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Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial

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Summary

Background: Vasomotor symptoms and bone loss are complications frequently induced by adjuvant treatment for breast cancer. Tibolone prevents both side-effects, but its effect on cancer recurrence is unknown. The aim of this study was to show non-inferiority of tibolone to placebo regarding risk of recurrence in breast-cancer patients with climacteric complaints.
Methods: Between July 11, 2002, and Dec 20, 2004, women surgically treated for a histologically confirmed breast cancer ($T_{1-3}N_{0-2}M_0$) with vasomotor symptoms were randomly assigned to either tibolone 2·5 mg daily or placebo at 245 centres in 31 countries. Randomisation was done by use of a centralised interactive voice response system, stratified by centre, with a block size of four. The primary endpoint was breast-cancer recurrence, including contralateral breast cancer, and was analysed in the intention-to-treat (ITT) and per-protocol populations; the margin for non-inferiority was set as a hazard ratio of 1·278. This study is registered with ClinicalTrials.gov, number NCT00408863.
Findings: Of the 3148 women randomised, 3098 were included in the ITT analysis (1556 in the tibolone group and 1542 in the placebo group). Mean age at randomisation was 52,7 years (SD 7,3) and mean time since surgery was 2,1 years (SD 1,3). 1792 of 3098 (58%) women were node positive and 2185 of 3098 (71%) were oestrogen-receptor positive. At study entry, 2068 of 3098 (67%) women used tamoxifen and 202 of 3098 (6,5%) women used aromatase inhibitors. The mean daily number of hot flushes was 6,4 (SD 5,1). After a median follow-up of 3,1 years (range 0·01-4·99), 237 of 1556 (15·2%) women on tibolone had a cancer recurrence, compared with 165 of 1542 (10,7%) on placebo (HR 1,40 [95% CI 1,14-1,70]; p=0·001). Results in the per-protocol population were similar (209 of 1254 [16,7%] women in the tibolone group had a recurrence *vs* 138 of 1213 [11,4%] women in the placebo group; HR 1,44 [95% CI 1·16-1·79]; p=0·0009). Tibolone was not different from placebo with regard to other safety outcomes, such as mortality (72 patients *vs* 63 patients, respectively), cardiovascular events (14 *vs* 10, respectively), or gynaecological cancers (10 *vs* 10, respectively). Vasomotor symptoms and bone-mineral density improved significantly with tibolone, compared with placebo.
Interpretation: Tibolone increases the risk of recurrence in breast cancer patients, while relieving vasomotor symptoms and preventing bone loss.
Funding: Schering-Plough (formerly NV Organon, Oss, Netherlands).

INTRODUCTION

Women successfully treated by surgery for early stage breast cancer often have severe flushes, resulting from adjuvant treatment with tamoxifen, aromatase inhibitors, gonadotropin-releasing hormone (GnRH) analogues, or chemotherapy.[1,2] Conventional oestrogen therapy, alone or combined with a progestagen, is effective in alleviating these complaints, but is contraindicated in patients with breast cancer, because it is feared that hormones can cause breast cancer to recur.[3,4]

Tibolone is a synthetic steroid with a pharmacological and clinical profile that is different from conventional sex steroids.[5,6] Tibolone is approved in 90 countries for treatment of menopausal symptoms and in 55 countries for the prevention of osteoporosis. Currently, many patients with breast cancer use tibolone to reduce climacteric symptoms. However, a history of breast cancer is a contraindication for tibolone use, although no reliable evidence of harm is available.

* *LIBERATE Study Group participants listed at end of paper*

The mode of action of tibolone is complex. Orally taken, tibolone is rapidly metabolised within the intestine and liver into active metabolites, two of which have an oestrogenic (mostly oestrogen-receptor-alpha mediated) action in various tissues (eg, bone and vagina), and a third metabolite, the delta-4-isomer, which binds to both progesterone and androgen receptors.[7,8]

In healthy postmenopausal women, tibolone causes less stimulation of breast tissue than conventional combined hormone therapy, as judged by mammographie breast density and fine-needle aspiration studies.[9-11] Observational studies provide limited and conflicting evidence on breast cancer risk with tibolone use.[12,13] Currently, there is only one randomised, placebo-controlled clinical trial with tibolone assessing breast-cancer risk. This study, in older osteoporotic women, had risk of vertebral fractures as the primary endpoint. Breast-cancer incidence, confirmed by independent adjudication, was significantly reduced after 3 years of tibolone use compared with placebo (hazard ratio 0·32 [95% CI 0·13-0· 80]) .[14]

Data for the use of tibolone in patients with breast cancer are scarce. In pilot studies, which involved patients with breast cancer receiving adjuvant treatment with tamoxifen or GnRH analogues, tibolone was effective in reducing vasomotor symptoms.[15-17] Additionally, no significant effect on tumour-cell proliferation was noted in oestrogen-receptor-positive breast tumours.[18]

The LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) trial was designed to test the primary postulation that the use of tibolone 2·5mg per day does not increase the risk of breast-cancer recurrence in women surgically treated for breast cancer who have hot flushes and other climacteric complaints.

METHODS

Patients

LIBERATE was a multinational, multicentre, randomised, double-blind, parallel group, placebo-controlled trial, designed to assess the safety and efficacy of tibolone in women with vasomotor symptoms and a history of breast cancer. Details of study design, methods, and baseline data of the LIBERATE study have been published previously.[19] Briefly, women with vasomotor symptoms who requested treatment for these symptoms were eligible if they had been surgically treated within the previous 5 years for histologically confirmed $T_{1-3}N_{0-2}M_0$ breast cancer. Participants had to be postmenopausal and younger than 75 years of age. Between June 20, 2002, and Dec 1, 2004, 3585 women were screened. At screening, non-hysterectomised women with endometrial abnormalities were excluded by transvaginal ultrasonography. The study was done at 245 clinical centres in 31 countries worldwide. The trial end was scheduled for December, 2007. The LIBERATE study protocol was approved by the institutional review board at each centre, and written informed consent was obtained from each participant.

Procedures

Eligible women were randomly assigned to receive orally either tibolone 2,5 mg daily or placebo in a one-to-one ratio. Randomisation was done by use of a centralised interactive voice response system, stratified by centre, with a block size of four. Participants, investigators, sponsor personnel, and outcome assessors were blinded to treatment assignment. The primary objective was to show that tibolone was non-inferior to placebo regarding breast-cancer recurrence; the primary endpoint was thus breast-cancer recurrence, including contralateral breast cancer. Recurrence was defined as locoregional recurrence, distant metastasis, or a new primary invasive tumour in the contralateral breast. Study participants had to attend their regular breast cancer follow-up visits. An independent adjudication committee assessed all recurrences reported.

Secondary endpoints were mortality, vasomotor symptoms, bone-mineral density (BMD), and health-related quality of life. The independent adjudication committee was responsible for reviewing the cause of death. The number and severity of vasomotor symptoms were recorded on diary cards during the first 12 weeks of treatment and on the Climacteric Symptoms Form throughout the trial. BMD of the lumbar vertebrae (L1-L4) and left proximal femur were measured by means of dual-energy X-ray absorptiometry (DXA) using Lunar or Hologic instruments at baseline and at week 104 in specialised centres in a subgroup of patients (N=763; restricted to 15 of 31 centres due to logistic reasons). Data were analysed at an independent central quality control and quality assurance facility. Health-related quality of life was assessed at weeks 13, 26, 52,78,104, and annually thereafter, using the nine domains in the Women's Health Questionnaire (WHQ) in a subgroup of patients (N=883; restricted to eight of 31 centres due to logistic reasons).

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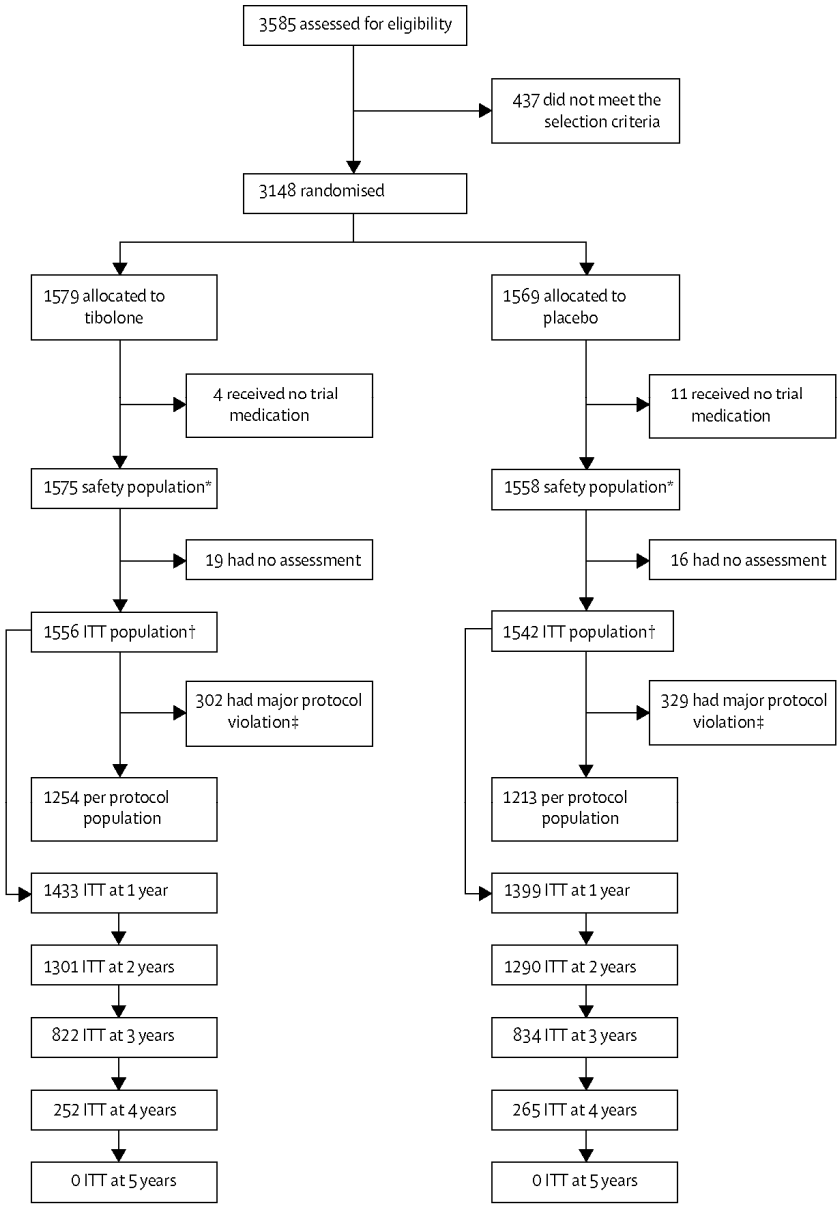
Figure 1: *Trial profile*
Reasons for discontinuation up to 5 years after randomisation include occurrence of breast-cancer recurrence, mortality, serious adverse events, insufficient relief of climacteric symptoms, withdrawal of informed consent, and loss to follow-up. *All-patients-treated population, ‡ Assessment of primary endpoint (breast-cancer recurrence). ‡ Extent of exposure to trial medication <60% of duration of trial participation, other than $T_{1-3}N_{0-2}M_0$ breast cancer history at entry, presence of breast-cancer recurrence or other malignancy, or hormonal comedication (except vaginal oestriol cream).



At follow-up visits, scheduled every 6 months, a physical examination and breast examination were done, vasomotor symptoms and vital signs recorded, and concomitant medication, vaginal-bleeding episodes, and adverse effects documented. A gynaecological examination, mammography, and blood sampling for routine laboratory safety assessment were done annually.

The protocol called for an endometrial biopsy at any time during the trial in women with persisting vaginal bleeding. If biopsies were categorised as any type of hyperplasia or cancer, trial medication was discontinued and the woman treated.

Women who did not have adequate relief of their vasomotor symptoms were allowed to use concomitant non-hormonal medication, such as soy products, clonidine, and antidepressants. Women who stopped trial medication

prematurely were encouraged to stay in the trial for inclusion in outcome analyses.

An independent data and safety monitoring board (DSMB) assessed the safety of the participants by reviewing unblinded data every 6 months, and advised as to the continuation, alteration, or cessation of the study.

Table 1: *Demographics and other baseline characteristics of the ITT population*

	Tibolone group (N=1556)	**Placebo group (N=1542)**
Age (years), n (%)		
<40	50(3·2)	38(2·5)
40-49	502(32·3)	469 (30·4)
50-59	723 (46·5)	764(49·5)
60-69	264 (17·0)	245 (15·9)
≥70	17 (1·1)	26 (17)
Mean (SD)	52·5 (7·4)	52·9(73)
Body-mass index (kg/m^2), mean (SD)	**26·9(4·9)**	**27·1(5·0)**
Ethnic origin, n (%)		
Asian	270 (17·4)	266 (173)
Black	8(0·5)	7(0·5)
White	1229(79·0)	1223 (79·3)
Other	49 (3·1)	46 (3·0)
Time since menopause (years), mean (SD)	**6·2(6·3)**	**6·2(6·5)**
Time since breast-cancer surgery (years), mean (SD)	2·1(1·3)	2·1(1·3)
Node status, n (%)		
Negative	**657(42·2)**	**646 (41·9)**
Positive	**898 (57·7)**	**894(58·0)**
Missing	**1 (0·1)**	**2 (0·1)**
Primary breast cancer stage, n (%)		
0	4(0·3)	3 (0·2)
I	463(29·8)	453 (29·4)
IIA	552(35·5)	517(33·5)
IIB	392(25·2)	418 (27·1)
IIIA	141 (9·1)	143 (9·3)
IIIB	1 (0·1)	6 (0·4)
Missing	3(0·2)	2 (0·1)
Type of surgery, n (%)		
Breast sparing	**661 (42·5)**	**662 (42·9)**
Mastectomy	**895 (57·5)**	**880 (57·1)**
Oestrogen-receptor status, n (%)		
Negative	294(18·9)	329 (21·3)
Positive	1112 (71·5)	1073 (69·6)
Unknown	150(9·6)	140 (9·1)
Progestagen receptor status, n (%)		
Negative	**361(23·2)**	**406 (26·3)**
Positive	**978(62·9)**	**922 (59·8)**
Unknown	**217(13·9)**	**214(13·9)**
Adjuvant therapy at entry*, n (%)		
Tamoxifen	1037 (66·6)	1031 (66·9)
Aromatase inhibitor	103 (6·6)	99 (6·4)
GnRH analogues	66 (4·2)	68 (4·4)
Overall	1139 (73·2)	1132 (73·4)
Chemotherapy before entry, n (%)	**1047 (67·3)**	**995 (64·5)**
Chemotherapy at entry*, n (%)	68 (4·4)	82 (5·3)
Ovariectomy at entry, n (%)	**276 (17·7)**	**238 (15·4)**
Hot flushes (n), mean (SD)		
Overall	6·3 (5·0)	6·4(5·2)
EMEA subgroup	12·8(4·6)	12·2(4·9)

GnRH=gonadotropin-releasing hormone. *Use within 14 days before baseline or at baseline according to defined AnatomicTherapeutic Chemical (ATC) codes; some patients received more than one drug.

Statistical analysis

The primary safety analysis for breast-cancer recurrence and the secondary analysis for mortality were done by fitting the Cox proportional hazard model stratified by (pooled) country, to obtain an estimate and a two-sided 95% CI for the hazard ratio (HR) between tibolone and placebo. Non-inferiority would be claimed if the upper two-sided 95% CI of the breast-cancer recurrence HR was less than the non-inferiority margin of delta=1 · 278 (corresponding to a relative risk <1·25). The sample size estimate of 3100 women assumed an incidence of breast cancer recurrence after 3 years of 15% in the placebo group, based on an expected 9% in lymph-node-negative patients and 24% in lymph-node-positive patients.[20] This would lead to a power of about 80% for claiming non-inferiority.

Table 2: **Incidence of breast-cancer recurrence in the ITT population**

	Tibolone group (N=1556), n (%)	Placebo group (N=1542), n (%)	HR (95%CI)*	p value †
Overall‡	237(15·2)	165 (10·7)	1·397 (1·144-1·704)	0·001
Location				
Local	48 (3·1)	33(2·1)	1·419 (0·911-2·211)	0·122
Contralateral	25(1·6)	17 (1·1)	1·387(0·742-2·594)	0·305
Distant	171 (11·0)	121 (7·8)	1·378 (1·092-1·740)	0·007

*Tibolone compared with placebo.† Wald test in Cox model, stratified by (pooled) country for the null hypothesis of no treatment difference.
‡402 patients were reported with a breast-cancer recurrence, of whom 13 had a recurrence at more than one site.

Statistical analysis of breast-cancer recurrence was done for the intention-to-treat (ITT) and the per-protocol populations. The ITT population consisted of all women receiving trial medication for whom information was available as to the presence or absence of breast-cancer recurrence. For the per-protocol population, all participants were excluded who had major protocol violations, such as sex-hormone coadministration (with the exception of vaginal oestriol cream; n=79) or lack of compliance (ie, exposure to trial medication less than 60% of duration of trial participation). Additionally, analyses were done for various predefined subgroups (ie, receptor status, lymph-node status, and comedication).

Data on hot flushes were analysed for the ITT population and for a subgroup of highly symptomatic patients (ie, those with at least five moderate or severe hot flushes a day) defined according to the European Agency for Evaluation of Medicinal Products (EMEA) guidelines, using the last-observation-carried-forward approach.[21] The mean number of hot flushes per 24-h period and the change and percentage change from baseline were calculated. Change and percentage change from baseline in lumbar vertebrae and hip BMD were analysed in a subgroup. For the analysis of hot flushes and BMD, an analysis of covariance (ANCOVA) model was used with treatment groups and centre as factors and the baseline value as the covariate. The estimates and corresponding two-sided 95% CI of the treatment effect were calculated per timepoint. Changes from baseline in the nine domain scores of the WHQ were analysed by use of a Wilcoxon rank test stratified by centre.

All statistical analyses were done with SAS version 9.1. This trial is registered with ClinicalTrials.gov, number NCT00408863.

Role of the funding source

The study sponsor did the trial and collected the data. An advisory board had overall scientific responsibility for study design and protocol, and advised the sponsor as to the conduct of the trial. After the trial end, the Board received all data analyses they requested. The Board was comprised of independent investigators and non-voting members from the sponsor. The corresponding author had full access to all the data. All authors were involved in the final decision to submit for publication.

RESULTS

The trial profile is shown in figure 1. Baseline characteristics were similar in the two groups of the ITT population (table 1). The mean age was 52,7 years (SD 73), and mean time since breast-cancer surgery was 2,1 years (SD 1·3). 1487 of 3098 women (48 0%) were between 50 and 59 years of age, 88 women (2,8%) were younger than 40 years of age, and 43 women (1,4%) were 70 years of age or older. Mean BMI was 27·0 kg/m^2 (SD 4,9). 2452 of 3098 women (79,1%) were white and 536 (17,3%) were Asian. Tumour stage was IIA or higher in 2170 of 3098 women (70·0%), and lymph-node status was positive (N_{1-2}) in 1792 women (57 · 8%). Surgery had been breast conserving in only 1323 of 3098 women (42·7%). Oestrogen-receptor status was

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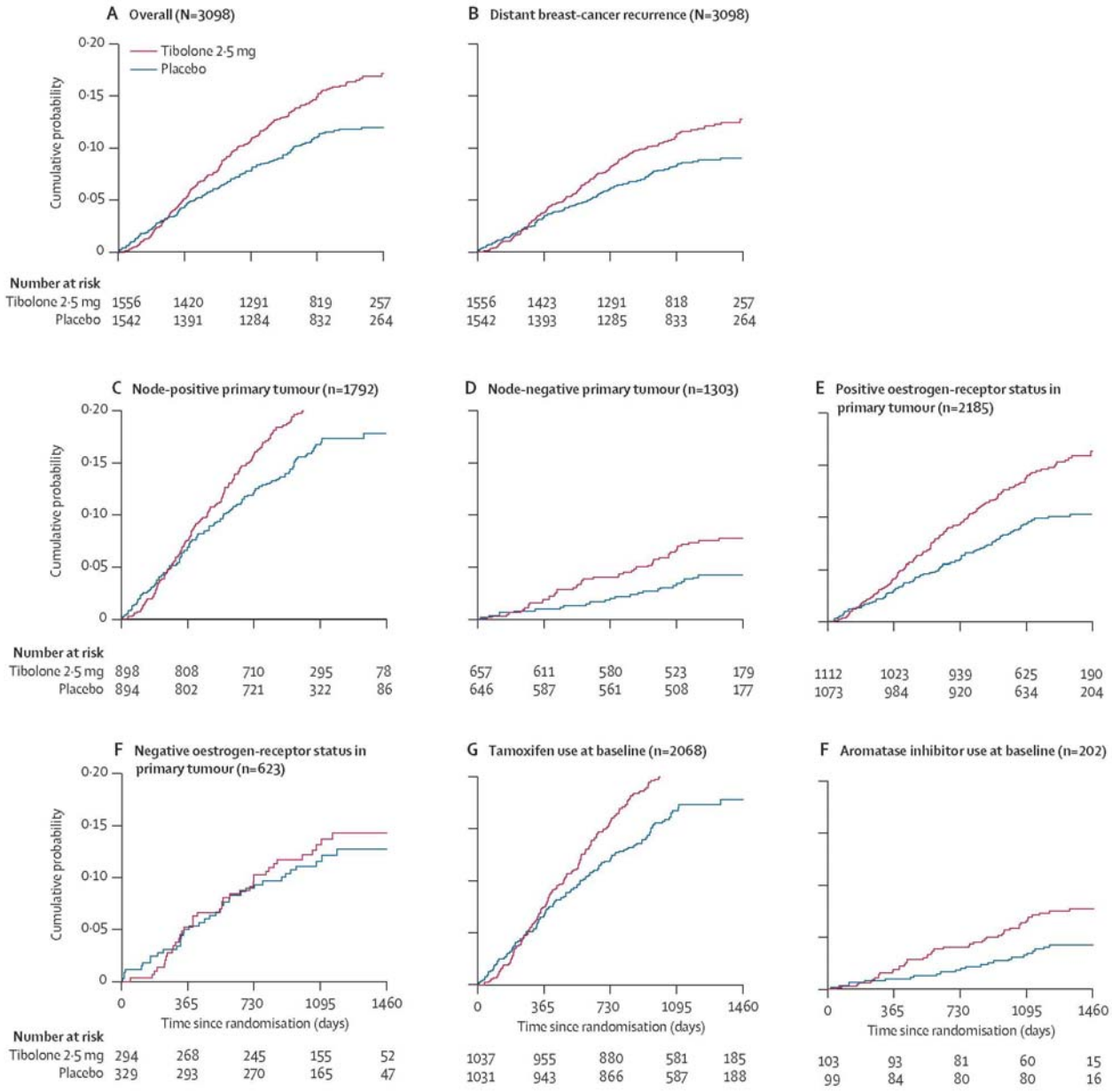
positive in 2185 women (77·8%) of the 2808 women in whom oestrogen-receptor status was known. At trial entry, most women used tamoxifen (n=2068 [66·8%]), with others receiving adjuvant aromatase inhibitors (n=202 [6·5%]), chemotherapy (n=150 [4·8%]), or GnRH analogues (n=134 [4·3%]). During the study period, 464 of 2068 women (22 · 4%) on tamoxifen switched to aromatase inhibitors (242 in the tibolone group, 222 in the placebo group). The mean daily number of hot flushes was 6·4 overall (SD 5·1) and 12·5 (SD 4·8) in the EMEA subgroup with severe complaints (table 1).

Figure 2: *Cumulative probability of breast-cancer recurrence versus time in the ITT population*



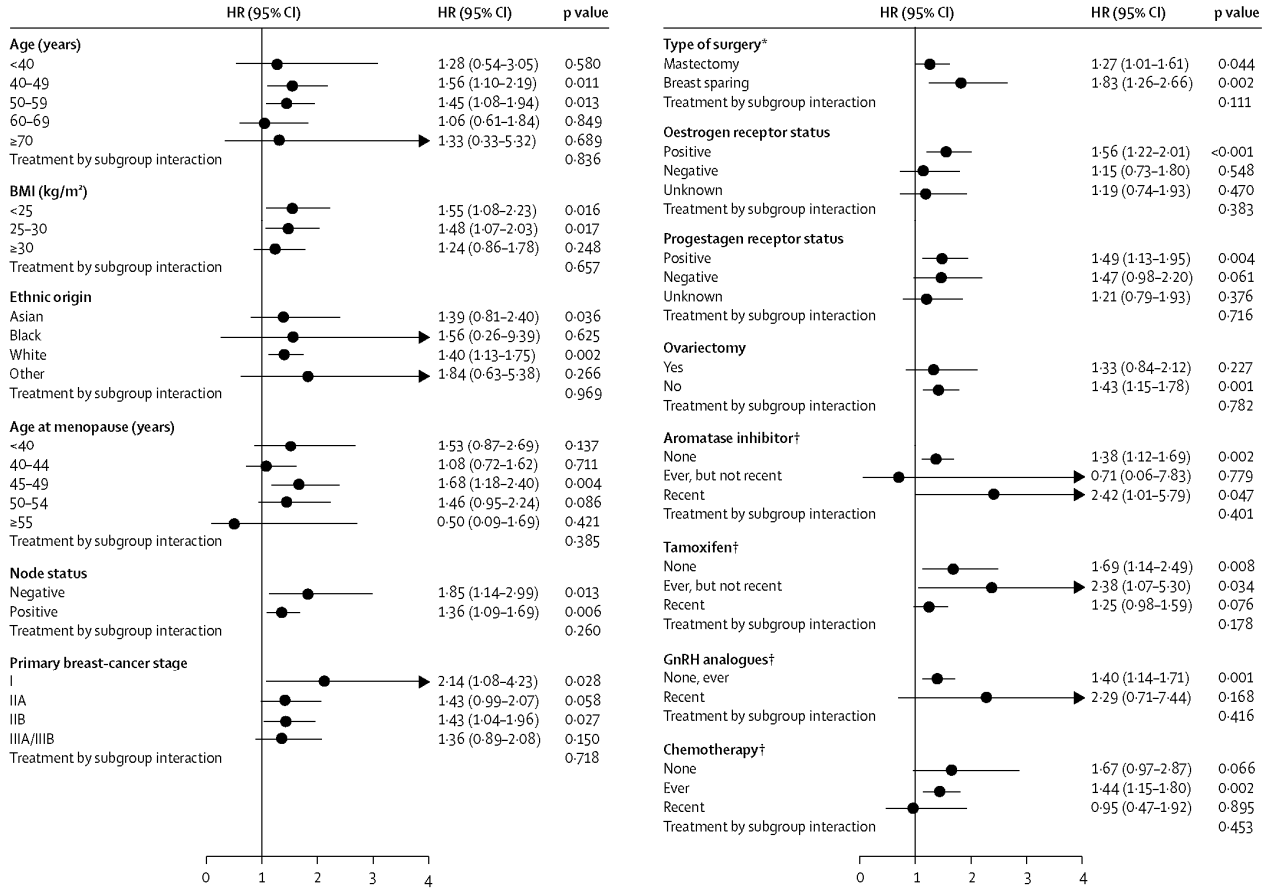
LIBERATE started screening patients in June, 2002, and ended prematurely on July 31, 2007 In March, 2007, the DSMB reported a trend for an excess of breast-cancer recurrences in the tibolone group. Because it seemed highly improbable that the predefined statistical criteria for non-inferiority could still be met, the scientific advisory board advised ceasing medication and the sponsor decided to end the trial prematurely.

Median duration of trial participation was 3 · 07 years (range 0·01-4·99; 4666 women-years in total) in the tibolone group and 3·14 years (range 0·01-4·94; 4633 women-years in total) in the placebo group. Median duration of treatment was 2·74 years (range 0·01-4·79) for tibolone and 2·76 years (range 0·01-4· 72) for the

placebo group, with a total of 3901 and 3874 women-years of exposure for tibolone and placebo, respectively.

In the ITT population, breast-cancer recurrences were reported and confirmed by adjudication for 402 patients: 237 of 1556 women (15 · 2%) in the tibolone group and 165 of 1542 women (10·7%) in the placebo group (HR 1·40 [95% CI 1·14-1 ·70]; p=0·001; table 2). In the per-protocol population, the results were similar (209 of 1254 [16·7%] women in the tibolone group had a recurrence vs 138 of 1213 [11·4%] women in the placebo group; HR 1·44 [95% CI 1·16-1·79]; p=0·0009). Most recurrences in the ITT population were distant metastases (n=292), 81 metastases were local, and the number of contralateral breast cancers detected was 42; 13 patients had a recurrence at more than one site. The HRs for the various sites were similar (table 2 and figure 2). Tibolone treatment was associated with an absolute risk of 51 breast-cancer recurrences per 1000 women-years and placebo with 36 recurrences per 1000 women-years. As expected, the overall incidence of breast-cancer recurrence was lower in lymph-node-negative patients compared with lymph-node-positive patients (5 · 6% [HR 1 · 85 (95% CI 1·14-2·99; p=0·013) vs 18·4% [HR 1·36 (95% CI 1·09-1·69; p=0·006)], respectively; figures 2 and 3). Patients with oestrogen-receptor-negative tumours had no increased risk of recurrence (HR 1·15 [95% CI 0·73-1·80]; p=0·058) by contrast with patients with oestrogen-receptor-positive tumours (HR 1·56 [95% CI 1·22-2·01]; p=0·0005). Users of aromatase inhibitors at baseline had a higher risk of recurrence than tamoxifen users (HR 2·42 [95% CI 1·01-5·79; p=0·047] vs HR 1·25 [95% CI 0·98-1·59; p=0·076]). In the subgroup of patients who were not on tamoxifen, aromatase inhibitors, or GnRH analogues at trial entry (26·7% of the ITT population; n=827) the HR was 1·73 (95% CI 1·18-2·53); p=0·005.

Figure 3: *Forest plots of hazard ratios for breast-cancer recurrences for tibolone compared with placebo in the ITT population*



p values calculated from Wald test in Cox model. *Worst case situation, † Recent use refers to use at entry (within 14 days before baseline or at baseline) according to defined ATC codes; ever use refers to pretrial use (not recent).

The outcomes of other safety outcomes, analysed in the all-patients-treated population are shown in tables 3 and 4. During the trial period 19 of 1575 women treated (1 · 2%) died in the tibolone group versus 20 of 1558 women (1·3%) in the placebo group (HR 0·94 [95% CI 0·50-1·76]; p=0·844). Overall, including the period after the individual end-of-trial visit until trial database closure, 72 of 1575 women (4·6%) died in the tibolone group

compared with 63 of 1558 women (4·0%) in the placebo group (HR 1·12 [95% CI 0·80-1·57]; p=0·509). Of these, 54 women (75%) and 49 women (78%), respectively, had been diagnosed with a breast-cancer recurrence before death. The remaining causes of death were predominantly cardiovascular.

No clinically meaningful differences were noted between the treatment groups during the in-treatment period with respect to the incidence of adverse events (table 4), serious adverse events, and the incidence of adverse events leading to discontinuation of trial medication. Adverse events occurred in 1342 of 1575 patients (85 · 2%) in the tibolone group compared with 1285 of 1558 patients (82·5%) in the placebo group; serious adverse events occurred in 323 of 1575 patients (20 · 5%) in the tibolone group versus 297 of 1558 patients (19·1%) in the placebo group and discontinuations occurred in 127 patients (8·1%) versus 112 patients (7·2%), respectively. The main serious adverse events were reproductive system and breast disorders (77 patients [4·9%] in the tibolone group, 47 [3·0%] in the placebo group); the most common adverse events that led to treatment discontinuation were also reproductive system and breast disorders (22 patients [1·4%] in the tibolone group, 13 [0·8%] in the placebo group). The number of women with adverse events judged by the investigator as possibly, probably, or definitely related to the trial medication was 437 of 1575 (27·7%) in the tibolone group and 340 of 1558 (21·8%) in the placebo group (p=0·0002). A clinical fracture was reported as an adverse event during the trial period for 60 of 1575 women (3·8%) in the tibolone group versus 77 of 1558 women (4·9%) in the placebo group (p=0·137); of these, most were noted in the wrist (table 3).

Table 3: *Main safety outcomes during the trial in the all-patients-treated population*

	Tibolone group (N=1575), n(%)	**Placebo group (N=1558), n(%)**	**p value**
Mortality			
During individual trial participation	19(1·2)	20 (1·3)	0·844*
Overall (until database closure)	72 (4·6)	63 (4·0)	0·509*
Primary malignancies (except breast-cancer recurrences)			
Endometrium	7(0·4)	4(0·3)	0·548†
Other gynaecological	3 (0·2)	6 (0·4)	0·341†
Gastrointestinal	7(0·4)	5 (0·4)	0·774†
Pulmonary	2 (0·1)	2 (0·1)	1·000†
Thyroid	3 (0·2)	2 (0·1)	1·000†
Other	5 (0·3)	6 (0·4)	0·773†
Cardiovascular events			
Venous thromboembolism	5 (0·3)	3 (0·2)	0·484‡
Coronary heart disease	4(0·3)	2 (0·1)	0·417‡
Cerebrovascular disease	5 (0·3)	5 (0·4)	0·997‡
Clinical fractures			
Wrist	13 (0·8)	20 (1·3)	0·225†
Overall	60(3·8)	77(4·9)	0·137†

*Wald test in Cox model, stratified by (pooled) country, † Fisher exact test two-sided. ‡ Wald test in Cox model.

During the in-treatment period, bleeding, spotting, or both, was reported for 208 of 1575 women (13·2%) women in the tibolone group versus 127 of 1558 women (8·2%) in the placebo group. A confirmed endometrial adenocarcinoma was diagnosed during the trial period in seven of 1575 women (0·4%) in the tibolone group compared with four of 1558 women (0·3%) in the placebo group. Nine of these eleven women had used tamoxifen for several years either before or at the time of diagnosis of their uterine cancer. One woman in the tibolone group and one in the placebo group did not use tamoxifen at any time. Endometrial biopsies were 1 · 8 times more frequently taken during the trial period in the tibolone group (n=249) compared with the placebo group (n=141).

On the basis of the diary card, the difference in mean number of hot flushes per day was significantly in favour of tibolone at week 4 (p=0·004), week 8 (p<0·0001), and week 12 (p<0·0001) (figure 4). In the highly symptomatic subgroup, according to the EMEA guidelines, tibolone resulted in significantly larger decreases in the mean number of hot flushes per day from baseline compared with placebo at week 8 (p=0·002) and week 12 (p<0·0001; figure 4). At week 12, the mean change from baseline for the average mean number of hot flushes was -5·4 (SD 4 · 7) in the tibolone group versus -3 · 2 (3 · 4) in the placebo group (p<0·0001). Assessed throughout the trial by use of the climacteric symptoms form, the tibolone group showed a significantly larger decrease from baseline than did the placebo group at all assessments (p<0·0001; figure 4).

In women who had bone-density assessments, increases in BMD from baseline by 3 · 3% at the lumbar spine and 2 · 9% at the hip were noted in the tibolone group (both p<0·0001) compared with the placebo group. The WHQ score showed a clinically meaningful improvement for the domains of sexual behaviour, sleep problems, and vasomotor symptoms (data not shown).

Table 4: *Adverse events during treatment with an incidence of >2% in the all-patients-treated population*

	Tibolone group (N=1575), n (%)	**Placebo group (N=1558), n (%)**
Infections		
Nasopharyngitis	116 (7·4)	106 (6·8)
Influenza	79 (5·0)	98 (6·3)
Upper respiratory tract infection	78(5·0)	85 (5·5)
Bronchitis	81 (5·1)	88 (5·6)
Vaginal infection	72 (4·6)	42 (2·7)
Vaginal candidiasis	56(3·6)	34(2·2)
Urinarytract infection	40(2·5)	56 (3·6)
Cystitis	27(1·7)	42 (2·7)
Sinusitis	29 (1·8)	35 (2·2)
Pharyngitis	26(17)	31 (2·0)
Neoplasms: benign, malignant and unspecified		
Uterine leiomyoma	62(3·9)	36(2·3)
Blood and lymphatic-system disorders		
Lymphadenopathy	31(2·0)	29 (1·9)
Metabolism and nutrition disorders		
Hypercholesterolaemia	39(2·5)	55 (3·5)
Type-2 diabetes mellitus	33(2·1)	21 (1·3)
Psychiatric disorders		
Depression	62(3·9)	73 (4·7)
Insomnia	59 (3·7)	76 (4·9)
Anxiety	30(1·9)	43 (2·8)
Nervous-system disorders		
Headache	158 (10·0)	160 (10·3)
Dizziness	54(3·4)	46 (3·0)
Ear and labyrinth disorders		
Vertigo	27(1·7)	21 (1·3)
Vascular disorders		
Hypertension	147 (9·3)	111 (7·1)
Lymphoedema	29 (1·8)	43 (2·8)
Respiratory, thoracic, and mediastinal disorders		
Cough	84 (5·3)	85 (5·5)
Gastrointestinal disorders		
Nausea	56(3·6)	50 (3·2)
Gastritis	42 (2·7)	39 (2·5)
Abdominal pain	42 (2·7)	31 (2·0)
Diarrhoea	38 (2·4)	40 (2·6)
Abdominal pain upper	40(2·5)	36(2·3)
Constipation	36(2·3)	27 (1·7)
Haemorrhoids	31(2·0)	18 (1·2)
Vomiting	31(2·0)	22 (14)
Hepatobiliary disorders		
Hepatic steatosis	24(1·5)	43 (2·8)
Musculoskeletal and connective-tissue disorders		
Arthralgia	220 (14·0)	212 (13·6)
Back pain	129 (8·2)	133 (8·5)
Pain in extremity	80 (5·1)	94(6·0)
Osteoarthritis	56(3·6)	63 (4·0)
Bone pain	39(2·5)	51 (3·3)
Osteopenia	31(2·0)	50 (3·2)
Musculoskeletal pain	48 (3·0)	50 (3·2)

	Tibolone group (N=1575), n (%)	Placebo group (N=1558), n (%)
(Continued from previous column)		
Osteoporosis	37 (2·3)	48 (3·1)
Myalgia	38 (24)	27(1·7)
Muscle spasms	24 (1·5)	38(2·4)
Spinal osteoarthritis	36(2·3)	27(1·7)
Reproductive system and breast disorders		
Vaginal or postmenopausal haemorrhage*	230 (14·6)	107(6·9)
Endometrial hypertrophy	71 (4·5)	48 (3·1)
Vaginal discharge	58(3·7)	29 (1·9)
Uterine polyp	41 (2·6)	31(2·0)
Breast pain	38 (2·4)	36(2·3)
Vulvovaginal dryness	19(1·2)	33(2·1)
Menopausal symptoms	31 (2·0)	29 (1·9)
General disorders and administration-site conditions		
Peripheral oedema	48 (3·0)	53 (3·4)
Fatigue	45 (2·9)	42 (2·7)
Investigations		
Weight increased†	110 (7·0)	87(5·6)
Blood glucose increased	35(2·2)	16 (1·0)
Weight decreased	34(2·2)	29 (1·9)
Surgical and medical procedures		
Breast reconstruction‡	36(2·3)	46 (3·0)

Data are ranged by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. *Considered as treatment-related by investigator in 134 patients (8·5%) on tibolone treatment and in 62 patients (4·0%) on placebo treatment. † Considered as treatment-related by investigator in 71 patients (4·5%) on tibolone treatment and in 50 patients (3·2%) on placebo treatment. ‡ Reported as a serious adverse event in 26 patients (1·7%) on tibolone treatment and in 31 patients (2·0%) on placebo treatment.

DISCUSSION

The LIBERATE trial set out to establish whether or not tibolone could be prescribed to women with a history of breast cancer to alleviate their climacteric complaints, without increasing their risk for recurrence. This is an important question for both doctors and patients, because many patients with breast cancer with bothersome complaints that do not respond sufficiently to non-hormonal treatment seek aid in the form of off-label use of tibolone. However, the trial was stopped prematurely 6 months before the planned end because, after adjudication of the reported events and unblinding of the data, we found that of 402 patients with breast cancer with a recurrence, significantly more of the recurrences occurred in the group of women randomly assigned to receive tibolone than in the placebo group. Although the trial was intended to show the non-inferiority of tibolone compared with placebo, the findings clearly show that, although effective against hot flushes, tibolone does increase the risk of breast-cancer recurrence in a population mostly using adjuvant systemic therapy for breast cancer. There are insufficient data to establish the safety of tibolone in women who have had breast cancer and do not require or have finished adjuvant therapy.

At the start of the trial, an assumption was made that the cumulative incidence of breast-cancer recurrences after 3 years would be 15% (in both groups). Such an incidence was indeed noted in the tibolone group (15 · 2%), but not in the placebo group (10·7%). The lower-than-expected recurrence in the placebo group cannot be explained by a low-risk profile of the study population, because most patients had a positive lymph-node status. Possibly, the low recurrence shown in the placebo group resulted from the high incidence of use of effective adjuvant breast-cancer treatment in the study population.

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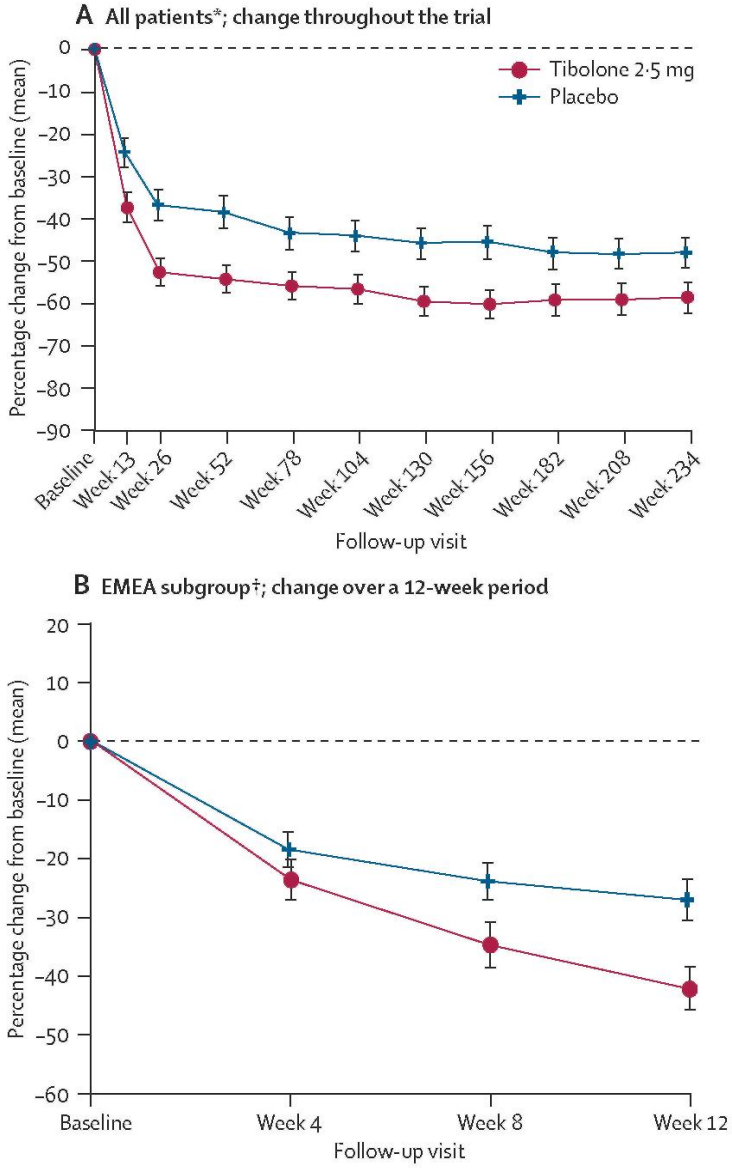
Figure 4: *Changes in number of hot flushes over time in the ITT population*
Mean percentage change in number of hot flushes per day from baseline and 95% CI of mean. *Number of hot flushes recorded throughout the trial period (n=3098). tEuropean Agency for Evaluation of Medicinal Products (EMEA) subgroup with at least five moderate or severe hot flushes per day at baseline (n=660); number of hot flushes taken from diary cards recorded during 12 weeks.



At study entry, 66 · 8% of women used tamoxifen and 6·5% used aromatase inhibitors, drugs with proven efficacy in reducing recurrence.[1] Tibolone is likely to interfere with the protective action of these agents. Subgroup analyses suggested that the interference of tibolone in users of aromatase inhibitors at entry is more severe than in tamoxifen users (HR 2·42 [95% CI 1·01-5·79; p=0·047] vs HR 1·25 [95% CI 0·98-1·59; p=0·076], respectively). The most likely explanation is that tibolone exerts an oestrogenic effect on occult, dormant breast-cancer metastasis (contrary to the underlying postulation of this trial). Such an oestrogenic action would have a greater effect within the oestrogen-depleted tissues of users of aromatase inhibitors than in those of users of tamoxifen, where the activation of the oestrogen receptor by the oestrogenic metabolites of tibolone is prevented by high-affinity hydroxy-tamoxifen molecules.[8]

Our finding that the risk of breast-cancer recurrence with tibolone is more evident in women with an oestrogen-receptor-positive tumour status than in women with an oestrogen-receptor-negative tumour status is in line with the assumption that tibolone exerts an oestrogenic action. However, in preclinical and clinical studies in healthy postmenopausal women, the effect of tibolone on the breast seemed to be non-oestrogenic.[9,10,22]

In the recently reported Long-term Intervention on Fractures with Tibolone (LIFT) trial, a daily dose of 1·25 mg tibolone (the optimum dose for treatment of osteoporosis)[23] decreased the risk of invasive breast cancer substantially, relative to placebo (HR 0·32 [95% CI 0·13-0·80]).[14] This discrepancy can be explained in various ways. First, the two populations are not comparable. The LIFT population (osteoporotic women, mean age 68 years [SD 5 · 2], mean BMI 25 ·7 kg/m^2 [3·4], no tamoxifen exposure) and the LIBERATE population (breast-cancer survivors, mean age 52·7 years (7·3), mean BMI 27·0 kg/m^2 (4·9), two-thirds with tamoxifen exposure) differ in many respects, including hormonal risk factors for breast-cancer events. Second, the effect of tibolone on healthy breast tissue most probably differs from its effect on cancer cells. Tibolone's power to inactivate oestrogenic substances by modulation of both sulphatase and sulphotransferase metabolic pathways, as shown in healthy breast tissue, might be lost in cancer cells.[2-5]

In the current study, tibolone was comparable to placebo regarding other safety outcomes, such as mortality, cardiovascular events, and gynaecological malignancies. Additionally, women with a history of breast cancer who use tibolone do seem to benefit in terms of efficacy outcomes: they have significantly fewer and less severe vasomotor symptoms, increased BMD of spine and total hip, and a subjective improvement of sex and sleep problems (data not shown).

Although it might be tempting to try to identify subgroups of patients that would benefit from tibolone use while incurring no or only a very low risk of breast-cancer recurrence with its use, this trial was not powered to assess such differences. On the basis of the present trial data, it is not possible to identify a specific subgroup of patients who could use tibolone without risk of increased breast-cancer recurrence. The results presented for various subgroups (figure 3) should be interpreted with utmost caution and restraint, in view of the dangers associated with multiple testing.

Our study has other potential limitations. We did not assess breast-cancer risk factors, such as family history or Gail-model score, nor did we provide an accurate histopathological classification of the primary tumours. Most of our study participants used tamoxifen, while future breast-cancer patients might use other adjuvant medication. Therefore, the generalisability of our study results to future populations of breast-cancer survivors is questionable. Modern developments in risk assessment (such as ERBB2 status) and in adjuvant treatment options are moving rapidly, and will result in a population of symptomatic breast-cancer survivors that differs from ours. The strengths of this unique multicentred international trial are its large size, adequacy of power for the primary outcome, low withdrawal rate, and quality of the data collection, which enhance the validity of the results for this population.

Randomised trials of menopausal hormone therapy in patients with breast cancer are scarce. Two recent clinical trials, the Stockholm trial[26] and the Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS) trial,[27,28] assessed the effects of conventional hormone therapy regimens versus best treatment without hormones in patients with early stage breast cancer who were free of recurrence and who had menopause symptoms deemed by the patient and the doctor to need treatment. Treatment with adjuvant tamoxifen was allowed. Populations of the two studies differed in various relevant aspects (ie, different hormone therapy regimens, more node-positive patients in the HABITS trial, and more tamoxifen users in the Stockholm trial). Both randomised studies were halted before enrolment could be completed. The Stockholm trial (with 378 women enrolled) was inconclusive due to lack of power, but did not show a risk increase for women on hormone therapy.[26] The HABITS study was a randomised, open-label, non-inferiority trial in which 447 women, after primary treatment for breast cancer and without signs of active disease, were randomly assigned to either hormone therapy or to best symptomatic treatment without hormones. Women in the hormone-therapy group had significantly more breast-cancer recurrences. After a median follow-up of 2·1 years (range 0·1-5·6) the HR was 3·3 (95% CI 1·5-7·4) and after 4·1 years (95% CI 0·1-7·8) the HR was 2·4(95% CI 1·3-4·2).[27,28] Although the populations and treatment regimens are not similar, the risk increase with conventional hormone therapy reported in the HABITS study seems to be larger than the risk increase shown for tibolone in the LIBERATE trial. Conventional hormone therapy could further increase patient concern, because it might impair the interpretation of mammograms, an effect unwanted during the follow-up of breast-cancer survivors.[29,30] Various studies have suggested that the risk of mammographic abnormalities with tibolone is lower than with conventional hormone therapy.[9,10]

The findings from the LIBERATE trial imply that the use of tibolone for women with a known, past, or suspected breast cancer will remain contraindicated. The findings of this trial will provide a better basis for general practitioners, gynaecologists, oncologists, and other doctors when counselling patients with breast cancer who are severely symptomatic with hot flushes and night sweats that interfere with sleep and impair quality of life. From our study, doctors can also learn from the long-lasting symptom relief seen in our placebo population, that personal attention and care for many women are highly successful and sufficient in this respect.

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Conflicts of interest

PK, NJB, J-MF, EK, BvS, PS, RV-S, CHY, and MWB have received honoraria for their membership of the LIBERATE advisory board. PK has received research grants and honoraria for consultancies from Organon, Schering-Plough, Procter and Gamble, Servier, and Pfizer. NJB has received honoraria for consultancies and postgraduate education lectures from Organon and has served on advisory boards for Organon, AstraZeneca, Novartis, and Pfizer. MWB has served on advisory boards for GlaxoSmithKline, Novartis, Astra-Zeneca, Sanofi Aventis, and Organon. JE, MM-A, RM, and SvO are employees of Schering-Plough (formerly NV Organon).

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