NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: Post Authorization Safety Study (PASS) of Conjugated Estrogens/Bazedoxifene (CE/BZA) in the US

Date: 26 March 2021

Name and affiliation of the main author: Sarah Hoffman, PhD, MS, MPH, (HealthCore)

Keywords: hormone therapy (HT), menopause, endometrial cancer, estrogen, bazedoxifene.

Rationale and background: Estrogen unopposed by progestin increases endometrial cancer risk. Progestin is commonly added to estrogen hormone replacement therapy to reduce the risk of endometrial cancer, however, this addition can increase breast cancer risk. In 2013, oral conjugated estrogen/bazedoxifene (CE/BZA) was authorized in the United States (US) for the treatment of moderate to severe vasomotor symptoms associated with menopause. Like progestin, bazedoxifene acts as an estrogen antagonist in the endometrium, but the real-world safety of CE/BZA has not been widely examined.

Research question and objectives: This study examined the incidence of endometrial cancer, endometrial hyperplasia, and other safety outcomes among postmenopausal women initiating CE/BZA or combined estrogen and progestin hormone therapy (E+P HT) during the first five years of CE/BZA availability in the US.

Study design: CE/BZA was contrasted with a comparator group consisting of oral, topical, and transdermal E+P HT. The study included new users (12-month minimum continuous enrollment lookback) of CE/BZA or E+P HT in 01 May2014 – 31 Aug 2019. Propensity score (PS)-matched incidence rates (IR) and ratios (IRR) were reported for all study outcomes.

Setting: This multi-database cohort study included five US healthcare insurance claims databases: HealthCore Integrated Research Database, MarketScan CCAE & Medicare Supplemental, MarketScan Medicaid, Optum Research Database, and Healthagen. Results were pooled using random effects meta-analysis.

Subjects and study size, including dropouts: Of approximately 90 million female patients with enrollment during the study period, 298,450 had used CE/BZA or E+P HT and met remaining inclusion criteria. After PS-matching, 75,455 were included in the analytic sample, of which 44,414 were included in the new user analysis (the remaining 31,041 were prevalent users and not included in comparative analyses).

Variables and data sources: Primary outcomes included endometrial cancer and endometrial hyperplasia identified via validated algorithms. Secondary outcomes included three acute cardiovascular and six cancer outcomes. Covariates included age, sex, Census region, total time in health plan prior to and including index date, calendar year of index date, pre-specified comorbidities and medications, and the 25 most common comorbidities and

medications in the pre-matched sample. All variables were assessed via diagnosis, procedure, or prescription codes present in claims. Data sources are described in "Setting."

Results: A total of 44,414 women were included in the PS-matched sample: 10,596 CE/BZA and 33,818 E+P HT new users. There were 39 endometrial cancer cases: 12 among CE/BZA users (IR_{pooled}=5.20 per 10,000 person-years; 95% confidence interval [CI]: 2.02, 8.38), and 27 among E+P HT users (IR_{pooled}=3.60 per 10,000 person-years; 95% CI: 1.13, 6.07). There were 48 endometrial hyperplasia cases: 14 among CE/BZA users (IR_{pooled}=11.00 per 10,000 person-years; 95% CI: 1.84, 20.17), and 34 among E+P HT users (IR_{pooled}=10.60 per 10,000 person-years; 95% CI: 6.13, 15.07). Comparing CE/BZA to E+P HT, the IRR_{pooled} was 1.50 (95% CI: 0.79-2.88; I^2: 0%) for endometrial cancer and 1.69 (95% CI: 0.51-5.61; I^2: 51%) for endometrial hyperplasia. The IRR_{pooled} for breast cancer was 0.79 (95% CI: 0.58-1.05; I^2: 0%). Rates of cardiovascular outcomes and any cancer were similar between CE/BZA and E+P HT users.

Discussion: This multi-database, new user/active comparator, PS-matched study noted a largely similar risk profile for cancer and cardiovascular outcomes between CE/BZA and E+P HT users. For the comparison of CE/BZA to E+P HT, the ratios of incidence rates for endometrial hyperplasia and endometrial cancer were both greater than 1.00 but with 95% CIs that included 1.00. These outcomes were uncommon, thus, the study had limited statistical power to estimate small or moderate magnitudes of effect. This study was able to estimate the effect of CE/BZA vs. E+P HT for breast cancer with greater precision than was available for endometrial cancer. No increased rate of breast cancer was found for CE/BZA relative to E+P HT.

Marketing Authorization Holder(s): Pfizer Limited

Names and affiliations of principal investigators: Renu Garg, PhD, MPH (Pfizer Inc.); Sarah Hoffman, PhD, MS, MPH (HealthCore, Inc.); Daniel Beachler, PhD, MHS (HealthCore, Inc.); Florence Wang, ScD (Optum), Cheryl McMahill-Walraven, MSW, PhD (Healthagen, currently known as CVS Health Clinical Trial Services as of 01 November 2020)

Document Approval Record

Document Name:	Duavive_B2311060_Final_Report_Abstract_fv
Document Title:	B2311060

Signed By:	Date(GMT)	Signing Capacity
Campbell, Ulka	29-Mar-2021 11:35:16	Final Approval
De Bernardi, Barbara	29-Mar-2021 12:53:04	Final Approval