

Novel SERM Tested in Vulvovaginal Atrophy

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NATIONAL HARBOR, MD. – A novel selective estrogen-receptor modulator called ospemifene was more effective than placebo for reducing symptoms of vaginal dryness and dyspareunia in a study of 919 postmenopausal women.

Only estrogen-based treatments have been approved in the United States to treat vulvovaginal atrophy (VVA) in postmenopausal women, but concerns about the effects of estrogen on breast and endometrial tissue have prompted doctors and patients to seek alternatives, said Dr. David Portman of the Columbus (Ohio) Center for Women's Health Research.

'We do need to find alternatives because many of our patients still have concerns even with local estrogen' to treat vulvovaginal atrophy.

"We do need to find alternatives because many of our patients still have concerns even with local estrogen," he emphasized.

Ospemifene (OSP), a selective estrogen-receptor modulator (SERM) – also referred to as a nonsteroidal estrogen-receptor agonist/antagonist – is distinct from other SERMs because its estrogenic activity occurs on the vaginal epithelium, "but not on the endometrium," said Dr. Portman.

Previous studies have shown that ospemifene is well tolerated, with a favorable pharmacologic profile in postmenopausal women with VVA, he added.

In a 12-week randomized, double-blind, placebo-controlled, phase III parallel group study, Dr. Portman and his colleagues assessed the efficacy, safety, and tolerability of ospemifene for women with moderate to severe vaginal dryness or moderate to severe dyspareunia.

Dyspareunia symptoms and severity were self-reported, and use of a non-hormonal vaginal lubricant was permitted as needed.

Demographic characteristics were similar between the two groups.

The women ranged from 40 to 80 years of age at baseline.

Those with a body mass index of 37 kg/m² or greater were excluded, as were those with clinically significant abnormal gynecologic findings other than vaginal atrophy and those using hormonal medications or other products with possible estrogenic or antiestrogenic effects within a timeframe too close to the study screening.

A total of 314 postmenopausal women who reported vaginal dryness

VITALS

Major Finding: In an intent-to-treat population, the change in the vaginal dryness severity score improved in the OSP group vs. the placebo group (–1.3 vs. –1.1).

Data Source: A 12-week study of 314 postmenopausal women who had vaginal dryness and were randomized to 60 mg of OSP orally each morning or a placebo.

Disclosures: The study was sponsored in part by Shionogi, which developed and markets ospemifene, and several coinvestigators were Shionogi employees. Dr. Portman has received consulting fees, honoraria, and/or grant support from multiple companies including Shionogi, Bayer, Boehringer Ingelheim, Teva, Warner Chilcott, and Watson Pharmaceuticals.

as their primary symptom were randomized to 60 mg of OSP orally each morning or a placebo, the researchers

said.

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score improved in the OSP group vs. the placebo group (–1.3 vs. –1.1).

In addition, the percentages of

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†This encompasses 85% of US household incomes. Source: 2009 US census data.

References: 1. Facts About Current Good Manufacturing Practices (cGMPs). Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm>. Accessed July 22, 2011. 2. CFR - Code of Federal Regulations Title 21. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21.4.0.1.1.11.6>. Accessed July 22, 2011.

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Please see next page for important safety information.

superficial and parabasal cells were significantly different in the OSP group vs. the placebo group (12% vs. 3% and -32% vs. -4%, respectively).

Measuring these types of cells indicates changes in the vaginal microflora, which have been shown to affect vaginal dryness and pain.

The mean change in vaginal pH was -1.01 in the OSP group, compared with -0.25 in the placebo group, respectively.

An additional 605 women who reported dyspareunia as their primary symptom were randomized to 60 mg

OSP orally each morning or a placebo.

In the intent-to-treat population, the change in the dyspareunia severity score improved in the OSP group vs. the placebo group (-1.5 vs. -1.2, $P = .0001$), a significant difference.

In addition, the percentages of superficial cells and parabasal cells were significantly different in the OSP vs. the placebo groups (12% vs. 2% and -40% vs. 0%, respectively).

The mean change in vaginal pH also differed significantly between the OSP and placebo groups (-1.0 vs. -0.06, respectively).

Overall, ospemifene had "a very clean safety profile," Dr. Portman said.

The total number of treatment-emergent adverse events was not significantly different between the OSP and placebo groups (290 vs. 232).

A total of 122 treatment-related adverse events occurred in the OSP group, compared with 62 in the placebo group.

The number of serious adverse events and severe adverse events were similar between the groups (6 vs. 7 and 28 vs. 29, respectively).

The most common treatment-emer-

gent adverse events in the OSP group were urinary tract infection (8%), hot flashes (7%), and vaginal discharge (5%).

No deaths, myocardial infarctions, and/or breast cancer cases were reported in any of the patients during the study period.

While the drug is not yet approved for VVA, "this investigational SERM has the potential to be an efficacious, nonestrogen oral prescription therapy for this prevalent, bothersome, and undertreated condition," according to Dr. Portman. ■

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Important safety information for Makena

- Makena should not be used in women with any of the following conditions:
 - Current or history of thrombosis or thromboembolic disorders
 - Known or suspected breast cancer, other hormone-sensitive cancer or history of these conditions
 - Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
 - Cholestatic jaundice of pregnancy
 - Liver tumors, benign or malignant, or active liver disease
 - Uncontrolled hypertension
- Makena should be discontinued if thrombosis or thromboembolism occurs
- Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil
- Women receiving Makena should be monitored if they:
 - Are prediabetic or diabetic
 - Have conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction
 - Have a history of clinical depression; Makena should be discontinued if depression recurs
 - Develop jaundice; consider whether benefit of use warrants continuation
 - Develop hypertension
- Certain pregnancy-related fetal and maternal complications or events were numerically increased in Makena-treated subjects as compared to placebo subjects, including miscarriage (2.4% vs. 0%) and stillbirth (2% vs. 1.3%), admission for preterm labor (16% vs. 13.8%), preeclampsia or gestational hypertension (8.8% vs. 4.6%), gestational diabetes (5.6% vs. 4.6%), and oligohydramnios (3.6% vs. 1.3%)
- The most common adverse reactions reported in ≥2% of subjects and at a higher rate in the Makena group than in the control group were injection site reactions (pain [35% vs. 33%], swelling [17% vs. 8%], pruritus [6% vs. 3%], and nodule [5% vs. 2%]), urticaria (12% vs. 11%), pruritus (8% vs. 6%), nausea (6% vs. 5%), and diarrhea (2% vs. 1%)

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