Breast Cancer Research

Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE Trial Bone Sub-study

Breast Cancer Research 2012, **14**:R13 doi:10.1186/bcr3097

Nigel J Bundred (bundredn@manchester.ac.uk)
Peter Kenemans (kenemans@vumc.nl)
Cheng Har Yip (yipch@um.edu.my)
Matthias W Beckmann (matthias.beckmann@uk-erlangen.de)
Jean-Michel Foidart (jmfoidart@ulg.ac.be)
Piero Sismondi (sismondi@mauriziano.it)
Bo von Schoultz (bo.vonschoultz@karolinska.se)
Rena Vassilopoulou-Sellin (rsellin@mail.mdanderson.org)
Rachid El Galta (rachid.elgalta@spcorp.com)
Eugenie Van Lieshout (eugenie.vanlieshout@spcorp.com)
Mirjam Mol-Arts (mirjam.mol@spcorp.com)
Juan Planellas (j.planellas@spcorp.com)
Ernst Kubista (ernst.kubista@meduniwien.ac.at)

ISSN 1465-5411

Article type Research article

Submission date 29 September 2011

Acceptance date 17 January 2012

Publication date 17 January 2012

Article URL http://breast-cancer-research.com/content/14/1/R13

Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE Trial Bone Sub-study

Nigel J Bundred[1,#], Peter Kenemans[2], Cheng Har Yip[3], Matthias W Beckmann[4], Jean-Michel Foidart[5], Piero Sismondi[6], Bo von Schoultz[7], Rena Vassilopoulou-Sellin[8], Rachid El Galta[9], Eugenie Van Lieshout[9], Mirjam Mol-Arts[9], Juan Planellas[9] and Ernst Kubista[10].

1. Department of Surgery, Univ of Manchester, Southmoor Road, Manchester, M23 9LT, United Kingdom

2. Department of Obstetrics and Gynaecology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands

3. Department of Surgery, University Malaya Medical Centre, Pusat Perubatan Universiti Malaya, Lembah Pantai, 59100, Kuala Lumpur, Malaysia

4. Department of Surgery, Universitätsklinikum Erlangen, Postfach 2306, D-91012 Erlangen, Germany

5. Department of Obstetrics and Gynecology, University of Liege, 81 bd de la Constitution, B-4020 Liege, Belgium

6. Department of Gynecological Oncology, University of Turin, C.So Svizzera, 185 - 10149 Torino, Italy

7. Department of Obstetrics and Gynecology, Karolinska Institutet SE-171 77 Stockholm, Sweden

8. Department of Pathology, The University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030, United States

9. Research Data and Quantitative Sciences, Schering-Plough, P.O. Box 20, 5340 BH, Oss, The Netherlands

10. Department of Special Gynecology, Medical University of Vienna, Borschkegasse 8a, A-1090 Vienna, Austria

[#] Corresponding author: bundredn@manchester.ac.uk

Abstract

Introduction:

Livial Intervention Following Breast Cancer; Efficacy, Recurrence and Tolerability Endpoints (LIBERATE - ClinicalTrials.gov number NCT00408863), a randomized, placebo controlled, double-blind trial which demonstrated that tibolone (Livial), a tissue selective hormone replacement therapy (HRT) increased breast cancer (BC) recurrence HR 1.40 (95% CI 1.14-1.70; *p=0.001*) entered a subgroup of women into a study of Bone Mineral Density (BMD).

Methods:

Women with surgically excised primary BC (T1-3, N0-2, M0) within the last 5 years complaining of vasomotor symptoms, were assigned to tibolone 2.5mg daily or placebo treatment for a maximum of 5 years. The BMD sub-study enrolled 763 patients utilizing dual-energy X-ray absorptiometry (DXA) scanning at baseline and at 2 years.

Results:

In the bone sub-study 699 out of 763 women were eligible (345 allocated to tibolone and 354 to placebo) after undergoing DXA scans, 300 (43%) women had normal BMD, 317 (45%) osteopenia and 82 (11.7%) osteoporosis. Low body mass index (<0.001), Asian race (*p<0.001*) and late age at menarche (p<0.04) predicted for low bone mass at baseline. Tibolone increased BMD by 3.2% at the lumbar spine and 2.9% at the hip compared to placebo (both *p<0.001*). The majority of fractures

(55%) occurred in osteopaenic patients. Women with normal BMD had increased recurrence on tibolone 15.6% (22/141) compared to placebo 6.9% (11/159) *p=0.016*, whereas no increased BC recurrence was seen in women with low BMD; 7.4% (15/204) on tibolone versus (6.7% (13/195) on placebo.

Conclusions:

Tibolone is contraindicated after BC treatment as it increases BMD and BC recurrence. Risk of BC recurrence was elevated in BC women with normal BMD (compared to low) who took tibolone.

{Keywords: Breast Cancer; Osteoporosis; Bone mineral density}

Introduction

Osteoporosis (reduced bone mineral density (BMD)) leads to fractures which impact severely on quality of life.[1] Postmenopausal women have increased bone loss due to estrogen deficiency resulting in an increased fracture risk. Fracture risk also increases after a diagnosis of breast cancer.[1,2] Breast cancer (BC) patients frequently suffer accelerated bone loss due to chemotherapy inducing premature menopause or aromatase inhibitor (AI) therapy lowering estrogen levels, thus increasing fracture rate.[3,4]

Although dual-energy X-ray absorptiometry (DXA) is proposed to identify women with low BMD in women commencing therapy, the incidence and frequency of osteoporosis in BC patients has not been widely studied. The bone sub-studies of the AI trials contained small numbers of patients.[5,6]

Tibolone (Livial®) is a synthetic steroid with a pharmacological and clinical profile different to conventional sex steroids which reduces vasomotor symptoms and prevents osteoporosis.[7] In the Longterm Intervention on Fractures with Tibolone (LIFT) trial, tibolone 1.25 mg/day prevented spinal fractures in osteoporotic older women compared to placebo, reducing the risk of BC (HR 0.32: 0.13-0.80).[8] Many women undergoing adjuvant therapy for BC suffer from vasomotor symptoms such as hot flushes; both osteoporosis and vasomotor symptoms can potentially be prevented by the use of tibolone.

The Livial Intervention Following Breast Cancer; Efficacy, Recurrence and Tolerability Endpoints (LIBERATE) study[9] set out to demonstrate non-inferiority of tibolone compared to placebo on BC recurrence but closed early due to increased breast cancer recurrence on Tibolone.

Studies have suggested that normal BMD is associated with an increased risk of BC development.[10,11] The LIBERATE bone sub-study therefore, assessed the changes in BMD on tibolone and determined the relationship between the effects on BMD and BC recurrence in this population.

Materials and methods

LIBERATE (ClinicalTrials.gov number NCT00408863) was a randomized, placebo-controlled, double-blind, parallel-group trial of tibolone (Livial®), 2.5 mg/day, on BC recurrence, aiming to demonstrate non-inferiority of treatment compared to placebo in women with climacteric symptoms and a history of BC.[9]

The primary endpoint was BC recurrence rate. Secondary study outcomes included vasomotor symptoms, health-related quality of life (HRQL), overall survival and BMD. A total of 3583 women were screened of whom 3148 were randomized in 245 centres in 31 countries; 1579 to tibolone and 1569 to placebo.[9]

The BMD sub-study utilized DXA scanning at baseline and after 2 years or at trial discontinuation as long as on trial medication. The aim was to explore the effect of tibolone compared to placebo on BMD of the lumbar vertebrae (L1-L4) and left proximal femur for hip density. Out of 763 women randomized to the BMD substudy, only 699 had BMD assessed at any site; 697 at the lumbar spine and 691 at the hip and entered the study (Figure 1).

BMD was measured using Lunar or Hologic instruments. Bone densitometry data were acquired by DXA technicians, trained by the Quality Control/Quality Assurance (QC/QA) centers according to protocols prepared by central QC/QA facilities. These facilities were also responsible for continuous safety monitoring of incoming data and for complete QC/QA procedures, including cross-calibration of instruments at all clinical trial sites and data analysis. This ensured comparability of the results over time and across different sites and machines. If a scan of the left femur was not possible then the right femur could be used, and was used consistently throughout the trial. DXA scans were performed at baseline, after 2 years or at trial discontinuation, as long as the patient remained on trial medication. Fractures were assessed by investigators reporting their presence as a serious adverse event.

Patients

Women with histologically confirmed BC (T1-3, N0-2, M0), surgically treated within the last 5 years, irrespective of hormone receptor status were randomized between July 2002 and December 2004. Patients were younger than 75 years of age, with the

last menstruation at least 12 months before study start or ovariectomized, hysterectomized or on GnRH analogues and suffering vasomotor symptoms, either related to natural menopause or resulting from prior or current adjuvant BC treatment. Use of tamoxifen, aromatase inhibitors, GnRH analogs or chemotherapy was allowed. Recent or current use of estrogenic or progestogenic substances as well as any non-registered investigational drug or Raloxifene hydrochloride were not allowed. Bisphosphonates were not allowed prior to study entry and only 7% of women ever used bisphosphonates in the LIBERATE trial. All women gave informed consent and the study was approved by the Ethics Committees and/or Health Authorities of the hospitals and countries involved.

Statistical analysis

All analyses were carried out for 699 women with a BMD value at baseline in the intent-to-treat (ITT) group. In order to deal with drop outs the observed case approach was used. The following populations were considered: overall population, Caucasian and Asian race.

According to the World Health Organization (WHO) criteria, BMD was divided into three categories based on the T-scores in the total hip: osteoporosis if T-score in at least one site ≤-2.5; osteopenia if T-score in both sites>-2.5 and at least for one site T-score ≤-1; and normal if T-score in both sites>-1.[1]

For lumbar spine and total hip, multiple regression analysis with forward stepwise selection was performed to identify predicting factors for BMD at baseline as continuous variable. Prognostic factors were further examined by fitting a logistic regression using the BMD classes osteoporotic and non-normal (osteopaenic and osteoporotic) as response variables.

For each of the sites change from baseline in BMD and percentage change from baseline in BMD were analyzed using an Analysis of Covariance (ANCOVA) model with as factors treatment group and center and as covariate the baseline value. Additionally both binary outcomes, osteopenia and osteoporosis, were analyzed using logistic regression models with as factors treatment group, race and as a covariate BMI.

Differences in bone loss (defined as any decrease in BMD from baseline) at both sites between tibolone and placebo groups were analyzed using Pearson's chi-square test.

The occurrence of fractures was analyzed using a logistic regression model with as factors treatment group, race (Caucasian vs. Asian), treatment by race interaction and BMD classes (osteoporotic vs. normal and osteopaenic vs. normal) and as covariates age, baseline body mass index (BMI) and age at menarche (and/or menopause).

Time to BC recurrence was analyzed using a Cox proportional hazards model, stratified by country, with factors for treatment and BMD classes and a covariate for baseline body mass index. Also a similar model is fitted with BMD class (osteopaenic and osteoporotic clumped into one class) as time dependent factor to account for updated BMD information during the first 2 years since randomization.

To examine a linear trend with regard to the effect of BMD classes on BC recurrence in tibolone group and placebo group similar models using BMD classes as a continuous variable were fitted to each treatment groups separately and the consistency of the linear trend across the treatment groups was tested.

Role of funding source

An Independent International Steering Committee advised on trial safety and conduct. The trial was funded by Schering Plough.

Results

As previously reported, tibolone increased BC relapse rates HR 1.4 (95% CI 1.14-1.70 *P*=0.001) and the trial closed prematurely[9].

Demographics and baseline characteristics of 699 subjects who consented to the bone sub-study and had a BMD assessment at baseline (≤ day 1) of either site are presented in Table 1 and Figure 1.

For both sites, (lumbar spine [LS] and hip) the tibolone group showed an absolute increase in BMD after 2 years of treatment compared to an absolute decrease in BMD seen on placebo (Figure 2/Additional file 1 Table S1: *P*<0.001).

The percentage change from baseline for LS BMD and total hip was 1.6% and 1.3% respectively in the tibolone group, with a decrease of 1.6% at both sites observed on placebo (Figure 2 and Additional file 1 Table S1).

The percentage change from baseline adjusted treatment effects were 3.12 (95% CI: [2.41; 3.84]) and 2.85 (95% CI: [2.20; 3.49] for the LS and total hip, respectively. The Asian and Caucasian subgroups were similar at both the LS (p=0.65) and total hip (*P*=0.14).

Prediction of osteoporosis at baseline and at treatment

At baseline, in total 697 subjects had information on BMD of LS (343 in the tibolone group vs. 354 in the placebo group), and 691 subjects had information on BMD of total hip (342 in the tibolone group vs. 349 in the placebo group). The majority of subjects were of Asian (37.2%) or Caucasian (61.1%) race. Overall, 82 (11.7%) had osteoporosis in either hip or LS, 317 (45.4%) osteopenia and 300 (42.9%) had normal BMD in both sites. Asian women (63.4%) contributed the majority of women with osteoporosis, followed by Caucasian women (35.4%). The osteopenia group consisted of 53.9% Caucasian and 43.9% Asian. The distribution of BMD categories based on T-score at both sites was comparable among the treatment groups as were demographics and baseline characteristics (Table 1).[12]

However, Asian women were more likely to be osteoporotic or osteopaenic (P<0.0001). Asian women had lower weight and height (wt 59.2kg:ht 156cm) compared to their Caucasian counterparts (wt 71.5kg:ht164cm) both *P*<0.0001.

After a stepwise selection procedure, Asian race, older age, late age at menarche, longer time since breast surgery and low BMI were found to be significant (all *P*-values < 0.05) with regard to both total hip and LS T-score at baseline (Table 2) and predicted non-normal BMD class (T-score <-1 at both sites) as well as osteoporosis

(T-score<-2.5) at baseline. Medical oophorectomy by GnRH analog use also predicted LS but not total hip T-score at baseline (*P*=0.039).

At baseline, 11.7% of subjects were osteoporotic but after 2 years of treatment, 15.4% in the placebo group and 10.2% in the tibolone group remained osteoporotic. In addition to osteoporosis at baseline, factors predicting osteoporosis after 2 years were BMI (OR 0.87: 95% CI 0.78; 0.98; *P*=0.019), and treatment (tibolone versus placebo OR 0.38: 95% CI 0.16; 0.88: *P*=0.024). For non-normal BMD class, ethnicity was also an additional risk factor (Asian race versus Caucasian OR 3.02: 95% CI 1.61; 5.68: p=0.0006).

For LS, the number of subjects who experienced bone loss was 99 (37.2%) on tibolone vs. 174 (66.4%) on placebo (LS p <0.0001) whereas total hip bone loss occurred in 86 (32.0%) women on tibolone vs. 176 (66.9%) in the placebo group (*P*<0.0001).

BMD and fractures

Thirty eight fractures occurred, of which the majority 21 occurred in the osteopaenic group, 12 in the normal BMD group and only 5 in the osteoporotic group (Table 3). Fractures occurred in 6.8% of osteopaenic, 6.2% of osteoporotic and 4.1% of normal BMD women. Logistic regression analysis including age, BMI, age at menarche and/or menopause, BMD classes at baseline, treatment, race and treatment by race interaction and race found no significant predictors of fracture were found (data not shown). No significant effect of tibolone on fracture rate was found although in the Caucasian women 7 out of 206 on tibolone developed fractures compared to 17 out of 221 on placebo (chi-squared p=0.054). Testing homogeneity of the tibolone to placebo odds ratios revealed no difference between the Asian and Caucasian races as indicated by lack of treatment by race interaction.

Analysis of BC recurrence restricted to subjects with BMD data

For subjects with BMD data, 61 women have experienced a BC recurrence. Univariate analysis of the effect of Tibolone treatment on inducing BC recurrence according to BMD at baseline; grouped as osteoporosis, osteopenia or normal, revealed recurrence on placebo was 4.7%, 7.2% and 6.9% respectively, whereas for

tibolone it was 7.5%, 7.3% and increased to 15.6% in women with normal BMD (p=0.03:Figure 3 and Additional file 2 Table S2).

Bisphosphonate use did not affect time to BC recurrence (HR 0.82 [95% CI 0.53 – 1.27]).

Results of fitting a proportional hazard Cox model with treatment, osteopenia status and osteoporosis status as factors and BMI as covariate indicate that tibolone and normal BMD increased the BC recurrence compared to placebo and osteopenia, respectively. Fitting the same model for tibolone and placebo groups separately suggested an increase in BC recurrence in patients with an increase in BMD seen in tibolone group (HR=0.47: 95% CI 0.26-0.85: p=0.017:Additional file 3 Table S3) but not in placebo group (HR 0.89: 95% CI 0.47-1.68; p=0.65) though testing the homogeneity of the linear trend over BMD classes indicated no differences between treatment groups (p-value=0.19).

Table 4 groups osteopaenic and osteoporotic patients together and uses this as a time dependant covariate to correct for changes in BMD during the course of the first 2 years of the trial. The results indicate again that tibolone and normal BMD are associated with increased BC recurrence.

Discussion

Treatment of BC survivors with tibolone (a specific tissue estrogenic activity regulator) led to increases in BMD and BC recurrence. Tibolone and other HRT are contraindicated after breast cancer treatment.

Recurrence on tibolone occurred mainly in women with normal BMD.

Osteoporosis increases with age, current smoking and low body mass index (BMI)[1,2,12] The lowering of estrogen levels increases BMD loss after the menopause and increases the risk of fracture.[2-6]

In BC survivors adjuvant therapies increase bone loss leading to increased fractures and lower health related quality of life.[2] The prevalence of osteoporosis has been

reported as up to 27% in BC survivors.[11] 11.7% of women recruited to the LIBERATE bone sub-study were osteoporotic and 45.4% osteopaenic, despite being only an average of 2.2 years since diagnosis.

The higher incidence of low BMD measurements (compared to the general population) and increased fracture rate observed in women after a diagnosis of BC[2] has resulted in ASCO and European Guidelines suggesting all women diagnosed with BC should undergo DXA scanning to detect those women at risk of fracture[7]and to initiate treatment at an early stage if osteoporosis is indicated by the DXA results.

BMD scanning identifies women with BC, at risk of fragility fracture but 55% of fractures occurred in the osteopaenic group compared to 13% amongst the "high risk" osteoporotic women (Table 3), indicating that BMD alone cannot be used to select patients for anti-resorptive therapy to prevent fragility fracture. Few (6.5%) patients in this study were on AI but the fracture rate (2.8% per annum) remains comparable with that reported in patients taking AIs in randomized trials.[3-6] Treatment with intravenous zoledronic acid 4 mg/day has been shown to increase BMD in pre and postmenopausal women with breast cancer[13] and recent results from the ABCSG-12/ZO-FAST trials suggest that when combined with endocrine therapy this combination improved disease free recurrence compared to endocrine therapy alone but the zoledronic acid adjuvant therapy (AZURE) trial results did not confirm a disease recurrence benefit. However, Bisphosphonates (not hormone replacement therapies) should be used in BC survivors with low BMD[13,14,15].

Current American Society of Clinical Oncology and UK guidelines recommend bisphosphonate therapy for women with a T score >-2.0. To prevent the majority of fractures would require all women with T scores greater than -1.0 to undergo anti-resorptive therapy.[7] An alternative approach in osteopaenic women with BC advocates commencing antiresorptive therapy in women with 1 other recognized risk factor for fracture such as history of fragility fracture, BMI<20, corticosteroid use or cigarette smoking habit.[16]

BMD is a function of the lifetime exposure of a woman to estrogen.[12,17] In the LIBERATE study, osteoporosis was associated with older age, lower BMI, late age at menarche and Asian race. Important racial differences in bone mineral density exist, with lower BMD in the Asian race compared to Caucasian. The application of Caucasian reference values to an Asian population may not reflect the true osteoporosis rate and fracture risk in Asians.[17,18] After adjusting for other factors such as height and weight, the BMD and bone mass are reported not to differ between Asians and Caucasians.[19] However trabecular BMD decreases at an earlier age in Asian women and the fracture threshold (especially spinal fracture) is lower[20] Fracture rates in the Asian population were comparable to that of Caucasians indicating a low BMD in Asian women is predictive of fracture risk.

In the LIFT trial, tibolone reduced fractures in osteoporotic women[8] and in the LIBERATE Caucasian population tibolone increased BMD and reduced fracture risk (OR= 0.42 p=0.06). Tibolone increased BMD regardless of ethnic background.

Breast cancer risk

BC risk is associated with a high lifetime exposure to estrogen and BMD may be a surrogate marker for this exposure. Studies have shown an association between higher BMD and increased risk of BC[11-13,15] The Women's Health Initiative study indicated that hip BMD predicted BC risk independently of Gail score.[21] The contribution of BMD in the prediction of postmenopausal BC score was significant in a Cox proportional hazards model and independent of the Gail score. Normal BMD appears to be associated with an increased BC risk.[22]

In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, women with low bone mass (T-score <-2) had a higher incidence of invasive, estrogen receptor positive BC than those with osteoporosis (HR 2.13, 95% CI 1.12-4.03). Raloxifene, an antioestrogen, reduced the incidence of BC development in this group.[11] In the LIFT trial, tibolone (1.25mg/day) likewise reduced BC risk in a population of osteoporotic women.[8]

In the LIBERATE study, which used tibolone 2.5mg/day in women after BC treatment, the incidence of BC recurrence increased. Recurrence was highest in the

group with normal BMD randomized to tibolone compared to those with low BMD. In the placebo group an increase in BC recurrence was seen in the normal and osteopaenic women, compared to osteoporotic women. The finding that normal BMD is associated with increased BC recurrence provides support to the concept that normal BMD is a surrogate for postmenopausal estrogen levels or women with normal BMD are more sensitive to estrogenic stimulation. BMD may be a biomarker of drug effect, so that as BMD gain occurred on tibolone, BC risk increased (Table 4). This is similar to the reduced BC risk seen in the MORE Trial with increased BMD gain on the antioestrogen raloxifene. Alternatively, women with higher BMD may harbor single nucleotide polymorphisms (SNPS) of the estrogen receptor alpha or CYP 17/19 genes which result in higher ER alpha at similar estrogen levels and reduce the risk of developing early osteoporosis and fracture.[23] Follow up of women with known BMD and ER SNP should allow this possibility to be explored.

Conclusions

Women with normal bone density not only have a higher lifetime exposure to estrogen but also have a lower threshold for estrogen stimulation of BMD increases and BC recrudescence. The placebo groups in studies protecting against AI induced bone loss using bisphosphonates will allow confirmation (or not) that low BMD is associated with a low risk of BC recurrence.

Tibolone and other HRT should not be used as osteoporosis treatment in women with breast cancer as they increase risk of recurrence.

Abbreviations

AI: aromatase inhibitor; ANCOVA: Analysis of Covariance; BC: breast cancer; BMD: Bone Mineral Density; BMI: body mass index; DXA: dual-energy X-ray absorptiometry; HRQL: health-related quality of life; HRT: hormone replacement therapy; ITT: intent-to-treat; LIBERATE: Livial Intervention Following Breast Cancer; Efficacy, Recurrence and Tolerability Endpoints; LIFT: Longterm Intervention on Fractures with Tibolone; LS: lumbar spine; MORE: Multiple Outcomes of Raloxifene Evaluation; QA: Quality Assurance; QC: Quality Control; SNPS: single nucleotide polymorphisms; WHO: World Health Organization.

Competing interests

PK, NJB, JMF, EK, BvS, PS, RVS, MWB and CHY have received honoraria for their membership of the LIBERATE Advisory Board. NJB was a member of the LIBERATE Steering Committee and has received fees for lecturing on Tibolone. Schering Plough is now owned by Merck.

PK has received research grants and honoraria for consultancies from the following pharmaceutical companies: Schering-Plough, Procter & Gamble, Servier and Pfizer.

NJB has received honoraria for consultancies and postgraduate education lectures from Schering-Plough and has served on advisory boards for Schering-Plough, Astra-Zeneca, Novartis and Pfizer.

MWB has served on advisory boards for GSK, Novartis, Astra-Zeneca, Sanofi Aventis and Schering-Plough.

JE, RM, MM-A and SvO are employees of Schering-Plough (formerly NV Organon).

Authors' contributions

All authors have read and approved this manuscript for publication. All authors are members of the Scientific Advisory Board or employee of Schering-Plough Corporation and contributed to the study concept, design and implementation, and to content and development of this manuscript.

LIBERATE study group

Advisory Board: P Kenemans (The Netherlands), JM Foidart (Belgium), NJ Bundred (UK), E Kubista (Austria), B von Schoultz (Sweden), P Sismondi (Italy), R Vassilopoulou-Sellin (USA), M Beckmann (Germany), and CH Yip (Malaysia).

Independent DSMB: M Baum (UK), R Gray (UK) and CW Burger (The Netherlands) .

Breast & Gynaecological Cancer Adjudication Committee: P.J. van Diest (The Netherlands), N. Harbeck (Germany) and R. Gray (UK)

Cardiovascular Adjudication Committee: MH Prins (The Netherlands), B. Davidson USA), R. Peters (The Netherlands), ML Longo (USA) and LJ Kappelle (The Netherlands)

Investigators: AUSTRALIA: R Baber, JA Eden, C Furnival, B Stuckey, E Farrell and AH MacLennan. AUSTRIA: CF Singer, E Kubista, C Marth, R Reitsamer, P Sevelda, H Salzer, I Thiel and R Winter. BELARUS: L Putyrski, V Belyakovski and Gedrevich.

BELGIUM: W Tjalma, J Desreux, M Dhont, H Depypere, R van den Broecke, JM Foidart, M L'Hermite, JP Nolens, S Rozenberg, Ph Simon, I Vergote, U Gaspard, D Janssens, H De Gezelle and E Merchiers. BRAZIL: JM Aldrighi, M Badalotti, VR Bagnoli, CE Fernandes, R Ferriani, AM Pinto Neto, CH Menke, DA Petti, A Urbanetz and A Del Giglio. CHILE: Cunill, H Sepulveda, L Soto, A Uribe and I Valdivia. COSTA RICA: J Baptista and Loaciga. CZECH REPUBLIC: M Bendova, K Buchta, V Pecha, T Reslova, O Hlavackova and M Mikulik. ESTONIA: R. Kütner and P Padrik. FINLAND: U Puistola, O Ylikorkala and K Mäenpää-Liukko. FRANCE: A Brémond, C Faure, P Seffert, T Delozier, M Espie, D Dupaigne, M Hoffet, F Laffargue, C Tunon de Lara, L Largillier, M Namer, L Dognon, T Routiot, P This and P Touraine. GERMANY: R Kimmig, S Kümmel, M Beckmann, Weiss, Sohn, G Bastert, C Nestle-Krämling, B Blümel, Engel, C Brucker, D Chatsiproios, B Conrad, HJ Hindenburg, C Höss, W Jonat, L Kiesel, B Krause-Bergmann, Dewitz, T Kühn, U Köhler, R Landthaler, D Langanke, H Leitsmann, Thomas, W Lichtenegger, P Mallmann, Neumann, Kulp, O Ortmann, C Schindler, P Schmidt-Rhode, W Schoenegg, V Seifert-Klauss, G Splitt, F Starflinger, Rühl, M Untch, JC de Waal, D Wallwiener and R de Wilde. HUNGARY: M Baki, Boér, J Boros, J Cseh, Faluhelvi, E Kövér, T Nagykálnai, A Ruzsa, J Erfán, F Fábián and K Páli. ITALY: AR Genazzani, S Ricci , R Mariani, A Martoni, G Scambia, N Biglia, P Sismondi, A Santoro, S Burlizzi, G Amunni and D Amadori. KOREA: DY Noh, JG Kim, SH Ahn, BM Kang, WC Noh, MH Kim, MH. Lee and JJ Lee LATVIA: G. Keire and D Baltina. MALAYSIA: N Nik Nasri, P Gomez, Sivalingam, S Muniandy and CH Yip . MEXICO:. J Cardenas, F Mainero, S Uscanga, A Fuentes and R Lugo. NETHERLANDS: H Heijmans, HS The, H Franke, J van Riel, S van der Vegt, E Boven, P Houben, A Kok, H van Weering, A van de Walle, Burggraaf and R Mulder. PANAMA: J. Alcedo. POLAND: J. Kornafel, M Litwiniuk, H Karnicka, L Bablok, Marianowski, A Basta and A Jakimiuk. ROMANIA: S. Curescu, ME Draganescu, AE Eniu, E Zbranca, G Peltecu, and V Ancar. RUSSIA: V Smetnik, A Petrossian, O Stekolschikova, A Popov, N Zoziouk, LI Krikunova, V Semiglazov, M Konstantinova, VF Bezhenar, A Diatchouk, G Manikhas, LY Korytova, V Vinogradov, V Sokurenko, Baranov, V.L. Arkhipovsky, IK Bogatova, LI Akhmadulina, Kuts, SA Susloparova, I Mitashok, AL Kanzaliev, VV Bryuzgin, EN Malygin, IE Sergeev, NM Pasman, Akishina, AV Tuev, EP Kullikov, M Kopp, VI Soloviev, ID Evtushenko, GV Ershov, NF Devyatchenko, YN Potapov, SV Cheporov, Ogurtsov, ON Chrustalev, DG

Lazareva, E Bryukhina and M Matrosova. SINGAPORE: SL Yu and PC Wong. SLOVAK REPUBLIC: O. Sadovsky, Z Petrovicova, L Masak and P Suska. SPAIN: JL. De Pablo, E García and J Iglesias. SWEDEN: L. Mattsson, G Granberg, L Berglund, and B Friberg. TAIWAN: .ST Chen, SN Chow, JN Lee, KL Wang and TS Yang. THAILAND: KK Limpaphayom, S Boonjong, M Jirapinyo, C Sakondhavat, N Taechakraichana, K Techatraisak and K Wilawan. UKRAINE: L Dudar, Koshukova, V Gyoyachyy, Y Hotko, I Kostynskyy, V Paramonov, T Pertseva, Y Shparyk, T Tatarchuk, O Tarasova, N Kosey, Y Solskiy, I Smolanka, VP Kvashenko, O Grishyna and G Dzyak. UNITED KINGDOM: NJ. Bundred, JP Drew, R Mansel, J Williamson, CR Kingsland, L Vishwanath, R Bliss, D Crawford, Z Winters, D Browell, M Paterson, T Ind, A Rostom and J Pitkin.

Acknowledgements

The LIBERATE trial was funded by Schering-Plough (formerly NV Organon, Oss, Netherlands).

References

1. Sambrook P, Cooper C: **Osteoporosis.** *Lancet* 2006, **17**:1369-81.

2. Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, Gass M, Leboff MS: **Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study**. *Arch Intern Med.* 2005, **165**:552-8.

3. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS; ATAC Trialists' Group: **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.

4. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, Jones SE, Alvarez I, Bertelli G, Ortmann O, Coates AS, Bajetta E, Dodwell D, Coleman RE, Fallowfield LJ, Mickiewicz E, Andersen J, Lønning PE, Cocconi G, Stewart A, Stuart N, Snowdon CF, Carpentieri M, Massimini G, Bliss JM, van de Velde C; Intergroup Exemestane Study: **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.

5. Coleman RE ,Banks IM,Girgis SL, Kilburn LS, Vrdoljak E, Fox J, Cawthorn SJ, Patel A, Snowdon CF, Hall E, Bliss JM, Coombes RC; Intergroup Exemestane Study group: **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).** *Lancet Oncology* 2007, **8**:119-27.

6. Eastell R, Adams JE, Coleman RE, Eastell R, Adams JE, Coleman RE, Howell A, Hannon RA, Cuzick J, Mackey JR, Beckmann MW, Clack G: **Effect of anastrozole on bone mineral density: 5-year results from the anastrazole, tamoxifen, alone or in combination trial 18233230**. *J Clin Oncol* 2008, **26**:1051-7.

7. Reid DM, Doughty J, Eastell R Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P, Coleman RE: **Guidelines for the management of Breast Cancer treatment induced bone loss: a consensus position statement from a UK expert group.** *Cancer Treat Rev* 2008, **34**:Supp 1:s3-18.

8. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R; LIFT Trial Investigators: **The effects of tibolone in older postmenopausal women.** *N Eng J Med.* 2008, 359:697-708.

9. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW; LIBERATE Study Group: **Safety and efficacy of tibolone in breast cancer patients with vasomotor symptoms: a double-blind, randomised noninferiority trial.** *Lancet Oncology* 2009, **10**:135-146.

10. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR: **Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group.** *JAMA* 1996, **276**:1404-8.

11. Lippman ME, Krueger KA, Eckert S, Lippman ME, Krueger KA, Eckert S, Sashegyi A, Walls EL, Jamal S, Cauley JA, Cummings SR: **Indicators of lifetime estrogen exposure: effect on breast cancer incidence and interaction with raloxifene therapy in the multiple outcomes of raloxifene evaluation study participants.** *J Clin Oncol.* 2001, **19**:3111-6.

12. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Glüer C, Goltzman D, Hans D, Krieg MA, La Croix A, McCloskey E, Mellstrom D, Melton LJ 3rd, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N: **The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women.** *Osteoporos Int.* 2007, **18**:1033-46.

13. Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, Neven P, von Minckwitz G, Miller JC, Schenk NL, Coleman RE: **Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results.** *Cancer* 2008**, 112**:1001-10.

14. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, Jakesz R, Seifert M, Hubalek M, Pristauz G, Bauernhofer T, Eidtmann H, Eiermann W, Steger G, Kwasny W, Dubsky P, Hochreiner G, Forsthuber EP, Fesl C, Greil R; Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria: **Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial.** *Lancet Oncol.* 2011, **12**:631-41.

15. Hadji P, Aapro MS, Body JJ, Bundred NJ, Brufsky A, Coleman RE, Gnant M, Guise T, Lipton A: **Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment.** *Ann. Oncol.* 2011, **22**:2546-55.

16. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Pugh J, Gaunt C, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R; AZURE Investigators: **Breast-cancer adjuvant therapy with zoledronic acid.** *N Engl J Med.* 2011,**365**:1396-405.

17. Burshell AL, Song J, Dowsett SA, Mershon JL, Delmas PD, Secrest RJ, Cauley JA: **Relationship between bone mass, invasive breast cancer incidence and raloxifene therapy in postmenopausal women with low bone mass or osteoporosis.** *Curr Med Res Opin.* 2008, **24**:807-13.

18. Walker MD, Babbar R, Opotowsky AR, Rohira A, Nabizadeh F, Badia MD, Chung W, Chiang J, Mediratta A, McMahon D, Liu G, Bilezikian JP: **A reference bone mineral density database for Chinese American women.** *Osteoporos Int.* 2006, **17**:878-87.

19. Russell-Aulet M, Wang J, Thornton JC, Colt EW, Pierson RN, Jr: **Bone mineral density and mass in a cross-sectional study of white and Asian women.** *J Bone Miner Res.* 1993, **8**:575-82.

20. Ito M, Lang TF, Jergas M, Ohki M, Takada M, Nakamura T, Hayashi K, Genant HK. **Spinal trabecular bone loss and fracture in American and Japanese women.** *Calcif Tissue Int.* 1997, **61**:123-8.

21. Chen Z, Arendell L, Aickin M, Cauley J, Lewis CE, Chlebowski R; Women's Health Initiative Program, National Heart, Lung and Blood Institute, US Department of Health and Human Services: **Hip bone density predicts breast cancer risk independently of Gail score: results from the Women's Health Initiative.** *Cancer.* 2008, **113**:907-15.

22. Kenemans P, Speroff L; International Tibolone Consensus Group: **Tibolone: clinical recommendations and practical guidelines. A report of the International Tibolone Consensus Group.** *Maturitas* 2005, **51**:21-8.

23. Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, Gudbjartsson DF, Walters GB, Ingvarsson T, Jonsdottir T, Saemundsdottir J, Center JR, Nguyen TV, Bagger Y, Gulcher JR, Eisman JA, Christiansen C, Sigurdsson G, Kong A, Thorsteinsdottir U, Stefansson K: **Multiple genetic loci for bone mineral density and fractures.** *N Engl J Med.* 2008, **358**:2355-65.

Table 1: Demographics and other baseline characteristics of subjects with BMD data at baseline

			Tibolone 2.5 mg (N=345)			Placebo (N=354)		
			Osteoporosis (N=39)	Osteopenia (N=165)	Normal (N=141)	Osteoporosis (N=43)	Osteopenia (N=152)	Normal (N=159)
		n	39	165	141	43	152	159
Age (years)		Mean (SD)	55.3 (7.3)	53.1 (7.3)	52.9 (7.4)	56.8 (7.2)	53.3 (7.0)	52.2 (6.4)
		Median (range)	55.0 (43, 73)	53.0 (32, 74)	53.0 (34, 72)	57.0 (42, 70)	53.0 (36, 71)	52.0 (39, 75)
		n	36	164	138	43	151	158
Body mass index (kg/m2)[1]		Mean (SD)	24.0 (3.5)	25.1 (4.6)	26.5 (3.8)	24.3 (4.0)	25.1 (4.1)	27.7 (4.8)
		Median (range)	23.9 (18, 33)	23.8 (17, 52)	25.7 (19, 37)	24.0 (19, 37)	23.9 (19, 39)	26.9 (19, 48)
		n	35	143	116	39	135	134
Time since menopause (years)[2]		Mean (SD)	10.5 (7.9)	6.9 (6.5)	7.3 (7.4)	8.4 (6.4)	7.1 (7.1)	5.0 (5.3)
		Median (range)	8.4 (1, 35)	4.3 (0, 30)	4.6 (0, 31)	5.1 (0, 24)	4.3 (1, 30)	3.1 (0, 30)
		n	39	165	141	43	152	159
Time since breast cancer surgery (years)		Mean (SD)	2.4 (1.2)	2.2 (1.2)	2.2 (1.3)	2.4 (1.5)	2.3 (1.3)	2.0 (1.2)
		Median (range)	2.3 (0, 5)	2.0 (0, 5)	2.1 (0, 5)	2.4 (0, 5)	2.1 (0, 5)	1.7 (0, 5)
		Asian	26 (66.7)	76 (46.1)	31 (22.0)	26 (60.5)	63 (41.4)	38 (23.9)
Race	**n (%)**	Black					1 (0.7)	1 (0.6)
		Caucasian	13 (33.3)	85 (51.5)	109 (77.3)	16 (37.2)	86 (56.6)	118 (74.2)
		Other		4 (2.4)	1 (0.7)	1 (2.3)	2 (1.3)	2 (1.3)
Smoking at baseline	**n (%)**	No	39 (100.0)	144 (87.3)	122 (86.5)	38 (88.4)	133 (87.5)	137 (86.2)
		Yes		21 (12.7)	19 (13.5)	5 (11.6)	19 (12.5)	22 (13.8)
Alcohol use at baseline	**n (%)**	No	36 (92.3)	111 (67.3)	78 (55.3)	32 (74.4)	96 (63.2)	83 (52.2)
		Yes	3 (7.7)	54 (32.7)	63 (44.7)	11 (25.6)	56 (36.8)	76 (47.8)
		Negative	12 (30.8)	36 (21.8)	21 (14.9)	12 (27.9)	49 (32.2)	30 (18.9)
Estrogen receptor status	n (%)	Positive	27 (69.2)	122 (73.9)	116 (82.3)	29 (67.4)	101 (66.4)	126 (79.2)
		Unknown		7 (4.2)	4 (2.8)	2 (4.7)	2 (1.3)	3 (1.9)
		Negative	11 (28.2)	45 (27.3)	28 (19.9)	16 (37.2)	58 (38.2)	39 (24.5)
Progestagen receptor status	n (%)	Positive	27 (69.2)	110 (66.7)	106 (75.2)	25 (58.1)	86 (56.6)	111 (69.8)
		Unknown	1 (2.6)	10 (6.1)	7 (5.0)	2 (4.7)	8 (5.3)	9 (5.7)
		None	33 (84.6)	149 (90.3)	132 (93.6)	39 (90.7)	139 (91.4)	144 (90.6)
Aromatase Inhibitor (*)	n (%)	Ever, but not recent	1 (2.6)	3 (1.8)		1 (2.3)	4 (2.6)	2 (1.3)
		Recent	5 (12.8)	13 (7.9)	9 (6.4)	3 (7.0)	9 (5.9)	13 (8.2)
		None	13 (33.3)	36 (21.8)	29 (20.6)	15 (34.9)	48 (31.6)	29 (18.2)
Tamoxifen (*)	n (%)	Ever, but not recent	4 (10.3)	16 (9.7)	9 (6.4)	1 (2.3)	10 (6.6)	14 (8.8)
		Recent	22 (56.4)	113 (68.5)	103 (73.0)	27 (62.8)	94 (61.8)	116 (73.0)
		None	34 (87.2)	159 (96.4)	133 (94.3)	41 (95.3)	144 (94.7)	147 (92.5)
GnRH analogs (*)	n (%)	Ever, but not recent	1 (2.6)	1 (0.6)	2 (1.4)	1 (2.3)	3 (2.0)	1 (0.6)
		Recent	4 (10.3)	5 (3.0)	6 (4.3)	1 (2.3)	5 (3.3)	11 (6.9)
		None	11 (28.2)	52 (31.5)	54 (38.3)	12 (27.9)	55 (36.2)	59 (37.1)
Chemotherapy (*)	n (%)	Ever, but not recent	25 (64.1)	109 (66.1)	83 (58.9)	28 (65.1)	94 (61.8)	96 (60.4)
		Recent	3 (7.7)	4 (2.4)	4 (2.8)	3 (7.0)	3 (2.0)	4 (2.5)
		Missing					1 (0.7)	
Node status	n (%)	Negative	18 (46.2)	90 (54.5)	86 (61.0)	20 (46.5)	80 (52.6)	93 (58.5)
		Positive	21 (53.8)	75 (45.5)	55 (39.0)	23 (53.5)	71 (46.7)	66 (41.5)

[1,2] Statistical analysis revealed no differences between groups for all of the above demographics and other baseline characteristics. Body mass index (p=0.06) and time since menopause (p=0.06) were the only 2 continuous variables close to significance.

Demographics and other baseline characteristics of subjects with Bone Mineral Density (BMD) data at baseline. Comparison between tibolone and placebo randomised patients at baseline demonstrated no difference between groups for all of the demographics and other baseline characteristics. Body Mass Index (p=0.06) and time since menopause (p=0.06) were the only two continuous variables which came close to significance.

Table 2: Factors predicting bone mineral density (lumbar spine and total hip)

Endpoint	Effect	Numerator DF	Denominator DF	F-Value	P-value
Lumbar spine	Race	2	665	26.19	<.0001
	BMI	1	665	17.06	<.0001
	Time since breast surgery (years)	1	665	7.74	0.006
	AGE	1	665	6.32	0.012
	Age at menarche (years)	1	665	4.74	0.030
	Node status	1	665	4.77	0.029
	GnRH analogs	2	665	3.26	0.039
Total hip	Race	2	660	63.33	<.0001
	BMI	1	660	149.15	<.0001
	Time since breast surgery (years)	1	660	6.15	0.013
	AGE	1	660	4.81	0.029

Factors predicting BMD at baseline. Asian women show significantly more osteoporosis (p=<0.001) at both hip and lumbar spine. Older age and lower BMI, both of which are recognised to predict bone mineral density, were also significant.

Table 3: Fractures by BMD classification at baseline (≤ day 1), Asian and Caucasian

		Tibolone 2.5 mg			Placebo			All		
		N	number of fractures	%	N	number of fractures	%	N	number of fractures	%
Asian	All	133	6	4.5	127	8	6.3	260	14	5.4
	osteoporosis	27	1	3.7	25	2	8.0	52	3	5.8
	osteopenia	75	4	5.3	64	5	7.8	139	9	6.5
	normal	31	1	3.2	38	1	2.6	69	2	2.9
Caucasian	All	206	7	3.4	221	17	7.7	427	24	5.6
	osteoporosis	12	0	0.0	17	2	11.8	29	2	6.9
	osteopenia	85	4	4.7	86	8	9.3	171	12	7.0
	normal	109	3	2.8	118	7	5.9	227	10	4.4
All	All	339	13	3.8	348	25	7.2	687	38	5.5
	osteoporosis	39	1	2.6	42	4	9.5	81	5	6.2
	osteopenia	160	8	5.0	150	13	8.7	310	21	6.8
	normal	140	4	2.9	156	8	5.1	296	12	4.1

Note: No significant reduction in fracture occurred in the group overall, although an almost-significant reduction occurred in Caucasian patients on tibolone (p=0.054).

Fractures according to baseline BMD classification. The percentage of women who developed bone fracture did not differ between those with osteoporosis and osteopaenia but because osteopaenia was the larger population group, more fractures occurred amongst osteopaenic patients.

Table 4: Anova table for BC recurrence restricted to subjects with any BMD assessment using a proportional hazard Cox model with treatment, osteopenia (defined as: T-score≤ -1) as time dependent factors and BMI as covariate

Parameter	Estimate	Std Error	Chi-Square	DF	P-value	Hazard ratio	95 % Confidence limits
Tibolone	0.50	0.26	3.75	1	0.05	1.64	0.99, 2.72
BMI	-0.01	0.03	0.07	1	0.79	0.99	0.93, 1.06
Osteopenia (T-score≤ -1)	-0.57	0.27	4.41	1	0.04	0.57	0.34, 0.96

For those patients with baseline and either two year or second bone mineral density measurements at trial end, an analysis was carried out to correct for changes in BMD on treatment. Osteopaenic and osteoporotic patients were grouped together to take account of changes in BMD during the course of the trial. Tibolone use in women with normal BMD were associated with increased breast cancer recurrence with a Hazard Ratio which reached significance.

Figure legends

Figure 1: CONSORT diagram of participant flow.

Figure 2: Bone mineral density change (%) from baseline after 2 Years.
Figures are Relative Change from baseline of BMD Mean (SD). Bone mineral density changes on tibolone compared to placebo between baseline and two years of treatment. Tibolone significantly increased bone mineral density whereas patients on placebo had a 2% loss of bone mineral density and had lower weight and height. Overall there was a 1.6% increase in bone mineral density at lumbar spine on tibolone and a 1.6% BMD loss on placebo and similar magnitudes of change were seen at the hip (both p = <0.01).

Figure 3: Baseline BMD and breast cancer recurrence. Incidence of breast cancer recurrence on tibolone or placebo according to baseline bone mineral density. Significantly more breast cancers occurred in women with normal bone

mineral density on tibolone (15.6%) compared to either osteopaenic or osteoporotic patients (7.3% and 7.7% respectively [p=<0.016]).

Additional files

Additional file 1: Summary statistics of the bone mineral density in the lumbar spine and total hip at baseline including change and percentage change from baseline.

Table showing the summary statistics of bone mineral density change on tibolone or placebo from baseline at the lumbar spine and hip. This represents the raw data from the basis of Figure 2 and Additional file Table 2. Analysis for breast cancer recurrence restricted subjects with any BMD assessment with a proportional Hazard Cox model for treatment osteopaenia as time-dependent factors with BMI as co-variate.

Additional file 2: Anova table for BC recurrence restricted to subjects with any BMD assessment using a proportional hazard Cox model with treatment, osteopenia (defined as: T-score≤ -1) as time dependent factors and BMI as covariate.

This analysis groups osteopaenic and osteoporotic patients together as approximately 50% of patients had normal bone mineral density and uses a co-variate to correct for changes in BMD during the course of the first two years of the trial. The results indicated that tibolone and normal BMD are associated with increased breast cancer recurrence.

Additional file 3: Breast cancer recurrence in the LIBERATE trial by BMI, race and lifestyle sub-groups.

The effect of tibolone on breast cancer recurrence occurred in all races although significance was only reached in Caucasians. Low or normal BMI was associated with increased breast cancer risk on tibolone (not high BMI).

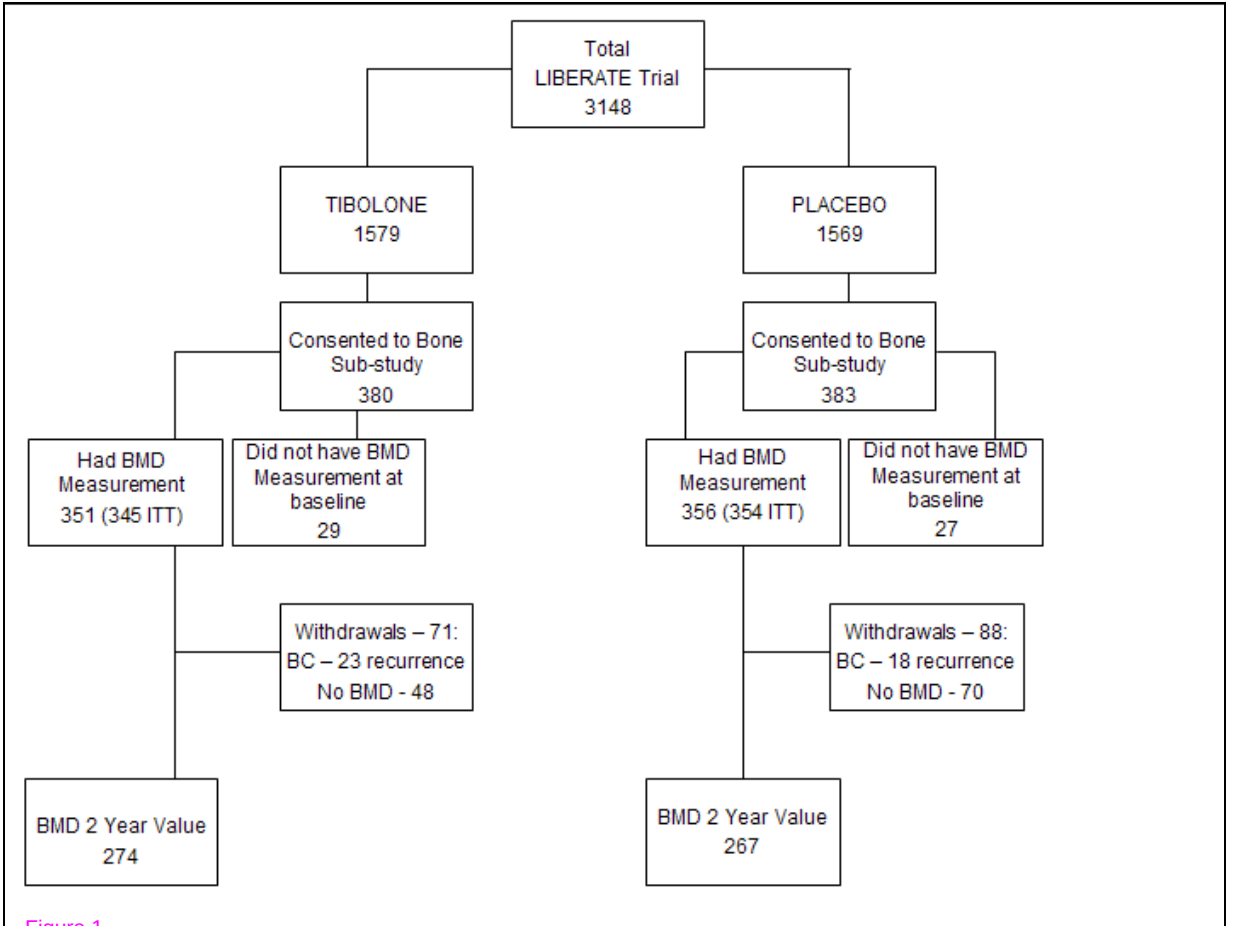
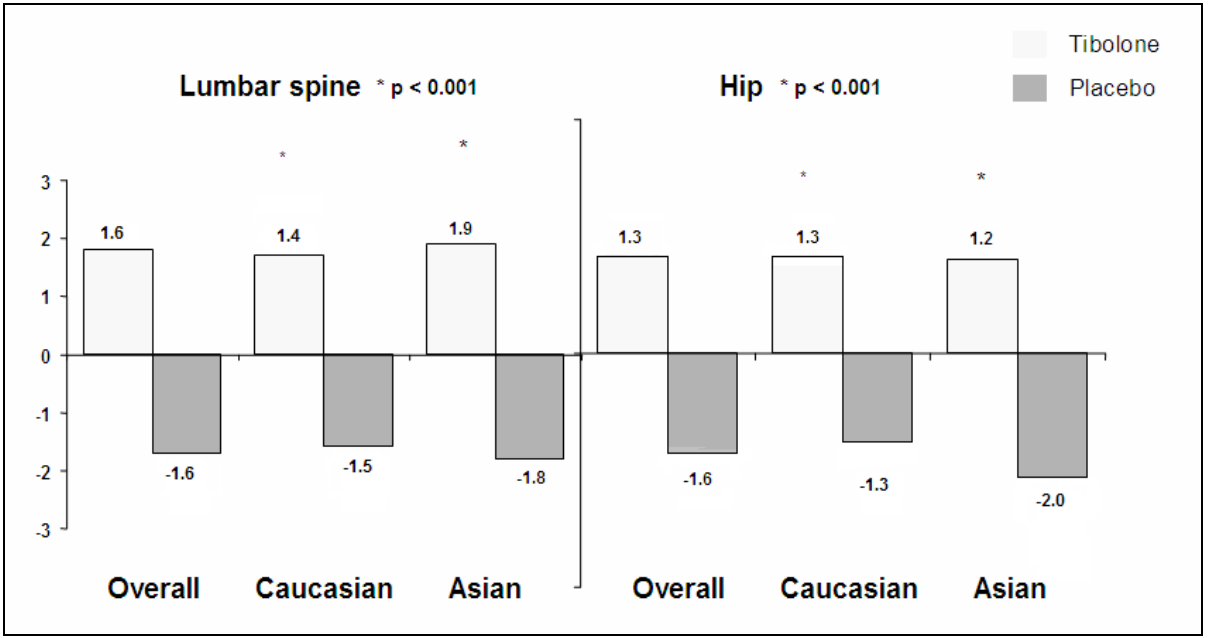
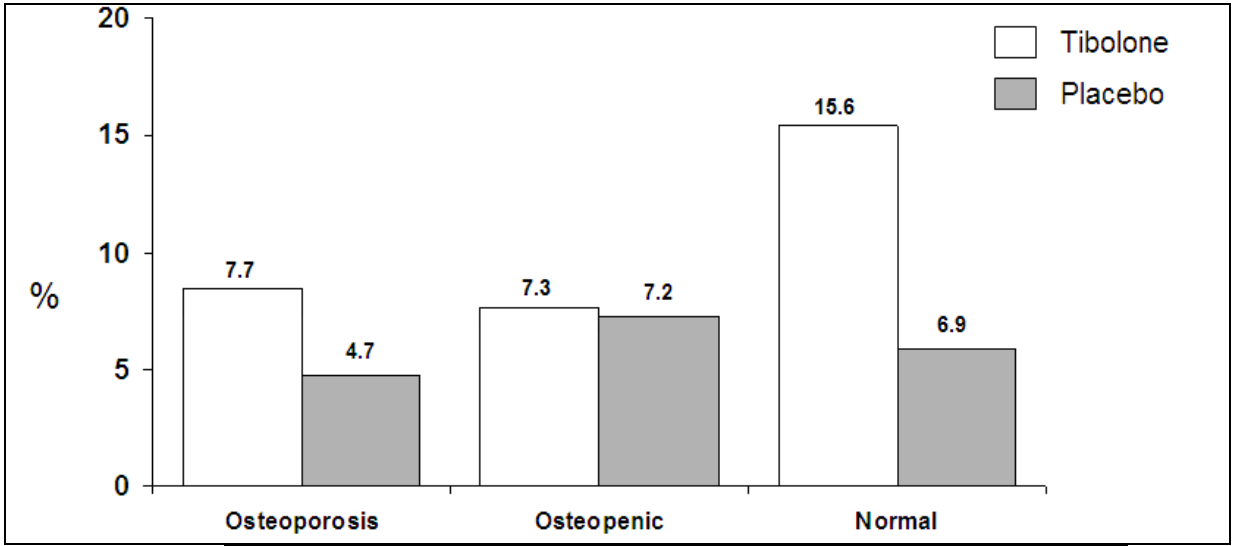

Total
LIBERATE Trial
3148
TIBOLONE
1579
PLACEBO
1569
Consented to Bone Sub-study
380
Consented to Bone Sub-study
383
Had BMD Measurement
351 (345 ITT)
Did not have BMD Measurement at baseline
29
Had BMD Measurement
356 (354 ITT)
Did not have BMD Measurement at baseline
27
Withdrawals – 71:
BC – 23 recurrence
No BMD - 48
Withdrawals – 88:
BC – 18 recurrence
No BMD - 70
BMD 2 Year Value
274
BMD 2 Year Value
267

Figure 1



Tibolone	1.6 (4.2)	1.4 (3.9)	1.9 (4.5)	1.3 (4.1)	1.3 (3.0)	1.2 (5.2)
Placebo	-1.6 (4.1)	-1.5 (4.0)	-1.8 (4.3)	-1.6 (3.4)	-1.3 (3.0)	-2.0 (3.7)

Figure 2



	Tib	Plac	Tib	Plac	Tib	Plac
n	39	43	165	152	141	159
BC Recurrence	3 (7.7%)	2 (4.7%)	12 (7.3%)	11 (7.2%)	22 (15.6%)	11 (6.9%)

Figure 3

Additional files provided with this submission:

Additional file 1: Supplementary Table 1.doc, 74K
http://breast-cancer-research.com/imedia/1845246266508671/supp1.doc
Additional file 2: Supplementary Table 2.doc, 26K
http://breast-cancer-research.com/imedia/1936052268650867/supp2.doc
Additional file 3: Supplementary Table 3.doc, 33K
http://breast-cancer-research.com/imedia/6302906416508692/supp3.doc