NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: Cohort Study of Venous Thromboembolism and Other Clinical Endpoints among Osteoporotic Women Prescribed Bazedoxifene, Bisphosphonates or Raloxifene in Europe.

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Rationale and background: Bazedoxifene (BZA) is a third-generation non-steroidal selective oestrogen receptor modulator (SERM) currently approved in the European Union (EU) for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. In clinical trials, women treated with BZA had an increased risk of venous thromboembolism (VTE) compared to placebo. VTE is included in the product labels of BZA as an important identified risk. This non-interventional cohort study has been conducted to characterise the risk of VTE and selected clinical endpoints of interest among a patient population prescribed BZA, raloxifene, or a bisphosphonate in usual clinical care outside of a randomised clinical trial setting.

This study is designated as a Post Authorisation Safety Study (PASS) and is a commitment to Committee for Medicinal Products for Human Use/European Medicines Agency (CHMP/EMA).

Research question and objectives: The objective of this PASS was to estimate and compare the incidence rates (IRs) of VTE and selected clinical endpoints in women receiving treatment with BZA, as compared to women receiving a bisphosphonate or raloxifene for the treatment of postmenopausal osteoporosis.

The primary endpoint of VTE is a composite measure of deep vein thrombosis (DVT), pulmonary embolism (PE), retinal vein and sinus thrombosis (RVST).

The selected secondary clinical endpoints included:

- Ischemic stroke
- Thrombotic and ischemic cardiac disorders (including myocardial infarction, myocardial ischemia, and coronary occlusion)
- Atrial fibrillation
- Biliary events: cholecystitis, cholelithiasis
- Hypertriglyceridemia
- Fractures
- Chronic and acute renal failure (including chronic renal insufficiency and end stage renal disease)

- Malignancies including breast, renal, ovarian, thyroid, gastrointestinal tract and lung cancers, as well as an aggregate of all malignancies
- Depression
- Selected ocular events including retinal vascular occlusions, disorders of the globe, iris, ciliary body, retina, eye adnexa and cornea
- Goitre

Study design: This cohort study was a non-interventional study that used extracted data from IQVIA electronic medical records (EMR) in Spain and Italy.

Setting: The total study period was 8 years. The patient inclusion/accrual period (also referred to as enrolment period) in each database began at the time of commercial launch of BZA in each country (September 2010 in Spain and April 2011 in Italy) and continued for approximately 3 years from the start of the study. The index date for each patient was the date of the first recorded prescription for either BZA or raloxifene or bisphosphonate during the enrolment period. Each patient must have had at least 6 months of data prior to the index prescription date in order to be included in the analysis (i.e., the baseline period). The study therefore consisted of 3 distinct periods:

- Baseline period: 6 months before the index prescription date of each patient.
- Accrual period: Approximately 3 years from launch day in a country.
- Follow-up period: at least 5 years of follow-up per patient from the index date.

Subjects and study size, including dropouts: There was no de novo patient enrolment in this study and all patients in the database who met the inclusion criteria during the recruitment period were included in the analysis. In the protocol, the precision of various estimated rate ratios (RRs) that could potentially be detected in the study, depending on several different hypothetical scenarios of patient accrual, was described. The assumptions underlying these scenarios are described below.

The precision estimates were based on the background incidence rate of VTE, since this was the primary endpoint. It was estimated that the incidence rate of VTE in women who were not treated with a SERM or hormone replacement therapy (HRT) was 1.74/1000 person-years, based on data from the placebo groups in the phase 3 pivotal clinical trials of BZA. The study had a 3-year accrual period and each woman was followed for at least 5 years from enrolment. Since osteoporosis therapies are chronic therapies, it is likely that women would be exposed to the drugs for more than 1 year. A conservative estimate of the proportion of patients lost to follow-up annually of 15% was used in the estimation.

A total of 1,111 BZA and 6,666 bisphosphonate patients (1:6) with at least one prescription were accrued during the study enrolment period and included in the study analyses. With this study size, an RR of 2.5 was detectable with 80.0% power and 0.05 significance level, with 3 years of accrual time and 5 years of follow up time, and 15% loss to follow-up in both BZA- and bisphosphonates-treated patients.

Variables and data sources: This study used IQVIA EMR databases form Spain and Italy. These are electronic medical records databases that collect clinical data from primary care physician practices. Variables defined and analyzed included: patient characteristics, comorbidities, medications, medical history, and the primary and secondary safety endpoints. For the VTE endpoint, the time-to-event was the time to any one of the 3 component event terms (DVT, PE, RVST), whichever occurred first. After that first event, the subject was censored for the primary VTE endpoint.

Results: Overall, 86,675 patients with at least one prescription of BZA, raloxifene or bisphosphonate were identified during the study accrual period (Spain, 01 October 2010- 30 April 2014; Italy, 01 May 2011- 30 April 2014). A total of 85,500 patients were included after the study exclusion criteria were applied. In all, 43,231 (50.6%) patients were from Italy and 42,269 (49.4%) were from Spain, with 99.6% and 95.6% of patients not reporting switching treatment during the study period in these two countries, respectively. Of these 85,500 patients, 1111 (1.3%) received BZA, 2720 (3.2%) received raloxifene, and 81,669 (95.5%) received bisphosphonate. As the bisphosphonate population in the database was much larger than the BZA (and raloxifene) population, a random sample of bisphosphonate users (without replacement) was obtained. Following the random selection there remained a total population of 10,497 patients; 1111 (10.6%) treated with BZA; 2720 (25.9%) treated with raloxifene; and 6666 (63.5%) treated with bisphosphonate.

Mean (SD) ages of the patients were 61.6 (9.0) years, 64.8 (8.8) years, and 71 (10.3) years for the BZA, raloxifene and bisphosphonate treatment groups, respectively. The median body mass index (BMI) for the 3 treatment groups ranged from 26.0 kg/m^2 for the bisphosphonate treatment group to 26.9 kg/m^2 for the BZA group. The proportion of patients with missing BMI in each of the 3 treatment groups were as follows: BZA, 66.7%; raloxifene, 52.6%; and bisphosphonates, 43.2%. The percentages of patients with a medical history of malignancies was 3.1% among BZA patients and 5.1% and 10.0% among raloxifene and bisphosphonate patients respectively. The medical charts showed ≤15% of any of the 3 treatment groups as being current or past smokers and for the remainder of patients, did not distinguish between non-smokers and patients with missing smoking information. The medical charts showed 12% of BZA, 21.5% of raloxifene, and 26.5% of bisphosphonate patients as being current alcohol consumers; for the remainder of patients, patients who did not drink alcohol could not be distinguished from patients who had missing alcohol uptake information.

A total of 17/1111 (1.5%, [event/N patients]) VTE events occurred in the BZA group during the study period. There were 60/2720 (2.2%) VTE events in the raloxifene treatment group and 305/6666 (4.6%) events in the bisphosphonate treatment group. DVTs were the most common VTE events in all 3 treatment groups.

In adjusted Cox proportional hazards analyses, the risk of VTE was significantly lower in the BZA group when compared with the bisphosphonate group (hazard ratio [HR] [95% CI]: 0.4 [0.2 – 0.6]; p<0.01). The risk for DVT, which was the most common component of the VTE endpoint, was similarly reduced (HR [95% CI]: 0.4 [0.2 – 0.6] p<0.01). No significant difference was found however between BZA and raloxifene regarding VTE or DVT endpoints (HR [95% CI]: 0.9 [0.4 – 2.2], p=0.91; 0.9 [0.4 – 2.0], p=0.73, respectively). In

general, fewer secondary endpoints were reported during the follow-up period in the BZA group, when compared to the raloxifene and bisphosphonate groups. No thyroid and renal malignancy events were observed in the BZA treatment group.

Discussion: Bisphosphonate patients in this study more frequently had VTE risk factors compared with BZA and raloxifene patients based on the available demographic and baseline characteristics. For example, the mean age in the bisphosphonate treatment group was 71.0 years and mean ages were 61.6 years and 64.8 years for BZA and raloxifene treatment groups, respectively. The percentage of patients with a medical history of malignancies was higher among bisphosphonate patients compared with BZA and raloxifene patients. These differences are noteworthy because older patients and cancer patients have a much higher risk of VTE than younger patients or patients without cancer.

Given that the BZA and raloxifene labels include warnings against treatment of patients with VTE risk factors, and evidenced by the demographic and medical history patient profiles, general practitioners (GPs) in Spain and Italy had a greater propensity of prescribing bisphosphonates, as against BZA or raloxifene, to patients with a higher risk of VTE. The resulting confounding by indication (ie, channelling bias) may not have been fully controlled in this study, thus impacting the BZA vs. bisphosphonates study results. Adequate control for confounding requires the collection of extensive information on other risk factors for VTE (potential confounders), which was missing in this study (e.g., information on body mass index (BMI), smoking status) and is a recognized limitation. In general, given the relatively low numbers of secondary events observed in this study, especially in BZA patients, the results of the comparative analyses should be interpreted cautiously.

In conclusion, data collected between 01 October 2010 and 30 April 2019 in the IQVIA EMR databases in Spain and Italy, indicates that BZA used in the real-world setting has a safety profile in women with postmenopausal osteoporosis similar to that observed in clinical trials.

Marketing Authorisation Holder(s): Pfizer Europe MA EEIG

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