



## Reversal of skeletal effects of endocrine treatments in the Intergroup Exemestane Study

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**Reversal of skeletal effects of endocrine treatments in the Intergroup  
Exemestane Study**

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## Reversal of skeletal effects of endocrine treatments in the IES

### Abstract

The adjuvant use of aromatase inhibitors in breast cancer is associated with adverse effects on bone health. We previously reported a decline in bone mineral density (BMD) following the switch from tamoxifen to exemestane in the Intergroup Exemestane Study (IES). Here we report effects of endocrine treatment withdrawal on BMD, bone turnover markers (BTM) and fracture rates.

4724 patients took part in IES, and 206 patients were included in a bone sub-study. BMD and BTM were assessed pre-randomization, during, and after the end of treatment (EOT). To evaluate treatment withdrawal effects, 12 and 24 month (m) post-EOT BMD results are available for 122 and 126 patients respectively. Similar patient numbers had BTM measured post EOT.

Following treatment withdrawal, the differences in BMD observed between the two endocrine strategies were partially reversed. At 24m from EOT, spine BMD increased by 1.53% (95% CI 0.63 to 2.43;  $p=0.001$ ) after stopping exemestane, and fell by 1.93% (95% CI -2.91 to 0.95;  $p=0.0002$ ) following tamoxifen withdrawal. A similar pattern of changes was observed at the hip. At 2 years post EOT, BMD changes from baseline were similar with both treatment strategies. Corresponding inverse changes in BTM were seen, with an increase following tamoxifen withdrawal and a reduction after exemestane. A higher number of fractures occurred during exemestane treatment, but fracture rates were similar after treatment withdrawal.

With the switch strategy used in IES, the on treatment adverse bone effects of exemestane are reversed. Ongoing monitoring of BMD is therefore not routinely required.

Word count: 249

### Introduction

Aromatase inhibitors (AI) have become part of standard care for the majority of postmenopausal women with estrogen receptor positive (ER+) early breast cancer. An AI may be started in the immediate post-operative period, typically for five years, or after a few years of tamoxifen in a sequencing strategy. Both approaches have been shown to be more effective than tamoxifen alone at preventing breast cancer recurrence. AI also have a generally more favorable side effect profile [1-4]. However, through their ability to profoundly suppress circulating and tissue based estrogens, AI are associated with musculoskeletal adverse events. These include arthralgia and accelerated bone loss which may lead to fragility fractures [5,6].

The role of exemestane, a steroidal AI, in the adjuvant treatment of postmenopausal women with early breast cancer has been tested in the Intergroup Exemestane Study (IES - ISRCTN number 11883920). In this trial, women on adjuvant tamoxifen and in remission following 2-3 years of treatment were randomized to either continue tamoxifen or switch to exemestane until the completion of 5 years adjuvant treatment [3]. Clear benefit in terms of disease-free survival and modest, but significant, improvement in overall survival were demonstrated and confirmed at subsequent updated analyses [7,8].

Within IES, we performed a detailed bone sub-study to assess changes in bone mineral density (BMD) and bone metabolism. The 24 month results of this sub-study, and the incidence of fractures within the main trial were published previously [9]. After switching to exemestane, a statistically significant reduction in BMD and increase in bone turnover markers (BTM) were observed. Here, we report the changes in BMD and bone metabolism that occur after the end of treatment (EOT) and assess the overall effects of both treatment strategies on bone health.

### **Patients and Methods**

#### **Study Design**

4724 postmenopausal women with histologically confirmed, completely resected, ER+ or ER unknown unilateral breast cancer, who were clinically disease-free and on tamoxifen following 2-3 years treatment, were randomized (double-blind design) to either continue tamoxifen 20mg daily or switch to exemestane 25mg daily to complete a total of 5 years of adjuvant endocrine therapy.

The bone sub-study was conducted in centers that had access to high quality dual-energy x-ray absorptiometry (DXA) facilities. The institutional review board or local ethics committee at each participating centre approved the sub-study, and all patients gave written informed consent to participate.

#### **Patient eligibility**

All patients from participating centers considered for IES were to be approached to enter the bone sub-study, subject to eligibility and patient choice. In addition, repeated accurate determination of BMD by DXA had to be technically possible, and baseline lumbar (L1-4) spine (LS) and total hip (TH) BMD T-scores needed to be above -2.5 SD. A history of fracture in the previous 6 months, treatment with bisphosphonates, calcium supplements for >1 month, or drug therapy with expected effects on bone metabolism at study entry or in the previous 6 months precluded entry into the bone sub-study.

#### **Study Measures**

BMD was measured by DXA of LS (L1-4) and the hip (total, femoral neck and Ward's triangle) prior to randomization into the main IES study. Follow-up measurements were performed at 6, 12 and 24 months (m), at the end of treatment (EOT) and at 12 and 24m after EOT. To improve precision and provide consistency, DXA scanning procedures were standardized and scans monitored and centrally analyzed by the Central Evaluation Facility (CEF) at Imperial College, London, UK. Throughout the study, instrument quality control

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procedures were undertaken at each scanning centre. These results were reviewed regularly by the CEF to confirm reliability and precision.

Serum and urine samples were collected for analysis of a panel of bone resorption and formation markers on two occasions prior to randomization. Follow-up samples were obtained at 3, 6, 9, 12, 18 and 24m on study medication, EOT and at 3, 12 and 24m after EOT. The second voided urine of the day was collected for urinary measurements, and results expressed as a ratio to urinary creatinine (Cr) concentration. Serum was taken whenever possible in the fasting state and at a similar time of day to minimize diurnal and dietary related effects. The bone resorption markers assessed were: urinary N-terminal (NTX) and serum C-terminal (CTX) cross-linked telopeptides of type 1 collagen (CTX), and urinary deoxypyridinoline (DPD). Bone formation markers measured were: serum bone alkaline phosphatase (B-ALP), osteocalcin (OC) and the C-terminal procollagen peptide fragment (PICP). 1,25 OH vitamin D levels were also measured at baseline.

Bone markers were analysed at Imperial College, London, UK. using ELISAs from Nordic Bioscience Diagnostics, Herlev, Denmark (CTX and OC); Quidel Corporation, San Diego, USA. (BAP, DPD and PICP) and Ostex International, Seattle, USA (NTX). The intra and inter assay CV were <8.4% for all markers. Vitamin D was measured by competitive enzyme immunoassay from Immunodiagnostic Systems Limited, Boldon, UK; the intra and inter assay CV were <9.0% for this marker.

The occurrence of clinical fractures was recorded throughout the study. In addition, the CEF reviewed lateral thoraco-lumbar spine radiographs taken prior to randomization, EOT and 2 years post EOT for vertebral fractures. During the conduct of the main IES trial, a specific case report form was introduced to capture data on fractures until 10 years after study entry. However, routine radiographs of the spine were not performed in the main IES trial; thus

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asymptomatic spinal fractures were typically not identified.

### **Study End-Points**

The primary end-point has been reported previously and described the change in LS and TH BMD from baseline to one and two years on study. Here we report secondary end-points which included within and between group changes in BMD and BTM after completion of endocrine treatment. Additionally, the number and annual rates of fractures in the main IES trial, both during and after endocrine therapy was withdrawn, were assessed.

### **Statistical Methods**

Analyses were conducted on a snapshot of data on 24/04/09 using Stata version 10.0 (Stata Corp, College Station, TX, USA). The primary analysis population was based on treatment actually and with data within pre-defined visit windows. These were set at +/- 1m of the follow-up date for the 3, 6, 9, 12 and 18m visits, -1m before or +2m after the 24m window, -3m before and +1m after the EOT visit, +/- 1m of the 3m post EOT follow-up date, +/- 3m of the 12m post EOT dates and +/- 6m for the final 24m post EOT assessment. Where the EOT assessment coincided with the 24m visit, these data were used for both visits. Percentage changes in BMD from baseline were derived and compared using two-sample (between treatment groups) and paired (within groups) T-tests.

As described previously [9], study subjects were censored at the start of any extended adjuvant therapy or bisphosphonate therapy, and at the date of relapse (using data from previous visit  $\geq 3$ m before any bone metastasis to minimize confounding effects on BMD and BTM). In addition, patients who stopped study treatment prior to 24m were also censored at the time of discontinuation. All data in the results section relate to this analysis population unless otherwise stated. Sensitivity analyses conducted for each time point to confirm the robustness of the primary analysis included the ITT population, and patients with complete follow-up. These produced results similar to those found in the primary analysis

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(data not shown).

Because BTM values were not normally distributed, medians and interquartile ranges were used instead of means and standard deviations as a measure of variability. The Mann-Whitney and Wilcoxon Sign Rank non-parametric tests were used to compare percentage change from baseline. Absolute values of the bone markers are shown to allow for the known inhibitory effects on bone turnover of pre-treatment with tamoxifen.

To account for the longitudinal nature of the data, a repeated measures approach was considered using generalized estimating equations. As these models produced similar results, T-tests and change from baseline are shown for simplicity, and to aid clinical interpretation.

Fractures were recorded for all patients as adverse events in the main IES trial, and analyzed according to treatment received, censoring for relapse as above. Analyses were performed on a snapshot of the main study on 08 June 2009, restricted to time on endocrine treatment as well as all available follow up (on and post treatment follow-up, on treatment only [defined as on treatment + 6m post treatment completion to account for treatment washout] and post treatment follow-up only). Time to fracture event analysis, taking into account multiple fractures per patient was conducted. Hazard ratios are presented adjusting for age and weight, time since menopause and country fracture risk as before [9]. In addition, incidence rates were analyzed by treatment group per 1000 women years. To be consistent with the safety reporting in the main IES trial, a p-value <0.01 was deemed statistically significant for fracture reporting to allow some adjustment for multiple testing, and thus 99% confidence intervals are reported.

## **Results**

### **Demographics**

Between April 2000 and February 2003, 206 patients (Exemestane [E]=101



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Tamoxifen [T]=105) were entered into the IES bone sub-protocol from 17 centers. Figure 1 illustrates the patient disposition (CONSORT diagram). The numbers of patients completing study treatment and post EOT follow-up, along with the most frequent reasons for withdrawal are shown. Following treatment, BMD results within the pre-defined visit windows are available for 122 (56E, 66T) and 126 pts (61E, 65T) at 12 and 24m after EOT respectively. Similar numbers of patients were available for BTM measurement at each time point.

The randomized groups were well balanced in terms of demographics and treatments received and have been detailed previously [9]. At baseline, there were no significant differences in BMD, T-score, the proportion of osteopenic patients or levels of bone markers (Table 1). Baseline vitamin D levels were available in 178 patients and similar although low in both groups: 16% sufficient ( $>75\text{nmol/L}$ ), 26% insufficient ( $50\text{-}75\text{nmol/L}$ ) and 58% deficient ( $<50\text{nmol/L}$ ).

### **Bone Mineral Density (BMD) Changes**

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Figures 2a and 2b show the percentage changes (including mean and 95% confidence intervals [CI]) from baseline in LS and TH BMD for each visit. As described previously, BMD remained stable on tamoxifen but fell following the switch to exemestane [9]. Following treatment withdrawal the decline in BMD seen earlier with exemestane was partially reversed. On withdrawal of exemestane, an increase in BMD from EOT to 24m post EOT of 1.53% (95%CI: 0.63 to 2.43;  $p=0.001$ ) was seen, while at the TH, BMD stabilized with a change of 0.05 (95%CI: -0.84 to 0.93;  $p=0.92$ ). Conversely, following tamoxifen withdrawal there was a significant fall in BMD of -1.93% at the LS (95%CI: -2.91 to -0.95;  $p=0.0002$ ) and -2.62% at the TH (95%CI: -3.33 to -1.91;  $p<0.0001$ ) between EOT and 24m post EOT. As a result (Figure 3), the mean changes in BMD from baseline to 24m post EOT (equivalent to 7-8 years after diagnosis) were similar for both treatment strategies: E-T mean % change in BMD at LS was +0.45% (95%CI: -1.15 to 2.03;  $p=0.58$ ); and at TH was +0.96% (95%CI: -0.41 to 2.32,  $p=0.17$ ).

The numbers of patients with osteopenia or osteoporosis at 24m post EOT were similar. 7 patients in each treatment group who had normal baseline BMD at the lumbar spine or hip had osteopenia at the LS or TH at this final time point, but none were osteoporotic. Of those with osteopenia at baseline, 2 patients in each treatment group were osteoporotic at 24m post EOT (Figure 4).

### Bone Markers

The changes in bone markers comparing baseline with on treatment effects have been described previously, with a significant increase in all BTM following the switch to exemestane [9]. Following treatment withdrawal, bone turnover increased after tamoxifen and decreased after exemestane (Figure 4). At 2 years post EOT, the values for the two treatment groups were similar for both bone resorption and formation markers.

### Fracture Incidence

In the main IES study, with a median follow-up in all surviving subjects of 91 months, a total of 494 fractures have been reported, occurring as single or multiple events in 439 patients. 280 of these were in 249 (10.7%) patients allocated to exemestane and 214 in 190 (8.1%) patients allocated tamoxifen (Odds ratio for total number of fractures, OR=1.36; 99%CI: 1.05 to 1.76;  $p=0.002$ ). Whilst study treatment continued there was an excess number of fractures in patients who switch to exemestane (117 vs 86: HR=1.39, 99%CI: 0.96-2.01;  $p=0.02$ ). However, on withdrawal of exemestane the fracture rate fell, and thereafter the difference in total number of fractures between the two treatment groups was not significantly different (163 vs 128: HR=1.20, 99%CI: 0.89-1.63;  $p=0.12$ ).

The fracture incidences/1000 women years of observation (safety analysis, all events) are shown in Figure 6. Two years after randomization the on treatment annual incidence rates per 1000 women years were 21.0 (99%CI: 14.0 to 31.3) and 12.3 (99%CI: 7.4 to 20.6) for the exemestane and tamoxifen groups respectively. Rates fell on treatment withdrawal, such that at 2 years post EOT they were very similar at 20.3 (99%CI: 13.35 to 30.78) and 20.6 (99%CI: 13.5 to 31.4) per 1000 women in the exemestane and tamoxifen groups respectively.

The number of fractures in patients who entered the bone sub-study was low and no inferences on relationships to BMD or bone marker changes can be made. There were 19 fractures in total, of which 4 were traumatic and 15 fragility, evenly distributed (8E, 11T) across the two treatment groups.

### Discussion

In postmenopausal women with recently diagnosed early breast cancer, the use of an aromatase inhibitor in the adjuvant setting has been associated with an average bone loss of around 2% per year in the LS and 1.5% at the hip [9-12]. In IES, we have previously reported that significant changes in BTM and BMD

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appeared within 6m of switching from tamoxifen to exemestane [9]. These were due, at least in part, to the cessation of bone turnover suppression induced by tamoxifen. The percentage median rates of bone loss during treatment with exemestane were -4.2% (95%CI: -5.3 to -3.0) and -3.10% (95%CI: -3.9 to -2.3) at the LS and TH respectively, and significantly different to continued tamoxifen.

Following completion of endocrine treatment, tamoxifen withdrawal was associated with a fall in BMD and an increase in bone turnover. BMD loss in patients who had previously switched to exemestane was partially reversed and the overall declines in BMD in these patients over 4-5 years of observation of -2.6% and -3.0% at the LS and TH approximate to the expected age related bone loss of 0.5-1% per year.

We have not observed a patient with normal baseline BMD (T score >-1) who developed osteoporosis. Although our sample size is quite small it is highly unlikely that such an event would occur with the treatment strategy proposed in IES, as bone loss of >12-15% would be necessary for transition from a normal to osteoporotic state, a degree of change that was not observed in any patient.

The only other study to investigate the withdrawal effects of an AI on the skeleton is the bone sub-protocol of the ATAC trial [11]. Here, in a smaller cohort of patients than studied in this study, withdrawal of anastrozole after 5 years treatment was associated with a mean increase in BMD of 4.0% ( $p=0.0004$ ) and 0.5% ( $p=0.80$ ) at the LS and TH respectively at 2 years after EOT. Both ATAC and MA-17 have reported a decline in BMD on tamoxifen withdrawal. In the ATAC and MA-17 studies respectively, the reductions two years after stopping tamoxifen in LS BMD were -0.3% ( $p=NS$ ) and -0.7% ( $p$  value not stated) and at the TH -2.5% ( $p=0.0002$ ) and -0.7% ( $p$  value not stated) [11,12].

In all studies reported to date, fracture rates with AI have been consistently higher than with tamoxifen. In the IES study, the incidence of fractures was

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significantly increased during exemestane treatment, but this difference was no longer apparent at 12m post EOT. These results are similar to those reported from the ATAC study. Throughout treatment in ATAC, there was a consistent increase in fracture risk (anastrozole 375 vs tamoxifen 324,  $p < 0.0001$ ), but after stopping treatment the annual fracture rates were similar (anastrozole 146 v tamoxifen 143,  $p = \text{NS}$ ) [8]. As shown previously for the effects on BMD [9], these fracture data from IES and ATAC indicate that the clinical significance of the increased bone turnover and subsequent accelerated bone loss and excess fracture risk is closely related to the duration of exposure to an aromatase inhibitor. Exposure to an AI for 2-3 years (as in IES) would be expected to result in an absolute fracture excess that is approximately one half of that seen with treatment for 5 years (as in ATAC). However, longer follow up is required to determine whether bone quality has been fully restored.

IES is the only study to report BTM changes both during and after endocrine treatment. The BTM profiles over the course of the study are consistent with the BMD changes. On completion of treatment, bone turnover increased after withdrawal of tamoxifen and decreased after exemestane was stopped.

In terms of monitoring patients receiving tamoxifen followed by exemestane, we would recommend a BMD assessment around the time of switching endocrine treatment along with life-style advice to maximize bone health, ensure adequate intake of calcium and vitamin D, and follow a risk-adapted strategy for monitoring and intervention with bisphosphonates in line with current clinical guidelines [13,14]. Consistent with other reports, vitamin D levels were deficient or insufficient in the majority of patients [15]. Further study is needed to see if this has any bearing on fracture risk during breast cancer treatment and whether vitamin D and calcium supplementation reduces fracture frequency.

In conclusion, the clinical advantage of the IES switch strategy [7] is achieved at the expense of short term, reversible decline in BMD, and loss of the protective

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effects of tamoxifen on bone. The disease related benefits of such a strategy clearly outweigh these adverse effects and most, if not all, women with ER+ postmenopausal breast cancer should receive an AI such as exemestane as part of adjuvant treatment.

Word count = 2994

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RE Coleman: Protocol development, steering committee, investigator, data interpretation and manuscript writing; LM Banks: Protocol development, study management, manuscript writing analysis of BMD and fracture incidence, provision of data, supervision of BMD measurements and DXA and data quality control; SI Girgis: Protocol development, supervision and provision of biochemical bone marker data, and manuscript writing; L Kilburn: Statistical analysis and manuscript writing; E Vrdoljak: Investigator, data collection, manuscript review and approval; JN Fox: Investigator, data collection, manuscript review and approval; S Cawthorn: Investigator, data collection, manuscript review and approval; A Patel: Investigator, data collection, manuscript review and approval; E Hall: Protocol development, statistical analysis, manuscript review and approval; JM Bliss: Protocol development, statistical analysis, manuscript writing; RC Coombes: Protocol development, main trial CI, data interpretation and manuscript writing.

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### Legend to Figures.

Figure 1: CONSORT diagram illustrating the IES study design and the timing of bone assessments in the bone sub-protocol.

Figure 2: % BMD change from baseline (medians and IQRs) at lumbar spine (a) and total hip (b). BL = baseline; EOT = end of treatment.

Figure 3: Percentage change from baseline in lumbar spine and total hip BMD between treatment groups

Figure 4: Transition between normal, osteopenic & osteoporotic states from baseline to 24 months post treatment. BL = baseline; EOT = end of treatment.

Figure 5: Median (+/- IQR) absolute bone marker values by treatment & visit for resorption (a & b) & formation markers (c & d). BL = baseline; EOT = end of treatment; PT = post treatment.

Figure 6: Annual fracture incidence rate, mean (+/- 99% CI)

**Table 1: Demographic and Baseline Characteristics**

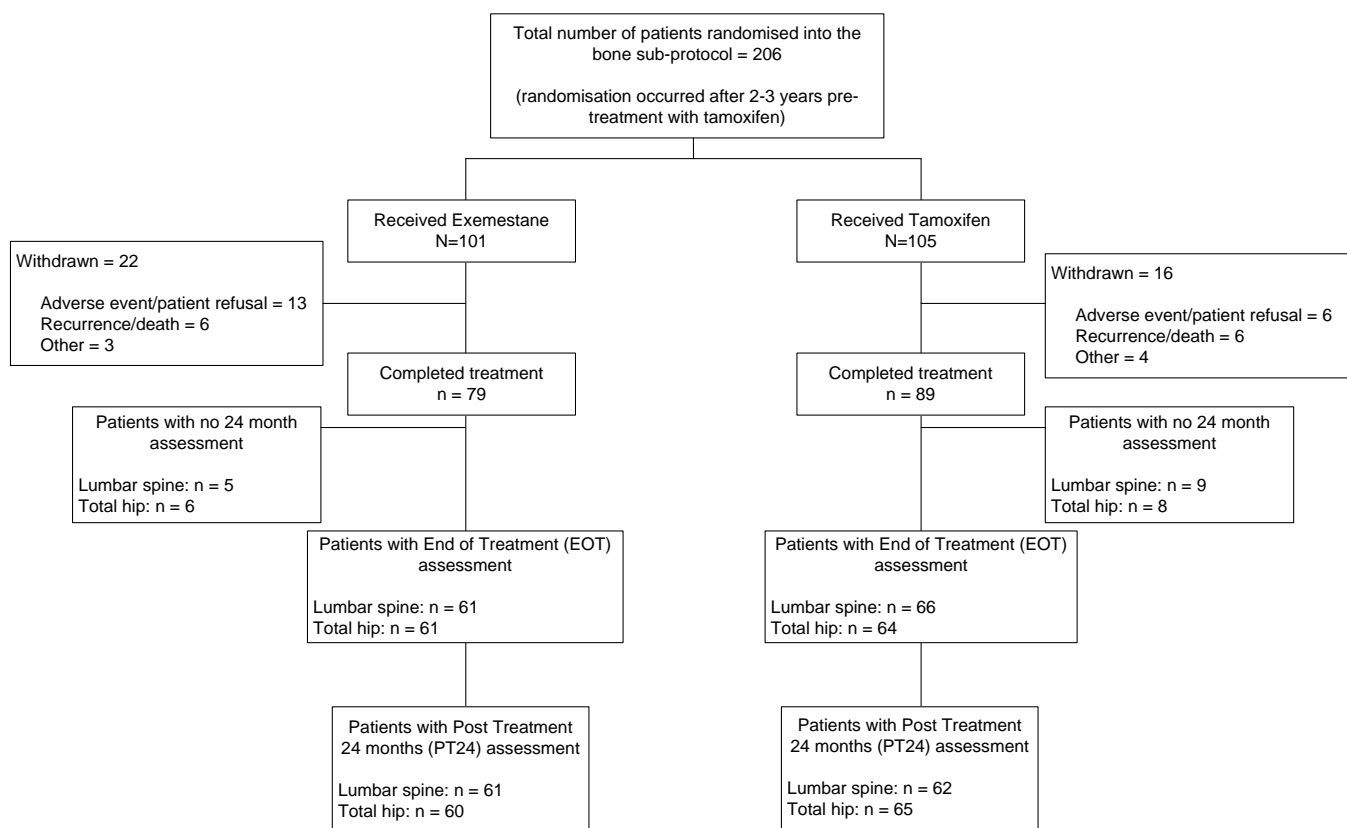
	<b>Exemestane (n=101)</b>	<b>Tamoxifen (n=105)</b>
<b>Age (years), mean (SD)</b>	61.3 (7.6)	59.7 (8.2)
<b>Time since last menses (years), median (IQR)</b>	10.5 (5.5, 16.0)	8.5 (5.0, 16.0)
<b>BMI (kg/m<sup>2</sup>), mean (SD)</b>	28.7 (5.3)	28.8 (5.8)
<b>Prior chemotherapy, n (%)</b>	36 (35.6)	43 (41.0)

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<b>Prior HRT, n (%)</b>		30 (29.7)	40 (38.1)
<b>Duration of initial tamoxifen (months), mean (SD)</b>		30.4 (4.0)	29.0 (3.7)
<b>BMD (g/cm<sup>2</sup>), mean (95%CI)</b>	<b>Lumbar spine</b>	1.06 (1.03, 1.09)	1.08 (1.05, 1.11)
	<b>Total hip</b>	0.96 (0.94, 0.99)	0.98 (0.95, 1.00)
<b>T-score, mean (95%CI)</b>	<b>Lumbar spine</b>	-0.56 (-0.79, -0.34)	-0.46 (-0.68, -0.24)
	<b>Total hip</b>	-0.22 (-0.42, -0.03)	-0.10 (-0.30, 0.10)
<b>DPD/Cr (nM/mM), median (IQR)</b>		5.4 (4.7, 6.4)	5.8 (4.9, 7.3)
<b>NTX/Cr (nM/mM), median (IQR)</b>		42.5 (34.9, 52.5)	40.1 (30.3, 57.3)
<b>CTX (pmol/L), median (IQR)</b>		2207.5 (1577.5, 3078.0)	2696.0 (2038.5, 3561.5)
<b>Bone ALP (U/L), median (IQR)</b>		24.4 (19.9, 29.1)	23.8 (19.5, 28.7)
<b>PICP (µg/L), median (IQR)</b>		82.8 (69.9, 102.6)	85.6 (71.4, 101.9)
<b>Osteocalcin (µg/L), median (IQR)</b>		10.0 (7.9, 14.3)	11.4 (8.4, 14.9)
<b>Vitamin D (nmol/L), median (IQR)</b>		46.3 (34.8, 65.0)	44.2 (31.9, 64.1)

**Figure 1**

## Reversal of skeletal effects of endocrine treatments in the IES



## Reversal of skeletal effects of endocrine treatments in the IES

Figure 2a: Lumbar Spine

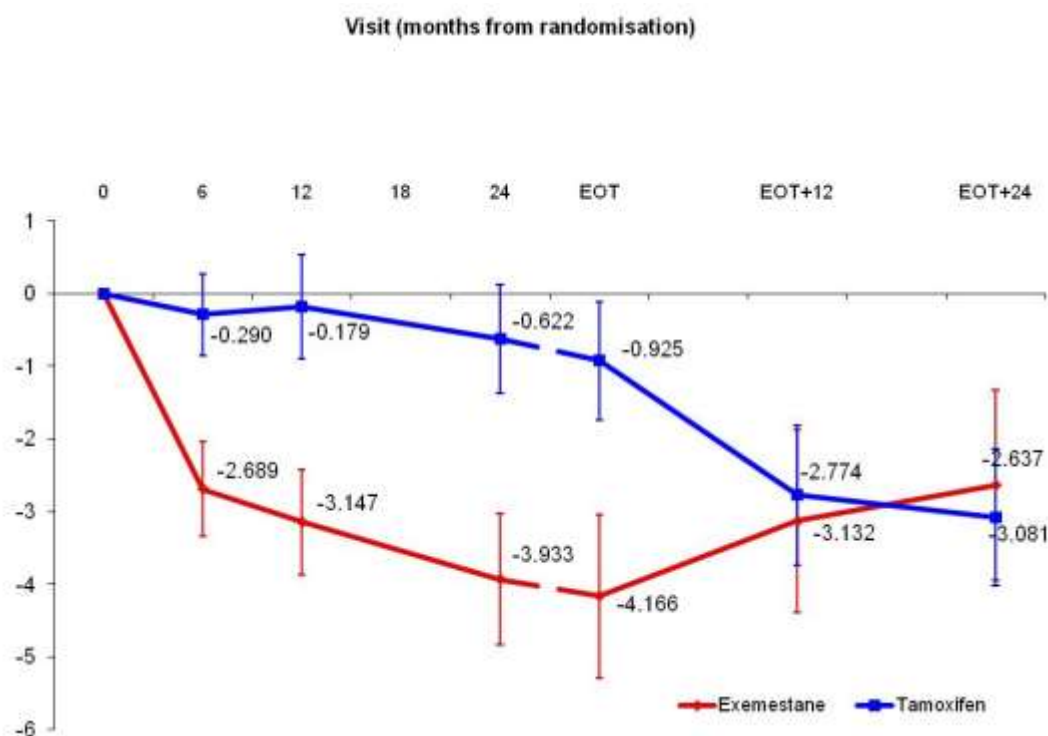
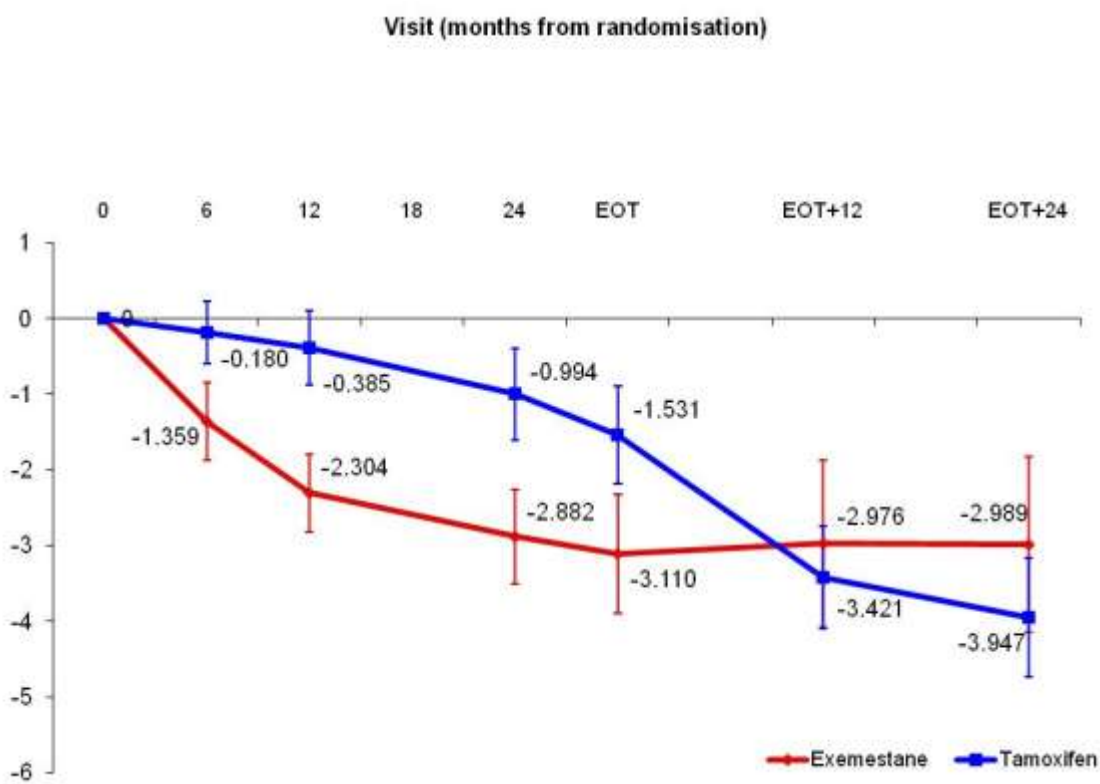
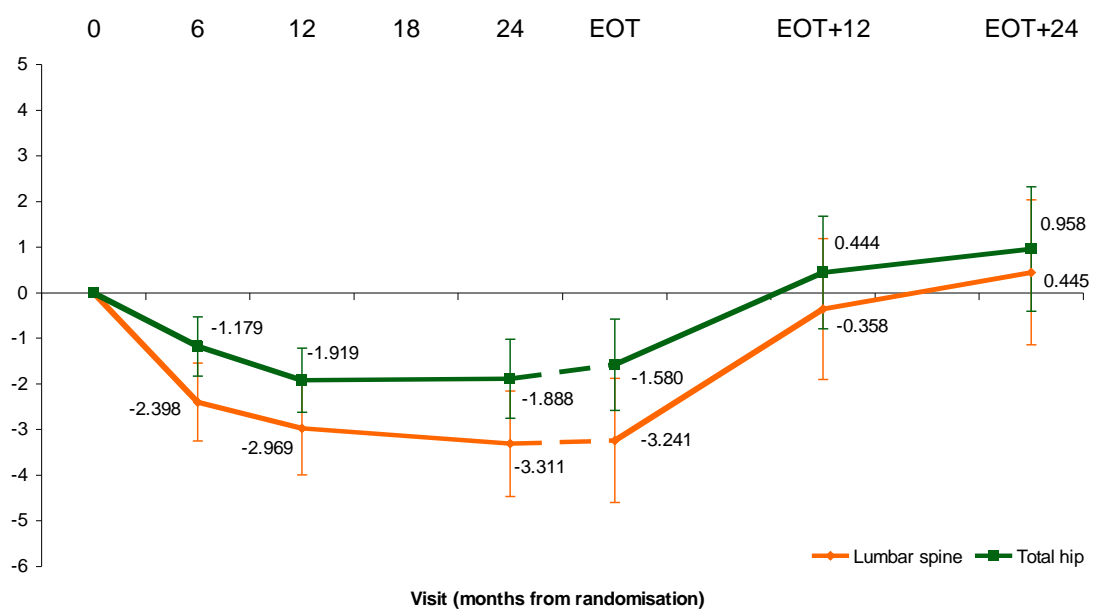


Figure 2b: Total hip



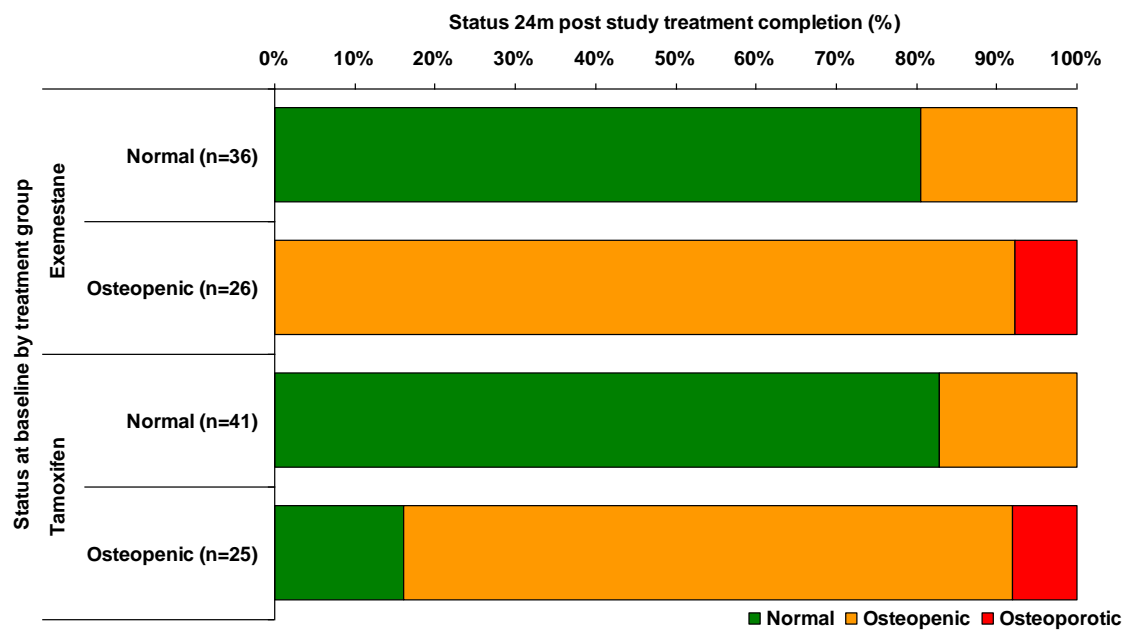
## Reversal of skeletal effects of endocrine treatments in the IES

Figure 3:



## Reversal of skeletal effects of endocrine treatments in the IES

Figure 4 :

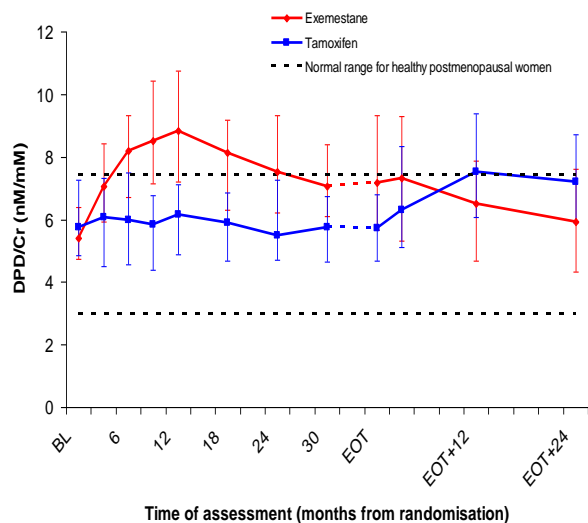




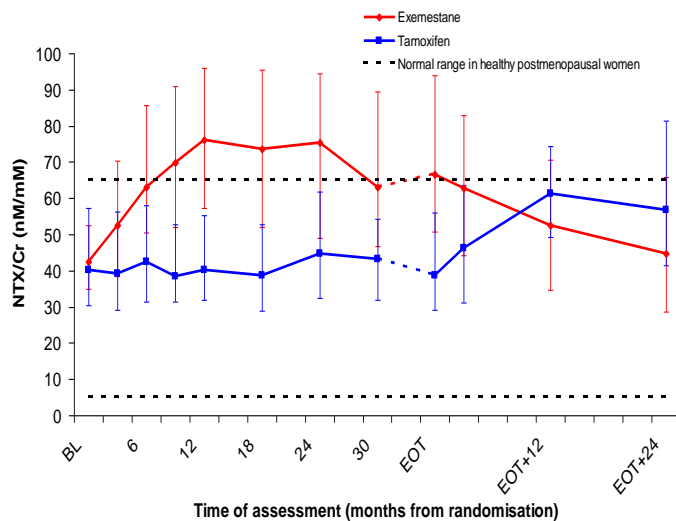
## Reversal of skeletal effects of endocrine treatments in the IES

**Figure 5:**

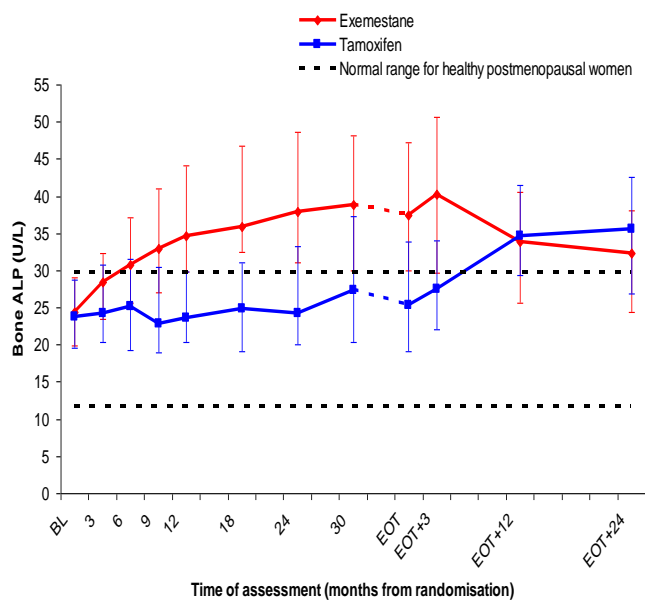
**a) DPD/Cr**



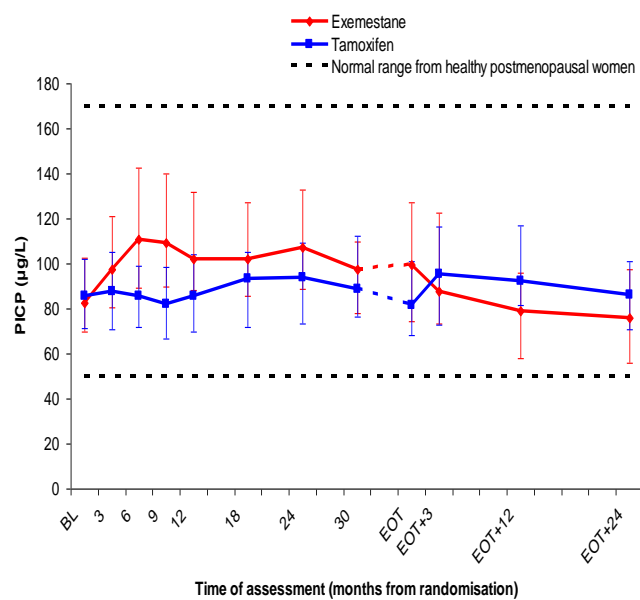
**b) NTX/Cr**



**c) BAP**



**d) PICP**



## Reversal of skeletal effects of endocrine treatments in the IES

Figure 6:

