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Effects of tibolone on climacteric symptoms and quality of life in breast cancer patients—Data from LIBERATE trial

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ABSTRACT

Background: Climacteric symptoms such as hot flushes and vaginal dryness are very common in breast cancer patients, resulting either from age or adjuvant therapy. Tibolone, a synthetic steroid, is effective in reducing these symptoms in healthy post-menopausal women, but this has never been studied in a large breast cancer population.
Objectives: The primary objective of LIBERATE trial was to study safety of tibolone 2.5 mg daily versus placebo as primary, in symptomatic breast cancer survivors. The aim of this present paper was to report effects of tibolone on climacteric symptoms, vaginal dryness and health-related quality of life in the study population. This trial is registered with ClinicalTrials.gov, n. NCT00408863.
Methods: The trial was conducted between June 2002 and July 2007. Concerning quality of life variables, a daily Diary Cards during the first three months and the Climacteric Symptoms Form and at each visit were used to register frequency and intensity of hot flushes. Mean vaginal dryness scores were calculated on the basis of individual ratings at baseline and at week 104. A subset of patients assessed their quality of life filling in the Women's Health Questionnaire (WHQ).
Results: Of the 3148 women recruited, 3133 received trial medication (1575 in the tibolone group and 1558 in the placebo group). The median duration of treatment was 2.75 years. In total 3098 women (1556 on tibolone, 1542 on placebo) were included in the intention-to-treat (ITT) population for efficacy analysis. Data on vaginal dryness are available for 2144 patients and 883 women (438 on tibolone, 445 on placebo) answered to WHQ. The mean change in number of hot flushes per day was 2.74 (43.1%) in the tibolone group and −1.77 (−27.5%) in the placebo group ($p < 0.0001$) at week 12 and −4.62 (−65.6%) on tibolone as compared to −3.73 (−52.5%) on placebo ($p < 0.0001$) at week 104. For the composite score the mean changes at week 12 were −0.19 (−10.6%) and −0.14 (−7.7%), respectively ($p = 0.0006$). Vaginal dryness score improved at week 104 in the tibolone group as compared to placebo (−0.46 versus −0.29, respectively; $p < 0.0001$). Across the assessments up to two years with WHQ, tibolone was more effective than placebo in improving sexual health, sleep quality and mood domains. Women using tamoxifen showed less improvement in climacteric symptoms with tibolone, than women only receiving tibolone without any adjuvant therapy.
Conclusion: The results of the LIBERATE trial show that tibolone is effective in symptomatic breast cancer patients and improves their quality of life. However, this finding should be judged within the context of the main outcome of the trial, showing that tibolone increases the risk of recurrence. The use of tibolone in women with breast cancer will remain contraindicated and any off-label use incurs a now proven risk.

1. Introduction

Breast cancer is the most common malignancy in Western women. Four out of five new cases of breast cancer are diagnosed in women over 50 years, with the peak in the 50–64 years age

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range. Many of these women suffer from climacteric symptoms such as hot flushes and night sweats. The majority of patients are given adjuvant tamoxifen and aromatase inhibitors which may exacerbate these symptoms, sometimes leading to discontinuation of their adjuvant therapy [1]. Alternatively, ovarian ablation, chemotherapy and Gonadotrophin Releasing Hormone (GnRH) analogues are used. These treatment modalities also commonly induce climacteric symptoms and/or bone loss [2].

Conventional oestrogen therapy, alone or combined with a progestagen, is effective in alleviating these complaints, but is contraindicated in breast cancer patients, as it has been shown that these hormones may cause breast cancer to recur [3,4]. The use of progestins like megestrol acetate have shown efficacy in reducing hot flushes in breast cancer patients [5] but long-term safety data on the use of progestins only therapy in breast cancer survivors are still missing.

Tibolone is a tissue selective synthetic steroid with a pharmacological and clinical profile that is different from conventional sex hormones [6,7]. Placebo-controlled trials have found that tibolone is effective in reducing menopausal symptoms in healthy post-menopausal women [8]. In pilot studies in breast cancer patients receiving adjuvant treatment with tamoxifen or GnRH-analogues, a similar effect was seen [9–11]. In the LIBERATE trial the primary hypothesis was tested that the use of tibolone 2.5 mg per day did not increase the risk for breast cancer recurrence in women surgically treated for breast cancer and suffering from flushes and other climacteric complaints. Secondary endpoints were mortality, climacteric symptoms, bone mineral density and health-related quality of life [12]. Tibolone was found to increase the risk of recurrence in breast cancer patients, while relieving climacteric symptoms and preventing bone loss [13,14].

In the current paper, dedicated to some secondary end points of the LIBERATE trial we describe more in detail the effects of tibolone on climacteric symptoms in study population and report on its effects on quality of life. We also analyze variation in efficacy of tibolone versus placebo in subgroups treated with different adjuvant regimens.

2. Materials and methods

2.1. Patients

LIBERATE was a multinational, multicentre, randomised, double-blind, parallel group, placebo controlled trial to investigate the safety and efficacy of tibolone in women with climacteric symptoms and a history of breast cancer. The trial was conducted between June 2002 and July 2007, at 245 clinical centres in 31 countries worldwide. The LIBERATE trial protocol was approved by the institutional review board at each centre, and written informed consent was obtained from each participant. Women with climacteric symptoms were eligible if they had been surgically treated within the previous five years for histologically confirmed $T_{1\text{-}3}N_{O\text{-}2}M_0$ breast cancer. Participants had to be postmenopausal and younger than 75 years of age. Of the 3585 women screened, a total of 3148 were randomly assigned to receive orally either tibolone 2.5 mg daily or placebo in a one to one ratio. The median duration of treatment was 2.75 years (range 0.01–4.79; 7775 women-years in total). Trial profile is reported in detail in Fig. 1 of the main publication [13].

2.2. Procedures

During the screening visit daily Diary Cards were handed over: the patient recorded number and severity of hot flushes on Diary Cards during 14 days before the baseline visit. During the baseline visit, the Cards were collected and analyzed, in order to check for the inclusion criteria and to establish a baseline record of hot flushes. Subsequently the women filled in the daily Diary Cards during the first three months of the trial. Hot flushes were recorded according to the following classifications:

- None = no sensation of heat on this day.
- Mild = sensation of heat without perspiration.
- Moderate = sensation of heat with perspiration, able to continue activity.
- Severe = sensation of heat with sweating causing you to stop activity.

For each day, a composite daily severity score was calculated using the following formula:

$$\frac{(\text{no. mild hot flushes}) \times 1 + (\text{no. moderate hot flushes}) \times 2 + (\text{no. severe hot flushes}) \times 3}{\text{Total number of hot flushes per day}}$$

These parameters were also assessed for highly symptomatic women (at least five moderate or severe hot flushes a day) defined according to the European Agency for Evaluation of Medicinal Products (EMEA) (CPMP/EWP/021/97).

In addition, the frequency and intensity of climacteric symptoms were also recorded at the investigational sites at baseline on a Climacteric Symptoms Form and at each visit during the total trial period for as long as the woman took trial medication.The following variables were calculated for each visit:

- Average number of hot flushes per day as well as absolute and relative change from baseline.
- The maximum intensity of climacteric complaints variables: hot flushes, sweats, interference of flushes/sweats with normal life, palpitations, joint pain, dryness of vagina and incontinence.

The frequency and intensity of these variables were rated for the last week before the visit as follows:

- None = no symptoms
- Mild = not interfering with daily activities or sleep
- Moderate = interfering with daily activities or sleep, but these activities could be continued
- Severe = interfering with daily activities or sleep and stopping them for maximally five minutes
- Very severe = interfering with daily activities or sleep, but activities had to be stopped for more than five minutes

Mean vaginal dryness scores were calculated on the basis of individual ratings at baseline and at week 104, whereas: None = 1; Mild = 2; Moderate = 3; Severe = 4; Very severe = 5.

A subset of 883 women (438 on tibolone, 445 on placebo), from eight countries (Austria, Belgium, Germany, Spain, France, United Kingdom, Italy, The Netherlands), assessed their quality of life throughout the trial with the aid of the Women's Health Questionnaire (WHQ). The WHQ is a "disease-specific" questionnaire developed for the purpose of addressing the particular problems associated with the menopause and contains 37 items distributed among nine domains (vasomotor symptoms, other somatic symptoms, sleep, sexual functioning, menstrual, memory, mood, attraction and anxiety) [15]. The WHQ is well validated in terms of its psychometric properties and has been successfully used in several clinical trials to monitor and detect treatment-induced

changes over time [16]. The domain 'Menstrual' is less applicable for breast cancer patients and will not further be discussed.

Each item on the WHQ, scored as:

- 1, 'yes definitely'.
- 2, 'yes sometimes'.
- 3, 'no not much'.
- 4, 'no not at all'.

was transformed to a binary (0/1) scale using the following rule.

- Score = 1 (poor health) for the positive responses 1 or 2.
- Score = 0 (good health) for the negative responses 3 or 4.

2.3. Statistical analysis

Efficacy was assessed within the intention-to-treat (ITT) population, comprising of all women receiving trial medication and for whom information was available as to the presence or absence of breast cancer recurrence. In addition, a baseline and at least one post-baseline result had to be recorded for a particular efficacy parameter to be included in the observed-cases approach analysis. The analysis of the Diary Cards was based on data obtained up to week 12, and the analysis of the Climacteric Symptoms Form was limited to data obtained up to week 104. The changes from baseline for a selection of climacteric symptoms (Number of hot flushes per day, composite severity score and vaginal dryness) were analyzed using an Analysis of Covariance (ANCOVA) with factors for treatment group, subgroup, interaction between treatment and subgroup and country and baseline value as covariates. The following subgroups were defined for baseline up to weeks 12 and 104:

- Tamoxifen use: NO (never or previous tamoxifen or AI use) and YES (without concomitant AI), both at baseline and at weeks 12 or 104, respectively.
- Aromatase Inhibitor (AI): NO (never or previous AI or tamoxifen use) and YES (without concomitant tamoxifen), both at baseline and at weeks 12 or 104, respectively.
- Chemotherapy: NO (never) and YES (previous or at baseline).
- Age: <50, 50–59 and ≥60 years (at baseline).

All tests were performed two-sided and considered statistically significant if the *P*-value was ≤0.05.

Comparisons between treatment groups with respect to changes from baseline using the observed-cases approach in the eight relevant WHQ domains were done at each post-baseline assessment (week 26, 52, 78 and 104) by applying the non-parametric Wilcoxon rank test stratified by centre. Attention was paid to potential interaction effects by age class and type of surgery (breast sparing/mastectomy) on WHQ scores. The LIBERATE trial is registered with ClinicalTrials.gov, number NCT00408863.

2.4. Role of the funding source

The sponsor conducted the trial and collected the data. An Advisory Board had overall scientific responsibility for trial design and protocol, and advised the sponsor as to the conduct of the trial [12,13]. The corresponding author had full access to all data relevant for the present publication and all authors were involved in its submission.

3. Results

Of the 3148 women who were recruited, 3133 received trial medication: 1575 in the tibolone group and 1558 in the placebo

Table 1
Demographics and other baseline characteristics of women receiving trial medication.

Parameter		Statistics	Tibolone 2.5 mg (*N* = 1575)	Placebo (*N* = 1558)	Total (*N* = 3133)
Age (years)	*n* (%)	<50	556 (34.3)	516 (33.1)	1072 (34.2)
		50–59	732 (46.5)	767 (49.2)	1499 (47.8)
		≥60	287 (18.2)	275 (17.7)	562 (18.0)
		Mean (SD)	52.5 (7.4)	52.9 (7.3)	52.7 (7.3)
		Median (Min;Max)	52.0 (29, 75)	52.0 (28, 75)	52.0 (28, 75)
Body mass index (kg/m^2)		Mean (SD)	26.9 (4.9)	27.1 (5.0)	27.0 (4.9)
		Median (Min;Max)	26.1 (17, 52)	26.3 (16, 50)	26.2 (16, 52)
Time since menopause (years)		Mean (SD)	6.2 (6.3)	6.2 (6.5)	6.2 (6.4)
		Median (Min;Max)	3.6 (0, 35)	3.5 (0, 40)	3.6 (0, 40)
Time since breast cancer surgery (years)		Mean (SD)	2.1 (1.3)	2.1 (1.3)	2.1 (1.3)
		Median (Min;Max)	1.8 (0, 6)	1.8 (0, 7)	1.8 (0, 7)
Primary breast cancer stage	*n* (%)	Missing, 0 or I	477 (30.3)	463 (29.7)	940 (30.0)
		IIA/B	956 (60.7)	946 (60.7)	1902 (60.7)
		IIIA/B	142 (9.1)	149 (9.6)	291 (9.3)
Type of surgery	*n* (%)	Breast sparing	674 (42.8)	672 (43.1)	1346 (43.0)
		Mastectomy	901 (57.2)	886 (56.9)	1787 (57.0)
Ovariectomized	*n* (%)	No	1296 (82.3)	1315 (84.4)	2611 (83.3)
		Yes	279 (17.7)	243 (15.6)	522 (16.7)
Aromatase inhibitor	*n* (%)	None or previous	1460 (93.3)	1458 (93.6)	2928 (93.5)
		At entry[a]	105 (6.7)	100 (6.4)	205 (6.5)
Tamoxifen	*n* (%)	None or previous	528 (33.5)	518 (33.3)	1046 (33.4)
		At entry[a]	1047 (66.5)	1040 (66.8)	2087 (66.6)
GnRH analogues	*n* (%)	None or previous	1508 (95.7)	1490 (95.6)	2998 (95.7)
		At entry[a]	67 (4.3)	68 (4.4)	135 (4.3)
Chemotherapy	*n* (%)	Never	448 (28.4)	469 (30.1)	917 (29.3)
		Previous or at entry	1127 (71.6)	1089 (69.9)	2216 (70.7)

[a] At entry refers to use within 14 days before baseline and/or at baseline.

Table 2
Treatment effects at weeks 12 (Diary Card) and 104 (Climacteric Symptoms Form) on climacteric symptoms – Observed Cases Approach in the ITT population.

Parameter	Week	Treatment group	*N*	Mean at baseline	Change from baseline		Treatment effect	*P*-Value[a]
					Mean (SD)	%		
Number of hot flushes per day	12	Tibolone 2.5 mg	1268	6.36	−2.74 (3.66)	−43.1	−0.97	<0.0001
		Placebo	1290	6.44	−1.77 (3.45)	−27.5		
	104	Tibolone 2.5 mg	1079	7.04	−4.62 (5.47)	−65.6	−0.89	<0.0001
		Placebo	1067	7.10	−3.73 (5.97)	−52.5		
Mean composite severity score	12	Tibolone 2.5 mg	1083	1.79	−0.19 (0.45)	−10.6	−0.05	0.0006
		Placebo	1148	1.81	−0.14 (0.44)	−7.7		
Vaginal dryness score	104	Tibolone 2.5 mg	1078	1.79	−0.46 (1.06)	−25.7	−0.18	<0.0001
		Placebo	1066	1.85	−0.29 (1.00)	−15.7		

Baseline population for ITT analysis: tibolone 1556, placebo 1542.
[a] *P*-Value for the test on treatment effect from an ANCOVA with factors for treatment group, country and baseline value as covariate.

group. Baseline characteristics were similar in the two groups (Table 1). On average, women were 52.7 years of age, the mean body mass index (BMI) was 27.0 kg/m^2, the mean time since menopause 6.2 years, 70.0% had a Stage II/III of their primary tumour, 57.3% had mastectomy and 16.7% were ovariectomized. Endocrine therapy at entry was given as tamoxifen, aromatase inhibitors (AI) or GnRH analogues to 66.6%, 6.5% and 4.3% of the women, respectively. Chemotherapy was given to 70.8% of the women, of which 4.9% still at entry.

In total 3098 women (1556 on tibolone, 1542 on placebo) were included in the intention-to-treat (ITT) population for efficacy analysis. At baseline, the mean number of hot flushes per day (Diary Card) was 6.4, the mean composite severity score 1.8 and the mean vaginal dryness score 1.8 (similar in both groups). The treatment

Table 3
Main effects (pooled over treatment groups) at weeks 12 (Diary Card) and 104 (Climacteric Symptoms Form) of covariates on climacteric symptoms – Observed Cases Approach in the whole ITT population.

Parameter	Week	Subgroup	*N*	Mean at baseline	Change from baseline		*P*-Value[a]
					Mean (SD)	%	
Number of hot flushes per day	12	No tamoxifen, no AI[b]	757	5.64	−2.51 (3.70)	−44.5	<0.0001
		Tamoxifen (no AI)[c]	1654	6.69	−2.08 (3.40)	−31.1	
		No tamoxifen, no AI[b]	757	5.64	−2.51 (3.70)	−44.5	0.0023
		AI (no tamoxifen)[d]	142	6.92	−2.82 (4.76)	−40.8	
		No chemotherapy[e]	757	6.96	−2.35 (3.48)	−33.8	NS
		Chemotherapy[f]	1801	6.17	−2.21 (3.63)	−35.8	
		Age < 50[g]	882	6.85	−2.50 (3.71)	−36.5	NS
		Age 50–59[g]	1237	6.42	−2.15 (3.66)	−33.5	
		Age ≥ 60[g]	439	5.45	−2.01 (3.07)	−36.9	
	104	No tamoxifen, no AI[b]	961	6.78	−4.48 (6.05)	−66.1	<0.0001
		Tamoxifen (no AI)[c]	1079	7.29	−3.90 (5.50)	−53.5	
		No tamoxifen, no AI[b]	961	6.78	−4.48 (6.05)	−66.1	0.049
		AI (no tamoxifen)[d]	106	7.46	−4.21 (5.17)	−56.4	
		No chemotherapy[e]	568	7.51	−4.25 (4.99)	−56.6	NS
		Chemotherapy[f]	1578	6.92	−4.15 (5.99)	−60.0	
		Age < 50[g]	769	7.54	−4.35 (5.94)	−57.7	NS (0.069)
		Age 50–59[g]	1009	7.05	−4.27 (5.83)	−60.6	
		Age ≥ 60[g]	368	6.16	−3.57 (5.00)	−58.0	
Mean composite severity score	12	No tamoxifen, no AI[b]	623	1.77	−0.19 (0.47)	−10.8	0.0019
		Tamoxifen (no AI)[c]	1485	1.80	−0.14 (0.43)	−8.0	
		No tamoxifen, no AI[b]	623	1.77	−0.19 (0.47)	−10.8	NS
		AI (no tamoxifen)[d]	118	1.86	−0.25 (0.47)	−13.7	
		No chemotherapy[e]	672	1.87	−0.15 (0.44)	−8.0	NS
		Chemotherapy[f]	1559	1.77	−0.17 (0.44)	−9.6	
		Age < 50[g]	780	1.77	−0.15 (0.42)	−8.5	NS
		Age 50–5[g]	1089	1.82	−0.17 (0.45)	−9.3	
		Age ≥ 60[g]	362	1.79	−0.18 (0.49)	−10.1	
Vaginal dryness score	104	No tamoxifen, no AI[b]	961	1.94	−0.46 (1.09)	−23.7	NS
		Tamoxifen (no AI)[c]	1077	1.66	−0.29 (0.93)	−17.2	
		No tamoxifen, no AI[b]	961	1.94	−0.46 (1.09)	−23.7	NS
		AI (no tamoxifen)[d]	106	2.27	−0.56 (1.34)	−24.5	
		No chemotherapy[e]	569	1.84	−0.34 (1.05)	−18.5	NS
		Chemotherapy[f]	1575	1.81	−0.39 (1.02)	−21.5	
		Age < 50[g]	769	1.81	−0.39 (1.04)	−21.5	NS
		Age 50–59[g]	1006	1.83	−0.39 (1.04)	−21.3	
		Age ≥ 60[g]	369	1.79	−0.31 (0.98)	−17.3	

[a] For treatment group based on an ANCOVA with factors for treatment group, subgroup, interaction between treatment and subgroup, country, and a covariate for baseline value.
[b] Absence of tamoxifen and AI use both at baseline and at week 12 or 104, respectively.
[c] Presence of tamoxifen and no AI use both at baseline and at week 12 or 104, respectively.
[d] Presence of AI and no tamoxifen use both at baseline and at week 12 or 104, respectively.
[e] As at baseline (and no previous chemotherapy).
[f] Previous chemotherapy or use at baseline.
[g] As at baseline.

Table 4
Interaction effects on climacteric symptoms at weeks 12 and 104 – Observed Cases Approach in the whole ITT population.[a]

Parameter	Week	Subgroup	Treatment	*N*	Mean at baseline	Change from baseline		*P*-Value[b] interaction
						Mean (SD)	%	
Number of hot flushes per day	12	No tamoxifen, no AI[c]	Tibolone 2.5mg	373	5.49	−3.33 (3.82)	−60.6	<0.0001
			Placebo	384	5.80	−1.71 (3.40)	−29.6	
		Tamoxifen (no AI)[d]	Tibolone 2.5mg	815	6.75	−2.40 (3.51)	−35.5	
			Placebo	839	6.64	−1.77 (3.26)	−26.7	
	104	No tamoxifen, no AI[c]	Tibolone 2.5mg	486	6.84	−5.28 (5.66)	−77.2	0.0005
			Placebo	475	6.73	−3.67 (6.33)	−54.5	
		Tamoxifen (no AI)[d]	Tibolone 2.5mg	542	7.20	−4.04 (5.14)	−56.1	
			Placebo	537	7.39	−3.76 (5.83)	−50.9	
Mean composite severity score	12	No tamoxifen, no AI[c]	Tibolone 2.5mg	285	1.78	−0.28 (0.51)	−15.6	0.0005
			Placebo	338	1.76	−0.12 (0.42)	−6.8	
		Tamoxifen (no AI)[d]	Tibolone 2.5mg	735	1.79	−0.15 (0.41)	−8.2	
			Placebo	750	1.81	−0.14 (0.44)	−7.9	

[a] Summary/descriptive statistics of combinations of treatment and subgroup for subgroups were the interaction effect was statistically significant at alpha is 0.05 (NB. No interaction effects were observed for the subgroups Aromatase Inhibitor, Chemotherapy and Age Classes.).
[b] For treatment group based on an ANCOVA with factors for treatment group, subgroup, interaction between treatment and subgroup, country, and a covariate for baseline value.
[c] As both at baseline and at week 12 or 104, respectively.
[d] Presence of tamoxifen and no AI use both at baseline and at week 12 or 104, respectively.

effects on the average number of hot flushes per day and average composite daily severity score at week 12 are presented in Table 2. The mean change in number of hot flushes per day was −2.74 (−43.1%) in the tibolone group and −1.77 (−27.5%) in the placebo group ($p < 0.0001$). For the composite score the mean changes were −0.19 (−10.6%) and −0.14 (−7.7%), respectively ($p = 0.0006$). For highly symptomatic women (EMEA definition) with 12.5 hot flushes on average per day at baseline, the change from baseline at week 12 was more pronounced in the tibolone group, with a mean change of −5.35 (−41.9%) in number of hot flushes per day, than in the placebo group with −3.33 (−27.7%); $p < 0.0001$ [13].

Data at week 104 (Table 2), based on the Climacteric Symptoms Form completed by the investigator, showed a reduction of the average number of hot flushes of −4.62 (−65.6%) on tibolone as compared to −3.73 (−52.5%) on placebo ($p < 0.0001$). Concerning vaginal dryness, data from 2144 patients show a significant improvement at week 104 in the tibolone group as compared to placebo (−0.46 versus −0.29, respectively; $p < 0.0001$).

Regarding the main effects of tamoxifen or AI adjuvant use (versus neither tamoxifen nor AI), chemotherapy and age on climacteric symptoms, summary/descriptive statistics for changes from baseline are presented in Table 3. At baseline, as expected, the number of hot flushes per day was higher for women who used adjuvants. Women receiving tamoxifen as the only adjuvant obtained less improvement in climacteric symptoms than non-users and this difference was statistically significant for average number of hot flushes per day at weeks 12 ($p < 0.0001$) and 104 ($p < 0.0001$) and for composite severity score at week 12 ($p = 0$ 0019). As Table 4 shows, the combination of tibolone and tamoxifen showed less improvement in number of hot flushes than tibolone without adjuvant therapy (−35.5% versus −60.6%), showing a statistically significant interaction effect for the average number of hot flushes per day at week 12 ($p < 0.0001$), maintained at week 104 ($p = 0.0005$). An interaction effect was also seen for the composite severity score at week 12 ($p = 0.0005$). No interaction effects were observed for AI adjuvant use, (previous) chemotherapy and age classes. The women who received AIs as the only form of adjuvant therapy had less relative improvement in number of hot flushes at weeks 12 and 104 as compared to those without any adjuvant therapy (Table 3). The absolute changes were statistically significant ($p = 0.0023$ and $p = 0.049$, respectively). Changes from baseline in number of hot flushes per day were analyzed for potential effect of adjuvant therapy (including switchers from tamoxifen to AIs), but no statistically significant differences could be observed (Table 5). Differences among chemotherapy and age subgroups were not statistically significant, although there was a suggestion that younger patients (age < 50 years) had more improvement from baseline compared to those over 50 years of age (Table 3). In addition, no differences in climacteric symptoms were observed due to GnRH-analogues use or ovariectomy (data not shown). In total, 73 women in the tibolone group and 91 in the placebo group neither received tamoxifen, AIs or GnRH-analogues at baseline, nor had an ovariectomy. In this subpopulation, the mean change in number of hot flushes per day at week 12 was −4.13 (−67.8%) in the tibolone group and −1.92 (−30.5%) in the placebo group ($p < 0.0001$).

Changes from baseline in WHQ scores at weeks 26, 52, 78 and 104 are presented in Table 6. Benefit with tibolone was clinically significant (change in score >0.100) (Hunter, 1992) for the domains vasomotor symptoms, sexual behaviour, sleep quality and mood. The decrease in the mean score of vasomotor symptoms with tibolone ranged from −0.331 (−34.3%) to −0.403 (−42.8%), whereby the decrease in the placebo group ranged from −0.167 (−17.3%) to −0.208 (−20.3%). For the domain sexual behaviour the decrease in the mean score ranged from −0.160 (−34.8%) to −0.196 (−43.6%) for tibolone, and from −0.023 (−5.9%) to −0.062 (−16.2%) for placebo. Regarding sleep problems the decrease in the mean score ranged from −0.124 (−16.8%) to −0.146 (−22.0%) for tibolone, and from −0.044 (−3.5%) to −0.079 (−10.3%) for placebo. Statistically significant treatment differences ($p < 0.05$) have been found for the following domains: vasomotor symptoms, sexual behaviour

Table 5
Effects of tamoxifen and/or aromatase inhibitor on number of hot flushes per day in placebo-treated patients at week 104 – Observed Cases Approach in the ITT population.[a]

Subgroup	*N*	Mean at baseline	Change from baseline	
			Mean (SD)	%
Overall	1067	7.10	−3.73 (5.97)	−52.5
No Tamoxifen, no AI[a]	475	6.73	−3.67 (6.33)	−54.5
Tamoxifen, no AI[a]	537	7.39	−3.76 (5.83)	−50.9
Tamoxifen at entry[b]	719	7.23	−3.74 (5.98)	−51.7
AI at entry[b]	63	7.73	−3.94 (3.84)	−51.0
AI at week 104[c]	206	7.46	−3.25 (5.37)	−43.6

[a] As both at baseline and at week 104.
[b] As at baseline.
[c] As at week 104, irrespective date of start and previous adjuvant use.

Table 6
Changes in WHQ score compared to baseline at weeks 26, 52, 78 and 104 – Observed Cases Approach.

Domain	Group	Baseline score[a]	Changes in WHQ score (%)			
			Week 26	Week 52	Week 78	Week 104
Vasomotor	Tibolone	0.928	**−0.331** (−34.3%)	**−0.334** (−36.2%)	**−0.359** (−36.9%)	**−0.403** (−42.8%)
	Placebo	0.950	−0.167 (−17.3%)	−0.187 (−18.5%)	−0.208 (−20.3%)	−0.206 (−19.4%)
Sexual	Tibolone	0.503	**−0.160** (−34.8%)	**−0.183** (−43.6%)	**−0.177** (−38.4%)	**−0.196** (−39.3%)
	Placebo	0.549	−0.062 (−16.2%)	−0.055 (−14.0%)	−0.023 (−5.9%)	−0.055 (−12.9%)
Sleep	Tibolone	0.649	**−0.124** (−17.4%)	**−0.129** (−16.8%)	**−0.146** (−22.0%)	**−0.136** (−20.7%)
	Placebo	0.664	−0.071 (−10.0%)	−0.079 (−10.3%)	−0.071 (−9.6%)	−0.044 (−3.5%)
Memory	Tibolone	0.552	−0.078 (−17.1%)	−0.088 (−16.6%)	−0.082 (−14.2%)	−0.101 (−20.5%)
	Placebo	0.577	−0.065 (−14.0%)	−0.052 (−10.7%)	−0.065 (−16.0%)	−0.070 (−16.9%)
Anxiety	Tibolone	0.312	−0.073 (−29.4%)	−0.083 (−30.9%)	−0.075 (−30.4%)	−0.049 (−28.2%)
	Placebo	0.316	−0.056 (−23.4%)	−0.064 (−24.5%)	−0.058 (−21.4%)	−0.057 (−21.2%)
Somatic	Tibolone	0.475	−0.060 (−5.4%)	−0.071 (−10.3%)	−0.081 (−9.5%)	−0.062 (−6.9%)
	Placebo	0.503	−0.066 (−8.9%)	−0.073 (−12.6%)	−0.067 (−8.4%)	−0.057 (−6.4%)
Attraction	Tibolone	0.405	−0.056 (−23.4%)	−0.058 (−21.7%)	**−0.081** (−27.8%)	−0.051 (−20.3%)
	Placebo	0.400	−0.020 (−18.8%)	−0.039 (−17.5%)	−0.011 (−14.9%)	−0.023 (−18.8%)
Mood	Tibolone	0.261	**−0.062** (−29.5%)	**−0.051** (−18.6%)	**−0.064** (−27.4%)	−0.050 (−22.9%)
	Placebo	0.270	−0.039 (−10.4%)	−0.024 (−4.5%)	−0.030 (−6.5%)	−0.028 (−13.5%)

Bold, statistically significant ($P < 0.05$) difference between scores in tibolone and placebo treatment groups. NB. Change in score > 0.100 considered as clinically significant. All changes reported are improvements compared to baseline. Domain 'Menstrual' not reported since less applicable for breast cancer patients.

[a] Baseline score; maximum $N = 438$ on tibolone and 445 on placebo; N will vary per domain at the various assessments due to missing data.

and sleep problems at weeks 26, 52, 78 and 104, mood at weeks 26, 52 and 78 and attraction at week 78. No interaction effect by age class or type of surgery (breast sparing/mastectomy) was observed (data not shown).

Psychological disorders reported as adverse event (depression, insomnia, anxiety) in the entire trial population showed a reduction on tibolone treatment consistent with the improved WHQ score. Urinary discomfort, which is usual in a patient population like the one in LIBERATE, was also less frequent in women on tibolone treatment as compared to placebo [13].

4. Discussion

The primary objective of LIBERATE trial (to demonstrate that tibolone could be prescribed to breast cancer patients suffering from climacteric complaints, without increasing the risk of recurrence) could not be met [13]. The secondary aim was to assess the effect of tibolone on bone mineral density, climacteric symptoms and health-related quality of life: these two last points are the subject of the present paper.

The survival rate of breast cancer patients has significantly increased due to earlier diagnosis and advances in adjuvant treatment. Many of these women experience climacteric symptoms, which result directly from therapy with tamoxifen, AIs, ovarian suppression, ovariectomy or chemotherapy [1,2,4]. Hot flushes affect approximately 65% of breast cancer patients after treatment and the majority of these women report them as severe. Hot flushes are even more prevalent among women treated with chemotherapy (78%) and with tamoxifen (72%) [17]. In young women, forced into menopause with chemotherapy and anti-oestrogen hormone therapy, the prevalence for climacteric symptoms reaches to 90% and hot flushes are more severe and last longer [11,18]. Despite the well-established efficacy of adjuvant treatments, up to 20% of breast cancer patients consider stopping or actually cease endocrine therapy because of menopausal symptoms.

Conventional oestrogen therapy, alone or combined with a progestagen is effective, but contraindicated in women with a history of breast cancer because of risk of recurrence [3]. The use of progestins like megestrol acetate have shown efficacy in reducing hot flushes in breast cancer patients [5] but long-term safety data on the use of progestins only therapy in breast cancer survivors are still missing. Non-hormonal therapy for severe climacteric symptoms is often ineffective and accompanied by side-effects [19]. Tibolone, a tissue selective synthetic steroid that is metabolized to compounds with androgenic, progestogenic and weak estrogenic effects was considered to be a valid alternative to HT in this group of symptomatic patients. Several studies have already demonstrated that tibolone is as effective as HT in relieving healthy postmenopausal women of climacteric symptoms and significantly improves mood, sleep and sexuality, with low rates of vaginal bleeding and breast pain [20,21]. Clinical trials preceding LIBERATE on the safety and efficacy of tibolone in women with a history of breast cancer were small in size and short in duration, but showed positive effects on climacteric symptoms [9,10].

In the LIBERATE trial, breast cancer patients who took tibolone reported a statistically significant reduction in number of hot flushes of 43.1% after three months of treatment versus 27.5% for the placebo group. After 2 years, the reduction was 65.6% and 52.5% in the tibolone and placebo group, respectively. Our results confirm previous smaller studies and also show a clear efficacy of tibolone in highly symptomatic breast cancer patients.

The statistically significant superiority of tibolone in reducing climacteric symptoms was evident. However, the placebo effect was impressive as well: the reduction in mean number of hot flushes was substantial and persisted after two years of treatment, consistent with results of many studies [22].

Tibolone was significantly less effective in relieving of vasomotor symptoms in tamoxifen users as compared to non-users: the reduction in number and severity of hot flushes was more evident in women treated with tibolone without adjuvant therapy (−60.6% versus −35.5%). This finding could be explained by the common target of the two compounds: the antiestrogenic activity of tamoxifen has been attributed to the avid binding of its active 4-hydroxy derivative to the oestrogen receptor (ER) and the hydroxyl metabolites of tibolone are full agonists for both ERs and bind preferentially ERα. Thus the efficacy of tibolone could be decreased because its target receptors are already bound by tamoxifen.

No significant interaction effect was observed between tibolone and AI, but this finding may be influenced by the low number of women receiving this adjuvant therapy.

In placebo group, the reduction in hot flushes registered after 2 years of follow-up was similar for women treated with or without adjuvant, regardless of tamoxifen or AI.

In addition to hot flushes, breast cancer survivors undergoing adjuvant treatment suffer from a broad range of physical symptoms, including vaginal dryness. In a recent study, vaginal dryness was reported by 23.4% and 70.8% of pre- and post-menopausal breast cancer patients, respectively [23]. In another trial, it was reported that it affects particularly women using AIs [24]; tamoxifen causes less vaginal dryness compared with AI due to its oestrogenic action on vaginal mucosa and endometrium.

Available data about vaginal dryness, concerning 2144 breast cancer patients, show a reduction in vaginal dryness in both tibolone and placebo groups; not surprisingly, the improvement was significantly larger in the tibolone group and the benefit persisted for up to two years of therapy, whereas placebo effect tended to be temporary. Decrease in vaginal dryness due to placebo is often subjectively reported by patients, but not demonstrated; on the other hand, tibolone improved the karyopycnotic and vaginal maturation indexes [20], after one year of therapy. This is associated with a major improvement in dyspareunia and urinary symptoms

The results of a subgroup analysis of this large trial confirm the positive impact of tibolone on relevant aspects of quality of life in breast cancer patients, such as sexuality, quality of sleep, anxiety and mood.

At least 50% of breast cancer patients report sexual problems, as dyspareunia, decreased libido and lack of lubrication [25]. Sexual difficulties are even more frequent in younger women, and more intense due to a negative body image [26] and poor communication with the partner [19,27]. In the LIBERATE trial, data from WHQ shown a significant improvement in sexual functioning in patients on tibolone compared with the placebo group The increase in libido, arousability and vaginal lubrication can be due to the well-demonstrated androgenic action of tibolone delta-4 isomer and the reduction of sex hormone binding globulin levels, resulting in increased free testosterone.

Tibolone has been reported to improve insomnia, a frequent and often overlooked clinical problem among breast cancer patients [28,29]. A majority of women treated for breast cancer complain about reduced total sleeping time due to pain, nycturia, coughing or snoring loudly and nocturnal hot flushes [30]. The LIBERATE trial results confirm the significant improvement in insomnia in our series and the superiority of tibolone over placebo became significantly prominent after six months of treatment.

The WHQ results showed a positive trend in the mood of our patients: tibolone was associated with a larger reduction in anxiety levels than placebo. This beneficial effect of tibolone on mood, well demonstrated in postmenopausal healthy women [7], is probably due to the increase in beta-endorphins level and to its androgenic activity [20].

The results of the LIBERATE trial show that tibolone, proven to be efficacious in the treatment of climacteric symptoms in healthy post-menopausal women, is also effective in breast cancer patients and improves their quality of life. The strong points of this randomized double-blind trial are its large size, the low dropout rate and the high quality of data collection. However, the finding concerning climacteric symptoms and quality of life should be judged versus the main outcome of the trial [13], showing that tibolone increases the risk of breast cancer recurrence, and requiring that its use in women with a known, past or suspected breast cancer will remain contra-indicated. Moreover, the results in the placebo group also show that extra care to breast cancer patients (as in a clinical trial setting) leads to improvement of their climacteric symptoms.

Contributors

All authors are members of the LIBERATE Scientific Advisory Board, investigators in the LIBERATE trial or employee of MSD, and contributed to content and development of this manuscript.

Competing interests

PS, EK and PK have received honoraria for their membership of the LIBERATE Advisory Board. In addition, PK has received research grants and honoraria for consultancies from the following pharmaceutical companies: Organon, Schering-Plough, Procter & Gamble, Servier and Pfizer. RK and NB has received honoraria for consultancies from the pharmaceutical company Organon. JE, RM, JP and MM-A are employees of MSD (legacy Organon, Schering-Plough, Oss, The Netherlands). No other potential conflict of interest relevant to this article was reported.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.maturitas.2011.09.003.

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