

# BREEZE 2: Gabapentin-ER Tamed Hot Flashes

BY RICHARD HYER

FROM THE ANNUAL MEETING OF  
THE NORTH AMERICAN MENOPAUSE SOCIETY

CHICAGO – An extended-release formulation of gabapentin for hot flashes showed the potential both to minimize peak adverse events and to allow for less frequent dosing in a randomized, controlled trial of 565 women, said Dr. Wulf Utian.

“The results of the BREEZE 2 study suggest that gabapentin-extended release 1,800 mg/day may be effective and well tolerated for the treatment of moderate to severe hot flashes in postmenopausal women,” he noted at the meeting.

Gabapentin-ER releases over 8 hours, potentially minimizing peak adverse events and allowing once daily or twice daily dosing, said Dr. Utian, the Arthur H. Bill Professor Emeritus of Reproductive Biology and Obstetrics and Gynecology at Case Western Reserve University in Cleveland.

Gabapentin is an anticonvulsant that is also used to relieve nerve-related pain.

BREEZE 2 is a prospective, multicenter, randomized, double-blind, placebo-controlled study in postmenopausal women aged 18-70 years at 45 sites across the United States.

The study had two active arms: gabapentin-ER 1,200 mg given once daily, and 1,800 mg given as 600 mg in the morning and 1,200 in the evening. Efficacy was assessed at 4 and 12 weeks, and the treatment duration was 3 months.

The primary efficacy end points were reductions in the mean frequency of moderate to severe hot flash-

es and the average severity of hot flashes.

The trial’s secondary end points were the proportion of patients categorized as “much improved” or “very much improved” at 12 weeks in the self-reported Patient Global Impression of Change scale. Investigators also recorded their impression of the results of the therapy using the Clinician Global Impression of Change scale.

Postmenopausal women who had been experiencing seven or more moderate to severe hot flashes per day (or at least 50 per week), accompanied by sweating during at least the previous 30 days, were the trial population.

Baseline characteristics were similar across the three groups. In the 1,800-mg group, for example, the average age was 54 years, the women were 71% white, and the average body mass index was less than 30 kg/m<sup>2</sup>.

Data were subjected to both parametric and nonparametric analysis, said Dr. Utian, because parametric analyses can be influenced by outliers.

At 4 weeks and 12 weeks, changes in the mean severity of moderate and severe hot flashes were -0.6 and -0.8 for 1,800-mg group, compared with the placebo group; both were significant differences.

More than 60% of patients in both active treatment

groups and more than 40% in the placebo group self-reported and were clinician reported as “very much improved” at 12 weeks. “This was a particularly high placebo response,” said Dr. Utian.

Nonparametric analysis showed a statistically significant change in median frequency of moderate to severe hot flashes at 4 weeks and 12 weeks in both active

groups, compared with the placebo group.

Dizziness was the most commonly reported adverse event in both the 1,800-mg and 1,200-mg groups, whereas headache was most commonly reported in the placebo group.

Somnolence was the second most common complaint in the active treatment groups.

A total of 48 patients across both active treatment groups discontinued because of adverse events.

“Essentially, this long-release product was well tolerated, adverse events were mild, the difference was a slight difference in dizziness and somnolence during the titration, and [there was] no real difference in the adverse events” between the 1,800-mg and the 1,200-mg dosing regimens, said Dr. Utian.

“The incidence of the adverse events declined markedly after 2-4 weeks of study therapy,” he added. ■

## VITALS

**Major Finding:** Gabapentin-ER 1,800 mg/day may be effective and well tolerated for the treatment of moderate to severe hot flashes in postmenopausal women.

**Data Source:** BREEZE 2 trial database of 565 postmenopausal women with moderate to severe hot flashes who were randomized to gabapentin-ER in two active arms (1,800 mg or 1,200 mg) or placebo for 13 weeks in this phase III, double-blind, placebo-controlled, randomized trial.

**Disclosures:** The trial was sponsored by Depomed Inc., maker of gabapentin-ER. Dr. Utian is a consultant to Depomed. Some of the study investigators are Depomed employees.

# Tissue-Selective Estrogen Complex Shows Metabolic Benefits

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF  
THE AMERICAN SOCIETY FOR  
REPRODUCTIVE MEDICINE

DENVER – A novel oral, once-daily, tissue-selective estrogen complex designed to treat postmenopausal symptoms more safely than traditional estrogen/progestin hormone therapy achieved an overall favorable effect on metabolic parameters in a large phase III clinical trial.

The combination of the selective estrogen receptor modulator (SERM) bazedoxifene and conjugated estrogens produced “very favorable” changes in lipid profiles and no clinically meaningful effects on coagulation parameters, fibrinolytic activity, or carbohy-

drate metabolism in the phase III SMART-1 trial, Dr. Hugh S. Taylor reported at the meeting.

The concept underlying the tissue-selective estrogen complex (TSEC) is that the SERM will serve as an antagonist to estrogen’s adverse effects on the uterus and breast without interfering with its favorable CNS effects on vasomotor symptoms, explained Dr. Taylor of Yale University, New Haven, Conn.

The Selective Estrogens, Menopause, and Response to Therapy (SMART-1) trial was a 2-year, double-blind, multicenter, placebo- and active comparator-controlled study involving 7,492 postmenopausal women aged 40-72 years with an intact uterus and acceptable baseline endometrial biopsy results. They were randomized to one of eight

treatment arms: bazedoxifene at 10, 20, or 40 mg, each combined with conjugated estrogens at 0.45 or 0.625 mg; raloxifene at 60 mg/day; or placebo.

There are three large randomized SMART trials in the bazedoxifene/conjugated estrogens development program. Prior reports from SMART-1 showed that the TSEC significantly increased bone mineral density while reducing hot flashes and vulvar/vaginal symptoms compared with placebo (Fertil. Steril. 2009; 92:1045-52 and 1025-38). TSEC

also was associated with low rates of endometrial hyperplasia and cumulative amenorrhea rates comparable to those with placebo (Fertil. Steril. 2009;92:1018-24 and 1039-44). In the overall SMART series, the thrombotic event rate in



**The fly in the lipid ointment was the 23% increase in triglyceride levels in the Aprela group.**

DR. TAYLOR

TSEC-treated patients was similar to that of estrogen alone. In other words, there was no synergistic effect on clotting events with the combined therapy. The TSEC had no effect on blood pressure, Dr. Taylor continued.

At the meeting, he presented for the first time the results of the SMART-1 metabolic substudy. Metabolic end points take on particular importance because menopause is often associated with unfavorable effects on the metabolic profile. Dr. Taylor focused on the subset of women treated with bazedoxifene 20 mg/conjugated estrogens 0.45 mg because that’s the regimen going forward in development under the trade name Aprela.

The metabolic substudy included 111 women randomized to Aprela and 108 on placebo. All were 1-5 years post-

menopausal, with an average of 3 years since their last menstrual period.

Patients who took Aprela had a mean 11% reduction in LDL cholesterol over a 2-year period compared with baseline, a significantly greater change than with placebo.

Other significant lipid changes in the Aprela group included a 4% decrease in total cholesterol, an 11% increase in HDL cholesterol level, a 28% rise in the cardioprotective HDL<sub>2</sub> subfraction, an 11% increase in apolipoprotein A-I, and a 19% drop in lipoprotein (a). Most of these favorable changes were significantly greater than with placebo at all time points in the study, with testing done at 6, 12, 18, and 24 months.

The fly in the lipid ointment was the 23% increase in triglyceride levels in the Aprela group, which was significantly greater than the 6% increase in the placebo arm. Most hormonal therapies have this unwelcome effect of boosting triglycerides, Dr. Taylor observed.

In terms of coagulation parameters, the Aprela group showed favorable changes in fibrinogen, antithrombin III activity, and plasminogen activator inhibitor-1 activity that were statistically significantly greater than with placebo, but small in size and not clinically meaningful. Fasting insulin, fasting glucose, plasma homocysteine, C-reactive protein, and thyroid-stimulating hormone levels were unaffected by Aprela, he said. ■

## VITALS

**Major Finding:** Patients who took bazedoxifene plus a conjugated estrogen had a mean 11% reduction in LDL cholesterol level over 2 years compared with baseline, a significantly greater change than with placebo. Other significant lipid changes in the Aprela group included a 4% decrease in total cholesterol and an 11% increase in HDL cholesterol.

**Data Source:** SMART-1 metabolic substudy including 111 women randomized to bazedoxifene and Aprela and 108 to placebo.

**Disclosures:** The SMART-1 trial was funded by Wyeth, which has been acquired by Pfizer. Dr. Taylor declared that he has received research grants from and has been on the speakers bureau for the companies.