Randomized, multicenter, double-blind, placebo-controlled trial to evaluate the efficacy and safety of synthetic conjugated estrogens B for the treatment of vulvovaginal atrophy in healthy postmenopausal women

James A. Simon, M.D.,[a] *Kathleen Z. Reape, M.D.,*[b] *Steve Wininger, M.D.,*[c] *and Howard Hait, M.S.*[b]

[a] Obstetrics and Gynecology, George Washington University School of Medicine and Health Sciences, Washington, District of Columbia; [b] Duramed Research, Inc., Bala Cynwyd, Pennsylvania; and [c] The Arizona Wellness Center for Women, Phoenix, Arizona

Objective: To evaluate the safety and efficacy of synthetic conjugated estrogens B (SCE-B; 0.3 mg/d) for 12 weeks in the treatment of vulvovaginal atrophy in symptomatic, postmenopausal women.
Design: Prospective, randomized, multicenter, double-blind, placebo-controlled trial.
Setting: Forty-two participating sites in the United States.
Patient(s): Postmenopausal women with at least one moderate to severe symptom of vaginal atrophy.
Intervention(s): Daily oral administration, in a randomized, placebo-controlled setting, of SCE-B (0.3 mg) or of placebo for 12 weeks.
Main Outcome Measure(s): Mean changes in vaginal maturation index, percentage of parabasal and superficial cells, vaginal pH, and severity of the most bothersome symptom (MBS) between baseline and predetermined time points were assessed. Safety and tolerability were evaluated.
Result(s): A total of 310 women (mean age, 58.6 y) were enrolled. Synthetic conjugated estrogens B yielded statistically significantly greater differences in vaginal maturation index and vaginal pH from baseline to the end of treatment. Vaginal dryness (44.4%) and pain during intercourse (30.2%) were the symptoms most commonly identified as the MBS. A statistically significant mean reduction in the severity of the MBS was noted for SCE-B. There were no clinically significant differences observed between the two groups for findings related to safety.
Conclusion(s): Synthetic conjugated estrogens B (0.3 mg/d) was effective in treating vulvovaginal atrophy in symptomatic postmenopausal women. Significant improvement was seen in vaginal maturation index, vaginal pH, and severity of MBS from baseline to the end of treatment. (Fertil Steril® 2008;90:1132–8. ©2008 by American Society for Reproductive Medicine.)

Key Words: SCE-B, synthetic conjugated estrogens, vulvovaginal atrophy, postmenopausal, vaginal dryness, dyspareunia, most bothersome symptom (MBS)

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Reprint requests: James A. Simon, M.D., C.C.D., Women's Health and Research Consultants, 1850 M Street, NW, Suite 450, Washington, DC 20036 (FAX: 202-463-6150; E-mail: simon@jamesasimonmd.com).

The declining levels of estrogen seen in postmenopausal women are associated with profound changes in the genitourinary tract, and about 40% of women have symptoms associated with these changes (1). The vaginal mucosa and vulvar skin become thinner; the labia flatten, shrink, and lose their hair; and the clitoris decreases in size (2). Vaginal pH increases from the normal range of 3.5–5.0 (which favors lactobacilli) to a range of 6.0–8.0 (which favors pathogenic organisms, including yeast and bacteria). The vaginal epithelium becomes dry, atrophic, and more prone to inflammation, with decreased elasticity and distensibility, resulting in discomfort, itching, and pain with intercourse. Cytologic examination of vaginal mucosa shows an increased proportion of parabasal cells and a decreased proportion of superficial cells (3).

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Estrogen or hormone therapy, in various forms, is an effective treatment for postmenopausal women with vulvovaginal atrophy (4, 5). Estrogen has been shown to revascularize and thicken the vaginal epithelium. This results in a decrease in vaginal pH, normalization of flora, and restoration of vaginal epithelial integrity with an increase in the percentage of superficial cells (6).

Synthetic conjugated estrogens B (SCE-B; Enjuvia; Duramed Pharmaceuticals, Inc., Pomona, NY) contains all 10 essential estrogenic components found in conjugated equine estrogens, including $\Delta^{8,9}$ dehydroestrone sulfate, which has been shown to have unique properties that may contribute to the overall biologic effects. Synthetic conjugated estrogens B, in a range of doses (0.3, 0.625, and 1.25 mg), has been shown to effectively and significantly reduce the frequency and severity of moderate to severe vasomotor symptoms associated with the menopause (7). This study was designed to evaluate the safety and efficacy of low-dose daily oral treatment with SCE-B (0.3 mg) compared with placebo for the treatment of moderate to severe symptoms of vulvovaginal atrophy that is associated with menopause.

MATERIALS AND METHODS

Study Design and Subjects

This was a double-blind, randomized, placebo-controlled, multicenter study conducted at 42 participating sites in the United States. It was designed to evaluate the safety and efficacy of SCE-B (0.3 mg) in postmenopausal women with symptoms of vulvovaginal atrophy. Before any study-related information was obtained, each patient provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and applicable guidelines for Good Clinical Practice; institutional review board approval was obtained at each participating site.

Randomization was performed sequentially, stratified by study site, in blocks of four, with equal allocation of patients to SCE-B or placebo in each block. Inclusion criteria were consistent with the January 2003 US Food and Drug Administration Draft Guidance for Industry for Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms (8). Participants had to be surgically or naturally postmenopausal, defined as [1] $\geq$12 months of spontaneous amenorrhea; [2] $\geq$6 weeks post-surgical bilateral oophorectomy, with or without hysterectomy; [3] 6 months of spontaneous amenorrhea with a serum FSH level of $>$40 mIU/mL; or [4] for hysterectomized patients without bilateral oophorectomy, serum FSH of $>$40 mIU/mL as well as an E_2 level of $<$20 pg/mL. Eligible patients also had to have a vaginal pH of $>$5.0 and $\leq$5% superficial cells on lateral vaginal wall smear at baseline. Patients who were on hormone therapy at the time of screening underwent a washout period of 1 to 6 months, depending on the product being used. A normal mammogram and endometrial biopsy also were required.

Study Procedures

After a screening phase of $\leq$4 weeks, there was a randomization (or baseline) visit and a 12-week double-blind treatment period. During the treatment period, patients were monitored at clinic visits on weeks 2, 3, 4, 8, and 12. A lateral wall smear to calculate the vaginal pH (using standardized pH paper) and vaginal maturation index (VMI, a measure of the estrogenic effect on the vaginal mucosa) were obtained at each visit. Vaginal maturation index was calculated using the following formula: VMI = (% parabasal cells $\times$ 0) + (% intermediate cells $\times$ 0.5) + (% superficial cells $\times$ 1.0). In addition, the investigator conducted a clinical assessment of vaginal atrophy at each visit.

Patients completed a self-assessment questionnaire of vaginal atrophy symptoms at all study visits, which consisted of questions about the severity of each of six individual symptoms of vulvovaginal atrophy. The symptoms evaluated were vaginal dryness (decreased vaginal lubrication, secretions, fluid, or mucus), vaginal irritation or itching, vaginal soreness, difficulty passing urine (such as sensations of burning, stinging, discomfort, or pain during urination and/or excessive sense of urgency or need to void), pain during intercourse (dyspareunia), and bleeding after intercourse. Symptoms could be ranked on a scale of 0–3 (none, mild, moderate, or severe). In addition, the symptoms related to sexual intercourse (pain during intercourse and bleeding after intercourse) could be rated as "not applicable" if the patient was not having intercourse. Each patient had to have at least one symptom that was moderate to severe in intensity at baseline to be enrolled in the study. Patients then were asked to indicate the one most bothersome symptom (MBS). The symptom selected as most bothersome had to be moderate or severe in intensity.

The investigators also rated the following seven clinical signs of vaginal atrophy at all study visits: vaginal color, vaginal dryness, vaginal rugosity, blanching of tissue, vaginal tissue integrity and friability, vaginal tissue petechiae, and overall vaginal atrophy. The investigator assessments were made by using the same 0–3 rating scale (0, none; 1, mild; 2, moderate; and 3, severe) that was used for the patient self-assessment of symptoms.

Adverse events, use of concomitant medications, and compliance with study medication were assessed at each study visit. Physical exams and standard clinical laboratory assessments (chemistry, hematology, lipids, coagulation tests) were performed at baseline and at the end of the study on all patients. A transvaginal ultrasound and endometrial biopsy were performed at the baseline and final visits on all patients who had a uterus, and these patients were provided with a 14-day course of micronized P (Prometrium; Solvay Pharmaceuticals Inc., Marietta, GA) or medroxyprogesterone acetate (for those with peanut allergy), to be taken after the last dose of study medication.

Analyses

The primary efficacy analysis consisted of the change from baseline to the end of treatment for each of the following three co-primary endpoints: [1] VMI (with additional analysis of superficial cells and parabasal cells), [2] vaginal pH, and [3] severity of the MBS.