Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: A randomised, placebo-controlled, phase III trial

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ABSTRACT

Objective: To evaluate the efficacy and safety of ospemifene, a novel selective oestrogen receptor modulator, in the treatment of vaginal dryness in postmenopausal women with vulvovaginal atrophy (VVA).

Study design: A 12 week, multicentre, randomised, double-blind, parallel-group phase III study of women (40–80 years) with VVA and self-reported vaginal dryness as their most bothersome symptom.

Main outcome measures: The co-primary efficacy endpoints were the change from baseline to Week 12 in (1) percentage of parabasal cells in the maturation index (MI), (2) percentage of superficial cells in the MI, (3) vaginal pH, and (4) severity of vaginal dryness. Safety assessments included physical examination, cervical Papanicolaou test and clinical laboratory analyses. Endometrial thickness and histology was also assessed.

Results: A total of 314 women were randomised to once-daily ospemifene 60 mg/day (n = 160) or placebo (n = 154). Significant improvements in the percentages of parabasal and superficial cells in the MI and vaginal pH were observed with ospemifene compared with placebo (p < 0.001 for all parameters). The mean change from baseline in severity score of vaginal dryness reported by women receiving ospemifene compared with those receiving placebo approached statistical significance (p = 0.080). Improvements in each of the four co-primary endpoints with ospemifene were statistically significant compared to placebo in the per protocol population. The majority of treatment-emergent adverse events were considered mild to moderate in severity.

Conclusions: Once-daily oral ospemifene 60 mg was effective for the treatment of VVA in postmenopausal women with vaginal dryness.

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1. Introduction

The vagina and surrounding tissues require oestrogen stimulation to maintain normal structure and function [1,2]. Declining oestrogen levels have been associated with physiological changes such as thinned epithelium and increased vaginal pH level [1,3]. These physiological changes underlie a range of symptoms including vaginal dryness, dyspareunia, burning, itching and irritation [1,3]. Vulvovaginal atrophy (VVA) is a chronic, often under-diagnosed condition that has a substantial negative impact on patients’ sexual health and quality of life (QoL) [4–8]. Symptoms of VVA have been reported by up to 40–60% of postmenopausal women in Europe and the USA [4,7,9]. Unlike well-recognised menopausal symptoms such as hot flushes that resolve over time in most women, the symptoms of VVA usually persist or increase in the absence of treatment [8,10].

Vaginal dryness and dyspareunia are the most bothersome symptoms (MBS) and the most common symptoms reported by
postmenopausal women with VVA [4,6,11,12]. Treatment of VVA seeks to alleviate these symptoms [13]. First-line therapies include non-hormonal, long-acting vaginal moisturisers and lubricants as well as vaginal oestrogen. However, long-term endometrial safety data are not available for vaginal oestrogen use, and endometrial carcinoma is associated with unopposed oestrogen [9,13]. Concerns about incorrect dose administration, leakage and mess of local application of creams [14] may impact upon compliance. Furthermore insufficient symptom relief with such treatments has been highlighted by 23–42% of users [6]. Non-vaginal therapies include transdermal and oral hormone therapy; however these are associated with low compliance due to safety concerns [4,9,13]. Furthermore, it has been estimated that 40% of patients receiving systemic oestrogen do not obtain adequate relief from vaginal dryness [15–17].

Ospemifene (OspheNaTM, Shionogi Inc.) is the first oral non-hormonal alternative to oestrogen [18–21]. It is a triphenylethylene

Table 1
Patient baseline demographics (ITT population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ospemifene 60 mg (n = 160)</th>
<th>Placebo (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>59.9 (6.7)</td>
<td>59.3 (7.0)</td>
</tr>
<tr>
<td>Age distribution, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>0 (0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>45–54 years</td>
<td>38 (23.8)</td>
<td>36 (23.4)</td>
</tr>
<tr>
<td>55–64 years</td>
<td>82 (51.3)</td>
<td>81 (52.6)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>40 (25.0)</td>
<td>35 (22.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>135 (84.4)</td>
<td>122 (79.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>12 (7.5)</td>
<td>21 (13.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (2.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5.0)</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>161.2 (6.6)</td>
<td>162.4 (5.8)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>70.9 (13.5)</td>
<td>69.9 (12.5)</td>
</tr>
<tr>
<td>BM1, mean (SD), kg/m²</td>
<td>27.2 (4.6)</td>
<td>26.5 (4.6)</td>
</tr>
</tbody>
</table>

BMI, body mass index; ITT, intent-to-treat; SD, standard deviation.

Table 2
Change from baseline for the ITT and PP population for parabasal cells, superficial cells, vaginal pH and severity scores for vaginal dryness as the most bothersome symptom at Week 12/LOCF.

<table>
<thead>
<tr>
<th>Change from baseline in:</th>
<th>ITT population</th>
<th>PP population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ospemifene 60 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Parabasal cells (LS mean ± SE)</td>
<td>−31.7 ± 2.11</td>
<td>−39 ± 2.18</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>% Superficial cells (median [min, max])</td>
<td>7.0 (−4.65)</td>
<td>0.0 (−11.57)</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Vaginal pH (LS mean ± SE)</td>
<td>−0.95 ± 0.067</td>
<td>−0.25 ± 0.068</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Severity of vaginal dryness (mean ± SD)</td>
<td>−1.3 ± 1.08</td>
<td>−1.1 ± 1.02</td>
</tr>
<tr>
<td></td>
<td>p = 0.080</td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

LS, least squares; SD, standard deviation; SE, standard error.

*p-Values for % parabasal cells, % superficial cells and vaginal pH were computed using ANCOVA where change from baseline is the response variable, baseline assessment is the covariate and treatment and centre are fixed effects. If ANCOVA assumptions were not met, a rank-based ANOVA, stratifying by study centre, was used instead, and median, min and max are presented instead of LS means. p-Value for severity of vaginal dryness was computed using Cochran–Mantel–Haenszel row mean score test controlling for centre.

Fig. 1. Study design. *Patients may be excluded from PP population for more than one reason. †Completers defined as patients who completed the study receiving on daily doses of ospemifene 60 mg or placebo for 12 weeks. ITT, intent to treat; od po, orally once daily; PP, per protocol.
Selective oestrogen receptor modulator (SERM) that exerts agonist effects on vaginal tissue [11]. Ospemifene 60 mg has been shown to reduce symptoms of both dyspareunia and vaginal dryness significantly compared with placebo in a randomised, phase III study [11]. The long-term safety of ospemifene up to one year has also been shown [22,23], with no significant oestrogenic or clinically relevant adverse effects reported on endometrial tissue in women with an intact uterus [22]. Improvement in bone growth in animal models, beneficial impact on bone resorption markers in humans and antagonistic effects on the MCF-7 cell line and other breast cancer models have been demonstrated with ospemifene and identify it as a SERM with unique tissue selectivity [24].

In a study of over 600 women who self-reported dyspareunia as their most bothersome symptom, once-daily oral ospemifene 60 mg significantly improved the maturation index (MI) and vaginal pH, in addition to reducing the severity of dyspareunia, compared to placebo [25]. Based on these pivotal phase III data, ospemifene has been approved by the FDA for the treatment of moderate to severe dyspareunia [26]. Here we report the efficacy of once-daily ospemifene 60 mg in the stratum of women reporting a MBS of vaginal dryness conducted in parallel to this previously reported study (NCT00729469) [25]. This is the first study that focuses on women with a self-reported MBS of vaginal dryness.

2. Methods

2.1. Study design

The study design and methods of this randomised, double-blind, parallel-group, multicentre phase III 12-week study in the USA

<table>
<thead>
<tr>
<th>AE category</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ospemifene 60 mg (n = 160)</td>
<td>Placebo (n = 154)</td>
</tr>
<tr>
<td>Treatment-emergent AEs</td>
<td>104 (65)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>43 (26.9)</td>
</tr>
<tr>
<td>Withdrawals due to AEs</td>
<td>12 (7.5)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Treatment-related serious AEs</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

AE, adverse events.
were eligible for study inclusion. VVA was assessed by the M1 of the vaginal smear (≤5% superficial cells) and vaginal pH (>5). Symptoms of vaginal dryness were self-reported on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe).

Key exclusion criteria included a body mass index (BMI) ≥ 37 kg/m², the presence of clinically significant abnormal gynaecological findings other than signs of vaginal atrophy and concomitant hormonal medications, SERMs, or products expected to have oestrogenic and/or antioestrogenic effects. The primary analysis set was the intent-to-treat (ITT) population, which consisted of all randomised participants who took at least one dose of the study medication. The per-protocol (PP) population completed at least 10 weeks of treatment, took ≥85% of the study medication and did not have any other major protocol violation, vaginal infection or any other medical condition that would confound the primary efficacy assessment.

2.3. Efficacy assessments

The co-primary efficacy endpoints were the change from baseline to Week 12 in (1) the percentage of parabasal cells, (2) the percentage of superficial cells, (3) vaginal pH, and (4) the severity of the MBS of vaginal dryness. Secondary endpoints included the primary endpoints assessed at Week 4 using observed cases, as well as sexual activity and lubricant use at Weeks 4 and 12.

A patient was defined post hoc as a ‘responder’ based on expert opinion of response, if all the following changes from baseline were seen: a 10-point increase in maturation value (MV), a decrease in vaginal pH of 0.5 and a 1-point decrease in severity of vaginal dryness.

1 MV = (S x 1) + (I x 0.5) + (P x 0) where S, percentage of superficial cells, I, percentage of intermediate cells and P, percentage of parabasal cells.

2.2. Patient population

Postmenopausal women, aged 40–80 years, with diagnosed VVA and moderate or severe symptoms of vaginal dryness as the MBS (NCT00729469) have been described elsewhere [25]. The study design is shown in Fig. 1.
Parabasal cells, superficial cells, and pH were evaluated using an analysis of covariance (ANCOVA) model. Within this model, the response variables were the change from baseline to Week 12; for missing values, the last observation was used (the last observation carried forward [LOCF]). The baseline value was the covariate, and treatment and study centre were the fixed effects. The change from baseline in vaginal dryness severity was analysed using the Cochran–Mantel–Haenszel row mean scores test, controlling for the study centre.

2.4. Safety assessments

Patients were questioned about adverse events (AEs) at every visit post-screening. Safety was also assessed by physical examination, breast palpation, cervical Papanicolaou test, clinical laboratory analyses, centrally read 12-lead electrocardiogram, vital signs, weight, and treatment compliance. Safety analyses were conducted on the ITT population. Endometrial thickness and histology were assessed in patients with an intact uterus at baseline and Week 12.

The protocol was reviewed and approved by the Copernicus Group Institutional Review Board (Durham, NC, USA) for most clinical sites; local institutional review boards were used for the remaining sites. The study was conducted in accordance with the Declaration of Helsinki and current Good Clinical Practice. All randomised patients provided a written informed consent form.

3. Results

A total of 314 patients with VVA who reported their MBS as moderate or severe vaginal dryness were randomised to ospemifene 60 mg once daily or placebo (Fig. 1). The patient baseline demographics of the ITT population are shown in Table 1.

Overall, 33.8% of the ospemifene treatment group were ‘responders’ compared with 7.1% of patients receiving placebo (p < 0.001). Statistical significance was seen for the co-primary endpoints of mean decrease from baseline to Week 12/LOCF for the ITT population in percentage of parabasal cells (Table 2, p < 0.001) and median increase from baseline to Week 12/LOCF in superficial cells (Table 2, p < 0.001) in the MI and mean decrease from baseline to Week 12/LOCF in vaginal pH (Table 2, p < 0.001). The mean change from baseline to Week 12/LOCF in severity score of vaginal dryness reported by women receiving ospemifene was −1.3 ± 1.08 compared with −1.1 ± 1.02 by those receiving placebo (p = 0.080) (Table 2). Similar results were observed in the secondary efficacy analyses for observed cases (change from baseline to Week 4 and Week 12 for the endpoints corresponding to the primary efficacy endpoints) (Fig. 2). Of note, the proportion of patients reporting no vaginal dryness at Week 12/LOCF was higher in the ospemifene group (30.0%) than in the placebo group (22.1%). Similarly, the reported severity of vaginal dryness at Week 12/LOCF was lower in the ospemifene group compared with the placebo group (Fig. 3a). Scores improving by 2–3 levels were reported by 46.3% of patients receiving ospemifene compared with 34.4% of patients receiving placebo (Fig. 4a).

Analysis of results in the PP population yielded similar results, with significant improvement in MI and vaginal pH endpoints in the ospemifene group compared with placebo (Table 2, p < 0.001). In addition, in the PP population, the mean improvement from baseline to Week 12/LOCF in severity score of vaginal dryness reported by women receiving ospemifene vs placebo was statistically significant (−1.4 ± 1.03 vs −1.1 ± 1.03, p = 0.014). There was a trend towards a higher proportion of patients reporting no or mild vaginal dryness at Week12/LOCF in the PP population than in the ospemifene group (29.9% and 38.6%, respectively) compared with the placebo group (23.4% and 29.9%, respectively) (Fig. 3b). Notably, 50.4% of patients in the ospemifene group reported scores improving by 2–3 levels compared with 34.3% of patients in the placebo group (Fig. 4b).

Similar proportions of patients receiving ospemifene vs placebo used lubricants during the first week of treatment (39.9% and 37.0% in the ospemifene and placebo groups, respectively). However, the decrease in the proportion of patients using lubricants was somewhat greater in the ospemifene group compared with placebo (21.7% and 33.0%, respectively) (Fig. 5). The frequency of sexual activity remained consistent across the study in both treatment groups.

3.1. Safety

Ospemifene was well tolerated (Table 3). Most treatment-emergent AEs (TEAEs) were classified as not related to the study drug or unlikely to be related to the study drug (66.5%). The most frequently reported TEAEs in the ospemifene group were urinary tract infection (12.5% of patients), hot flush (7.5%) and nasopharyngitis (5.6%). Only two patients experienced serious AEs; of which one was considered probably treatment related (deep vein thrombosis). There were no more withdrawals due to AEs in the ospemifene group, however the majority of AEs were rated as mild or moderate by the treating physician. Three patients receiving ospemifene reported worsening of hot flushes which led to discontinuation of the study drug. Further information on TEAEs can be found in the online appendix (Supplementary Fig. 1).

A slight increase in endometrial thickness from baseline was seen in women with an intact uterus receiving ospemifene compared with a decrease in thickness in the placebo group (Table 4). No patients had an endometrial thickness ≥5 mm at baseline in either treatment group. Three patients (3/51; 5.9%) in the ospemifene group and one patient (1/58; 1.7%) in the placebo group had an endometrial thickness ≥5 mm after 12 weeks of treatment (Table 4). Of these, two patients (2/51; 3.9%) in the ospemifene group had an endometrial thickness ≥8 mm at Week 12. Endometrial histology samples for these patients revealed one who had insufficient tissue for diagnosis and one was classified as having atrophic endometrium. Overall, endometrial histology assessments showed four cases of weak proliferation in the ospemifene group and three cases in the placebo group. No cases of endometrial hyperplasia, endometrial polyps, or carcinoma were observed in the endometrial biopsy samples. Vaginal bleeding was reported in two patients in each treatment group.

4. Discussion and conclusions

This study provides further evidence of the efficacy and tolerability of oral ospemifene for treating symptoms of VVA associated with menopause, particularly in women with VVA who report vaginal dryness as their MBS. Improvements in the proportion of parabasal and superficial cells in the MI as well as vaginal pH were seen by 4 weeks and maintained throughout the study. Although improvements in the self-reported MBS severity score of vaginal dryness did not reach statistical significance in the ITT population during the study, a greater proportion of women receiving ospemifene compared with placebo rated their vaginal dryness as mild or none at Week 12/LOCF. Furthermore, in the PP population (patients with ≥85% compliance, at least 10 weeks of treatment and no known conditions that might confound the efficacy assessment), the mean reduction from baseline to Week 12/LOCF in the severity score of vaginal dryness reported by women receiving ospemifene vs placebo was statistically significant. The overall efficacy of ospemifene is highlighted by the significantly greater number of ‘responders’ receiving active treatment vs placebo. In this study, the
definition of ‘responder’ combines the assessment of both objective physiological and subjective symptoms and therefore ensures improvements in vaginal dryness are clinically relevant.

The parallel strata of ospemifene-treated women with VVA with a MBS of dyspareunia, published by Portman and colleagues [25], reported similar improvements in the objective symptoms of VVA. However, statistically significant beneficial changes were reported in all four co-primary efficacy endpoints including a significant reduction in the severity of dyspareunia after 12 weeks of treatment in women receiving ospemifene compared with those receiving placebo in the ITT population. As in the present study, improvements were seen in vaginal pH, percentage of parabasal cells, and percentage of superficial cells after just four weeks of treatment [25].

Interestingly, an earlier, smaller study of ospemifene in women with VVA and a MBS of dyspareunia or vaginal dryness demonstrated significant improvements in the ospemifene group compared with placebo for both the vaginal dryness and the dyspareunia strata after 12 weeks [11]. The mean reduction in symptom scores was similar to the scores observed in the present study for those receiving ospemifene 60 mg after 12 weeks of treatment (1.26). However, the reduction in the score of the placebo group at 12 weeks was lower (0.84) compared to the present larger dryness study, suggesting that the placebo effect is a key driver in the findings in this study and may be difficult to overcome in even a large well-powered trial. The reasons for this are unknown but could relate to differences in the baseline characteristics of the two study populations (such as differences in BMI between treatment populations). Additionally, the permis sibility of lubricants in the study makes it more difficult for the subjective symptom of dryness to be assessed (unlike pain, which can often be more defined by the woman, and which may not respond as well to lubricants alone). The placebo control is in actuality a lubricant-treated group, which may make it more difficult to see statistically a difference with active treatment when dryness alone is the MBS.

Although the data presented here suggest improvement in self-reported MBS severity score of vaginal dryness, statistical significance was not achieved for this endpoint. The use of MBS as an FDA-recommended clinical study endpoint may be meaningful, however, it is a subjective patient-reported endpoint and therefore may be subject to response bias [27] and a greater placebo effect. A substantial placebo effect was observed for the MBS of vaginal dryness endpoint in this study, which did not decrease from Week 4 to Week 12. Other studies of female sexual dysfunc tion have also reported clinically significant improvement in sexual function during treatment with placebo [28]. It has been suggested that the contextual and procedural aspect of clinical trials, such as support from sexual partners and clinical staff encounters and counselling, may influence outcomes in the absence of an active drug treatment. A better understanding and acknowledgement of placebo response in VVA and trials of female sexual dysfunction is an important issue to explore further as other treatments for these conditions emerge and undergo investigation.

There are several inherent difficulties in demonstrating statistical efficacy at the MBS of dryness in clinical trials. In fact, to date, only one treatment – oral synthetic conjugated oestrogens B – has demonstrated efficacy using the dryness MBS endpoint [29] and is approved in the USA for the treatment of both moderate to severe vaginal dryness and pain with intercourse associated with menopause (Enjuvia®, Teva Pharmaceuticals Inc.). No lubricants were permitted in that trial and treatment was an oral therapy, allowing for less confounding from the vaginal route of administration and lubricant use, and for statistical separation from placebo in both domains. In the MBS studies of conjugated equine oestrogen cream, 0.5 g twice weekly, only dyspareunia, and not dryness, met statistical significance compared to placebo. The emollient effect of a vaginal placebo cream may have confounded the dryness results by increasing placebo improvement, and thus this effective, established vaginal oestrogen regimen only has a labelled indication in the USA for dyspareunia for this dose [30]. The MBS, albeit a useful way to separate out individual domains of symptom relief, creates distinction and separation that are somewhat arbitrary [12]. Patients must select their one most bothersome symptom, and follow that one throughout the study period. Most women studied had multiple bothersome symptoms and some became more bothersome than others over the course of a study, making the MBS measures limiting and quite challenging, and it fails to address the constellation of symptoms of women with VVA. Additionally, the MBS approach has not undergone any rigorous validation process. Better patient-reported outcome instruments for VVA clinical trial and diagnostic purposes are needed and currently under development.

Ospemifene was shown to be safe and well tolerated, as has been reported in other trials in women with VVA [11,22,23,25]. Over 1200 women have been studied for safety with the 60 mg dose and represent one of the largest prospective, randomised cohorts studied for VVA [31]. No significant oestrogenic effects on endometrial tissue or new clinically important AEs were reported in the present study either. Although hot flushes occurred more frequently in the ospemifene group, as has been observed in other trials with ospemifene [11,25], this led to discontinuation of only three patients receiving ospemifene. However, it is noteworthy that the numbers of patients who experienced hot flushes while receiving ospemifene was still low, given the age of the patient population. No significant increases in endometrial thickness or endometrial proliferation, a key consideration for chronic SERM use [32], was seen in this study as similarly reported in the parallel 12 week trial [25]. Although endometrial thickness increased slightly, no biopsies indicated endometrial hyperplasia or carcinoma. A 12-month study of endometrial safety with ospemifene (n = 426) confirmed minimal stimulation of the endometrium with only one case of simple hyperplasia, representing a rate of 0.3%, well below the expected background rate of 1% [33]. This study also supports the tissue selectivity of ospemifene.

Ospemifene 60 mg is a non-oestrogen oral treatment that is a safe and effective option for the treatment of postmenopausal women with VVA and a MBS of vaginal dryness in the PP population and exploratory responder analysis of the present study. Patients also reported less lubricant use, which may be a surrogate for improved vaginal moisture and lubrication. VVA is a prevalent symptom complex found among postmenopausal women due to the chronic hypo-oestrogenic state of menopause with dryness and dyspareunia the most common complaints [4,7,9]. Unlike other symptoms of hypo-oestrogenism, VVA does not resolve over time, and non-oestrogenic and oral options for this common condition are needed. Ospemifene 60 mg offers a well-tolerated oral therapeutic alternative to vaginal oestrogens for postmenopausal women with VVA irrespective of their MBS.

Contributors

Authors: David Portman, Santiago Palacios, Rosella E. Nappi, Alfred O. Mueck
All authors contributed to the design of the research and writing of the paper.
All authors take responsibility for the content.
The manuscript has been approved for publication by all the authors involved.
Competing interest

AOM declared he has no conflict of interest.

During the past 2 years REN has had financial relationships (lecturer, member of advisory boards and/or consultant) with Bayer-Schering Pharma, Ely Lilly, Gedeon-Richter, HRA Pharma, Merck Sharp & Dohme, Novo Nordisk, Pfizer Inc, Shionogi Limited and TEVA/Theramex.

DP declared that he has acted as a consultant and advisory board member for Bayer, Noven Pharmaceuticals, Palatin Technologies, QuatRx Pharmaceuticals Company, Shionogi, Sprott Pharmaceuticals, Teva Pharmaceuticals, Apricus Bioscience, Actavis Pharmaceuticals, Pfizer and Agile. He has also received grant/research support from Bayer, Boehringer Ingelheim, Noven Pharmaceuticals, Palatin Technologies, Pfizer Inc, QuatRx Pharmaceuticals Company, Teva Pharmaceutical Industries Ltd, Amn XS Pharmaceuticals, Warner Chilcott, Trimmel, Agile, Endoecutics, Watson Pharmaceuticals and Therapeutics MD. He has served on speakers’ bureaux for Teva Pharmaceutical Industries, Warner Chilcott, Noven Pharmaceuticals and Shionogi.

SP declared that he has acted as a consultant and advisory board member for Servier, Pfizer, Glaxo Smith Kline, Abbott, Ferrer, Bioiberica, Shionogi and Amgen. He has also received grant/research support from Pfizer, Servier, Amgen, Merck Sharp & Dohme, Preglem, Leon Farma, Gynea, Sandoz, Bayer, Amgen.

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Ethical approval, consent or animal equivalent

The protocol was reviewed and approved by the Copernicus Group Institutional Review Board (Durham, NC, USA) for most clinical sites; local institutional review boards were used for the remaining sites. The study was conducted in accordance with the Declaration of Helsinki and current Good Clinical Practice. All randomised patients provided a written informed consent form.

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Appendix A. Ospemifene study group (clinical centres – principal investigators)


We thank the study staff at each site and all the women who participated in this study.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.maturitas.2014.02.015.

References


