

PLENARY SCIENTIFIC ABSTRACT SESSION #1

S-1.

The Effects of Bazedoxifene/Conjugated Estrogens on Breast Density in Postmenopausal Women

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Objective: Increased mammographic breast density may be a risk factor for breast cancer, but the etiology of this relationship is not well understood. Certain medications, including combined estrogen/progestin therapy, have been shown to increase breast density. Published phase 3 studies have demonstrated the efficacy and safety of bazedoxifene/conjugated estrogens (BZA/CE), a tissue selective estrogen complex (TSEC), in the treatment of menopausal symptoms and prevention of postmenopausal osteoporosis without an increase in breast pain or breast cancer. The effects of BZA/CE on breast density were evaluated in a substudy of the Selective Estrogens, Menopause, And Response to Therapy (SMART)-5 trial. **Design:** In this phase 3, double-blind, placebo (PBO)-controlled study of postmenopausal women with a uterus (N = 1,843), subjects were randomized to receive BZA 20 mg/CE 0.45 or 0.625 mg, BZA 20 mg, CE 0.45 mg/medroxyprogesterone acetate (MPA) 1.5 mg, or PBO daily for 12 months to evaluate efficacy and safety. A subset of these women met inclusion criteria and were enrolled in a breast density substudy. Breast density changes were assessed by digitized mammograms that were centrally read by a single radiologist using specifically developed software. Comparison of the adjusted mean difference in percent breast density at 12 months for each group versus PBO was based on a non-inferiority test with a pre-defined margin of 1.5%. **Results:** A total of 940 women (mean age \pm standard deviation (SD), 54.0 \pm 4.0 y; mean years since last menstrual period, 4.4 \pm 3.6 y) participated in the breast density substudy: BZA 20 mg/CE 0.45 mg (n = 231), BZA 20 mg/CE 0.625 mg (n = 247), BZA 20 mg (n = 122), CE 0.45 mg/MPA 1.5 mg (n = 100), or PBO (n = 240). At 12 months (Figure), BZA 20 mg/CE 0.45 and 0.625 mg demonstrated non-inferiority versus PBO (the upper bound of the 95% confidence interval [CI] was 0.51% and 0.44%, respectively). However, CE 0.45 mg/MPA 1.5 mg showed a significant increase in mean percent breast density at 12 months versus PBO (P < 0.001; upper bound of the 95% CI, 2.7%). **Conclusion:** Women treated with BZA 20 mg/CE 0.45 or 0.625 mg for 12 months showed no differences in breast density compared with those treated with PBO, suggesting a potential advantage of BZA/CE over conventional estrogen/progestin therapy.

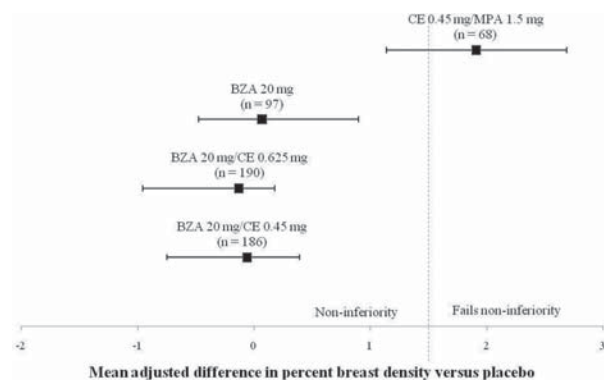


Figure. Mean Adjusted Difference (95% CI) in Percent Breast Density Versus Placebo at 12 Months.

S-2.

Effect of Estrogen and Hormone Therapy Withdrawal on Health and Quality of Life after Publication of The Women's Health Initiative in New York City

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Objective: Since July of 2002, when the results of the Women's Health Initiative (WHI) were published, a large number of women stopped hormone therapy (HT) due to concerns over risks of heart attacks and breast cancer(1). This sudden discontinuation of therapy is probably the largest single decrease of a medication over a short period of time in the history of American medicine. The initial drop in sales amounted to 33% and has continued at rate of approximately 6% a year(2,3). These events represent an unparalleled opportunity to answer questions of risk and benefit in women who initiated therapy at menopause and subsequently chose to stop therapy. Evidence exists that the hypoestrogenic menopausal state is associated with weight gain and changes in body composition. Such changes increase visceral fat and the secretion of inflammatory factors and predispose women to chronic diseases such as diabetes, heart disease and the metabolic syndrome. The time elapsed since 2002 presents an appropriate interval for observation of the consequences of this experience, as women who were in the 49-64 age

group when the results of WHI were announced are now 57-73 years of age and thus at greater risk for cardiovascular and other chronic disease. This group started HT at the normal age of menopause, unlike two thirds of the women in the WHI study(1). **Design:** The aim of this retrospective cohort study was to test differences in the incidence of obesity, hypertension, and hyperlipidemia, as well as the use of medications among women ages 57 to 73 who used HT for at least 5 years and subsequently stopped its use compared to those who continued HT use. The study also assessed quality of life and medical morbidity. The study enrolled women born between 4/1/1938 and 3/31/1953 who previously used HT for at least five years. Recruitment is ongoing; to date 250 women have been enrolled of which 209 are considered complete. Interviews and measurements were conducted at doctors' offices in the New York City area. Three groups were compared: women who have remained on HT ("Continued HT," n= 101), women who discontinued HT use for a minimum of 6 months and have since resumed HT ("Resumed HT", n=33), and women who discontinued HT and have not resumed its use ("Discontinued HT," n=75). **Results:** Of the women who discontinued HT, 67% cited adverse media as a reason for discontinuation, 29% cited a physician's recommendation, and 11% stated other reasons. The overall mean age at interview was 64.8 \pm 4.0 years. The Discontinued HT group was slightly older than the Continued HT group; 65.7 \pm 3.9 vs. 64.1 \pm 4.0 years (p<0.05) but similar to the Resumed HT group (65.1 \pm 4.0 years, n.s.). 95% were Caucasian, and 87% had a college education or greater. Patients started HT at 49.2 \pm 5.0 years. Mean weight was 63.2 \pm 11.2 kg and mean body mass index (BMI) was 23.8 \pm 4.2. No differences were noted between the groups with respect to weight, height, BMI, waist/hip ratio, blood pressure, triglycerides or cholesterol levels. Women on HT (Continued HT and Resumed HT) scored higher than the Discontinued HT group on the 115 point Utian Quality of Life scale (87.7 \pm 13.3 vs. 81.8 \pm 13.3, p<.01). In particular, women on HT scored higher than the Discontinued HT group on the 35 point occupational satisfaction scale subset (26.5 \pm 7.2 vs. 23.5 \pm 7.8, p<.02). The Discontinued HT group scored higher than those on HT with respect to the Greene climacteric vasomotor scale (1.2 \pm 1.4 vs. 0.7 \pm 1.1, p<.02). Vaginal dryness was also greater (1.9 \pm 1.1 vs. 1.4 \pm 0.6, p<.001). Finally, the Discontinued HT group was on significantly more antihypertensive medications (29.9% of the Discontinued HT group vs. 15.9% of Continued HT group and 6.5% of Resumed HT group). Combining the groups on HT, 13.8% of women currently on HT were on antihypertensive medications compared with 29.9% of women not on HT (p<.01). **Conclusion:** These results suggest that discontinuation of HT may place some women at risk for the development of hypertension, which may be an early indication of the metabolic syndrome and those remaining on HT score higher on scale of quality of life, particularly that which focuses on satisfaction with profession and occupation. REFERENCES: 1. Rossouw, JAMA 2002. 2. Grady, Obstet Gynecol 2003. 3. IMS Health, WSJ 2006

S-3.

Hot flashes and lipids in the Study of Women's Health Across the Nation

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Objective: Vasomotor symptoms, or hot flashes (HF) and night sweats (NS), reported by 75% of peri- and postmenopausal women, are thought to have quality of life, but few medical implications. However, recent findings link HF to cardiovascular disease (CVD) risk. The reasons for these associations are not fully understood, but evidence suggests that HF may be associated with an adverse lipid profile. Our aim was to examine the relations between HF and lipids, controlling for other CVD risk factors, estradiol (E2), and follicle stimulating hormone (FSH) over a 7 year period. **Design:** Participants were 3201 women ages 42-52 years at baseline in the Study of Women's Health Across the Nation (SWAN). Participants at entry completed interviews (HF and NS: none, 1-5, \geq 6 days in past 2 weeks; affect), physical measures (body mass index (BMI)), and a blood draw (low density lipoprotein (LDL), high density lipoprotein (HDL), apolipoprotein(a) (apo(a)), apolipoprotein(b) (apo(b)), lipoprotein(a) (Lp(a)), triglycerides, E2, FSH) at baseline and approximately yearly for 7 years thereafter. HF were examined in relation to each lipid with covariates age; site; race/ethnicity; education; BMI; menopausal status; parity; alcohol use; smoking; physical activity; diabetes status; diagnosed cardiovascular disease; depression/anxiety symptoms; and anti-hypertensive, anticoagulant, and lipid lowering medication use. E2 and FSH were added in separate steps. Data from visits with reported hormone therapy use were excluded. **Results:** In linear mixed models adjusted for all covariates except hormones, more frequent HF were significantly associated with higher levels of all of the lipids assessed except Lp(a): LDL [vs. no HF, 1-5 days: β (95%CI)=1.48(0.57-2.40, p=.002); \geq 6 days: B(95%CI)=2.13(0.91-3.35, p=.0006)], HDL [vs. no HF, 1-5 days: B(95%CI)=-30(-0.06-0.65, p=.10); \geq 6 days: B(95%CI)=-77(0.30-1.25, p=.001)], apo(a) [vs. no HF, 1-5 days: B(95%CI)=92(-0.01-1.85, p=.05); \geq 6 days: B(95%CI)=1.97(0.76-3.19, p=.002)], apo(b) [vs. no HF, 1-5 days: B(95%CI)=1.41(0.61-2.20, p=.0006); \geq 6 days: B(95%CI)=2.51(1.45-3.57, p<.0001)], and triglycerides [(vs. no HF, 1-5 days: % change (95%CI)=2.91(1.41-4.43, p=.0001); \geq 6 days: % change(95%CI)=5.90(3.86-7.97, p<.0001)]. These associations remained significant for LDL, HDL, apo(a), apo(b), and triglycerides after adjustment for E2, and for HDL, apo(a), apo(b), and triglycerides after adjustment for FSH. Findings for NS were consistent with those for HF. **Conclusion:** HF were associated with higher LDL, HDL, apo(a), apo(b), and triglycerides during a 7-year follow up period, controlling for CVD risk factors and E2 concentrations. Lipids should be considered in examining links between HF and CVD risk. SWAN has support from the NIH, DHHS, through NIA, NINR and NIH ORWH (NR004061; AG012505, AG012535, AG012531, AG012539,

AG012546, AG012553, AG012554, AG012495). The content of this abstract is solely the responsibility of the authors and does not necessarily represent the views of the NIA, NINR, ORWH or NIH.

S-4.

Does Route of Administration for Estrogen Hormone Therapy and Estradiol Transdermal System Dosage Strength Impact Risk of Venous Thromboembolism

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Objective: Hormone therapy (HT) is regularly used in the treatment of symptoms associated with menopause, such as hot flashes and vulvovaginal atrophy. Venous thromboembolism (VTE) is among the most serious complications associated with HT. A recent study has shown that transdermal estrogen administration was associated with a lower risk of VTE relative to oral estrogen administration. The objective of the current follow-up analysis was to evaluate the impact of high dose estradiol transdermal system (ETS; Vivelle-Dot®) on the risk of VTE events as compared to the use of oral estrogen-only HT agents. **Design:** A health insurance claims analysis was conducted using the Thomson Reuters MarketScan database from January 2002 through October 2009. Patients ≥35 years old with continuous insurance coverage, newly initiated on an ETS or oral estrogen-only HT with ≥2 dispensings were analyzed. VTE was defined as ≥1 diagnosis code for deep vein thrombosis (DVT; ICD-9 codes: 451.1x, 451.2, 453.4x, 453.8, 453.9) or pulmonary embolism (PE; ICD-9 codes: 415.1x). Patients with a prior history of VTE or using any estrogen HT agents within 180 days before the first ETS or oral estrogen-only HT drug dispensing were excluded. The study observation period started on the date of ETS or oral estrogen HT treatment initiation (index date) until 90 days following the index treatment interruption or discontinuation (i.e., continuous use of therapy). Cohorts of ETS and oral estrogen-only HT were matched 1:1 based on both exact factor and propensity score matching methods to ensure balanced patient characteristics at baseline. The incidence rates of VTE events were calculated as number of patients with an event divided by patient-years of observation, censored at the time of the first event. The incidence rate ratio (IRR), assessed through Poisson regression was used to compare the rates of VTE events for ETS relative to oral estrogen-only HT cohorts. ETS dosage strength ranged from 0.025 to 0.1 mg/day. To assess the impact of ETS dosage, IRRs of VTE were also reported for subgroups of women initiating high dose ETS based on two definitions: (i) 0.075 or 0.1 mg/day and (ii) 0.1 mg/day, relative to their corresponding matched oral estrogen-only HT users. **Results:** Among the 30,547 patients treated with ETS and 159,281 receiving oral estrogen-only HT, 27,018 ETS users and an equal number of oral estrogen-only HT users were matched to form the overall study population. The mean ages of the matched cohorts (SD) were 48.9 (7.1) years; in each cohort 6,044 (22.4%) and 1,788 (6.6%) patients had a hysterectomy and an oophorectomy at baseline, respectively. The mean (median) drug exposure for the ETS and oral estrogen-only HT cohorts was 391 (264) and 401 (272) days, respectively. Based on the matched analysis of the overall study population, a total of 115 ETS users developed VTE compared to 164 subjects in the oral estrogen-only HT cohort (IRR: 0.72; 95% CI: 0.57-0.91, P=0.006). Furthermore, the lower risk for VTE events associated with ETS relative to oral estrogen-only HT remained statistically significant in women initiating high dose ETS. In the matched cohorts of ETS and estrogen-only HT users where ETS was initiated at 0.075 or 0.1 mg/day (11,570 women in each cohort), 45 ETS users and 80 oral estrogen-only HT users developed VTE (IRR=0.58; 95% CI: 0.40-0.84, P=0.004), while in the matched cohorts where high dose ETS was defined as 0.1 mg/day (8,956 patients in each cohort), 32 ETS users and 65 oral estrogen-only HT users developed VTE (IRR=0.52; 95% CI: 0.34-0.80, P=0.003). **Conclusion:** This large population-based study of over 50,000 patients based on real-world data suggests that patients receiving ETS (Vivelle-Dot®) have significant lower incidence of VTE of approx 30% compared to patients receiving oral estrogen-only HT. Data from this study also showed that the lower risk for VTE associated with ETS remained significant in women initiating high dose ETS relative to matched oral estrogen-only HT women.

S-5.

Efficacy of a novel SERM, ospemifene, in the treatment of moderate-to-severe vaginal dryness symptoms of vulvovaginal atrophy associated with menopause

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Objective: Ospemifene, a novel, selective estrogen receptor modulator (SERM) that exerts estrogenic, pharmacologic activity in the vaginal epithelium, is presently being studied for treatment of symptoms of vulvovaginal atrophy (VVA) in postmenopausal women. This study assessed the efficacy, safety and tolerability of ospemifene 60 mg/d in the treatment of VVA symptoms. **Design:** A 12-wk, 1:1 randomized, double-blind, placebo-controlled, parallel-group study enrolling 919 postmenopausal women 40 to 80 years of age with VVA in two strata based on their self-reported most bothersome symptom (MBS) of vaginal dryness or vaginal pain (dyspareunia). Two study populations were analyzed: the intent-to-treat (ITT) (primary analysis) and per protocol (PP). Subjects

in each stratum were randomized to receive 60 mg/d ospemifene or placebo and were provided with a nonhormonal vaginal lubricant to use as needed (PRN). For each stratum, changes from baseline to Wk 12 (LOCF) for the four co-primary endpoints were assessed: vaginal pH, percentages of superficial cells and parabasal cells in the maturation index and the severity of the MBS. This abstract reports the Dryness Stratum results. **Results:** In the ITT analysis, at Wk 12 ospemifene demonstrated significant efficacy vs placebo for 3 of 4 co-primary endpoints from baseline. Significant mean changes from baseline to Wk 12 for vaginal pH and percentages of superficial (LS mean) and parabasal cells (Median) were evident (Table 1). Significant improvement was observed as early as 4 wks. Improved mean change was observed for the MBS vaginal dryness at Wk 12, which approached statistical significance (P=0.0803). A higher % of subjects treated with ospemifene reported no vaginal dryness, and the subjects' self-reported symptom severity, which was assessed on a 4-point scale improved by 2 to 3 points in 46.3% ospemifene vs 34.4% placebo subjects. The PP analysis showed statistically significant improvement for all 4 co-primary endpoints (pH, % superficial and % parabasal cells, all P<0.0001 and vaginal dryness, P=0.0143) and similar improvements in dryness severity. The main difference between the ITT and the PP populations was in study drug compliance, which was higher in the PP population. The numbers of subjects with ≥1 adverse event (AE) at Wk 12 in both strata combined is summarized in Table 2. Discontinuation rates were similar in the ospemifene (10.2%) and placebo (11.6%) groups. Endometrial histology assessments showed no cases of hyperplasia and 2 (1.0%) cases of active proliferation in the ospemifene group vs 0% in the placebo group. Vaginal bleeding was reported in 2 (0.4%) and 4 (0.9%) subjects in the ospemifene and placebo groups, respectively; 1 subject on ospemifene experienced deep vein thrombosis was discontinued from the study. There were no cases of myocardial infarction, breast cancer or death. **Conclusion:** In postmenopausal women with the self-reported MBS of vaginal dryness, these data demonstrate that treatment with ospemifene 60 mg/d provides clinically and statistically significant efficacy and was well tolerated. With greater improvement in symptom severity scale changes and in markers of vaginal health, this novel SERM may prove to be the first non-estrogen to effectively treat the symptoms of VVA.

Table 1 Change from BL to Wk 12 LOCF (ITT)*

Parameter	Ospemifene 60mg (n=160)	Placebo (n=154)	P-value
Vaginal pH (LS mean ± SE)	-0.95 ± 0.067	-0.25 ± 0.068	<0.0001
% Parabasal cells (LS mean ± SE)	-31.7 ± 2.11	-3.9 ± 2.18	<0.0001
% superficial cells (median [min, max])	7.0 (-4, 65)	0.0 (-11, 57)	<0.0001

* Similar results were reported for the PP analysis.

Table 2 Adverse Events

Subjects with ≥1 AE at wk 12 (ITT, combined strata)	Ospemifene 60mg (n=163)	Placebo (n=156)
TEAE, n (%)	200 (62.6)	232 (50.9)
AE causing discontinuation, n (%)	26 (5.6)	15 (3.3)
SAE, n (%)	6 (1.3)	7 (1.5)

S-6.

Vasomotor Symptoms in Premenopausal Women by Race: the LEAVES Study

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Objective: Prevalence of vasomotor symptoms among women over age 45 who report regular periods have not been well described. Prevalence variability by race/ethnicity is expected. **Design:** We performed a population-based mailed survey of 18,500 women, ages 45-58, enrolled at Group Health Cooperative in Washington State, identified from automated databases as not using hormones (50% response rate). The purpose of this analysis was to describe self-reported hot flashes and night sweats, by race/ethnicity among all premenopausal women surveyed who reported regular menses. We excluded women who had had a bilateral salpingo-oophorectomy. Generalized linear models were used to calculate differences in vasomotor symptoms by race, adjusted for age (*P<0.05; †P<0.001). **Results:** There were 1,575 premenopausal women who responded to the survey, 73% were white, the mean age was 48.5±2.5 years, 32% reported ever having hot flashes and 48% reported ever having night sweats. Premenopausal native Hawaiians/Pacific Islanders were most likely to report ever having hot flashes (46%), followed by African American women (39%), American Indian (38%), Hispanic nonwhite (37%), white (34%), Filipino (30%), Vietnamese (29%), Japanese (26%), Asian Indian (22%), Chinese (19%), and Hispanic white (18%). Controlling for age, Chinese women were 11% less likely to have ever had hot flashes as compared with white women (P<0.01). Premenopausal American Indian women were most likely to report ever having night sweats (62%), follow by African American (61%), white (51%), Hawaiian/Pacific Islanders (46%), Hispanic nonwhite (41%), Hispanic white (35%), Japanese* and Asian Indian (33%), Filipino* (30%), and Chinese† and Vietnamese* (24%). **Conclusion:** Among women over age 45, who were most likely in the early to mid transition, Asian women were least likely to report having hot flashes and night sweats. African-American reported hot flashes and night sweats more commonly than white or Asian women.