Ospemifene’s effects on lipids and coagulation factors: a post hoc analysis of phase 2 and 3 clinical trial data

David F. Archer, MD,1 Corrado Altomare, MD,2 Wei Jiang, PhD,2 and Susannah Cort, MD2

Abstract

Objective: To evaluate the effect of ospemifene 60 mg on the lipid and coagulation parameters of postmenopausal women using data from five phase 2 and 3 clinical trials.

Methods: Data for lipids and coagulation factors for 2,166 postmenopausal women were pooled from five randomized, placebo-controlled studies. Lipid and coagulation parameters included in this analysis were total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, activated partial thromboplastin time (aPTT), fibrinogen, antithrombin antigen, protein C Ag, and protein S Ag free.

Results: Mean percent changes in HDL and LDL were significantly greater with ospemifene versus placebo at month 3 (HDL: 4.4% vs 0.2%; LDL: −5.2% vs 2.4%), month 6 (HDL: 5.1% vs 1.5%; LDL: −6.7% vs 2.4%), and month 12 (HDL: 2.3% vs −1.9%; LDL: −7.0% vs −2.1%; P < 0.05, for all comparisons). Ospemifene significantly reduced total cholesterol at 6 months (−1.8% vs 1.6%; P = 0.0345 versus placebo), and changes in triglycerides with ospemifene were similar to placebo at all three time points. In subgroup analyses based on age, body mass index, and baseline triglyceride level, ospemifene increased HDL and decreased LDL, but had no significant effect on total cholesterol and triglycerides relative to placebo. Ospemifene significantly improved fibrinogen and protein C antigen levels relative to placebo at months 3 (−8.7% vs −0.8% and −2.7% vs 0.5%, respectively), 6 (−6.0% vs 6.7% and −3.6 vs 8.0%), and 12 (−8.7% vs 7.3% and −4.5% vs 6.6%; P < 0.01, for all). The levels of all coagulation factors remained within the normal range throughout the studies.

Conclusion: Ospemifene 60 mg does not have a detrimental effect on lipid and coagulation parameters of postmenopausal women with up to 12 months of use.

Key Words: Coagulation factors – Dyspareunia – Fibrinogen – Lipids – Ospemifene – Vulvar and vaginal atrophy.

Estrogen decline at the onset of menopause can leave the vasculature vulnerable to cardiovascular disease, which is associated with changes in surrogate markers such as lipids and coagulation factors. Postmenopausal women have been shown to have significantly higher levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and very-LDL (VLDL) cholesterol, and a lower level of high-density lipoprotein (HDL) cholesterol than premenopausal women.1 Hormone therapy (HT) has been shown to offset the detrimental effect of menopause on lipids by decreasing total cholesterol and LDL, and increasing HDL in postmenopausal women.2-8 Clinical studies have shown HT’s effect on the risk of thrombotic diseases differs based on the route of administration. Oral HT has been shown to increase fibrinolysis and coagulation in postmenopausal women, with clinical studies showing an increased risk for venous thromboembolism (VTE), and increased fibrinolysis and coagulation with oral compared with transdermal HT.9-12 Activated partial thromboplastin time (aPTT), fibrinogen, antithrombin antigen, protein C Ag, and protein S Ag free are regularly measured as surrogate markers for thrombophilia; however, the clinical impact of abnormal changes in these markers is not fully understood.13-16

Received December 22, 2016; revised and accepted March 7, 2017.

From the 1Jones Institute for Reproductive Medicine, Norfolk, VA; and 2Shionogi Inc, Florham Park, NJ.

Funding/support: Data analyses were conducted by Shionogi, Inc. Also, Shionogi, Inc provided financial support for medical writing assistance supplied by Disha Patel, PhD (Precise Publications, LLC).

Financial disclosure/conflicts of interest: D.F.A. (within the past 3 years) has received research support from Actavis (previously Allergan, Watson Pharmaceuticals, Warner Chilcott), Bayer Healthcare, Endoecutics, Glenmark, Merck (previously Schering Plough, Organon), Radius Health, Shionogi Inc, and TherapeuticsMD; and has served as a consultant to Abbvie (previously Abbott Laboratories), Actavis (previously Allergan, Watson Pharmaceuticals, Warner Chilcott), Agile Therapeutics, Bayer Healthcare, Endoecutics, Exeltis (previously CHEMO), InnovaGyn, Merck (previously Schering Plough, Organon), Pfizer, Radius Health, Sermonix Pharmaceuticals, Shionogi, Inc, Teva Women’s Healthcare, and TherapeuticsMD. C.A., W.J., and S.C. are employees of Shionogi, Inc.

Address correspondence to: David F. Archer, MD, Eastern Virginia Medical School, 601 Colley Avenue, Norfolk, VA 23507. E-mail: archerd@evms.edu

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permisible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
Ospemifene is an estrogen receptor agonist/antagonist (ERAA, also referred to as a selective estrogen receptor modulator [SERM]) approved by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe dyspareunia, a symptom of vulvar vaginal atrophy (VVA, which is also a component of genitourinary syndrome of menopause1) due to menopause.18 Clinical and preclinical studies have shown that ospemifene can elicit tissue-specific estrogenic or antiestrogenic effects in the vagina,19,25 bone,26-30 and breast.27,31,32 However, limited data are available characterizing ospemifene’s effect on the surrogate markers for cardiovascular health of postmenopausal women. Two 3-month, phase 2 clinical studies have characterized the effect of ospemifene on lipids and coagulation factors relative to placebo and the SERM raloxifene (60 mg).20,33 Data from both studies suggest that ospemifene may have a beneficial effect on levels of HDL, LDL, and fibrinogen.

A post hoc analysis of pooled data from 5 randomized, placebo-controlled clinical trials16-21,25,33,34 was conducted to assess the effect of systemic ospemifene exposure on lipids and coagulation factors in postmenopausal women.

METHODS

Study design
The effect of once-daily oral ospemifene 60 mg on lipids and coagulation factors in postmenopausal women (40-80 years in age) was evaluated in a post hoc analysis using data from five randomized, double-blind, parallel-group, placebo-controlled, phase 2 and 3 clinical trials (15-50718,25 1506002,16,33 15-50615,34 15-50310,21 and 15-5082123,24), including a 40-week extension of a phase 3 study (15-50310x22). Details of the study design and inclusion criteria for all five clinical trials have been previously reported.16,21-25,33,34

Briefly, the studies ranged from 6 weeks to 12 months in length, with 1,242 randomized to ospemifene 60 mg and 924 to placebo (Fig. 1). Study completion rate was similar between the ospemifene (85.4%) and placebo (86.8%) groups. Discontinuation due to adverse events was 7.6% (n = 95) for ospemifene and 3.7% (n = 34) for placebo (Fig. 1).

Age, race, and BMI were comparable between the ospemifene and placebo groups (Table 2). The trial participants were predominantly white with a mean age of approximately 59 years and a mean BMI of approximately 26 kg/m². The percentage of postmenopausal women with an intact uterus was numerically higher for ospemifene (68.5%) versus placebo (58.8%), and a similar percentage of women had a prior history of HT use with ospemifene (21.1%) and placebo (18.8%).

Lipids
Mean percent increases in HDL from baseline were significantly greater with ospemifene versus placebo at 3 months (4.4% vs 0.2%; P < 0.0001), 6 months (5.1% vs 1.5%; P = 0.0359), and 12 months (2.3% vs −1.9%; P = 0.0086; Fig. 2A). Similarly, mean percent changes in LDL from baseline were significantly greater with ospemifene versus placebo at 3 months (−5.2% vs 2.4%; P < 0.0001), 6 months (−6.7% vs 2.4%; P = 0.0002), and 12 months (−7.0% vs −2.1%; P = 0.0293; Fig. 2A). Ospamifene significantly reduced total cholesterol at 6 months compared with placebo (−1.8% vs 1.6%; P = 0.0345; Fig. 2B). The increase in triglycerides with ospemifene use was similar to those found with placebo (Fig. 2B).

The subgroup analyses based on age found that ospemifene significantly increased HDL in postmenopausal women 60 years of age or older at 3, 6, and 12 months, but only at 3 months in women less than 60 years of age (Table 3). LDL levels in contrast were significantly decreased by ospemifene at 3 and 6 months in both age groups. Ospamifene evaluated by each study are described in Table 1. The changes from baseline to 3, 6, and 12 months for each lipid and coagulation factor were evaluated in this post hoc analysis. For each parameter, the mean percent change from baseline was calculated and the Welch’s t test was used to compare ospemifene 60 mg and placebo.

Lipid and coagulation factor data were evaluated for 2,166 postmenopausal women participating in five placebo-controlled studies, ranging from 6 weeks to 12 months in length, with 1,242 randomized to ospemifene 60 mg and 924 to placebo (Fig. 1). Study completion rate was similar between the ospemifene (85.4%) and placebo (86.8%) groups. Discontinuation due to adverse events was 7.6% (n = 95) for ospemifene and 3.7% (n = 34) for placebo (Fig. 1).

RESULTS

Participant disposition, demographics, and baseline characteristics
Lipid and coagulation factor data were evaluated for 2,166 postmenopausal women participating in five placebo-controlled studies, ranging from 6 weeks to 12 months in length, with 1,242 randomized to ospemifene 60 mg and 924 to placebo (Fig. 1). Study completion rate was similar between the ospemifene (85.4%) and placebo (86.8%) groups. Discontinuation due to adverse events was 7.6% (n = 95) for ospemifene and 3.7% (n = 34) for placebo (Fig. 1).

Age, race, and BMI were comparable between the ospemifene and placebo groups (Table 2). The trial participants were predominantly white with a mean age of approximately 59 years and a mean BMI of approximately 26 kg/m². The percentage of postmenopausal women with an intact uterus was numerically higher for ospemifene (68.5%) versus placebo (58.8%), and a similar percentage of women had a prior history of HT use with ospemifene (21.1%) and placebo (18.8%).

Lipids
Mean percent increases in HDL from baseline were significantly greater with ospemifene versus placebo at 3 months (4.4% vs 0.2%; P < 0.0001), 6 months (5.1% vs 1.5%; P = 0.0359), and 12 months (2.3% vs −1.9%; P = 0.0086; Fig. 2A). Similarly, mean percent changes in LDL from baseline were significantly greater with ospemifene versus placebo at 3 months (−5.2% vs 2.4%; P < 0.0001), 6 months (−6.7% vs 2.4%; P = 0.0002), and 12 months (−7.0% vs −2.1%; P = 0.0293; Fig. 2A). Ospamifene significantly reduced total cholesterol at 6 months compared with placebo (−1.8% vs 1.6%; P = 0.0345; Fig. 2B). The increase in triglycerides with ospemifene use was similar to those found with placebo (Fig. 2B).

The subgroup analyses based on age found that ospemifene significantly increased HDL in postmenopausal women 60 years of age or older at 3, 6, and 12 months, but only at 3 months in women less than 60 years of age (Table 3). LDL levels in contrast were significantly decreased by ospemifene at 3 and 6 months in both age groups. Ospamifene
15-5071825 Phase 3, 15-5082123, 24 Phase 3, aPTT, activated partial thromboplastin time; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL-BCD, baseline conjugated dienes of low-density lipoprotein.

15-5031021/150600216, 33 Phase 2, decreased LDL levels from baseline to 3 months in women age (Table 3). ceride levels of postmenopausal women, regardless of their no significant effects, compared with placebo, on the trigly- ceride levels. Total cholesterol and triglyceride levels at 3 months remained unchanged, regardless of the BMI or triglyceride levels. None of these changes were outside the range of normal values for each parameter.

**TABLE 1. Descriptions of the five phase 2 and 3 clinical trials included in this report**

| Study number | Study design | Study duration | Treatment administered | Lipid and coagulation factors measured |
|--------------|--------------|----------------|------------------------|----------------------------------------|
| 15-5061524 | Phase 2, placebo-controlled | 6 wks | Once-daily oral dose of ospemifene 60 mg (n = 100) Placebo (n = 98) | Coagulation factors: Factor V Leiden and thromboplastin time Evaluated at screening and wk 6 |
| 150600216, 33 | Phase 2, placebo-controlled | 12 wks | Once-daily oral doses of ospemifene 30 mg (n = 40) 60 mg (n = 40) 90 mg (n = 40) Placebo (n = 40) | Lipids: HDL, LDL, LDL-BCD, Lp (a), total cholesterol, and triglycerides Coagulation factors: Endothelin-1, plasma nitric oxide, prostacyclin, fibrinogen, prothrombin fragments 1 + 2, thrombin-antithrombin III complex, D-dimer, tissue-type plasminogen activator, plasminogen activator inhibitor-1, and homocysteine in plasma Evaluated at screening and wks 12 and 14 to 16 (after treatment discontinuation) |
| 15-5031023 | Phase 3, placebo-controlled | 12 wks | Once-daily oral dose of ospemifene 60 mg (n = 463) Placebo (n = 456) | Lipids: HDL, LDL, total cholesterol, and triglycerides Coagulation factors: Factor V Leiden, antithrombin III, fibrinogen, protein C, protein S, and thromboplastin time Evaluated at screening and wk 12 |
| 15-50310x2, 15-50310x2a | Phase 3, placebo-controlled | 40-wk extension | Once-daily oral dose of ospemifene 30 mg (n = 62) 60 mg (n = 69) Placebo (n = 49) | Lipids: HDL, LDL, total cholesterol, and triglycerides Coagulation factors: aPTT, fibrinogen, antithrombin III antigen, protein C antigen, and free protein S antigen Evaluated at wks 26 and 52 |
| 15-5071823 | Phase 3, placebo-controlled, safety study | 52 wks | Once-daily oral dose of ospemifene 60 mg (n = 363) Placebo (n = 63) | Lipids: HDL, LDL, total cholesterol, and triglycerides Coagulation factors: Factor V Leiden, antithrombin III, protein C, and protein S Evaluated at screening and wks 12, 26, and 52 |

*Evaluated only at screening.

significantly decreased total cholesterol relative to placebo in women less than 60 years of age only at 6 months and had no effect among women aged 60 years or older. Ospemifene had no significant effects, compared with placebo, on the triglyceride levels of postmenopausal women, regardless of their age (Table 3).

Ospemifene also significantly increased HDL and decreased LDL levels from baseline to 3 months in women with BMI less than 32 kg/m² and those with triglyceride levels less than 250 mg/dL (P < 0.0001 vs placebo for all; data not shown). In contrast, ospemifene had no significant effect on HDL or LDL among women with high BMI or triglyceride levels. Total cholesterol and triglyceride levels at 3 months remained unchanged, regardless of the BMI or triglyceride level.

**Coagulation factors**

Mean percent changes in fibrinogen and protein C antigen levels from baseline were significantly greater with ospemifene versus placebo at 3 months (−8.7% vs −0.8%; P < 0.0001, and −2.7% vs 0.5%; P = 0.0008, respectively), 6 months (−6.0% vs 6.7%; P = 0.0019, and −3.6% vs 8.0%; P < 0.0001), and 12 months (−8.7% vs 7.3%; P = 0.0029, and −4.5% vs 6.6%; P < 0.0001) were significantly greater with ospemifene versus placebo (Fig. 3). Ospemifene numerically lowered aPTT levels from baseline to 3 and 6 months, with the change being significantly greater than that for placebo at 3 months (−1.9% vs 0.7%; P = 0.0009). Antithrombin III antigen levels also decreased from baseline to 3 months with ospemifene, with the change being greater than that with placebo (−2.9% vs −0.8%; P = 0.0004). Ospemifene numerically increased free protein S antigen levels at all measured time points (Fig. 3B), with the change being significantly greater than placebo at 3 months (5.8% vs 1.6%; P < 0.0001).

**DISCUSSION**

This post hoc analysis of pooled data from five placebo-controlled clinical studies found ospemifene 60 mg increased HDL and decreased LDL levels in postmenopausal women with no adverse effects on total cholesterol and triglycerides. Ospemifene 60 mg also decreased the levels of fibrinogen (a risk factor for coronary heart disease) from baseline, with a significant difference from placebo; however, the postbaseline fibrinogen level remained within the normal range for the

 Menopause, Vol. 24, No. 10, 2017 1169
A negative effect on lipid and coagulation factors in postmenopausal women.

Data characterizing ospemifene’s effect on lipid and coagulation factors relative to placebo was previously limited to a 3-month, phase 2 clinical trial (study 1506002, included in this pooled dataset) of 160 healthy, postmenopausal women randomized to either ospemifene at doses of 30, 60, and 90 mg or placebo.

Ospemifene increased HDL and decreased total cholesterol and LDL from baseline to 3 months, but the changes were not significant versus placebo and vanished within 2 to 4 weeks of treatment cessation.

Triglycerides increased significantly with ospemifene 90 mg relative to placebo (P = 0.017). Ospemifene also decreased plasma fibrinogen levels (P < 0.05), which returned to baseline levels upon treatment cessation.

More specifically, fibrinogen levels significantly decreased with ospemifene 60 mg (P = 0.0145) and 90 mg (P = 0.0232) relative to placebo at 3 months. The results from our post hoc analysis further extend initial data from study 1506002 and demonstrate that ospemifene 60 mg, the clinical US FDA-approved dose, does not negatively influence lipids and coagulation factors in postmenopausal women either in good health or diagnosed with VVA.

The significant improvement in HDL and LDL with ospemifene observed in this post hoc analysis is consistent with the majority of the clinical literature for estrogen therapies and other ERAAs/SERMs, including raloxifene and bazedoxifene.

However, ospemifene has no significant effect on triglycerides, which is in contrast with the increase in triglycerides typically seen with oral estrogens, but is consistent with clinical data for bazedoxifene. A 3-month...
FIG. 2. Mean percent change in serum lipid levels (A: HDL- and LDL- Cholesterol; B: Total Cholesterol and Triglycerides) of postmenopausal women treated with ospemifene 60 mg for up to 12 months in five placebo-controlled studies (15-50718, 1506002, 15-50615, 15-50310, and 15-50821). The values of n for each group appear at the base of each bar. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. HDL, high-density lipoproteins; LDL, low-density lipoproteins.

TABLE 3. The effect of age on the mean percent change in serum lipid levels of postmenopausal women treated with ospemifene 60 mg from studies 15-50718, 1506002, 15-50615, 15-50310, and 15-50821.

| Time point, mos | Mean percent change from baseline (n) |
|-----------------|--------------------------------------|
|                 | HDL 60 mg (n = 664) | Placebo (n = 545) | P          | LDL 60 mg (n = 578) | Placebo (n = 379) | P          |
|                 |                        |                    |            |                        |                    |            |
| HDL             |                        |                    |            |                        |                    |            |
| 3               | 3.5068 (498)           | 0.4212 (418)       | 0.0005     | 5.2473 (479)           | −0.0429 (297)      | <0.0001    |
| 6               | 3.7713 (162)           | 4.4413 (43)        | 0.7886     | 6.1076 (212)           | −0.9090 (52)       | 0.0027     |
| 12              | 2.4799 (150)           | −1.0935 (40)       | 0.1614     | 2.1321 (192)           | −2.5809 (48)       | 0.0204     |
| LDL             |                        |                    |            |                        |                    |            |
| 3               | −4.5125 (263)          | 2.9522 (163)       | <0.0001    | −5.7298 (301)          | 1.8122 (145)       | 0.0010     |
| 6               | −5.2666 (160)          | 3.3872 (43)        | 0.0144     | −7.8387 (212)          | 1.5365 (52)        | 0.0075     |
| 12              | −6.4397 (148)          | −3.3896 (40)       | 0.3080     | −7.3690 (192)          | −1.0783 (48)       | 0.0525     |
| Triglycerides   |                        |                    |            |                        |                    |            |
| 3               | 10.7071 (498)          | 8.0956 (418)       | 0.2944     | 9.1318 (479)           | 9.4346 (297)       | 0.9086     |
| 6               | 17.0465 (162)          | 19.8375 (43)       | 0.6828     | 12.7093 (212)          | 18.5546 (52)       | 0.3768     |
| 12              | 12.6197 (150)          | 15.7714 (40)       | 0.6416     | 13.8306 (192)          | 19.1875 (48)       | 0.3778     |
| Total cholesterol |                        |                    |            |                        |                    |            |
| 3               | −0.655 (498)           | 0.0740 (418)       | 0.3649     | −1.5039 (479)          | −0.4904 (297)      | 0.3652     |
| 6               | −1.2853 (162)          | 3.4364 (43)        | 0.0473     | −2.2008 (212)          | 0.1701 (52)        | 0.2919     |
| 12              | −2.7399 (150)          | −2.0868 (40)       | 0.7407     | −3.1654 (192)          | −1.1288 (48)       | 0.325      |

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
phase 2 clinical study comparing ospemifene (30, 60, and 90 mg) with raloxifene 60 mg showed no significant differences in the triglyceride levels between the four treatment groups (changes from baseline were not reported). However, raloxifene’s effect on triglycerides varies from no change reported by several studies to a significant increase ($P < 0.05$) at 4 years in the Multiple Outcomes of Raloxifene Evaluation (MORE) study. Additional longer-term, placebo, and active-controlled clinical trials are needed to fully confirm the initial results from this analysis, which suggest ospemifene is likely to improve HDL and LDL levels in postmenopausal women with no detrimental effect on their triglyceride levels.

Ospemifene, like HT and raloxifene, also does not have a negative effect on fibrinogen levels of postmenopausal women. The significant decrease in fibrinogen levels with ospemifene 60 mg (mean percent change of 8.7%; $P = 0.0145$) initially observed at 3 months in study 1506002 extends for up to 12 months of treatment (mean percent change of 8.7%) in this post hoc analysis. A 6-month, placebo-controlled study, which compared the effect of raloxifene (60 and 120 mg) with placebo and HT (0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate [CE/MPA]) in 390 healthy, postmenopausal women, reported a 10% to 12% decrease compared with baseline fibrinogen levels with the two raloxifene doses ($P < 0.001$ vs placebo), whereas CE/MPA...
OSPEMIFENE’S EFFECTS ON CARDIOVASCULAR MARKERS

CONCLUSIONS

Post hoc analysis of pooled data from five randomized, placebo-controlled studies found ospemifene 60 mg to significantly increase HDL and decrease LDL, while having little effect on triglycerides relative to placebo. Significant decreases in fibrinogen were also reported with 12 months of ospemifene treatment; however, this was not considered to be of clinical significance as the values remained within the normal range for both parameters. Taken together, ospemifene 60 mg, when prescribed for postmenopausal symptoms of VVA or GSM, does not have adverse effects on lipid levels and coagulation factors.

Acknowledgments: The authors thank Yasunori Uragari for the statistical analyses, and Disha Patel, PhD, of Precise Publications, LLC, for the medical writing assistance, which was supported by Shionogi, Inc.

REFERENCES

1. Reddy KS, Chandala SR. A comparative study of lipid profile and oestriadiol in pre- and post-menopausal women. J Clin Diagn Res 2013; 7:1596-1598.
2. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen-Progestin Interventions (PEPI) trial. JAMA 1995;273:199-208.
3. Prestwood KM, Unson C, Kulldorff M, Cushman M. The effect of different doses of micronized 17beta-estradiol on C-reactive protein, interleukin-6, and lipids in older women. J Gerontol A Biol Sci Med Sci 2004;59:827-832.
4. Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. Fertil Steril 2001;76:13-24.
5. Archer DF, Thorneycroft IH, Foegh M, et al. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. Menopause 2005;12:716-727.
6. Rossouw JE, Cushman M, Greenland P, et al. Inflammatory, lipid, thrombotic, and genetic markers of coronary heart disease risk in the Women’s Health Initiative trials of hormone therapy. Arch Intern Med 2008;168:2245-2253.
7. Espeland MA, Marcovina SM, Miller V, et al. Effect of postmenopausal hormone therapy on lipoprotein(a) concentration. PEPI Investigators. Postmenopausal Estrogen-Progestin Interventions. Circulation 1998;97:979-986.
8. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progesteron for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-613.
9. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 2007;115:840-845.
10. Roach RE, Lijfering WM, Helmerhorst FM, Cameron SC, Rosendaal FR, van HV. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. J Thromb Haemost 2013;11:124-131.
11. Scarabin PY, Alenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Asach M. Effects of oral and transdermal estrogen/progestogen regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. Arterioscler Thromb Vasc Biol 1997;17:3071-3078.
12. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrone-replacement therapy with venous thromboembolism. Lancet 2003;362:428-432.
13. Marlar RA, Gausman JN. Laboratory testing issues for protein C, protein S, and antithrombin. Int J Lab Hematol 2014;36:289-295.
14. Grimes DA, Schulz KE. Surrogate end points in clinical research: hazardous to your health. Obstet Gynecol 2005;105:1114-1118.
15. Franchini M, Martinelli I, Mannucci PM. Uncertain thrombophilia markers. Thromb Haemost 2015;115:25-30.
16. Rutanen EM, Heikkinen J, Halonen K, Komi J, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: a double-blind, randomized trial. Menopause 2003;10:433-439.
17. Portman DJ, Gass ML. Geriatric syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women’s Sexual Health and the North American Menopause Society. Menopause 2014;21:1063-1068.
18. Mirkin S, Komm BS. Tissue-selective estrogen complexes for postmenopausal women. Maturitas 2013;76:213-220.
19. Voipio SK, Komi J, Kangas L, Halonen K, DeGregorio MW, Erikkola RU. Effects of ospemifene (FC-1271a) on uterine endometrium, vaginal maturation index, and hormonal status in healthy postmenopausal women. Maturitas 2002;43:207-214.
20. Komi J, Lankinen KS, Harkonen P, et al. Effects of ospemifene and raloxifene on hormonal status, lipids, genital tract, and tolerability in postmenopausal women. Menopause 2005;12:202-209.
21. Bachmann GA, Komi J. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 2010;17:480-486.
22. Simon JA, Lin VH, Radoevich C, Bachmann GA; Group IOS. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013;20:418-427.
23. Portman D, Palacios S, Nappi RE, Mueck AO. 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. Maturitas 2014;78:91-98.
24. Portman DJ, Bachmann GA, Simon JA. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause* 2013;20:623-630.

25. Goldstein SR, Bachmann GA, Konincks PR, Lin VH, Portman DJ, Ylikorkala O. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. *Climacteric* 2014;17:173-182.

26. Qu Q, Harkonen PL, Vaananen HK. Comparative effects of estrogen and antiestrogens on differentiation of osteoblasts in mouse bone marrow culture. *J Cell Biochem* 1999;73:500-507.

27. Qu Q, Zheng H, Dahllund J, et al. Selective estrogenic effects of a novel triphenylethylene compound, FC1271a, on bone, cholesterol level, and reproductive tissues in intact and ovariectomized rats. *Endocrinology* 2000;141:809-820.

28. Michael H, Harkonen PL, Kangas L, Vaananen HK, Hentunen TA. Differential effects of selective oestrogen receptor modulators (SERMs) tamoxifen, ospemifene and raloxifene on human osteoclasts in vitro. *Br J Pharmacol* 2007;151:384-395.

29. Komi J, Heikkinen J, Rutanen EM, Halonen K, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women. *Gynecol Endocrinol* 2004;18:152-158.

30. Komi J, Lankinen KS, DeGregorio M, et al. Effects of ospemifene and raloxifene on biochemical markers of bone turnover in postmenopausal women. *J Bone Miner Res* 2006;21:314-318.

31. Taras TL, Wurz GT, DeGregorio MW. In vitro and in vivo biologic effects of ospemifene (FC-1271a) in breast cancer. *J Steroid Biochem Mol Biol* 2001;77:271-279.

32. Kangas L, Harkonen P, Vaananen K, Keskitalo J, Eigelien N. Effects of ospemifene on breast tissue morphology and proliferation: a comparative study versus other selective estrogen receptor modulators in ovariectomized rats. *Horm Metab Res* 2014;46:328-332.

33. Ylikorkala O, Cacciato A, Halonen K, et al. Effects of ospemifene, a novel SERM, on vascular markers and function in healthy, postmenopausal women. *Menopause* 2003;10:440-447.

34. Constantine G, Archer DF, Pollycove R, Jiang W, Altomare C, Pinkerton J. Effects of ospemifene on vasomotor symptoms in phase 2 and 3 clinical trials. *Menopause* 2016;23:957-964.

35. Danesh J, Lewington S, Thompson SG, et al. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 2005;294:1799-1809.

36. Miller PD, Chines AA, Christiansen C, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. *J Bone Miner Res* 2008;23:525-535.

37. Collins P, Mosca L, Geiger MJ, et al. Effects of the selective estrogen receptor modulator raloxifene on coronary outcomes in the raloxifene use for the Heart trial: results of subgroup analyses by age and other factors. *Circulation* 2009;119:922-930.

38. Christiansen C, Chensun Lii CH, Badi J, et al. Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled phase 3 study of postmenopausal women with osteoporosis. *BMC Musculoskelet Disord* 2010;11:130.

39. Anderson GL, Limacher M, Assaf AR, et al; Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women’s Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-1712.

40. Delmas PD, Bjarnason NH, Mittak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337:1641-1647.

41. Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998;279:1445-1451.

42. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;287:847-857.

43. Zegura B, Guzic-Salobir B, Sebestjen M, Keber I. The effect of various menopausal hormone therapies on markers of inflammation, coagulation, fibrinolysis, lipids, and lipoproteins in healthy postmenopausal women. *Menopause* 2006;13:643-650.

44. Mackie IJ, Kinchen S, Machin SJ, Lowe GD. Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. Guidelines on fibrinogen assays. *Br J Haematol* 2003;121:396-404.