (tamoxifen exemestane adjuvant multinational) prospective randomized phase III trial in hormone sensitive postmenopausal early breast cancer. *SABCS* 2008.
12. Coombes RC, Hall E, Gibson LJ et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004 350:1081–92.
13. Coombes RC, Kilburn LS, Beare S et al. Survival and safety post study treatment completion: an updated analysis of the Intergroup Exemestane Study (IES). *ECCO 15-ESMO 34 meeting* 2009, oral presentation.
14. Rea DW, Hasenburg A, Seynaeve C et al. Five years of exemestane as initial therapy compared to 5 years of tamoxifen followed by exemestane: The TEAM trial, a prospective, randomized, phase III trial in postmenopausal women with hormone-sensitive early breast cancer. *SABCS* 2009.
15. Jones S, Stokoes.C., Sborov M. The effect of tamoxifen or exemestane on bone mineral density during the first 2 years of adjuvant treatment of postmenopausal women with early breast cancer. *Clin Breast Cancer* 2008;8:527–32.
16. Hadji P, Ziller M, Kieback DG et al. Effects of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial: results of a German, 12-month, prospective, randomised sub-study. *Ann Oncol* 2009;20:203–7.
17. Hadji P, Ziller M, Kieback DG et al. The effect of exemestane or tamoxifen on markers of bone turnover: results of a German sub-study of the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial. *Breast* 2009;18:159–64.
18. van Nes JGH, Papapoulos SE, Braun JJ et al. Effect of exemestane on bone turnover markers and bone mineral density (BMD): 2 year results of the Dutch/Belgian Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial. *SABCS* 2008.
19. van Nes JGH, Seynaeve C, Jones S et al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries. *Br J Surg* 2010;97:671–9.
20. Lönning PE, Geisler J, Krag LE et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005;23:5126–37.
21. Coleman RE, Banks LM, Girgis SI et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007;8:119–27.
22. Eastell R, Adams JE, Coleman RE et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008;26:1051–7.
23. Howell A, Cuzick J, Baum M et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60–2.
24. Rabaglio M, Sun Z, Price KN et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. *Ann Oncol* 2009;20:1489–98.
25. Coleman RE, Banks LM, Girgis SI et al. Reversal of skeletal effects of endocrine treatments in the intergroup exemestane study. *SABCS* 2008.
26. Hozumi Y, Aihara T, Suemasu K et al. The effect of exemestane and anastrozole on bone mineral density and bone turnover markers in postmenopausal early breast cancer patients: final results of 3 years after randomization of N-SAS (national surgical adjuvant study) BC04, the TEAM Japan sub-study. *European Breast Cancer Conference*, 2010; poster presentation.
27. Goss PE, Qi S, Cheung AM et al. Effects of the steroidal aromatase inhibitor exemestane and the nonsteroidal aromatase inhibitor letrozole on bone and lipid metabolism in ovariectomized rats. *Clin Cancer Res* 2004;10:5717–23.
28. Goss PE, Hadji P, Subar M et al. Effects of steroidal and nonsteroidal aromatase inhibitors on markers of bone turnover in healthy postmenopausal women. *Breast Cancer Res* 2007;9:R52.
29. Hadji P. Aromatase inhibitor-associated bone loss in breast cancer patients is distinct from postmenopausal osteoporosis. *Crit Rev Oncol Hematol* 2008;69:73–82.
30. McCloskey EV, Hannon RA, Lakner G et al. Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. *Eur J Cancer* 2007;43:2523–31.
31. Miller WR, Bartlett J, Brodie AM et al. Aromatase Inhibitors: Are There Differences Between Steroidal and Nonsteroidal Aromatase Inhibitors and Do They Matter? *Oncologist* 2008;13:829–37.
32. Coleman RE, Bolten WW, Lansdown M et al. Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations. *Cancer Treat Rev* 2008;34:275–82.
33. Hadji P, Body JJ, Aapro MS et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. *Ann Oncol* 2008;19:1407–16.

