NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

COHORT STUDY OF VENOUS THROMBOEMBOLISM AND OTHER CLINICAL ENDPOINTS AMONG OSTEOPOROTIC WOMEN PRESCRIBED BAZEDOXIFENE, BISPHOSPHONATES OR RALOXIFENE IN EUROPE

Compound Number:	PF-05208749
Compound Name:	Bazedoxifene
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1. INTRODUCTION

1.1. Background and Rationale

Osteoporosis is characterized by a decrease in bone mass and architectural deterioration of bone tissue. Subtle modifications of bone remodeling, 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. 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 estrogen, at the time of the menopause, results in an accelerated rate of bone loss in women.

Bazedoxifene (BZA) is a third generation non-steroidal selective estrogen 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 estrogen 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 current dosing consists of once daily administration of a 20 mg tablet. BZA (Conbriza) was approved in Europe via the centralized authorization procedure in April 2009. The first EU launch occurred in Spain in September 2010 which will be 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 remodeling, and are widely used for the prevention and treatment of osteoporosis.

In clinical trials, BZA-treated women had an increased risk of venous thromboembolic events (VTEs) compared to placebo. VTEs are included in the product label as an important identified risk.

This observational cohort study is being conducted to further characterize selected adverse events of interest among a patient population prescribed bazedoxifene, raloxifene, or a bisphosphonate in usual clinical care outside of a randomized clinical trial setting. This post-authorization safety study (PASS) is a post-authorization commitment to the CHMP/EMA.

The product Summary of Product Characteristics (SmPC) will be used as the single reference safety document for expedited safety reporting purposes for this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1.1. 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.

2.1.2. 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 (listed as secondary endpoints in section "2.2 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 (listed as secondary endpoints in section "2.2 Endpoints") among women receiving bazedoxifene and women receiving raloxifene for treatment of osteoporosis.

2.2. Endpoints

The clinical endpoints for this study were determined based on the clinical and pre-clinical data from the bazedoxifene development program, class effects of other SERMs, and recommendations of the EU Rapporteurs.

Potential endpoints will be identified by an electronic search of the coded diagnosis fields of the medical records. The relevant diagnostic codes that will be used as operational definitions of each of the endpoints will be listed in the statistical analytic plan of the study. The available medical record of the identified cases for the primary endpoint will be retrieved and reviewed to confirm the diagnosis.

2.2.1. Primary endpoints:

- Venous thromboembolism (VTE) defined as deep vein thrombosis (DVT), pulmonary embolism (PE), retinal vein thrombosis, and sinus thrombosis

2.2.2. Secondary endpoints:

- 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.
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3. STUDY DESIGN

This post-authorization safety study (PASS) is an observational, non-interventional epidemiologic cohort study using data from a European database of electronic medical records.

3.1. Data Source

This study will use the Cegedim Longitudinal Patient Database (LPD), an electronic medical records database that collects clinical data from primary care physician practices in the following European countries i.e., Spain, Italy, Germany, France, Belgium and UK. (In the UK the database is known as The Health Improvement Network (THIN).) For this study the Cegedim LPD in Italy and Spain will be used. If during the recruitment period of the study bazedoxifene is launched in other European countries where Cegedim LPD is available, the study may be expanded to include those countries.

The Cegedim LPD obtains medical information from a proprietary 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, the patient population is representative of the respective country population according to age and sex distribution, as provided by national statistic authorities.

Table 1: Doctor and patient populations in the Cegedim LPD by country

	France	UK	Italy	Germany	Spain
Number of physicians in the panel	1200	1200	700	550	300
Average number of patients who consulted GP at least once in a year	1,600,000	1,400,000	800,000	680,000	320,000

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

3.2. Contents of the Cegedim LPD

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

Anonymized patient data collected from each GP practice includes:

- 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 by Cegedim in each country participating in the LPD varies to some extent to accommodate local needs. However, all countries collect data on medical comorbidities and outcomes, prescriptions, demographics, and physician characteristics.

In the Cegedim electronic medical record system diagnosis of clinical events are recorded as diagnostic codes. These codes from the different participating countries will be harmonized based on prespecified algorithms developed prior to the analysis and listed in the statistical analytic plan.

Table 2: Data coding conventions in the different countries

	France	UK	Italy	Germany	Spain
Drug code dictionary	Claude Bernard	Multilex	Farmadati	Abdata	Vademecum
Therapy classification	European Pharmaceutical Marketing Research Association (EphMRA)	British National Formulary (BNF)	Anatomical Therpeutic Chemical (ATC)	ATC	ATC
Disease classification	Home grown thesaurus *mapped to International Classification of Diseases-10 (ICD-10) and International Classification of Primary Care-2 (ICPC-2)*	Read Codes	ICD-9	ICD-10	Code CIAP mapped to ICD-9

Cegedim LPD does not collect hospitalization data directly except in the UK THIN database. Information on hospitalizations is 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 is not systematically collected and there is no established linkage between the medical records at the general practices and at the hospitals.

4. STUDY POPULATION

All women in the Cegedim database meeting the inclusion criteria will be included in the analysis without any sampling process.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for inclusion into the study:

1. Female
2. At least one prescription for bazedoxifene, raloxifene, or any bisphosphonate during the study inclusion period (index prescription);
3. A recoded diagnosis code of osteoporosis on or within 60 days prior to the index prescription date;
4. Age >=45 at the date of the index prescription; and
5. At least 6-months of follow-up data in the electronic medical record system prior to the date of the index prescription

4.2. Subject Accrual Period

The study will operationally launch after bazedoxifene becomes commercially available in the participating countries. However, the subject inclusion period in the database will begin at the time of the commercial launch of bazedoxifene in each country (e.g., September 2010 in Spain, April 2011 in Italy) and will continue for three (3) years from the start of the study.

5. STUDY TREATMENT AND DURATION

This study involves retrospective analysis of prospectively collected data in an existing electronic database for the purpose of usual clinical care. It is expected that osteoporosis medications will be used on the basis of the approved SmPCs and will be adjusted solely according to medical and therapeutic necessity. As this is a non-interventional study there is no study mandated dosing regimen or visit schedule. Physicians will be prescribing the drugs according to the standard clinical practice in the participating countries. There is no study mandated duration of therapy.

6. STUDY PROCEDURES

6.1. Follow up time and drug exposure time

6.1.1. Follow up:

Each woman will be followed for identification of the selected endpoints for a period of up to five years from the date of the index prescription record for bazedoxifene, raloxifene or a bisphosphonate. The follow up will continue even if the woman discontinues the index medication or switches to a different medication during the five year period.

The follow up duration of an individual woman may be shorter than the five year period if the woman transfers out of her GP office that wrote the index prescription, or if the database records the death of the woman. In these situations the data will be censored on the date of transfer or the date of death.

6.1.2. Drug exposure:

Exposure to the drugs under study will be ascertained by searching the prescription records for the relevant product codes. For each prescription the duration of exposure will be

estimated based on the dose and quantity of the prescribed medication. For each prescription, person-time exposed to the drug will begin to accrue from the date of the prescription. The follow up time will be categorized into:

- **Current exposure:** defined as the duration of the prescription
- **Recent exposure:** defined as the 60-day period following the end of the duration of prescription
- **Past exposure:** defined as any follow up time accrued after 60 days following the end of the duration of the prescription.

A sensitivity analysis will be conducted with a different definition of exposure categories (e.g., using a 90-day window to define recent exposure).

Given the discontinuous nature of osteoporosis medication use, it is likely that a large number of women in this study will accrue 'current use', 'recent use' and 'past use' exposure time to multiple osteoporosis drugs during the 5-year period of follow up.

Drug exposure will also be categorized with respect to the cumulative exposure to each drug (e.g., 0-days, 1-30-days, 31-90-days, 91-180-days, 181-365-days, >365-days) to evaluate whether or not the incidence (hazard) of a specific adverse event varies with increased duration of use.

6.2. Study Period

It is expected that this study will take at least nine (9) years to complete, with a 3 year subject accrual period, 5 years of follow-up per patient and 1 year for data cleaning, analysis and report generation. Depending on the rate of uptake of bazedoxifene in the participating countries the accrual period may need to be extended to ensure adequate sample size. The patient accrual data will be reviewed annually to determine whether the uptake is sufficient to complete the study in the proposed time period.

6.3. Endpoint identification

The relevant diagnostic codes for each of the endpoints will be specified in the statistical analytic plan. Endpoints will be identified based on an electronic search for the relevant diagnostic codes in the diagnosis fields of the medical records during the follow up period. For the identified potential cases, the electronic medical record will be retrieved and reviewed by a clinical expert to confirm the diagnosis for the following endpoints:

The primary endpoint:

a. Venous thromboembolism (VTE) defined as deep vein thrombosis (DVT), pulmonary embolism (PE), retinal vein thrombosis, and sinus thrombosis.

Secondary endpoints

b. Ischemic stroke
c. Thrombotic and ischemic cardiac disorders (including myocardial infarction, myocardial ischemia, and coronary occlusion; and includes both acute and chronic disorders).
d. Malignancies: Breast, ovarian, renal, thyroid and endometrial.
e. Any ocular event with a vascular etiology (possibly indicative of retinal vein thrombosis, e.g. retinal arterial thrombosis, retinal hemorrhage, visual field defects of vascular origin).

7. DATA ANALYSIS/STATISTICAL METHODS

The details of the data analysis will be documented in a Statistical Analysis Plan (SAP) document, which will be maintained by the sponsor. The SAP will elaborate, and may modify the analytic plans outlined in the protocol; however, any major modifications will be reflected in a protocol amendment.

7.1. Sample Size Calculation

There is no active de novo patient enrollment in this study and all women in the database who meet the inclusion criteria during the recruitment period will be included in the analysis. Therefore, the focus of the sample size calculation was to determine the precision of the estimated incidence rate ratios (IRR) that can potentially be achieved in the study depending on several different hypothetical scenarios of subject accrual. Depending on drug uptake in the participating countries, speed of accrual, event rates, and actual dropout rates, the precision of the estimated incidence rate ratio may change.

The estimates are based on the expected incidence rate of VTE as the primary endpoint. It is estimated that the incidence rate of VTE in women who are not treated with a SERM or HT is 1.74/1000 patient-years (PY), based on data from the placebo groups in bazedoxifene clinical trials. It is assumed that women treated with raloxifene would have a higher incidence of VTE, of 2.17/1000 PY, based on data from the Phase III pivotal trials of bazedoxifene. The rate of VTE observed in the raloxifene arm of the bazedoxifene pivotal trials is lower than the rate reported in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial [1]. In the MORE trial, the incidence rate of VTE was 3.5/1000 patient-years in women randomized to raloxifene. Therefore, our calculations are likely to be substantially more conservative than estimates based on rates in the literature.

All estimates (Table 3, Table 4) were calculated with two-sided 95% confidence intervals. According to the study plan, there will be a 3-year accrual period and each woman will be followed for up to 5 years from enrollment. Since osteoporosis therapies are chronic therapies, it is likely that women will be exposed to the drugs for more than one year. A conservative annual loss to follow up rate of 15% was used in the estimation. Estimates were based on Wald 95% confidence intervals [2]

Table 3: 95% Confidence Intervals (CI) for Incidence Rate Ratios (IRR) with different numbers of patients in the BZA arm and the primary comparator arm

Bazedoxifene	Bisphosphonate	BZA:Bisphosphonate	Underlying Incidence Rate Ratio (IRR)		
			1	1.5	2
(n)	(n)		95% CI of observed point estimate of IRR		
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

The estimated 95% CI of the incidence rate ratios (IRR) in Table 3 imply that if the underlying (true) IRR comparing BZA users to bisphosphonate users is 2, then the point estimate of IRR in the study will lie between 1.3 and 3.2 indicating (a) that the study will be able to rule out equality of the IRRs (i.e., IRR>1) and (b) that the study would not be able to rule out the possibility that the true IRR could be as high as 3.2 or as low as 1.3.

Table 4: 95% Confidence Intervals (CI) for Incidence Rate Ratios (IRR) comparing BZA users and Raloxifene users assuming equal number of patients in the two arms

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

The estimated 95% CI of the incidence rate ratio (IRR) in table 4 implies that if the underlying (true) IRR comparing BZA users to raloxifene users is 2, then the point estimate of IRR in the study will lie between 1.2 and 3.4 indicating (a) that the study will be able to rule out equality of the IRRs (i.e., IRR>1) and (b) that the study would not be able to rule out the possibility that the true IRR could be as high as 3.4 or as low as 1.2.

7.2. Safety Analysis

Descriptive statistics on available patient characteristics (e.g., age, BMI, smoking and alcohol use, history of relevant medical diagnoses, use of relevant concomitant medications) will be reported for all exposure groups at baseline.

Incident cases of study endpoints will be included in the analysis. Women with a history of study outcomes recorded in the medical records prior to the index prescription will not be included in the primary analysis for that specific outcome, but will be analyzed separately. For example, a woman with a history of VTE prior to the index prescription will be categorized as a prevalent case and will be excluded from the primary VTE analysis. A

separate analysis for women with a medical history of VTE will be performed and the woman would remain eligible for the analysis of other outcomes as normal. Depending on the number of patients in these subgroups of prevalent cases of each endpoint, this supplemental analysis is likely to have low power to perform any statistical comparison and will be descriptive in nature.

Incidence rates will be calculated for all endpoints in all treatment groups; incidence rate ratios and 95% confidence intervals will be calculated and compared. Stratifications by risk factors of interest (e.g., age, BMI, history of selected medical comorbidities, selected concomitant medications) will be performed for each outcome depending on availability of the data. A multiple regression model may be fit for the primary objective of the study depending on the completeness of the data on potential confounders and accrual of a sufficient number of endpoints.

A time to event analysis may be conducted as a secondary analysis.

All analyses will be conducted for each country separately, as well as after pooling the data from all participating countries.

Given the rarity of certain malignancies in this population, the incidence rates observed in this study may be small and imprecise. In such case, to better characterize the rates obtained in this study, an additional analysis using external reference data for the malignancies may be conducted. The observed frequency of malignancies in all three treatment groups will be compared with the expected frequency calculated from an age and gender matched population-based reference group (e.g., GloboCan) This ratio of observed versus expected events and 95% confidence interval, will be reported.

7.3. Interim Analysis

An interim analysis will be conducted once, after four (4)years of study data become available.
This interim analysis will include a calculation of crude event rates for the study outcomes in each exposure group. The observed rates of the primary endpoint will be used to determine if the rates are sufficient to continue the study as planned. Based on the results of this interim analysis, the study may be extended in order to accrue the number of events required to preserve the precision of the incidence rate ratios. There will be no other changes in the study design nor will there be any changes needed to the originally planned analysis as a result of this interim analysis.

8. DATA COLLECTION AND DATA MANAGEMENT

8.1. Case Report Forms/Electronic Data Record

There is no data collection form designed for this study. The data to be used in this study are being collected in an existing electronic health care database.

8.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including serious adverse event forms, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9. ADVERSE EVENT REPORTING AND SERIOUS ADVERSE EVENT REPORTING

This study uses de-identified patient-level electronic health related databases (e-HRD), in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Furthermore, while the identifiable patient criterion may be met, the identifiable reporter criterion will not. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

However, this study protocol requires review of the patient medical chart and/or a narrative field in the dataset. If the reviewer identifies a SAE with explicit attribution to any Pfizer drug via patient chart and/or narrative review (and with an identifiable reporter), these SAEs should be reported to Pfizer or its representative for submission to regulatory authorities.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (i.e., at immediate risk of death due to the event);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize

the patient or may require intervention to present one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If there is a written notation in the medical chart/narrative field indicating that a physician attributed a serious adverse event to a Pfizer drug, Pfizer or its representative will complete an SAE form within 24 hours and submit it to Pfizer Safety. Such information will not include any patient or physician identifying information such as name, address, or phone number.

10. POTENTIAL WEAKNESSES

Lack of hospitalization data: The Cegedim LPD collects data from GP offices. Therefore, complete records of events requiring hospitalization 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).

Data collection in routine care: The Cegedim LPD collects real life clinical practice information from the actual medical records of the patients. No study specific CRF will be used to collect supplemental information that are not entered in the medical records as part of the patient's routine clinical care. Also, as a non-interventional study, this protocol does not mandate any study specific visits, procedures or laboratory tests.

Dependence on market uptake of the study medication: Bazedoxifene is a newly launched product in the participating countries. Since there is no active enrollment of patients (i.e., in contrast to a de novo prospective follow up study), the final sample size will be based on the rate of the uptake of the drug in the participating countries during the subject accrual period.

Potential for missing data: The data for this study will come from routine clinical care. No individual patient identifiers will be available. Therefore it is not possible to query the physicians providing the data for any missing information.

Difference in indication for Bazedoxifene and Raloxifene: Bazedoxifene is indicated for the treatment of post-menopausal osteoporosis whereas Raloxifene is indicated for both the prevention and treatment of post-menopausal osteoporosis. As a result the characteristics of the cohort of women receiving Raloxifene may differ from the women who are receiving Bazedoxifene. It is possible that the Raloxifene cohort will have a higher proportion of healthier, younger women.

11. ETHICS

11.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of Cegedim to have prospective approval of the study protocol, protocol amendments, from an appropriate IRB/EC as necessary in the participating countries. All correspondence with the IRB/EC should be retained in the study File.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

11.3. Subject Information and Consent

Not applicable.

12. COMMUNICATION AND PUBLICATION OF STUDY RESULTS

12.1. Communication of results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on www.clincaltrials.gov regardless of the reason for registration; OR

- All other studies for which the results have scientific or medical importance as determined by Pfizer.

Results are posted in two formats:

- The results of studies applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA) and/or An Act Regarding Advertising by Drug Manufacturers and Disclosure of Clinical Trials (state of Maine Reporting Requirements) are posted on ClinicalTrials.gov in a tabular format called Basic Results.

- The results of all required studies (even if not previously registered to ClinicalTrials.gov) and any voluntarily registered studies are posted on ClinicalStudyResults.org in a format called a Pharmaceutical Research and Manufacturers of America (PhRMA) website synopsis (PWS), the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products already approved in any country and applicable under FDAAA and/or state of Maine, Pfizer posts results within one year of the primary outcome completion date (PCD). For all other studies that do not involve a Pfizer product, Pfizer posts results one year from last, subject last visit (LSLV);

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days after US regulatory approval. or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year after such discontinuation.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

13. REFERENCES

1. Grady, D., et al., Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol, 2004. 104(4): p. 837-44.
2. Agresti, A., Categorical Data Analysis. Wiley, 2002. 2nd Edition.