The Effect of Conjugated Estrogens/Bazedoxifene on Body Weight in Postmenopausal Women

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*Dr Mirkin was an employee of Pfizer at the time of this analysis.

INTRODUCTION

• A commonly held misperception that hormone therapy can cause weight gain contributes to some women’s hesitation about its use—often imaging the process greater than the actual weight change.

• There is currently no clinical evidence that hormone therapy-induced weight gain and some women believe that weight gain may even promote estrogenic risk factors. The view is a widespread one that has contributed to the belief that hormone therapy use leads to postmenopausal weight gain, and some studies support this view.

• A recent meta-analysis that pooled data from clinical trials of up to 2 years of use found that conjugated estrogens alone (0.625 mg) modestly increased postmenopausal body weight in women with a uterus in clinical trials of up to 2 years of use—often imaging the process greater than the actual weight change.

• The primary endpoints in the current sample were on-treatment change from baseline in body weight and BMI (kg/m²) and BMI categories.

• We believe that hormone therapy use is associated with weight gain, and some women believe that weight gain may even promote estrogenic risk factors. The view is a widespread one that has contributed to the belief that hormone therapy use leads to postmenopausal weight gain, and some studies support this view.

RESULTS

Table 1. Study Designs of the SMART Trials

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Duration</th>
<th>Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART-1 (N=1607)</td>
<td>12 weeks</td>
<td>Aged 40 to 65 years, postmenopausal, ≥1 moderate to severe daily hot flushes, baseline BMI ≥20 kg/m², and ≥5 years since menopause.</td>
</tr>
<tr>
<td>SMART-2 (N=1256)</td>
<td>1 year (extension)</td>
<td>Aged 40 to 65 years, postmenopausal, ≥1 moderate to severe daily hot flushes, baseline BMI ≥20 kg/m², and ≥5 years since menopause.</td>
</tr>
</tbody>
</table>

Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Years since menopause</th>
<th>BMI (kg/m²)</th>
<th>Average hot flush severity</th>
<th>Average hot flush frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE/BZA 0.45 mg/BZA 20 mg</td>
<td>56.2</td>
<td>6.8</td>
<td>26.0</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>CE/BZA 0.625 mg/BZA 20 mg</td>
<td>56.1</td>
<td>6.9</td>
<td>26.0</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>PBO</td>
<td>56.0</td>
<td>6.9</td>
<td>26.0</td>
<td>2.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table 3. Changes in Body Weight and BMI

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in Body Weight (kg)</th>
<th>Change in BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE/BZA 0.45 mg/BZA 20 mg</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>CE/BZA 0.625 mg/BZA 20 mg</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>PBO</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Daily treatment with conjugated estrogens for up to 2 years was not associated with clinically meaningful changes in body weight, BMI, or BMD in this group of postmenopausal women (SMART trials).

• There are no data to support the belief that hormone therapy use leads to postmenopausal weight gain, and some studies support this view.

• The view is a widespread one that has contributed to the belief that hormone therapy use leads to postmenopausal weight gain, and some studies support this view.

• As an exploratory analysis, the interaction between treatment effects on hot flush severity and frequency and subjects’ baseline BMI categories (World Health Organization classification

Figure 1. Adjusted Mean Change From Baseline in (A) Body Weight and (B) Body Mass Index (BMI) Over Time

BMI Category: Underweight, Normal, Overweight, Obese

Figure 2. Shifts in Body Mass Index (BMI) Category From Baseline to Follow-up. The Follow-up BMI Category Was Based on the Visit at the End of the Last Month of Treatment

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ACKNOWLEDGMENTS

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1University of Manitoba, Winnipeg, Manitoba, Canada; 2Pfizer Inc, New York, NY, United States; 3Pfizer Inc, Groton, CT, United States; 4Pfizer Inc, Quakertown, PA, United States; 5Pfizer Canada Inc, Kirkland, QC, Canada

4Dr Mirkin was an employee of Pfizer at the time of this analysis.

Presented at the Annual Meeting of the North American Menopause Society; October 15–18, 2014; National Harbor, MD.
**INTRODUCTION**

- A commonly held misperception that hormone therapy can cause weight gain contributes to some women’s hesitation about its use,\(^2\) despite its proven benefits.\(^3\)
  - There is currently no clinical evidence that hormone therapy use leads to postmenopausal weight gain, and some studies suggest it may even prevent it.\(^4\)
- A new menopausal therapy that purposefully pairs conjugated estrogens (CE) with the selective estrogen receptor modulator (SERM) bazedoxifene (BZA) was evaluated in five phase 3 studies known as the Selective estrogens, Menopause And Response to Therapy (SMART) trials.\(^5\)\(^-\)\(^12\)
  - CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg reduced moderate to severe vasomotor symptoms and vulvar-vaginal atrophy (VA), and also preserved bone mass, without increasing breast density or uterine hyperplasia in postmenopausal women with a uterus in clinical trials of up to 2 years of use.\(^6\)\(^-\)\(^9\)
- The objective of these pooled analyses was to evaluate the effect of CE/BZA on body weight and body mass index (BMI) in postmenopausal women in the SMART trials.

**METHODS**

- Data were pooled from five randomized, double-blind, placebo (PBO)- and active-controlled studies in nonhysterectomized postmenopausal women aged 40 to 75 who received CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, or PBO for up to 2 years (Table 1).\(^8\)\(^-\)\(^12\)

<table>
<thead>
<tr>
<th>Table 1. Study Designs of the SMART Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART-1(^8)</td>
</tr>
<tr>
<td>N(^*)</td>
</tr>
<tr>
<td>Key eligibility criteria</td>
</tr>
<tr>
<td>Age at baseline</td>
</tr>
<tr>
<td>BMI, body mass index</td>
</tr>
<tr>
<td>Primary end points</td>
</tr>
<tr>
<td>BMD, bone mineral density; BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; PBO, placebo; SMART, Selective Estrogens, Menopause And Response to Therapy; VVA, vulvar-vaginal atrophy.</td>
</tr>
</tbody>
</table>

\(^*\)Number of participants who were randomized and received ≥1 dose of study medication (valid population).

- The primary end points in the current analysis were on-treatment change from baseline in body weight and BMI (kg/m\(^2\)), and BMI category
  - BMI categories (World Health Organization classification\(^14\)): underweight BMI <18.5 kg/m\(^2\), normal 18.5 to <25 kg/m\(^2\), overweight 25 to <30 kg/m\(^2\), and obese ≥30 kg/m\(^2\)
- Change in body weight over time was analyzed by mixed model repeated measures (MMRM) with study, month, treatment group, month by treatment group interaction, and baseline body weight included in the model
- A categorical longitudinal model was used to analyze change in BMI category
- As an exploratory analysis, the interaction between treatment effects on hot flush severity and frequency and subjects’ baseline body weight and BMI was evaluated
  - Only SMART-1 and SMART-2 contributed hot flush frequency and severity data
  - Number and severity of hot flushes over time were analyzed by MMRM with study, month, treatment group, month by treatment group interaction, and baseline body weight tertile and BMI included in the model
  - Treatment effect modification by baseline weight/BMI was tested (significance level α=0.15)
**RESULTS**

**Subjects and Baseline Characteristics**

- There were 4461 women randomly assigned to CE 0.45 mg/BZA 20 mg (n=1607), CE 0.625 mg/BZA 20 mg (n=1598), or PBO (n=1256) in the five SMART trials.
- Baseline characteristics were balanced between treatment groups except for a significantly higher percentage of women with menopause onset within 5 years in the CE 0.625 mg/BZA 20 mg group (Table 2), which was not adjusted for in the pre-specified model.
- Of the randomized participants, 4006 (89.8%) had baseline and follow-up body weight data available (CE 0.45 mg/BZA 20 mg, n=1444; CE 0.625 mg/BZA 20 mg, n=1439; PBO, n=1123); there were no imputations for missing data.

**Table 2. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CE 0.45 mg/BZA 20 mg (N=1607)</th>
<th>CE 0.625 mg/BZA 20 mg (N=1598)</th>
<th>PBO (N=1256)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since menopause, least squares mean (95% CI)</td>
<td>6.3 (6.1–6.5)</td>
<td>5.9 (5.7–6.2)</td>
<td>6.3 (6.0–6.6)</td>
<td>0.056</td>
</tr>
<tr>
<td>Range, y</td>
<td>0.01–30.8</td>
<td>0.5–31.7</td>
<td>0.5–35.1</td>
<td></td>
</tr>
<tr>
<td>&lt;5 years, n (%)</td>
<td>854 (53.2)</td>
<td>914 (57.2)</td>
<td>663 (52.8)</td>
<td>0.027</td>
</tr>
<tr>
<td>≥5 years, n (%)</td>
<td>751 (46.8)</td>
<td>684 (42.8)</td>
<td>593 (47.2)</td>
<td></td>
</tr>
<tr>
<td>BMI, least squares mean (95% CI) kg</td>
<td>26.0 (25.8–26.1)</td>
<td>26.0 (25.8–26.1)</td>
<td>26.1 (25.9–26.3)</td>
<td>0.610</td>
</tr>
<tr>
<td>Range, kg/㎡</td>
<td>16.8–40.0</td>
<td>16.4–35.6</td>
<td>16.2–35.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO BMI category, n (%)</th>
<th>Underweight (&lt;18.5 kg/m²)</th>
<th>Normal (18.5 to &lt;25 kg/m²)</th>
<th>Overweight (25 to &lt;30 kg/m²)</th>
<th>Obese (≥30 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (0.8)</td>
<td>672 (41.9)</td>
<td>655 (40.8)</td>
<td>266 (16.6)</td>
</tr>
<tr>
<td>Fasting glucose, least squares mean (95% CI), mmol/L</td>
<td>4.97 (4.94–4.99)</td>
<td>4.94 (4.91–4.97)</td>
<td>4.93 (4.90–4.96)</td>
<td>0.111</td>
</tr>
<tr>
<td>Daily number of moderate/severe hot flushes, least squares mean (95% CI)</td>
<td>3.7 (3.3–4.2)</td>
<td>3.8 (3.4–4.3)</td>
<td>3.3 (2.7–3.8)</td>
<td>0.216</td>
</tr>
<tr>
<td>Range</td>
<td>0–53.1</td>
<td>0–62.9</td>
<td>0–72.0</td>
<td></td>
</tr>
<tr>
<td>Average hot flush severity score, least squares mean (95% CI)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.1 (1.0–1.2)</td>
<td>0.550</td>
</tr>
<tr>
<td>Range</td>
<td>0–3.0</td>
<td>0–3.0</td>
<td>0–3.0</td>
<td></td>
</tr>
</tbody>
</table>

**Changes in Body Weight and BMI**

- In all 3 treatment groups, adjusted mean body weight increased <0.9 kg and adjusted mean BMI increased <0.4 kg/m² over the course of the studies (Figure 1).
  - The CE 0.625 mg/BZA 20 mg group had statistically significantly less weight gain (difference of ~0.34 kg; P=0.015); and BMI increase (difference of ~0.13 kg/m²; P=0.014) compared with PBO at month 12; otherwise, there were no statistically significant between-group differences.
Data were pooled from five randomized, double-blind, placebo (PBO)- and active-controlled studies in nonhysterectomized postmenopausal women in the SMART trials.

METHODS

Key eligibility criteria: Generally healthy postmenopausal women with a uterus.

- Treatments administered:
  - CE 0.45 mg/BZA 20 mg
  - CE 0.625 mg/BZA 20 mg
  - PBO

Table 1. Study Designs of the SMART Trials

BMI category

- Underweight
- Normal
- Overweight
- Obese

The Effect of Conjugated Estrogens/Bazedoxifene on Body Weight in Postmenopausal Women

The CE 0.625 mg/BZA 20 mg group had statistically significantly less weight gain (difference of –0.34 kg; \(P=0.015\)) compared to the PBO group. No statistically significant interactions were found between change in hot flush frequency during CE/BZA treatment and baseline BMI or diabetes status.

Patterns of BMI category shifts were similar in the CE/BZA and PBO groups (global chi-square test, \(P=0.453\)).

Figure 1. Adjusted Mean Change From Baseline in (A) Body Weight and (B) Body Mass Index (BMI) Over Time

**BMI Category Shifts**

- Patterns of BMI category shifts were similar in the CE/BZA and PBO groups (global chi-square test, \(P=0.294\); **Figure 2**)
  - The CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, and PBO groups had similar proportions of subjects who gained weight, shifting BMI category to overweight (14.7%, 14.3%, 14.7%, respectively) or obese (10.5%, 12.8%, 15.1%, respectively)
  - The CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, and PBO groups had similar proportions of subjects who lost weight, shifting to underweight (1.0%, 1.2%, 0.7%, respectively), normal (13.0%, 15.9%, 15.7%, respectively), or overweight (22.3%, 22.3%, 18.3%, respectively)
The primary endpoints in the current analysis were on-treatment change from baseline in body weight and BMI (kg/m²). The objective of these pooled analyses was to evaluate the effect of CE/BZA on body weight and body mass index (BMI) in a new menopausal therapy that purposefully pairs conjugated estrogens (CE) with the selective estrogen receptor modulator (SERM) bazedoxifene (BZA) was evaluated in five phase 3 studies known as the Selective Estrogens, Menopause And Response to Therapy (SMART) trials. A commonly held misperception that hormone therapy can cause weight gain contributes to some women's hesitation about its use, despite its proven benefits. The Effect of Conjugated Estrogens/Bazedoxifene on Body Weight in Postmenopausal Women was presented at the Annual Meeting of the North American Menopause Society, October 15–18, 2014, National Harbor, MD.

METHODS

INTRODUCTION

- Treatment effect modification by baseline weight/BMI was tested (significance level α=0.15).
- Number and severity of hot flushes over time were analyzed by Mixed Model with Random Effects (MMRM) with study, month, treatment group, month by treatment group interaction, and baseline body weight included in the model.

<table>
<thead>
<tr>
<th>Table 1. Study Designs of the SMART Trials</th>
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</thead>
<tbody>
<tr>
<td>SMART-18</td>
</tr>
<tr>
<td>3-year</td>
</tr>
<tr>
<td>N=1607</td>
</tr>
<tr>
<td>CE 0.45 mg/BZA 20 mg</td>
</tr>
<tr>
<td>81.0% 19.0%</td>
</tr>
</tbody>
</table>

In all 3 treatment groups, adjusted mean body weight increased <0.9 kg and adjusted mean BMI increased <0.4 kg/m² over the 1-year extension. Of the randomized participants, 4006 (89.8%) had baseline and follow-up body weight data available (CE 0.45 mg/BZA 20 mg, n=1444; CE 0.625 mg/BZA 20 mg, n=1607; PBO, n=1122). Baseline body weight was not significantly different across treatment groups (P>0.05).

Influence of Body Weight/BMI on Treatment Efficacy

- No statistically significant interactions were found between change in hot flush frequency during CE/BZA treatment and baseline body weight (interaction P=0.267) or baseline BMI (interaction P=0.453).
- A marginal, but statistically significant interaction was found between change in hot flush severity with CE/BZA and baseline BMI (interaction P=0.112) but not baseline body weight (P=0.271).
  - A liberal threshold was used for statistical significance (P<0.15 instead of <0.05) to compensate for low power to detect interaction effects; as a result, the interaction between hot flush severity and BMI may have been a spurious finding.

CONCLUSIONS

- Daily treatment with CE/BZA for up to 2 years was not associated with clinically meaningful changes in body weight, BMI, or shifts in BMI category in this pooled analysis of the five SMART trials.
  - CE/BZA effects on body weight and BMI were minimal and similar to PBO.
  - Baseline BMI influenced efficacy for hot flush severity, but not frequency.

REFERENCES


ACKNOWLEDGEMENT

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