NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	Cohort Study of Venous Thromboembolism and Other Clinical Endpoints Among Osteoporotic Women Prescribed Bazedoxifene, Bisphosphonates or Raloxifene in Europe.
Protocol number	B1781044
Version identifier of the final study report	1.0
Date	24 April 2020
EU Post Authorisation Study (PAS) register number	ENCEPP/SDPP/5395
Active substance	Bazedoxifene
Medicinal product	CONBRIZA
Product reference	EMEA/H/C/000913, EU/1/09/511/001-005
Procedure number	EMEA/H/C/000913/ MEA 012
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG
Joint PASS	No
Research question and objectives	Primary Objective: To estimate and compare the incidence rates of venous thromboembolism (VTE) among women receiving bazedoxifene and women receiving a bisphosphonate for treatment of osteoporosis. Secondary Objective:

	• To estimate and compare the incidence rates of VTE among women receiving bazedoxifene and women receiving raloxifene for treatment of osteoporosis. • To estimate and compare the incidence rates of selected clinical endpoints among women receiving bazedoxifene and women receiving a bisphosphonate for treatment of osteoporosis. • To estimate and compare the incidence rates of selected clinical endpoints among women receiving bazedoxifene and women receiving raloxifene for treatment of osteoporosis.
Countries of study	Spain and Italy
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1. ABSTRACT (Stand-Alone Document)

Please refer to the stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AT	As-treated
BMI	Body mass index
BZA	Bazedoxifene
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CP	Centralised procedure
CR	Cumulative risk
CRF	Case report form
DVT	Deep vein thrombosis
e-HRD	Electronic health related databases
EMA	European Medicines Agency
EMR	Electronic Medical Records
EU	European Union
GP	General practitioner
GPP	Good Pharmacoepidemiology Practices
HR	Hazard ratio
HRT	Hormone replacement therapy
IEC	Independent Ethics Committee
IR	Incidence rate
IRB	Institutional review board
IRR	Incidence rate ratio

ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LPD	Longitudinal patient database
MAH	Marketing Authorisation Holder
MORE	Multiple Outcomes of Raloxifene Evaluation
NI	Non-interventional
NIS	Non-interventional study
OR	Odds ratio
PAS	Post Authorisation Study
PASS	Post Authorisation Safety Study
PE	Pulmonary embolism
PhRMA	Pharmaceutical Research and Manufacturers Association
PRAC	Pharmacovigilance Risk Assessment Committee
RR	Rate ratio
RVT	Retinal vein thrombosis
RVST	Retinal vein and sinus thrombosis
SAP	Statistical analysis plan
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SmPC	Summary of product characteristics
ST	Sinus thrombosis
TG	Triglycerides

VTE	Venous thromboembolism
WTS	Without treatment switch

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

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4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date
Start of data collection	01 October 2010	01 October 2010
End of data collection	30 April 2019	30 April 2019
Registration in the EU PAS register	12 December 2013	12 December 2013
1st Annual Progress Report	15 December 2012	11 December 2012
2nd Annual Progress Report	20 December 2013	17 December 2013
3rd Annual Progress Report	19 December 2014	19 December 2014
Interim report	25 April 2016	21 January 2016
Final study report	30 April 2020	24 April 2020

6. RATIONALE AND BACKGROUND

Osteoporosis is characterised by a decrease in bone mass and architectural deterioration of bone tissue.[1] Subtle modifications of bone remodelling, related to abnormalities of bone turnover, can induce a substantial loss of bone over a prolonged period of time. A period of asymptomatic bone loss results in reduced bone strength. When bone loss is sufficient to cause mechanical weakness, fractures may occur spontaneously or as a result of minimal trauma.[1] Osteoporotic fractures cause substantial clinical and economic burden for society. Age and menopause are the two main determinants of osteoporosis. The cessation of ovarian production of oestrogen at the time of the menopause results in an accelerated rate of bone loss in women.[1]

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. BZA is an oestrogen receptor ligand that exhibits tissue-specific activity: BZA functions as an agonist in the bone and an antagonist in the breast and uterine endometrium. BZA was developed in tablet form and its current dosing consists of once daily administration of a 20 mg tablet. BZA (Conbriza®) was approved in Europe via the centralised authorisation procedure in April 2009. The first EU launch occurred in Spain in September 2010, which was followed by launch in Italy in April 2011.

Currently, one other SERM, raloxifene (Evista®) is marketed in Europe for the treatment and prevention of postmenopausal osteoporosis. Bisphosphonates are non-hormone compounds that bind to the bone surface and are then taken up by osteoclasts. Bisphosphonates have a profound effect on bone remodelling and are widely used for the prevention and treatment of osteoporosis.

In clinical trials, women treated with BZA had an increased risk of venous thromboembolism (VTE) compared to placebo.[2] VTE is included in the product labels of BZA and raloxifene as an important identified risk.

This non-interventional cohort study was conducted to characterise the risk of VTE and other safety events 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 was designated as a Post Authorisation Safety Study (PASS) and is a commitment to European Medicines Agency (EMA).

7. RESEARCH QUESTION AND OBJECTIVES

7.1 Research Question

The overall aim of this PASS was to compare the incidence rates (IRs) of VTE and selected clinical endpoints in women receiving BZA, 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

7.2 Objectives

Primary Objective
To estimate and compare the IRs of VTE among women receiving BZA and women receiving a bisphosphonate for treatment of osteoporosis.

Secondary Objectives

- To estimate and compare the IRs of VTE among women receiving BZA and women receiving raloxifene for treatment of osteoporosis.
- To estimate and compare the IRs of selected clinical endpoints (listed above) among women receiving BZA and women receiving a bisphosphonate for treatment of osteoporosis.
- To estimate and compare the IRs of selected clinical endpoints (listed above) among women receiving BZA and women receiving raloxifene for treatment of osteoporosis.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	24 April 2012	Substantial	Section 2.2 (Secondary endpoints)	Addition of selected ocular events as a secondary endpoint	To estimate the incidence of ocular events, safety events of interest, in the study population
2	26 June 2012	Substantial	Section 2.2 (Secondary endpoints)	Addition of goitre as a secondary endpoint	To estimate the incidence of goitre, a safety event of interest, in the study population
3	3rd September, 2013	Substantial	Section 4.2 Patient accrual period	Extension of study accrual period	To increase study sample size

9. RESEARCH METHODS

9.1. Study design

This PASS was a non-interventional retrospective cohort study using extracted data from IQVIA electronic medical records (EMR) databases ((formerly named Longitudinal Patients Databases (LPD) maintained by Cegedim and processed by IQVIA) in Spain and Italy. This study was conducted to characterise the risk of VTE and other selected safety endpoints of interest among a patient population prescribed BZA, raloxifene, or a bisphosphonate in usual clinical care outside of a randomised clinical trial setting.

9.2. Setting

The IQVIA EMR databases of Spain and Italy contain all drug prescriptions, diagnoses, demographic data, medical history (event data, risk factors) and other types of data electronically collected by participating general practitioners (GPs). The eligible population was constructed from these anonymized IQVIA EMR databases.

The total study period was 8 years, (see Table 2). BZA (Conbriza®) was approved in EU via the Centralised Procedure (CP) in April 2009. This study was launched after BZA became commercially available in the participating countries, Spain and Italy. The patient inclusion/accrual period (also referred to as the enrolment period) in the 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 BZA or raloxifene or

bisphosphonates during the enrolment period. Each woman must have had at least 6 months of data prior to index prescription date 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 for 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.

Table 2. Study Timelines by Country

	Accrual Period 3 Years*	**Follow-Up Period**
Spain	01 October 2010- 30 April 2014	01 May 2014- 30 April 2019
Italy	01 May 2011- 30 April 2014	01 May 2014- 30 April 2019

* Due to low enrolment/accrual into the study, the original end of the study accrual period was extended from 30 September 2012 in Spain, and 30 April 2013 in Italy, to 30 April 2014 for both Spain and Italy. Extending the accrual period to April 2014 extended the study timelines by 1 year. The new accrual period for Spain is 43 months (01 October 2010- 30 April 2014) and the new accrual period for Italy is 36 months (01 May 2011-30 April 2014).

Each patient was followed for identification of selected endpoints for a minimum period of 5 years from their index prescription date for BZA, raloxifene, or bisphosphonates, when possible, and for the maximum period available in the dataset for each patient. The follow-up continued even if the woman discontinued the index medication or switched to a different medication during the five-year follow-up period. The follow-up duration of an individual patient may have been shorter than 5 years if the woman transferred out of the general practitioner (GP) office that wrote the index prescription or if she died. In these situations, in the absence of any qualifying events, the data was censored on the date of last visit. This study used the IQVIA EMR database, an electronic medical records database. However, the Spanish and Italian databases of IQVIA do not have recorded events of death and date of death. The discontinued patients' records indicate loss to follow-up for various other reasons, such as patient's moving from the catchment areas, patient's change of GPs or other various reasons. Therefore, it is unknown whether a 'lost to follow-up' patient was lost because he or she died. A minimum of a 6-month history in the IQVIA EMR database prior to the index date (at least one GP visit, whatever the motive of the visit to GP) was required for inclusion of population, in order to obtain baseline data.

In summary, follow-up for each endpoint was from the index date to whichever of the following occurred first:

- Occurrence of study endpoint
- Last patient visit
- Study end date, 30 April 2019

9.3. Subjects

Inclusion Criteria
Patients must have met all of the following inclusion criteria to be eligible for inclusion into the study:

1. Female;
2. At least one prescription for BZA, raloxifene, or any bisphosphonate during the study accrual period (index prescription);
3. Age ≥45 years at the date of the index prescription; and
4. At least 6-months of follow-up data in the electronic medical record system prior to the date of the index prescription.

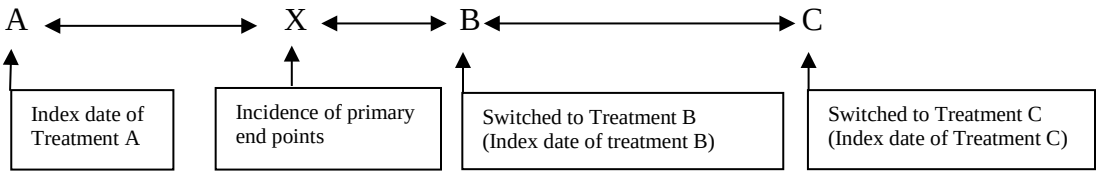
The study protocol includes an inclusion criterion "A recorded diagnosis code of osteoporosis on or within 60 days prior to the index prescription date". Because it was anticipated that many patients might not have this diagnosis code and the criterion might therefore introduce selection (bias), the applicability this criterion was evaluated through a sensitivity analysis during the interim analyses (data lock point of 15 April 2016). Results of the sensitivity analysis are described in section 9.9.4. Following the analysis, the decision was made (and communicated in the interim analyses) not to apply this inclusion criterion.

As patients were able to receive multiple (sequential, not concomitant) treatments for osteoporosis during the follow-up period (switched treatment), patients were classified and analysed in two ways:

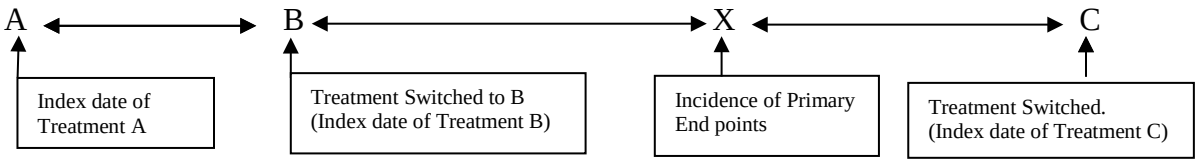
1. **As-treated (AT) approach,** where patients were analysed according to the treatment they actually received. Patients were counted in multiple sequential treatment groups if they switched treatment. Events were counted in the treatment group in which they occurred or the last treatment they received, if treatment had been stopped (Figure 1). Each event type could only be counted once for each patient even if the patient switched treatment. For VTE, only the first occurrence of deep vein thrombosis (DVT), pulmonary embolism (PE), retinal vein thrombosis or sinus thrombosis (RVST) during the follow-up period was counted.[3]

Cumulative Risk (CR) approach, where patients were counted in the group of their first treatment during the study accrual period and were considered in this group during all of the follow-up, similar to an 'intention to treat' analysis.[3]

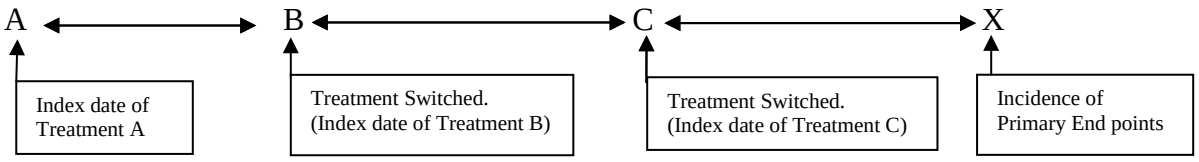
Figure 1. Calculating the duration of treatment for patients that switched treatment using the as-treated (AT) approach



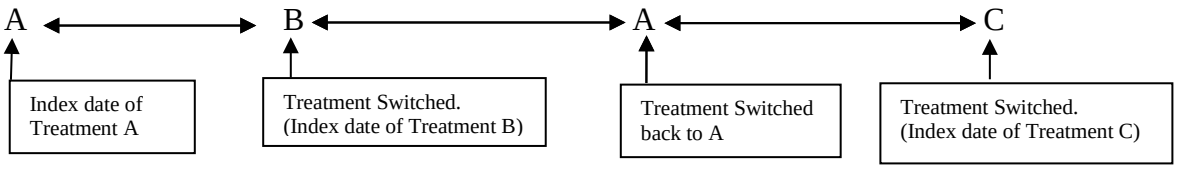
The person-time will be apportioned as a time varying exposure such that this person accrues person-time for exposure A until point X. The event, X, is only associated with exposure A assuming no induction period, but person-time from drugs A and B would contribute to respective exposure groups for other events. This apportioning of person-time is also applicable to the other study endpoints, not only the primary endpoint.



The person-time will be apportioned as a time varying exposure such that this person accrues person-time for exposure A until point B, B until point X. The event, X, is only associated with exposure B assuming no induction period, but person-time from drugs A and B would contribute to respective exposure groups for other events. This apportioning of person-time is also applicable to the other study endpoints, not only the primary endpoint.



The person-time will be apportioned as a time varying exposure such that this person accrues person-time for exposure A until point B, then accrues toward exposure B until point C, and then accrues to exposure C until point X. The event, X, is only associated with exposure C assuming no induction period, but person-time from drugs A and B would contribute to respective exposure groups for other events. This apportioning of person-time is also applicable to the other study endpoints, not only the primary endpoint.



This person accrues person-time for exposure A until point B, then accrues person-time for exposure B until the next point A, then accrues person-time for exposure A until point C.

A, B, C: Treatment cohort types. X= Incidence date of primary end point as an example. These examples are equally applicable to all the study endpoints.

Due to the large number of bisphosphonate users that were accrued in the study database relative to BZA (approximately 74:1), and to prevent the study from being over powered, in accordance with guidance from the Pharmacovigilance Risk Assessment Committee (PRAC) (Ref: EMA/PRAC/165687/2015), a random selection of bisphosphonate users were selected with a target ratio of 6:1 BZA users within the 4 age strata of 45-49, 50-59, 60-69, ≥70 years.

9.4. Variables

Exposure

A BZA exposed patient was defined as having at least one prescription of BZA during the study accrual period.

Comparators/reference groups:
A bisphosphonate exposed patient was defined as having at least one prescription of bisphosphonate during the study accrual period.

A raloxifene exposed patient was defined as having at least one prescription of raloxifene during the study accrual period.

For each index drug exposure, the person-time was measured from first prescription to the end of the observation period for that patient with no extension (see section 9.9 Statistical methods). Therefore, each patient was considered as exposed to the index drug until the end of the study or till the patient switched treatment, whichever occurred first. There was no consideration of days of supply or treatment gaps in determining duration of exposure.

Outcomes

Primary endpoints:

- Events of VTE defined as DVT, PE or RVST

Secondary endpoints:

Events of:

- 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

Endpoint verification

Endpoints were identified based on an electronic search for the relevant diagnostic codes (see Diagnostic codes in Annex 1) in the diagnosis fields of the medical records during the follow-up period. For each potential endpoint, structured data from the patient's electronic medical record were retrieved, de-identified and provided to two clinical experts for review and confirmation of the diagnosis.

All potential primary endpoints BZA and raloxifene users were evaluated. As the bisphosphonate group was very large, 176/305 (58%) of the primary endpoints were randomly selected and evaluated. Overall, 5-10% of potential secondary endpoints were randomly selected and evaluated depending on the specific endpoint. Each event was reviewed independently by two clinicians blinded to patients' treatment group to confirm the diagnosis of the primary and secondary endpoints.

Endpoints were adjudicated as:

- Confirmed - an event had definitely occurred;
- Possible - an event had possibly occurred;
- Not confirmed – could not confirm that an event had occurred.

The study project manager reconciled the decisions of the two clinical experts and identified the cases on which they did not agree. These disagreements were discussed by the two experts and their discussion was documented. After discussion, if they were agreed then it was not necessary to submit the case to a third expert for a tie breaking decision.

Results of this evaluation are in section 10.5.4.

Covariates

The following patients' demographic and baseline characteristics known to be risk factors for VTE were assessed at index date:

- Age (years): derived by difference between the year of time of interest and year of birth. Age is presented as a continuous variable and in categories: 45-49, 50-59, 60-69 and ≥70 years
- Weight (kg): recorded at the given date, or if not available, at the most recent date before or after it. Weight was used in the calculation of BMI and not presented separately.

- Height (cm): the value at the given date or, if not available, at the most recent date before or after it. Height was used in the calculation of BMI and not presented separately.
- BMI (kg/m²), calculated from weight and height as defined previously. BMI is presented as a continuous variable and in categories: <18.5 (Underweight), 18.5- <25 (Normal), 25- <30 (Overweight), ≥30 (Obese)
- Alcohol use
- Smoking status
- Time since diagnosis of osteoporosis: derived by the difference between the index date and the diagnosis date (in the entire patient medical history available)
- Previous treatment for osteoporosis (before index date) (yes versus no)
- History of VTE (any time before index date)
- History of major lower extremity (hip, knee) arthroplasty, arthroscopic surgery (information on arthroscopic surgery not available in Italian database) (<1 month prior to incidence of VTE)*
- General surgery, major orthopaedic surgery (<1 month prior to incidence of VTE)* (information on general surgery not available in Italian database)
- Multiple trauma, (<1 month prior to incidence of VTE)*
- Hip, pelvis, or leg fracture (<1 month prior to incidence of VTE)*
- Stroke (<1 month prior to incidence of VTE)*
- Acute spinal cord injury (paralysis) (<1 month prior to incidence of VTE)*

*If available, descriptive information only provided for patients experiencing a VTE in each treatment group.

The multivariate analyses included the following variables as potential confounders:

- Age
- Smoking status
- Alcohol use
- History of osteoporosis
- History of diabetes
- History of hypertension
- History of malignancies
- History of DVT.
- History of PE
- History of RVST

9.5. Data sources and measurement

This study used IQVIA EMR databases (formerly named LPD, maintained today by Cegedim and processed by IQVIA) in Spain and Italy, an electronic medical records database that collects clinical data from primary care physician practices located in Spain and Italy (Table 3).

The IQVIA EMR database results from medical information registered via a practice management software, used during physician office visits to capture clinical data in an electronic medical record system. Physicians use the practice management software developed by Cegedim to maintain electronic medical records of their patients. In each country a panel of physicians using this electronic system volunteered to make available anonymized patient-level information from their practices for clinical research purposes. Since these data are being collected in usual clinical care in a non-interventional way, they reflect routine clinical practice in these countries. The panel of contributing physicians is maintained as a representative sample of the primary care physician population in each country according to age, sex, and geographical distribution. Additionally, in most countries (including Spain and Italy), the patient population is representative of the respective country population according to age and sex distribution, as provided by national statistic authorities.

Table 3. Doctor and Patient Populations in the IQVIA EMR databases by Country at Study Inception

	Italy	Spain
Number of physicians in the panel	700	300
Average number of patients with at least one GP visit annually	800,000	320,000

GP: general practitioner, EMR: Electronic Medical Records

The patient data in the IQVIA EMR databases form a nationally representative sample. Data have been collected in Spain since 2006 and in Italy since 2004, providing several years of medical history, including comorbidity and concomitant medication use information. Of the patients included in the Spanish and Italian IQVIA EMR databases, there were currently approximately 68,000 women with osteoporosis who were being treated with a pharmaceutical agent. Between 1 and 6% of these women were taking raloxifene, depending on the region; most of the rest were prescribed a bisphosphonate (IQVIA, data on file).

Data were entered regularly during usual patient care, submitted daily to the Cegedim coordinating centre, cleaned and de-identified, and then made available for research.

Anonymized patient data collected from each GP practice included:

- Demographic information (age, gender)
- Medical history (event dates, diagnoses, risk factors, referrals to specialists)
- Therapeutic history (date/length of prescription, molecule/product, dosage)
- Additional information (test results, immunizations, height, weight, blood pressure)

Patient data collected in each country participating in IQVIA EMR databases varied to some extent to accommodate local needs. However, all countries collected data on medical comorbidities and outcomes, prescriptions, demographics, and physician characteristics.

In the Cegedim electronic medical record system diagnoses, diagnosis of clinical events was recorded as diagnostic codes (see Diagnostic codes in Annex 1). These codes from Spain and Italy differ, and were harmonized based on pre-specified algorithms developed prior to the analysis and listed in the statistical analysis plan (SAP).

Cegedim's software did not collect hospitalisation data directly in Spain and Italy. Information on hospitalisations was captured in the patient's general practice file during follow-up visits with the patient's general practice physician following discharge from the hospital. However, this information was not systematically collected and there was no established linkage between the medical records at the general practices and at the hospitals.

9.6. Bias

Several approaches were implemented in the study design and analyses to reduce bias in this study. Raloxifene was selected as a second comparator to BZA based on an assessment of comparability of mechanism of action (both drugs are SERMs), indication, and drug label, which indicated greater similarity between BZA and raloxifene users, as compared with bisphosphonate users. The feasibility assessment showed indication to be an important contributing factor to imbalances in baseline characteristics across cohorts. Therefore, the study was restricted to prescriptions for the osteoporosis indication (indication for use was inferred by evidence of an osteoporosis diagnosis in medical records) to strengthen the internal validity of the study.

Stratification and multivariate analyses were used to further adjust for confounding. Variables for inclusion in the regression models were determined a priori and defined in the study protocol, including covariates hypothesized to be associated with exposures and study outcomes that do not mediate the potential effects of interest.

Further discussion of potential sources of bias in the study, including under-ascertainment of endpoints and channelling bias, is provided in Section 11.2 Limitations.

9.7. Study size

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.[2] It

was assumed that women treated with raloxifene would have a higher incidence of VTE, of 2.17/1000 person-years, based on data from the phase 3 pivotal trials of BZA.[2] The rate of VTE observed in the raloxifene arm of the BZA pivotal trials was lower than the rate reported in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.[4] In the MORE trial, the incidence rate of VTE was 3.5/1000 patient-years in women randomised to raloxifene.

All estimates (Table 4, BZA vs. bisphosphonates; Table 5, BZA vs. raloxifene) were calculated with two-sided 95% CIs. 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. Estimates were based on Wald 95% CIs.[5]

Table 4. 95% CI for RR with Different Numbers of Patients in the BZA Exposed Group and the Bisphosphonate Exposed Group

Bazedoxifene (n)	Bisphosphonate (n)	BZA: Bisphosphonate	Underlying RR		
			1	1.5	2
			95% CI of observed point estimate of RR		
2150	8600	1:4	0.6, 1.7	1.0, 2.4	1.3, 3.0
2000	8000	1:4	0.6, 1.8	0.9, 2.4	1.3, 3.1
1750	10,500	1:6	0.6, 1.8	0.9, 2.5	1.3, 3.1
1500	12,000	1:8	0.5, 1.9	0.9, 2.5	1.3, 3.2

BZA: bazedoxifene, CI: confidence interval, RR: rate ratio

Table 5. 95% CI for RR Comparing BZA Users and Raloxifene Users Assuming Equal Number of Patients in the Two Arms

Bazedoxifene (n)	Raloxifene (n)	BZA: Raloxifene	RR		
			1	1.5	2
			95% CI of observed point estimate of RR		
2150	2150	1:1	0.5, 1.9	0.9, 2.7	1.2, 3.4

BZA: bazedoxifene, CI: confidence interval, RR: rate ratio

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 2.50 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.

9.8. Data transformation

Detailed methodology for data transformations are documented in the SAP, which is dated, filed and maintained by the Sponsor (see Annex 1. List of stand-alone documents).

9.9. Statistical methods

Detailed methodology for data transformations are documented in the SAP, which is dated, filed and maintained by the Sponsor (see Annex 1. List of stand-alone documents). Analyses were conducted separately for Spain and Italy as well as pooled. The pooled results are presented in this report and country-specific results are included in the Supplementary tables in the appendices.

9.9.1. Main summary measures

Descriptive statistics on available patient characteristics (e.g., age, body mass index (BMI), smoking, history of relevant medical diagnoses) are reported for all exposure groups (i.e. BZA, raloxifene, and bisphosphonate users) at index date.

Incidence rates (IRs) were calculated for all endpoints in all cohort groups i.e. BZA, raloxifene, and bisphosphonate users.

The incidence of each endpoint was estimated using both the cumulative incidence approach (incidence proportion) and an incidence density (person-time) approach.

Cumulative Incidence = (Total new cases during follow-up period / Total persons at risk during follow-up period)

For this equation, the numerator was defined as the total number of patients with a diagnosis of primary endpoints or secondary endpoints during follow-up period. The denominator was the total number of all patients at risk in the specific treatment group during the follow-up period. Patients that switched treatment appeared in the numerator and denominator of the respective treatment groups.

Secondly, an incidence density approach calculated time at risk in person-years, measured from first prescription to the end of the observation period. The incidence rate was reported as per 1000 person-years of observation, as shown in the following formula:

*Incidence rate = (Total new cases during follow-up period / Total person-years at risk during follow-up period)*1000*

The numerator was defined as the total number patients with end points of interest during follow-up period. The denominator was defined as the sum of person-years of patients during the follow-up period.

9.9.2. Main statistical methods

The study used regression analyses to estimate the incidence of selected clinical endpoints associated with BZA versus bisphosphonates, and BZA versus raloxifene. Specifically, hazard ratios (HRs) for BZA vs. bisphosphonates, and BZA vs. raloxifene were estimated using a Cox proportional hazards model.

For patients who have incidence of primary or secondary end points, person-time was equal the sum of days from their first prescription of treatment (index prescription) until the date of the incident condition (diagnosis of primary or secondary end points). For patients who did not experience an incidence of primary or secondary end points, person-time was equal to the sum of days from the first prescription of treatment (index prescription) to a censoring event or to the end of the study (at which all patients were censored), whichever occurred first. There was no consideration of days of supply or treatment gaps in determining duration of exposure.

In the determination of person-years, the date of first prescription of treatment was used as a surrogate for time of first exposure to treatment, since the date when the patient used their first treatment for osteoporosis may not have been consistently ascertainable. The same definition of person-time was used for all the study endpoints, provided they were all chronic diseases or malignancies with potentially long latency periods.

DVT, PE, RVST are component endpoints of the composite endpoint VTE. For this 3-component VTE endpoint, the time-to-event was the time to any one of those 3 component event terms, whichever occurred first. After that first event, the subject was censored for the primary VTE endpoint.

The study used multivariate regression analyses to estimate the risks of VTE (primary endpoint) and selected clinical endpoints (secondary endpoints) associated with BZA versus bisphosphonates, and BZA versus raloxifene, adjusting for potential confounders described above in section 9.4. Specifically, HRs for BZA vs. bisphosphonates and BZA versus raloxifene were estimated using an adjusted Cox proportional hazards model. Separate models were used for each reference group.

9.9.3. Missing values

For each variable, the number and proportion of patients in each treatment group with missing data were specified. Smoking status, alcohol consumption, height and/or weight (BMI) values were known to be missing for approximately 40-60% patients in IQVIA EMR databases based on previous studies. Dates are automatically recorded in the IQVIA EMR databases and doctors can select diseases codes from the pre-defined lists. In all analyses, if a comorbidity other than the diagnosis of osteoporosis was not recorded, it was assumed to be absent.

Handling of missing values is described in more detail in section 7 of the final statistical analysis plan.

9.9.4. Sensitivity analyses

The applicability of the third inclusion criterion *(i.e., a recorded diagnosis code of osteoporosis on or within 60 days prior to the index prescription date)* was evaluated through a sensitivity analysis during the interim analyses (data lock point of 15 April 2016). The evaluation involved comparing the risk of VTE between patients with a recorded diagnosis of osteoporosis within 60 days prior to the index prescription date, to those without a recorded

diagnosis within 60 days. This comparison was deemed necessary due to a significant number of patients (> 45%) missing a recorded diagnosis of osteoporosis. If the VTE rates of the two groups i.e., those with and without a recorded diagnosis osteoporosis were comparable (i.e., difference within 20%), this criterion was not included as this implied that the impact of excluding this criterion on the VTE rates was minimal, i.e., the potential for confounding of the estimation of the risk of VTE by the absence of a recorded diagnosis of osteoporosis was minimal.

A significant proportion of patients were missing the third eligibility criterion of having an osteoporosis diagnosis within 60 days before the index date (Table 6).

Table 6. Summary information on Inclusion Criterion of Osteoporosis Diagnosis (Interim Analyses)

		Bazedoxifene (N=1263)		**Raloxifene (N=2427)**		**Bisphosphonate (N=11405)**	
		N	%	N	%	N	%
Osteoporosis diagnosis	60 days before index date	680	53.8	1233	50.8	7645	67
	Anytime throughout medical history *	83	6.6	188	7.7	1116	9.8
	Missing	500	39.6	1006	41.5	2644	23.2

* Excluding patients with diagnosis 60 days before index date. Pooled analysis Italy + Spain.

The utility of the third eligibility criterion was evaluated through performing a sensitivity analysis comparing those with osteoporosis diagnosis code within 60 days before the index date and those without the diagnosis code within 60 days before the index date (Table 7). The VTE rates of the two groups were comparable; 2.2% (for those with osteoporosis diagnosis code within 60 days) vs. 2.0% (those without osteoporosis diagnosis within 60 days) (i.e., difference within 20%), and the decision was made (and communicated in the interim report) to combine the two groups and therefore include all patients for further analyses (i.e., in the interim and final study analyses), regardless of the presence of an osteoporosis diagnosis code.

Table 7. Sensitivity Analysis of Inclusion Criterion of Osteoporosis Diagnosis - Incidence Rates of Venous Thromboembolism

	Osteoporosis diagnosis*					
	Yes (N=9558)		No (N=5537)		Total (N=15095)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
VTE	215	2.2 (2.0 -2.6)	113	2.0 (1.7 – 2.4)	328	2.2 (2 – 2.4)
DVT	192	2.0 (1.7 – 2.3)	95	1.7 (1.4 – 2.1)	287	1.9 (1.7 – 2.1)
PE	23	0.2 (0.2 – 0.4)	17	0.3 (0.2 – 0.5)	40	0.3 (0.2 – 0.4)
RVST	3	0.0 (0.0 – 0.1)	4	0.1 (0.0 – 0.2)	7	0.0 (0.0 – 0.1)

CI: confidence interval; DVT: deep vein thrombosis; PE: pulmonary embolism; RVST: retinal vein and sinus thrombosis. VTE: venous thromboembolism
* Patients with diagnosis within 60 days before index date. Pooled analysis Italy + Spain.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

IQVIA's research team documented the progress, as well as the scientific and quality review of all study activities and deliverables, and also documented the quality assurance measures performed for each study activity during the conduct of the study.

Data validation occurred throughout the data management and analysis processes. Data quality checks included, but were not limited to, programming checks for the study for internal dataset consistency, and checks to ensure that protocol criteria were met. If validation checks were not satisfied then an examination of the problem was performed on the dataset or datasets in question, and the problem resolved.

9.11. Protection of human subjects

Subject information and consent

Not applicable, since this was a secondary data collection study using fully anonymized data.

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

All database records were de-identified and fully compliant with European and National regulations.

IRB/Ethics Committee approvals were not necessary because the study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE)[6], the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidance, and Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines.

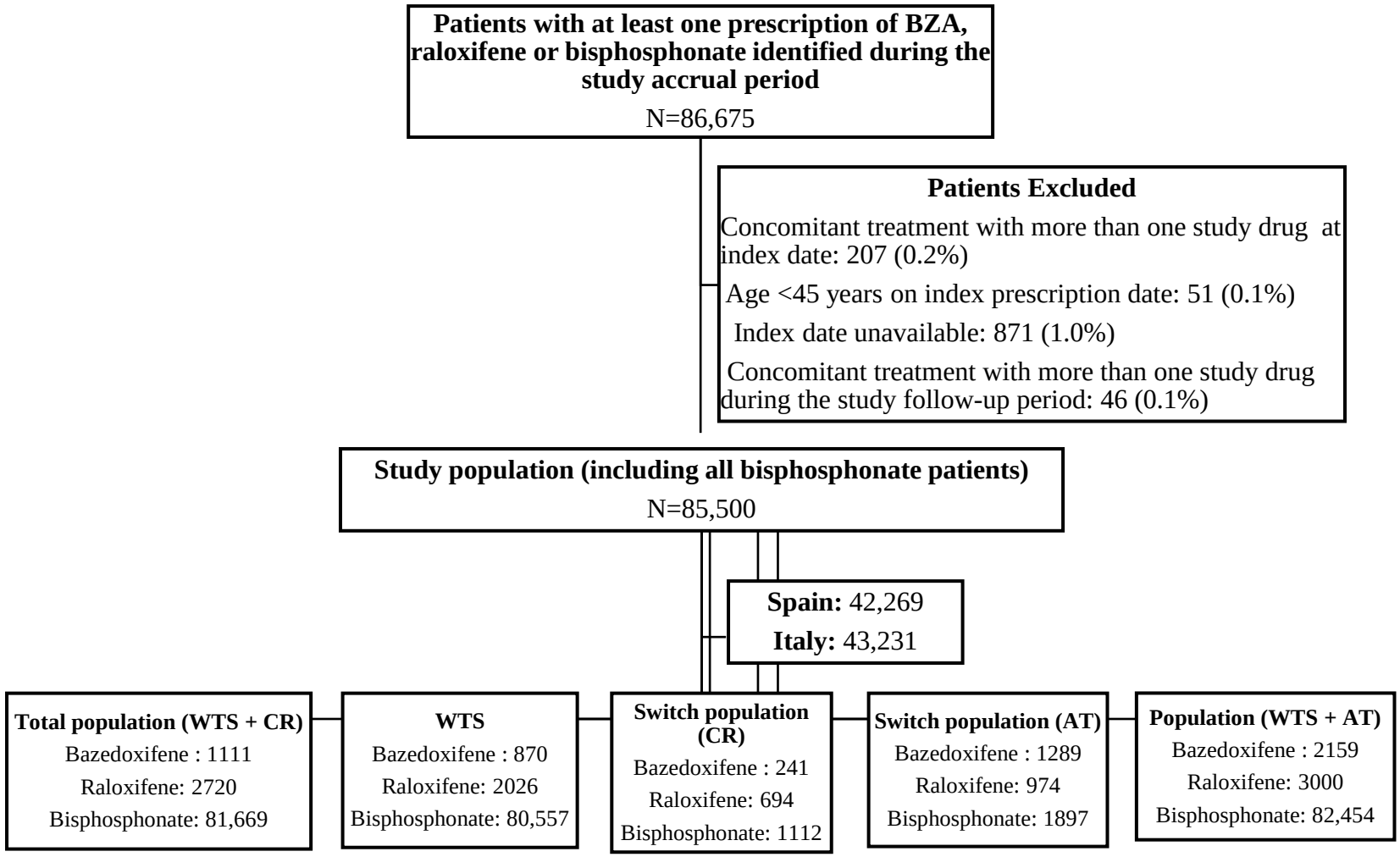
10. RESULTS

10.1. Participants

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). The reasons for exclusion from the study population are described in Figure 2: 'Concomitant treatment with more than one study drug at index date', 207 (0.2%); 'Age <45 years on index prescription date' 51 (0.1%); 'Index date unavailable', 871 (1.0%); and 'Concomitant treatment with more than one study drug during the study follow-up period', 46 (0.1%). A total of 85,500 patients remained after the exclusion criteria were applied.

Overall, 43,231/85,500 (50.6%) patients were from Italy and 42,269/85,500 (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. The low percentage of patients who reported switching treatment is noteworthy as it has implications for the distinction between as-treated and ever-treated analyses and the impact of these analyses on the overall study results.

Figure 2. Identification of the study population



AT: as-treated; CR: cumulative risk; FU: follow-up, WTS: Without treatment switch.

Of these 85,500 patients, 1111(1.3%) received BZA, 2720 (3.2%) received raloxifene, and 81,669 (95.5%) received bisphosphonate (CR approach + without treatment switch) (Figure 2).

As the bisphosphonate recipient population in the database was much larger than the BZA (and raloxifene) population, at the recommendation of PRAC, a random sample of bisphosphonate patients (without replacement, target ratio bisphosphonate: BZA of 6:1) was included in the analysis.

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 (Table 8).

Table 8. Summary of Identification of Study Population

Parameter	Population (including all bisphosphonate patients)		Population (including randomly selected sample of bisphosphate patients)	
	n	%	n	%
Patients with at least one prescription of BZA, raloxifene or bisphosphonate identified during the study accrual period	N=86,675		-	
Population (including all bisphosphonate patients)	86,675	100.0	-	-
Total patients excluded	1175	1.4	-	-
Concomitant treatment with more than one study drug at index date	207	0.2	-	-
Age <45 years on index prescription date	51	0.1	-	-
Index date unavailable	871	1.0	-	-
Concomitant treatment with more than one study drug during the study follow-up period	46	0.1	-	-
Study population	N=85,500		N=10,497	
Patients without treatment switch (WTS)	83,453	97.6	9468	90.2
Patients who switched treatment	2047	2.4	1,029	9.8
Italy	N=43,231		N=3822	
Patients without treatment switch (WTS)	43,062	99.6	3,700	100
Patients who switched treatment	169	4.4	122	3.2
Spain	N=42,269		N=6675	
Patients without treatment switch (WTS)	40,391	95.6	5768	86.4
Patients who switched treatment	1878	4.4	907	13.6

BZA: bazedoxifene, WTS: without treatment switch

10.1.1. Patient follow-up

The mean length of follow-up was over 70 months for all 3 treatment groups. Mean (standard deviation [SD]) length of follow-up was the highest for the raloxifene group at 77.7 (28.2) months, followed by BZA at 76.5 (21.4) months and bisphosphonate at 70.3 (28.0) months. The mean (SD) number of prescriptions for the index treatment during follow-up was highest for the raloxifene group at 35.3 (29.4), followed by the bisphosphonate group at 22.1 (22.6) and BZA at 21.5 (25.3) (Table 9).

Table 9. Summary of Patient follow-up Information

		Bazedoxifene (N=1111)	**Raloxifene (N=2720)**	**Bisphosphonate (N=6666)**
Average length of follow-up* (in months)	Mean (SD)	76.5 (21.4)	77.7 (28.2)	70.3 (28.0)
	Median	82.8	92.1	75.9
Length of follow-up* (in months)	0	3 (0.3%)	4 (0.1%)	11 (0.2%)
	1-11	17 (1.5%)	49 (1.8%)	223 (3.3%)
	12-17	12 (1.1%)	46 (1.7%)	167 (2.5%)
	18-23	13 (1.2%)	47 (1.7%)	158 (2.4%)
	24-35	38 (3.4%)	155 (5.7%)	432 (6.5%)
	36-41	15 (1.4%)	99 (3.6%)	255 (3.8%)
	42-49	21 (1.9%)	130 (4.8%)	389 (5.8%)
	≥50	992 (89.3%)	2190 (80.5%)	5031 (75.5%)
Number of prescriptions of the index treatment during follow-up	Mean (SD)	21.5 (25.3)	35.3 (29.4)	22.1 (22.6%)
	Median	11	29	15
	Range	1 – 269	1 – 136	1 – 285

SD: standard deviation
* Follow-up is calculated from index date to first incident primary event or date of last contact.

The proportion of patients missing an osteoporosis diagnosis in medical records in the 60 days before index date, in all of the available medical history before index date, and time since osteoporosis diagnosis, in months, are reported in Table 10. Given that a considerable proportion of patients were missing a recorded diagnosis of osteoporosis, the initial eligibility criterion of having an osteoporosis diagnosis within 60 days before the index date, was not applied to the study. The proportion of patients missing diagnosis of osteoporosis decreased when reviewing data from all the available medical history prior to the index date. The mean (SD) time from osteoporosis diagnosis to the index date was the longest in bisphosphonate patients (44.9 [38.9] months), followed by raloxifene patients (41.4 [42.8] months) and BZA patients (19.7 [22.7] months).

Table 10. Summary of Recording of Osteoporosis Diagnosis

		Bazedoxifene (N=1111)		Raloxifene (N=2720)		Bisphosphonate (N=6666)	
		n	%	n	%	n	%
Osteoporosis diagnosis recorded in the 60 days before index date	Yes	557	50.1	1406	51.7	4448	66.7
	No	554	49.9	1314	48.3	2218	33.3
		n	%	n	%	n	%
Osteoporosis diagnosis recorded in entire history before index date	Yes	643	57.9	1643	60.4	5122	76.8
	No	468	42.1	1077	39.6	1544	23.2
Time from date of recorded osteoporosis diagnosis* to index date (months)	N (%)	643 (100)	-	1643 (100)	-	5122 (100)	
	Mean (SD)	19.7 (22.7)	-	41.4 (42.8)	-	44.9 (38.9)	-
	Median	11. 3	-	32.6	-	33.9	-
	Range	0	118	0	806.2	0	250.3

*Most recent recorded diagnosis prior to index date
SD: standard deviation
Pooled analysis Italy + Spain.

10.2. Descriptive data

10.2.1. Demographic and baseline characteristics

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 (Table 11). A larger percentage of bisphosphonate users were ≥70 years of age (56.2%) compared to the other two groups (BZA: 17.9%; raloxifene: 27.5 %).

Any BMI ≤ 14 kg/m^2 was considered to be an error and the value was set to 'missing'. The median 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.

Table 11. Patient Demographic and Baseline Characteristics

		Bazedoxifene (N=1111)		Raloxifene (N=2720)		Bisphosphonate (N=6666)	
Age	N (%)	1111 (100)	-	2720 (100)	-	6666 (100)	-
	Mean (SD)	61.6 (9.0)	-	64.8 (8.8)		71.0 (10.3)	-
	Median	60	-	64	-	71	-
	Range	45	90	45	97	45	101
		n	**%**	**n**	**%**	**n**	**%**
Age Group (years)	45-49	51	4.6	78	2.9	88	1.3
	50-59	479	43.1	665	24.4	915	13.7
	60-69	382	34.4	1229	45.2	1915	28.7
	≥70	199	17.9	748	27.5	3748	56.2
BMI kg/m^2 (only BMI >14 kg/m^2)	N (%)	370 (33.3)	-	1289 (47.4)	-	3784 (56.8)	-
	Mean (SD)	27.3 (5.29)	-	27.1 (4.85)	-	26.8 (5.05)	-
	Median	26.9	-	26.7	-	26	-
	Range	16	49	15	47.9	14.5	52.1
	Missing, N (%)	741 (66.7)	-	1431 (52.6)	-	2882 (43.2)	-
		n	**%**	**n**	**%**	**n**	**%**
BMI Group kg/m^2	<18.5 (Underweight)	8	2.2	21	1.6	86	2.3
	18.5- <25 (Normal)	125	33.8	423	32.8	1404	37.1
	25- <30 (Overweight)	132	35.7	508	39.4	1358	35.9
	≥30 (Obese)	105	28.4	337	26.1	936	24.7
	Missing (N)	741	-	1431	-	2882	-
		n	**%**	**n**	**%**	**n**	**%**
Smoker	Yes	92	8.3	408	15.0	884	13.3
	No/missing	1019	91.7	2312	85.0	5782	86.7
		n	**%**	**n**	**%**	**n**	**%**
Alcohol	Yes	133	12.0	585	21.5	1768	26.5
	No/missing	978	88.0	2135	78.5	4898	73.5

BMI: body mass index; SD: standard deviation.

Pooled analysis Italy + Spain.

10.2.2. Patient medical history

Information regarding any past medical history is provided in Table 12. Patients on bisphosphonate reported higher medical history of VTEs (DVT, PE, or RVST), and comorbidities, as compared to patients on BZA or raloxifene.

Table 12. Patient Medical History

		Bazedoxifene (N=1111)		Raloxifene (N=2720)		Bisphosphonate (N=6666)	
		n	%	n	%	n	%
History of Diabetes	Yes	70	6.3	222	8.2	874	13.1
	No	1041	93.7	2498	91.8	5792	86.9
History of Hypertension	Yes	303	27.3	1,008	37.1	3498	52.5
	No	808	72.7	1712	62.9	3168	47.5
History of Malignancies	Yes	34	3.1	138	5.1	666	10.0
	No	1077	96.9	2582	94.9	6000	90.0
History of DVT	Yes	13	1.2	41	1.5	317	4.8
	No	1098	98.8	2679	98.5	6349	95.2
History of PE	Yes	1	0.1	3	0.1	35	0.5
	No	1110	99.9	2717	99.9	6631	99.5
History of RVST	Yes	1	0.1	-		15	0.2
	No	1110	99.9	2720	100	6651	99.8

DVT: deep vein thrombosis; PE: pulmonary embolism; RVST: retinal vein and sinus thrombosis.
Pooled analysis Italy + Spain.

10.3. Outcome data

10.3.1. Cumulative incidence of primary endpoints

The primary endpoint, VTE, was a composite endpoint of either DVT, PE or RVST. The first component event to occur constituted the VTE event. As a single patient may have experienced more than 1 component event, the number of component events do not sum to the number of composite VTE events for the raloxifene and bisphosphonate groups. 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 (Table 13).

Table 13. Cumulative Incidence of Primary Endpoints

	Bazedoxifene (N=1111)		**Raloxifene (N=2720)**		**Bisphosphonate (N=6666)**	
	n	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
VTE (Primary endpoint)	17	1.5 (1.0-2.4)	60	2.2 (1.7-2.8)	305	4.6 (4.1-5.1)
DVT	15	1.4 (0.8-2.2)	52	1.9 (1.5-2.5)	256	3.8 (3.4-4.3)
PE	2	0.2 (0.0-0.7)	7	0.3 (0.1-0.5)	53	0.8 (0.6-1.0)
RVST	-	-	2	0.1 (0.0-0.3)	7	0.1 (0.1-0.2)

CI: confidence interval, DVT: deep vein thrombosis; PE: pulmonary embolism; RVST: retinal vein and sinus thrombosis; VTE: venous thromboembolism

10.3.2. Cumulative incidence of secondary endpoints

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.

Most secondary events occurred in the bisphosphonate group, fractures were most frequently reported event (12.8%), followed by ocular events (10.8%) and depression (8.6%). In the raloxifene group, ocular events were the most frequently reported (12.5%), followed by hypertriglyceridemia (10.6%), and depression (9.2%). The most frequently reported secondary endpoint in the BZA group was depression (10.1%), followed by hypertriglyceridemia (9.7%) and ocular events (8.0%) (Table 14).

Table 14. Cumulative Incidence of Secondary Endpoints

	Bazedoxifene (N=1111)		Raloxifene (N=2720)		Bisphosphonate (N=6666)	
	n	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
Ischemic Stroke	24	2.2 (1.5-3.2)	71	2.6 (2.1-3.3)	449	6.7 (6.2-7.4)
Cardiac Disorders	22	2 (1.3-3.0)	82	3 (2.4-3.7)	443	6.6 (6.1-7.3)
All Malignancies	35	3.2 (2.3-4.3)	120	4.4 (3.7-5.2)	441	6.6 (6-7.2)
Malignancies - Thyroid	-	-	3	0.1 (0-0.3)	13	0.2 (0.1-0.3)
Malignancies - Breast	4	0.4 (0.1-0.9)	17	0.6 (0.4-1.0)	92	1.4 (1.1-1.7)
Malignancies - Renal	-	-	2	0.1 (0.0-0.3)	6	0.1 (0.0-0.2)
Malignancies - Genital / Urogenital	6	0.5 (0.2-1.2)	10	0.4 (0.2-0.7)	31	0.5 (0.3-0.7)
Malignancies - Lung	3	0.3 (0.1-0.8)	10	0.4 (0.2-0.7)	22	0.3 (0.2-0.5)
Malignancies - Gastrointestinal	12	1.1 (0.6-1.9)	30	1.1 (0.8-1.6)	101	1.5 (1.2-1.8)
Malignancies - Respiratory	1	0.1 (0.0-0.5)	-	-	4	0.1 (0.0-0.2)
Ocular Events	89	8.0 (6.6-9.8)	339	12.5 (11.3-13.8)	723	10.8 (10.1-11.6)
Atrial Fibrillation	31	2.8 (2.0-3.9)	116	4.3 (3.6-5.1)	436	6.5 (6.0-7.2)
Fractures	49	4.4 (3.4-5.8)	224	8.2 (7.3-9.3)	850	12.8 (12.0-13.6)
Renal Effects	9	0.8 (0.4-1.5)	63	2.3 (1.8-3.0)	317	4.8 (4.3-5.3)
Biliary Events	20	1.8 (1.2-2.8)	55	2.0 (1.6-2.6)	264	4.0 (3.5-4.5)
Depression	112	10.1 (8.4-12.0)	251	9.2 (8.2-10.4)	572	8.6 (7.9-9.3)
Hypertriglyceridemia	108	9.7 (8.1-11.6)	287	10.6 (9.5-11.8)	397	6.0 (5.4-6.5)
Goitre (Thyroid)	18	1.6 (1.0-2.5)	67	2.5 (1.9-3.1)	256	3.8 (3.4-4.3)

CI: confidence interval

10.4. Main results

10.4.1. Incidence rate of primary endpoints

The bisphosphonate group had the highest IR [95% CI] of the primary endpoint VTE (8.0 [7.1 − 8.9]), followed by the raloxifene group (3.5 [2.6 – 4.3]), and the BZA group (2.4 [1.3 – 3.6]) (Table 15).

Table 15. Incidence Rate of Primary Endpoints

	Bazedoxifene (N=1111)		**Raloxifene (N=2720)**		**Bisphosphonate (N=6666)**	
	IR	**(95% CI)**	**IR**	**(95% CI)**	**IR**	**(95% CI)**
VTE / 1000 PY (Primary endpoint)	2.4	(1.3-3.6)	3.5	(2.6-4.3)	8.0	(7.1-8.9)
DVT / 1000 PY	2.1	(1.1-3.2)	3.0	(2.2-3.8)	6.7	(5.9-7.5)
PE / 1000 PY	0.3	(0.0-0.7)	0.4	(0.1-0.7)	1.4	(1.0-1.7)
RVST / 1000 PY	0.0	(0.0-0.0)	0.1	(0.0-0.3)	0.2	(0.1-0.3)

CI: confidence interval; DVT: deep vein thrombosis; IR: incidence rate; PE: pulmonary embolism; PY: person-years; RVST: retinal vein and sinus thrombosis; VTE: venous thromboembolism
Pooled analysis Italy + Spain.

10.4.2. Incidence rate of secondary endpoints

In general, lower IRs of secondary endpoints were observed in BZA group compared to the raloxifene and bisphosphonate groups. No thyroid and renal malignancy events were observed in the BZA treatment group (Table 16).

The highest IRs observed in each group were for fractures among bisphosphonate users (IR 23.4 [95% CI: 21.9 – 25.0]), ocular events among raloxifene users (IR 21.0 [95% CI: 18.8 – 23.3]), and depression among BZA users (IR 16.7 [95% CI: 13.6 – 19.8]), per 1000 person-years (Table 16).

Table 16 Incidence Rate of Secondary Endpoints

	Bazedoxifene (N=1111)		**Raloxifene (N=2720)**		**Bisphosphonate (N=6666)**	
	IR	**(95% CI)**	**IR**	**(95% CI)**	**IR**	**(95% CI)**
Ischemic Stroke / 1000 PY	3.4	(2.1-4.8)	4.1	(3.1-5.0)	11.9	(10.8-13.0)
Cardiac disorders / 1000 PY	3.1	(1.8-4.5)	4.7	(3.7-5.8)	11.7	(10.6-12.8)
All Malignancies / 1000 PY	5.0	(3.4-6.7)	7.0	(5.7-8.2)	11.7	(10.6-12.8)
Malignancies-Thyroid / 1000 PY	0.0	(0.0-0.0)	0.2	(0.0-0.4)	0.3	(0.2-0.5)
Malignancies-Breast / 1000 PY	0.6	(0.0-1.1)	1.0	(0.5-1.4)	2.4	(1.9-2.9)
Malignancies-Renal / 1000 PY	0.0	(0.0-0.0)	0.1	(0.0-0.3)	0.2	(0.0-0.3)
Malignancies-Genital/Urogenital / 1000 PY	0.9	(0.2-1.5)	0.6	(0.2-0.9)	0.8	(0.5-1.1)
Malignancies-Lung / 1000 PY	0.4	(0.0-0.9)	0.6	(0.2-0.9)	0.6	(0.3-0.8)
Malignancies-Gastrointestinal / 1000 PY	1.7	(0.7-2.7)	1.7	(1.1-2.3)	2.6	(2.1-3.1)
Malignancies-Respiratory / 1000 PY	0.1	(0.0-0.4)	0.0	(0.0-0.0)	0.1	(0.0-0.2)
Ocular Events / 1000 PY	13.2	(10.5-16.0)	21.0	(18.8-23.3)	19.9	(18.5-21.4)
Atrial Fibrillation / 1000 PY	4.4	(2.9-6.0)	6.7	(5.5-7.9)	11.5	(10.4-12.6)
Fractures / 1000 PY	7.1	(5.1-9.1)	13.3	(11.6-15.0)	23.4	(21.9-25.0)
Renal Effects / 1000 PY	1.3	(0.4-2.1)	3.6	(2.7-4.5)	8.3	(7.4-9.3)
Biliary Events / 1000 PY	2.8	(1.6-4.1)	3.2	(2.3-4.0)	6.9	(6.1-7.8)
Depression / 1000 PY	16.7	(13.6-19.8)	15.2	(13.3-17.0)	15.5	(14.3-16.8)
Hypertriglyceridemia / 1000 PY	16.0	(13.0-19.0)	17.4	(15.4-19.4)	10.6	(9.6-11.6)
Goitre (Thyroid) / 1000 PY	2.6	(1.4-3.8)	3.9	(2.9-4.8)	6.7	(5.9-7.5)

CI: confidence interval; IR: incidence rate; PY: person-years,
Pooled analysis Italy + Spain

10.4.3. Hazard ratios for primary endpoints

Crude and adjusted hazard ratios for the primary endpoint are shown in Table 17. Two separate models for each event were run: (1.) BZA versus bisphosphonate; and (2.) BZA versus raloxifene.

In the results from the adjusted Cox proportional hazards analyses, the risk of VTE was significantly lower in the BZA group when compared with the bisphosphonate group (HR [95% CI]: 0.4 [0.2 – 0.6]; p<0.01). A similar lower risk of DVT, the most common component of the VTE composite endpoint, was observed in the BZA group when compared to the bisphosphonate group (HR [95% CI]: 0.4 [0.2 – 0.6] p<0.01). However, no statistically significant difference was found between BZA and raloxifene regarding VTE or DVT endpoints (0.9 [0.4 – 2.2], p=0.91; 0.9 [0.4 – 2.0], p=0.73, respectively). Cox proportional hazards analyses were not performed for PE and RVST because the number of events in those groups were too few.

Table 17. Crude and Adjusted Hazard Ratios for Primary Endpoint

Event	Comparator	Reference	Crude Hazard Ratio			Adjusted Hazard Ratio		
			HR	(95% CI)	P-value	HR	(95% CI)	P-value
VTE (primary endpoint)								
	Bazedoxifene	Bisphosphonate	0.3	(0.2-0.4)	<0.01	0.4	(0.2-0.6)	<0.01
	Bazedoxifene	Raloxifene	0.9	(0.4-2.1)	0.81	0.9	(0.4-2.2)	0.91
DVT								
	Bazedoxifene	Bisphosphonate	0.3	(0.2-0.4)	<0.01	0.4	(0.2-0.6)	<0.01
	Bazedoxifene	Raloxifene	0.8	(0.3-1.9)	0.62	0.9	(0.4-2.0)	0.73

CI: confidence interval, DVT: deep vein thrombosis; HR: hazard ratio; PE: pulmonary embolism, RVST: retinal vein and sinus thrombosis, VTE: venous thromboembolic event.
The following variables were included in the adjusted models: Group treatments, Age group, Smoker, Alcohol, Osteoporosis in all history, Medical history of diabetes, Medical history of hypertension, Medical history of malignancies, Medical history of DVT.
In the multivariate analyses a backward selection method for covariates was utilized with the treatment group variable forced into the models.
Too few events to compute HR for PE and RVST endpoints.

10.4.4. Hazard ratios for secondary endpoints

Crude and adjusted hazard ratios for the secondary endpoints are shown in Table 18. Two separate models for each event were run: (1.) BZA versus bisphosphonate; and (2.) BZA versus raloxifene.For the adjusted analyses of secondary events, a significantly lower risk ($p<0.01$) was identified in the BZA group, when compared to the bisphosphonate group for the following endpoints: ischemic stroke, cardiac disorders, malignancies, ocular events, fractures, renal effects, biliary events, hypertriglyceridemia and goitre (thyroid). Moreover, there was a significantly lower risk in the BZA group when compared to the raloxifene group for fractures ($p=0.01$).

Table 18. Crude and Adjusted Hazard Ratios for Secondary Endpoints

Event	Comparator	Reference	Crude Hazard Ratio			Adjusted Hazard Ratio		
			HR	(95% CI)	P-value	HR	(95% CI)	P-value
Ischemic Stroke								
	Bazedoxifene	Bisphosphonate	0.3	(0.2-0.4)	<0.01	0.5	(0.3-0.7)	<0.01
	Bazedoxifene	Raloxifene	1.1	(0.5-2.4)	0.81	1.1	(0.5-2.4)	0.76
Cardiac disorders								
	Bazedoxifene	Bisphosphonate	0.3	(0.2-0.4)	<0.01	0.6	(0.3-0.9)	0.01
	Bazedoxifene	Raloxifene	0.7	(0.3-1.3)	0.24	0.7	(0.4-1.5)	0.37
Malignancies								
	Bazedoxifene	Bisphosphonate	0.4	(0.3-0.6)	<0.01	0.5	(0.3-0.7)	<0.01
	Bazedoxifene	Raloxifene	0.7	(0.4-1.2)	0.22	0.8	(0.5-1.4)	0.38
Ocular Events								
	Bazedoxifene	Bisphosphonate	0.7	(0.6-0.9)	<0.01	0.8	(0.6-1.0)	0.03
	Bazedoxifene	Raloxifene	0.7	(0.5-1.0)	0.08	0.8	(0.6-1.1)	0.19
Atrial Fibrillation								
	Bazedoxifene	Bisphosphonate	0.4	(0.3-0.6)	<0.01	0.7	(0.5-1.1)	0.1
	Bazedoxifene	Raloxifene	0.7	(0.4-1.2)	0.15	0.7	(0.4-1.2)	0.19
Fractures								
	Bazedoxifene	Bisphosphonate	0.3	(0.2-0.4)	<0.01	0.4	(0.3-0.6)	<0.01
	Bazedoxifene	Raloxifene	0.6	(0.4-0.9)	0.01	0.6	(0.4-0.9)	0.01
Renal Effects								
	Bazedoxifene	Bisphosphonate	0.1	(0.1-0.3)	<0.01	0.3	(0.1-0.5)	<0.01
	Bazedoxifene	Raloxifene	0.3	(0.1-0.8)	0.02	0.4	(0.2-1.0)	0.06
Biliary Events								
	Bazedoxifene	Bisphosphonate	0.4	(0.2-0.6)	<0.01	0.4	(0.3-0.7)	<0.01
	Bazedoxifene	Raloxifene	0.9	(0.4-2.1)	0.84	1.0	(0.4-2.2)	0.9
Depression								
	Bazedoxifene	Bisphosphonate	1.1	(0.9-1.4)	0.42	1.2	(0.9-1.5)	0.24

Event	Comparator	Reference	Crude Hazard Ratio			Adjusted Hazard Ratio		
			HR	(95% CI)	P-value	HR	(95% CI)	P-value
	Bazedoxifene	Raloxifene	1.1	(0.8-1.6)	0.51	1.1	(0.8-1.6)	0.59
Hypertriglyceridemia								
	Bazedoxifene	Bisphosphonate	2.0	(1.6-2.6)	<0.01	1.9	(1.4-2.5)	<0.01
	Bazedoxifene	Raloxifene	0.9	(0.7-1.3)	0.74	0.9	(0.7-1.3)	0.74
Goitre (Thyroid)								
	Bazedoxifene	Bisphosphonate	0.3	(0.2-0.5)	<0.01	0.3	(0.2-0.5)	<0.01
	Bazedoxifene	Raloxifene	0.6	(0.3-1.1)	0.11	0.6	(0.3-1.3)	0.24

CI: confidence interval; HR: hazard ratio,
The following variables were included in the adjusted models: Group treatments, Age group, Smoker, Alcohol, Osteoporosis in all history, Medical history of diabetes, Medical history of hypertension, Medical history of malignancies, Medical history of deep vein thrombosis. In the multivariate analyses a backward selection method for covariates was utilized with the treatment group variable forced into the models.

10.5. Other analyses

Stratification of primary and secondary endpoints by age and BMI did not provide any further significant insight into the study results, partly due to few events in the BZA group. For more details regarding stratification of primary and secondary endpoint incidences by age and BMI (see Supplementary tables in Annex 1)

10.5.1. Cumulative incidence and incidence rate of primary and secondary endpoints stratified by age and BMI

There were no changes in the overall trends previously observed in the main analyses (cumulative incidence and IRs of primary and secondary endpoints) and when further stratified by age and BMI; the bisphosphonate group continued to present the highest IRs (see Supplementary tables in Annex 1). Most results, when stratified by age or BMI, largely followed the pattern of results shown in Table 15 (primary endpoint) and Table 16 (secondary endpoints) as compared to the total population without stratification.

10.5.2. Patients who switched treatment

As patients were able to receive multiple (sequential, not concomitant) treatments for osteoporosis during the follow-up period (switch treatment), patients who switched treatment groups were also classified and analysed in two ways, using the AT approach and CR approach. The AT patients were analysed according to the treatment they actually received. Patients could have been counted in multiple treatment groups if they received more than one treatment. The CR patients were counted in the group of their first treatment during the study accrual period and were considered in this group during all of the follow-up, similar to an ‘intention to treat’ analysis.

10.5.2.1. Demographic and baseline characteristics

In the CR population, the distribution of patients was BZA 241/1029 (23.4%), raloxifene 694/1029 (67.4%), and bisphosphonate 94/1029 (9.1%), (Table 19). In the AT group, the

distribution of patients was BZA 501/2101 (23.8%), raloxifene 721/2101 (34.3%) and bisphosphonate 879/2101 (41.8%).

The mean (SD) ages of patients were 60.3 (8.5), 64 (8.1), and 63 (7.1) years for BZA, raloxifene and bisphosphonates treatment groups, respectively, within the CR population. Within the AT population the mean (SD) ages were 62.3 (8.3), 63.9 (8.1), and 65.6 (8.4) years for BZA, raloxifene and bisphosphonates, respectively.

BMI was comparable in the CR and AT populations. Overall, there were more missing values for BMI in the CR and AT populations, ranging between 55.2% - 71.3% compared to the 43.2% - 66.7% in the study population with the random selection of bisphosphonate patients (Table 11, Table 19).

Regarding smoking and alcohol intake, the main difference was that there were more smokers and alcohol consumers in the bisphosphonate group within the study population (13.3% and 26.5%, respectively) compared to the CR (7.4% and 12.8%) and AT populations (11.3% and 14.3%) (Table 19).

Table 19. Patient Demographic and Baseline Characteristics -Patients who Switched Treatment.

		CR						AT					
		Bazedoxifene (N=241)		Raloxifene (N=694)		Bisphosphonate (N=94)		Bazedoxifene (N=501)		Raloxifene (N=721)		Bisphosphonate (N=879)	
Age	N %	241 (100)	-	694 (100)	-	94 (100)	-	501 (100)	-	721 (100)	-	879 (100)	-
	Mean (SD)	60.3 (8.46)	-	64 (8.09)	-	63 (7.14)	-	62.3 (8.25)	-	63.9 (8.05)	-	65.6 (8.36)	-
	Median	59	-	64	-	62.5	-	62	-	64	-	65	-
	Range	46	90	45	93	47	82	45	94	45	93	46	93
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**
Age Group	45-49 (%)	11	4.6	22	3.2	3	3.2	16	3.2	22	3.1	14	1.6
	50-59 (%)	118	49	191	27.5	27	28.7	182	36.3	199	27.6	209	23.8
	60-69 (%)	81	33.6	311	44.8	49	52.1	214	42.7	324	44.9	390	44.4
	≥70 (%)	31	12.9	170	24.5	15	16	89	17.8	176	24.4	266	30.3
BMI kg/m^2 (only BMI >14 kg/m^2)	N (%)	72 (29.9)	-	311 (44.8)	-	27 (28.7)	-	152 (30.3)	-	317 (44)	-	282 (32.1)	-
	Mean (SD)	25.7 (4.67)		26.3 (4.6)		26.1 (3.61)		26.2 (4.39)	-	26.3 (4.58)	-	26.3 (4.48)	-
	Median	25.1	-	26	-	26.1	-	25.7		26		26	
	Range	18.4	41.2	17	43.4	20.2	35.7	18.4	41.2	17	43.4	14.8	43.4
	Missing N (%)	169 (70.1)	-	383 (55.2)	-	67 (71.3)	-	349 (69.7)		404 (56)		597 (67.9)	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**
BMI Group kg/m^2	<18.5 (Underweight)	1	1.4	5	1.6	-	-	1	0.7	5	1.6	6	2.1

		CR						AT					
		Bazedoxifene (N=241)		**Raloxifene (N=694)**		**Bisphosphonate (N=94)**		**Bazedoxifene (N=501)**		**Raloxifene (N=721)**		**Bisphosphonate (N=879)**	
	18.5- <25 (Normal)	33	45.8	126	40.5	7	25.9	64	42.1	128	40.4	107	37.9
	25- <30 (Overweight)	29	40.3	115	37	16	59.3	62	40.8	119	37.5	112	39.7
	≥30 (Obese)	9	12.5	65	20.9	4	14.8	25	16.4	65	20.5	57	20.2
	Missing (N)	169	-	383	-	67	-	349	-	404	-	597	-
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Smoker	Yes	24	10	97	14	7	7.4	36	7.2	103	14.3	99	11.3
	No/missing	217	90	597	86	87	92.6	465	92.8	618	85.7	780	88.7
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alcohol	Yes	31	12.9	141	20.3	12	12.8	55	11	146	20.2	126	14.3
	No/missing	210	87.1	553	79.7	82	87.2	446	89	575	79.8	753	85.7

AT: as-treated, BMI: body mass index, CR: cumulative risk, SD: standard deviation

10.5.2.2. Incidence rate of primary endpoints

In the CR and AT populations, the IRs of the primary endpoints were lowest in the BZA group compared to the raloxifene and bisphosphonate treatment groups, (Table 20).

Table 20. Incidence Rate of Primary Endpoints - Patients who Switched Treatment

	CR						AT					
	Bazedoxifene (N=241)		Raloxifene (N=694)		Bisphosphonate (N=94)		Bazedoxifene (N=501)		Raloxifene (N=721)		Bisphosphonate (N=879)	
	IR	(95% CI)	IR	(95% CI)	IR	(95% CI)	IR	(95% CI)	IR	(95% CI)	IR	(95% CI)
VTE / 1000 person-years (Primary endpoint)	1.2	(0.0-2.9)	2.3	(1.0-3.7)	2.8	(0.0-6.7)	1.6	(0.0-3.3)	3.4	(0.7-6.2)	2.1	(0.5-3.6)
DVT / 1000 person-years	1.2	(0.0-2.9)	2.1	(0.8-3.4)	1.4	(0.0-4.1)	1.0	(0.0-2.5)	3.4	(0.7-6.2)	1.8	(0.4-3.2)
PE / 1000 person-years	0.0	(0.0-0.0)	0.0	(0.0-0.0)	1.4	(0.0-4.1)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.3	(0.0-0.9)
RVST / 1000 person-years	0.0	(0.0-0.0)	0.2	(0.0-0.6)	0.0	(0.0-0.0)	0.5	(0.0-1.5)	0.0	(0.0-0.0)	0.0	(0.0-0.0)

AT: as-treated; CI: confidence interval; CR: cumulative risk; DVT: deep vein thrombosis; IR: incidence rate; PE: pulmonary embolism; RVST: retinal vein and sinus thrombosis; VTE: venous thromboembolism

10.5.3. Entire bisphosphonate treatment group

10.5.3.1. Demographic characteristics

As described earlier, a random selection was performed to reduce the number of patients in the bisphosphonate group. However, in the analyses in this section, all bisphosphonate patients are included the analyses and the analyses were not limited to only the randomly selected bisphosphonate subgroup of patients. Therefore, the raloxifene and BZA patient count and results stayed the same, but the number of bisphosphonate patients increased to the original number prior to the random selection, (Table 21).

Table 21. Patient Demographic Characteristics- Study Population with Entire Group of Bisphosphonate Patients

		Bazedoxifene (N=1111)		**Raloxifene (N=2720)**		**Bisphosphonate (N=81,669)**	
Age	N (%)	1111 (100)	-	2720 (100)	-	81,669 (100)	-
	Mean (SD)	61.6 (9)	-	64.8 (8.77)	-	71 (10.26)	-
	Median	60		64		71	
	Range	45	90	45	97	45	105
		n	**%**	**n**	**%**	**N**	**%**
Age Group	45-49	51	4.6	78	2.9	1134	1.4
	50-59	479	43.1	665	24.4	11,220	13.7
	60-69	382	34.4	1229	45.2	23,440	28.7
	≥70	199	17.9	748	27.5	45,875	56.2
BMI (only >14 kg/m^2)	N (%)	370 (33.3)	-	1289 (47.4)	-	46,497 (56.9)	-
	Mean (SD)	27.3 (5.29)	-	27.1 (4.85)	-	26.9 (5.7)	-
	Median	26.9	-	26.7	-	26.3	-
	Range	16	49	15	47.9	14	60
	Missing (N)	741 (66.7)	-	1,431 (52.6)	-	35,172 (43.1)	-
BMI Group	<18.5	8	2.2	21	1.6	1055	2.3
	18.5-25	125	33.8	423	32.8	16,536	35.6
	25-30	132	35.7	508	39.4	17,315	37.2
	≥30	105	28.4	337	26.1	11,591	24.9
	Missing (N)	741	-	1431	-	35,172	-
Smoker	Yes	92	8.3	408	15.0	10,921	13.4
	No/missing	1019	91.7	2,312	85.0	70,748	86.6

		Bazedoxifene (N=1111)		Raloxifene (N=2720)		Bisphosphonate (N=81,669)	
Alcohol	Yes	133	12.0	585	21.5	22,041	27.0
	No/missing	978	88.0	2135	78.5	59,628	73.0

BMI: body mass index, SD: standard deviation

10.5.3.2. Incidence rate of primary endpoints

There were no major differences in the random subgroup (Table 15) vs. entire bisphosphonate populations, with regards to the IR of primary endpoints in the bisphosphonate patient group (Table 22). Similar to the randomly selected subgroup, in the entire population, the bisphosphonate group had the highest IR (95% CI) of the primary endpoint VTE (8.1 [7.8 – 8.4]) , followed by the raloxifene group (3.5 [2.6 – 4.3]), and the BZA group with the lowest IR (2.4 [1.3 – 3.6]) (Table 22).

Table 22. Incidence of Primary Endpoints- Study Population with Entire Group of Bisphosphonate Patients

	Bazedoxifene (N=1111)		Raloxifene (N=2720)		Bisphosphonate (N=81669)	
	IR	**(95% CI)**	**IR**	**(95% CI)**	**IR**	**(95% CI)**
VTE/ 1000 person-years (Primary endpoint)	2.4	(1.3-3.6)	3.5	(2.6-4.3)	8.1	(7.8-8.4)
DVT / 1000 person-years	2.1	(1.1-3.2)	3.0	(2.2-3.8)	7.0	(6.7-7.2)
PE / 1000 person-years	0.3	(0.0-0.7)	0.4	(0.1-0.7)	1.1	(1.0-1.2)
RVST / 1000 person-years	0.0	(0.0-0.0)	0.1	(0.0-0.3)	0.2	(0.2-0.3)

CI: confidence interval; DVT: deep vein thrombosis; IR: incidence rate; PE: pulmonary embolism; RVST: retinal vein and sinus thrombosis; VTE: venous thromboembolism

10.5.3.3. Adjusted hazard ratios for primary endpoint

The risk of VTE was significantly lower in the BZA group when compared to the entire bisphosphonate group (HR [95% CI]: 0.4 [0.2 – 0.7]; p<0.01). Regarding the DVT endpoint, there was also a significantly lower risk in the BZA group when compared to the bisphosphonate group (HR [95% CI]: 0.4 [0.2 – 0.7] p<0.01). However, no significant difference was found between the BZA and raloxifene group regarding VTE or DVT endpoints (p=0.91; p=0.73, respectively) (Table 23). These results are similar to that of the study population with the randomly selected subgroup of bisphosphonate patients Cox proportional hazards analyses were not performed for PE and RVST because the number of events in those groups were too few.

Table 23. Adjusted Hazard Ratios for Primary Endpoint- Study Population with Entire Group of Bisphosphonate Patients

Event	Treatment	Comparator	HR	(95% CI)	P-value
Primary endpoints (VTE)	Bazedoxifene	Bisphosphonate	0.4	(0.2-0.7)	<0.01
Primary endpoints (VTE)	Bazedoxifene	Raloxifene	1.0	(0.4-2.2)	0.91
DVT	Bazedoxifene	Bisphosphonate	0.4	(0.2-0.7)	<0.01
DVT	Bazedoxifene	Raloxifene	0.9	(0.4-2.0)	0.73

CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio; VTE: venous thromboembolism

Similar results were obtained in the comparison of hazard ratios of secondary endpoints between the entire bisphosphonate group and with the randomly selected subgroup of bisphosphonate patients (results not shown).

10.5.4. Results summary of endpoint verification

All the potential primary endpoints in the BZA and raloxifene groups were evaluated. A total of 17/17 (100.0%) BZA, 57/60 (95.0%) raloxifene were confirmed cases of VTE. As the bisphosphonate group was very large, 176/305 (58%) of the potential primary endpoints were randomly selected and evaluated. A total of 158/176 (89.8%) of potential VTE endpoints in bisphosphonates users were confirmed. None of the potential primary events were adjudicated as ‘not confirmed’ in the BZA and raloxifene groups and 4/176 (2%) primary events were adjudicated as ‘not confirmed’ in the bisphosphonates group. The non-adjudicated cases were presumed confirmed and included in the analyses and no potential event was excluded from the analyses based on the verification exercise.

Overall 5-10% of potential secondary endpoints were randomly selected and evaluated depending on the category. A total of 21/23 (91.3%) BZA, 128/149 (85.9%) raloxifene, and

292/354 (82.5%) of bisphosphonate potential primary endpoints were confirmed. Among the events that were evaluated, none (0/23) were adjudicated as 'not confirmed' for BZA, 1/149 (0.7%) of events were adjudicated as 'not confirmed' for raloxifene and 10/354 (2.8%) events were 'not confirmed' in the bisphosphonate group. The non-adjudicated cases were presumed confirmed and included in the analyses and no potential event was excluded from the analyses based on the verification exercise.

10.6. Adverse events / Adverse reactions

This study involved de-identified patient-level electronic health related databases (e-HRD), data that existed as structured data by the time of study start. In this data source, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. DISCUSSION

11.1. Key results

Overall, 86,675 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 left after the study exclusion criteria were applied. In all, 43,231/85,500 (50.6%) patients were from Italy and 42,269/85,500 (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 larger than the BZA (and raloxifene) population, a random sample of bisphosphonate patients (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.

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

In adjusted Cox proportional hazards analyses, the risk of VTE was significantly lower in the BZA group when compared to the bisphosphonate group (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). However, no significant difference was found between the BZA and raloxifene groups regarding VTE or DVT (HR [95% CI]: 0.9 [0.4 – 2.2], p=0.91; 0.9 [0.4 – 2.0], p=0.73, respectively).

In the study sample size and study length calculations the expected IR of VTE in women who are not treated with a SERM or HRT was 1.74/1000 patient-years, based on data from the placebo groups in clinical trials of BZA. In women treated with raloxifene the expected IR was 2.17/1000 patient-years. In the 3-year phase 3 clinical trial of healthy postmenopausal osteoporotic women (mean age, 66.4 years) who were randomised to daily doses of bazedoxifene 20 mg (n=1886) or 40 mg (n=1849), raloxifene 60 mg (n=1872), or placebo (n=1885) for 3 years, VTE events, primarily DVTs, were more frequently reported in the active treatment groups compared with the placebo group; rates were similar with bazedoxifene and raloxifene.[2] There were no significant differences in the risk of any VTE, including DVT, PE, and RVT (retinal vein thrombosis), between the bazedoxifene and raloxifene treatment groups. The rates of any VTE per 1000 women-years were 2.8 with bazedoxifene 20 mg, 2.9 with bazedoxifene 40 mg, 2.0 with raloxifene 60 mg, and 1.7 with placebo; corresponding HRs (95% CIs) relative to placebo were 1.6 (0.68, 3.94), 1.7 (0.70, 4.07), and 1.1 (0.44, 2.96). Overall, the incidence of adverse events, serious adverse events, and discontinuations due to adverse events in the bazedoxifene groups was not different from that seen in the placebo group.

The observed rates of VTE obtained in bisphosphonate treated patients in the interim and final analyses are much higher than the expected rates (not treated with SERM) and the observed rates of VTE in the BZA and raloxifene treatment groups were within the expected range. Accordingly, in both the interim and final analyses, women receiving BZA had a lower risk of VTE compared to the bisphosphonate treatment group.

In 2010, Danish researchers conducted a study on the use of bisphosphonates (including alendronate, clodronate, etidronate, risedronate) and raloxifene and risk of DVT and PE in a nationwide register-based cohort in Denmark.[7] In crude analyses of patients prior to the start of treatment, the cases consisted of users of bisphosphonates, raloxifene, and other drugs

used in the treatment of osteoporosis between 1996 and 2006. For each case, three age- and gender-matched controls from the general population were selected. Before the start of treatment, an increased risk of DVT/PE was present in the crude analysis for alendronate, etidronate, and risedronate as compared with matched controls; odds ratio (OR) (95% CI), for alendronate, etidronate, and risedronate were 1.28 (1.20–1.35), 1.56 (1.46–1.67) and 1.45 (1.04–2.02) respectively. Before the start of raloxifene, compared with controls, a decreased risk of DVT/PE was present, OR =0.64 (0.48-0.86). After the start of a drug, compared with the background population, alendronate (HR = 1.20, 95% CI, 1.00-1.43), clodronate (HR = 4.06, 95% CI, 1.47-11.2), and etidronate (HR = 1-37, 95% CI, 1.23-1.51) were all associated with an increased risk of DVT/PE, while the association was weak for raloxifene (HR = 1.64, 95% CI, 0.97-2.77). No dose-response relationship was present except for alendronate, where the risk was inversely associated with dose, i.e., the risk of DVT/PE decreased with increasing average daily dose. The HR for DVT/PE was higher with clodronate and etidronate than with alendronate. Alendronate and raloxifene carried the same risk for DVT/PE. The authors concluded that “bisphosphonates seem associated with an increased risk of DVT/PE but the association does not seem to be causal”. As in our study, confounding by indication seems a more plausible explanation for their findings (see section 11.2).

11.2. Limitations

BZA (Conbriza®) was approved in Europe in April 2009 and the first EU launch occurred in Spain in September 2010 which was followed by launch in Italy in April 2011. At the time of study design, the IQVIA EMR databases of Spain and Italy contained the most drug prescriptions for BZA along with patient diagnoses, demographic data, medical history (event data, risk factors) and other types of data, electronically collected by participating GPs. Although the databases have many strengths in their comprehensive structure, large number of variables, and electronic accessibility, there were gaps in the data as described below:

Lack of hospitalisation data: The IQVIA EMR database collects data from GP offices. Therefore, complete records of events requiring hospitalisation are not available in the database. Since no patient identifiers are available, it is also not possible to link to any available national or regional registries to obtain additional information (e.g., vital status, diagnosis of malignancies) and under-ascertainment of outcomes that require hospitalisation is likely to have occurred. However, there is no evidence to suggest that this limitation was differential across treatment groups.

Data collection in routine care: The IQVIA EMR database collects real life clinical practice information from the actual medical records of the patients. No study specific case report form (CRF) was used to collect supplemental information that is not entered in the medical records as part of the patient’s routine clinical care. Also, as an observational study, this

study did not mandate any study specific visits, procedures or laboratory tests. To enable the study achieving consistent, accurate, independent, and an unbiased assessment of the study endpoints suspected clinical events reported by GPs were adjudicated by a blinded evaluation process. All potential VTE events in BZA and raloxifene treated patients, a random selection of potential VTE events in bisphosphonate patients, and a random selection of potential secondary endpoints were adjudicated, with the vast majority confirmed.

Potential for missing data: The data for this study were obtained from routine clinical care records. No individual patient identifiers were available. Therefore, it was not possible to query the physicians providing the data for any missing information and data was missing for key variables such as osteoporosis diagnosis, smoking status and BMI. As a result, control of confounding in the multivariate analyses was likely inadequate as variables such as smoking status and BMI, strong risk factors for VTE[10], and for which a significant proportion of patients had missing information, were included as confounders.

Potential for confounding: Per the BZA summary of product characteristics (SmPC)[8] "*Use of CONBRIZA is not recommended in women at an increased risk for venous thromboembolic events. CONBRIZA is associated with an increased risk of venous thromboembolism (VTE). In clinical trials, the highest rate of VTE was observed during the first year of treatment, with a relative risk of 2.69 compared to placebo. After 3 years the relative risk was 1.63 and after a 5-year study period the relative risk was 1.50; after 7 years the relative risk was 1.51. The risk factors associated with VTE cases in clinical trials included: advanced age, obesity, immobilisation, surgery, major trauma and malignancy. CONBRIZA should be discontinued prior to and during prolonged immobilisation (e.g., post-surgical recovery, prolonged bed rest), and therapy should be resumed only after the patient is fully ambulatory*".

A similar warning exists in the raloxifene SmPC[9]: "*Raloxifene is associated with an increased risk for venous thromboembolic events that is similar to the reported risk associated with current use of HRT. The risk-benefit balance should be considered in patients at risk of venous thromboembolic events of any aetiology. Evista should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible in case of the illness, or from 3 days before the immobilisation occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile*".

To the best of our knowledge, bisphosphonates do not increase the risk of VTE and there are no warnings in any label or literature. From the available demographic and baseline results in this study, bisphosphonate patients in this study more frequently had VTE risk factors compared with BZA and raloxifene patients. For example, the mean ages of patients were 61.9 years, 64.8 years, and 71.0 years for BZA, raloxifene and bisphosphonate treatment

groups, respectively. The percentage of patients with a medical history of malignancies was higher among bisphosphonate patients compared with BZA and raloxifene patients. This is noteworthy because older patients and cancer patients have a much higher risk of VTE than younger patients or patients without cancer. [10]

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.

11.3. Interpretation

The incidence rate of VTE in women receiving bazedoxifene were similar to the rates reported from clinical trials, but the observed rate among women receiving bisphosphonate treatment were higher. In Cox proportional hazards analyses, the risk of VTE was therefore significantly lower in the BZA group when compared to the bisphosphonate group and this difference remained after adjustment for available demographic and clinical characteristics. No significant difference was found between BZA and raloxifene regarding the risk of VTE.

In both absolute and relative frequency terms, a low number of secondary events were observed, with most occurring in the bisphosphonate group and fewer secondary endpoints occurring in the BZA group; however, the most frequently occurring secondary endpoint was depression in the BZA group.

The results of this study, especially with regards to the primary objective of estimating and comparing the IRs of VTE among women receiving BZA and women receiving a bisphosphonate for treatment of osteoporosis are in contrast with other published clinical trial studies that have examined a similar research question.[2,4] However, results are consistent with that observed in a previously published observational study.[7] Residual confounding via channelling of patients with VTE risk factors to bisphosphonates given the labelled VTE risk for BZA is a likely (but perhaps partial) explanation of the differences in clinical trial and observational study results.

The results of this study with regards to the secondary objective of estimating and comparing the IRs of VTE among women receiving BZA and women receiving raloxifene for treatment

of osteoporosis are consistent with other published studies that have examined a similar research question. This study (B1781044) results do not suggest an increased risk of VTE associated with BZA use. However, incomplete control of channelling bias is likely (e.g., as evidenced by similar VTE risks observed between BZA and raloxifene users). 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.

11.4. Generalizability

This analysis includes data from Spain and Italy to assess the risk of VTE and select secondary endpoints in women aged 45 years and older prescribed BZA, raloxifene, or bisphosphonates for the treatment of osteoporosis. As supportive treatment for osteoporosis, comorbid conditions, and diagnosis of the other safety events differ from country to country based on country-specific treatment guidelines, caution should be exercised when generalising the findings to more diverse age, ethnic or racial female populations in whom the baseline risks of these safety events may differ.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

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.

14. REFERENCES

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15. LIST OF SOURCE TABLES AND FIGURES

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

16. Appendices

16.1. Annex 1. List of stand-alone documents

16.1.1. Study protocol

16.1.2. Statistical analysis plan

16.1.3. Supplementary tables

16.1.4. Diagnostic codes