NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	Post Authorization Safety Study (PASS) of Conjugated estrogens/Bazedoxifene (CE/BZA) in the US
Protocol number	B2311060
Protocol version identifier	Amendment 6, Final Version
Date of last version of protocol	29 April 2019
EU Post Authorisation Study (PAS) register number	EUPAS11599
Active substance	Conjugated estrogens/bazedoxifene (CE/BZA)
Medicinal product	DUAVEE® 0.45 mg/20 mg tablets
Product reference	**EU MA number: EU/1/14/960/001** (EU marketing authorization granted 16 December 2014)
Procedure number	**EMEA/H/C/002314/MEA 002**
Marketing Authorization Holder (MAH)	Pfizer Europe MA EEIG
Joint PASS	No
Research question and objectives	Compare the incidence of safety endpoints, in patients exposed to CE/BZA with patients exposed to estrogen + progestin (E+P) combination hormone therapy (HT)
Country(-ies) of study	United States

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Marketing Authorization Holder(s)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AMCP	Academy of Managed Care Pharmacy
AE	Adverse event
AEM	Adverse Event Monitoring
BBCIC	Biologics and Biosimilar Collective Intelligence Collaborative
BMI	Body Mass Index
CDHP	Consumer Directed Health Plans
CE/BZA	Conjugated estrogens/Bazedoxifene
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DCC	Data Coordinating Center
DRN	Distributed Research Network
DSAs	Data Sharing Agreements
E+P	Estrogen + Progestin
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPI	Generic Product Identifier
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HIRD	HealthCore Integrated Research Database℠
HMO	Health Maintenance Organization
HR	Hazard Ratio
HT	Hormone therapy
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IEC	Independent Ethics Committee
IMEDS	Innovation in Medical Evidence Development and Surveillance
IR	Incidence Rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IUD	Intrauterine Device
MAH	Marketing Authorization Holder
MI	Myocardial infarction
NCHS	National Center for Health Statistics
NDCs	National Drug Codes
NDI	National Death Index
NIH	National Institute of Health
NIS	Non-interventional study

Abbreviation	Definition
ORD	Optum Research Database
PASS	Post-Authorization Safety Study
PCORI	Patient-Centered Outcomes Research Institute
PHI	Protected Health Information
PII	Personal Identified Information
POS	Point of Service
PPO	Preferred Provider Organization
PPV	Positive Predictive Value
PRAC	Pharmacovigilance Risk Assessment Committee
ROC	Receiver Operating Characteristic
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCDM	Sentinel Common Data Model
SERM	Selective estrogen receptor modulator
SOP	Standard Operating Procedure
TIA	Transient ischemic attack
UB-92	Uniform Billing Code of 1992
US	United States
VMS	Vasomotor Symptom
VTE	Venous Thromboembolism

1. RESPONSIBLE PARTIES

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2. ABSTRACT

Title: Post-Authorization Safety Study (PASS) of conjugated estrogens/bazedoxifene (CE/BZA) in the United States

Protocol: Amendment 6, Final, 23 August 2019

Authors: Leo Russo, PhD, Pfizer Inc., Vera Frajzyngier, PhD, Pfizer Inc., Geetanjoli Banerjee, MPH, PhD, HealthCore, Inc., Stephan Lanes, PhD, MPH, HealthCore, Inc.

Rationale and background: Conjugated estrogens/bazedoxifene (CE/BZA) is authorized in the European Union (EU; as Duavive®) for the treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate. It became commercially available in the EU in 2015. In the United States (US), the product, approved as Duavee® by the Food and Drug Administration (FDA), has been commercially available since May 2014 for use in women with a uterus for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause and for the prevention of postmenopausal osteoporosis. It is important to collect real-world safety data regarding actual use in the populations for which the product is prescribed. This protocol describes a non-interventional study (NIS) designated as a Post-Authorization Safety Study (PASS) that will be conducted in the US in order to fulfill a post-authorization commitment to the European Medicines Agency (EMA).

During the first four years after introduction of CE/BZA in the US (01 May 2014 through 31 May 2018), the rate of uptake of new users of this medication was lower than projected. As a result, fewer new users of CE/BZA have accrued than had been anticipated during study design. Current trends indicate this PASS will not accumulate enough patients in the HealthCore Integrated Research Database℠ (HIRD) alone in the next 5 years, as originally planned, to conduct a meaningful assessment of the risk of the primary safety events (endometrial hyperplasia and endometrial cancer), comparing new users of Duavee and estrogen + progestin (E+P) combination hormone therapies (HT). Therefore, the study has been expanded to include additional US databases to minimize the time needed to achieve an adequate study size.

Research question: The overall aim of this PASS is to evaluate the safety profile of *Duavee* in comparison to E+P HT in the US.

Objectives:

- Primary objective: to estimate the incidence and compare the risk of endometrial hyperplasia and endometrial cancer among postmenopausal women initiating *Duavee* and postmenopausal women initiating E+P HT.
- Secondary objective: to estimate the incidence and compare the risk of selected secondary safety endpoints listed in Section 7.3.2.2, among postmenopausal women initiating *Duavee* and postmenopausal women initiating E+P HT.

Study design: This PASS is a cohort study utilizing multiple US healthcare claims data sources. Two treatment groups of new initiators (*Duavee* and E+P HT) will be defined and followed for each specified endpoint until the occurrence of the endpoint, the end of the study period, hysterectomy, treatment switch, disenrollment from the database, diagnosis of cancer, or death. The total planned study duration has been extended from four years to five years and will follow new initiators identified in 2014-2019.

Study Population: All patients who have received at least one prescription for *Duavee* or E+P HT since May 2014 (US commercial launch date) and have a baseline period of at least 12 months prior to their first dispensing of a study medicine, will be considered for inclusion. Patients without a uterus and those with a previous cancer diagnosis will be excluded. Only new initiators will be included in the primary analysis. To be a new initiator, patients need to have no recorded use of either *Duavee* or E+P HT products in their baseline period. Patients with prior use of single-entity estrogen and progestin therapy in either the *Duavee* or E+P HT cohort will be excluded from the primary analyses but will be included in secondary analyses. Similarly, patients with a history of unopposed estrogen use in their baseline period will be analyzed in secondary analyses but excluded from the primary analyses. Figure 4 details the analysis populations.

Variables: Variables will be defined and analyzed that represent patient characteristics, comorbidities, medications, medical history, and safety endpoints.

Data sources: This study will include five US healthcare claims data sources: HealthCore, Healthagen, Optum, IBM Truven MarketScan® Commercial and Medicare, and IBM Truven Marketscan Medicaid.

Study size: Endometrial hyperplasia and endometrial cancer are the endpoints used for the power calculation. There was a total of 1,502 new users of CE/BZA in the HealthCore database between 01 May 2014 and 31 May 2018. It is projected that the addition of the Healthagen, Optum, and MarketScan databases and the extension of this study for an additional 15 months (to 31 August 2019), will add approximately 12,000 more CE/BZA new users. Therefore, a final study size of approximately 13,000 patients who are new users of CE/BZA is anticipated, which is estimated to have 80% power to detect a hazard ratio of 1.8 for endometrial hyperplasia and 2.1 for endometrial cancer.

Data analysis: Analyses will focus on the comparison between women initiating either *Duavee* or E+P HT. Baseline characteristics will be compared across the two cohorts of new users to assess potential confounding variables. For each safety endpoint (venous thromboembolism [VTE], stroke, coronary heart disease [CHD], breast cancer, ovarian cancer, endometrial hyperplasia, and endometrial cancer, etc.), univariate and adjusted hazard ratios (HRs) will be estimated that compare incidence of the first occurrence of each safety event between *Duavee* and E+P HT users.

Milestones: A final report will be submitted to the EMA/Committee for Medicinal Products for Human Use (CHMP) cumulatively covering patients in all five databases who initiate *Duavee* or E+P HT in 2014-2019.

3. 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	28 November 2017	Administrative	**7.3.2**	An additional end point of any cancer, excluding basal cell carcinoma, was added, in addition to the original end point of any cancer.	Because basal cell carcinoma is common and non-fatal with a behavior similar to benign tumor, it is often excluded when assessing all-cause cancer in epidemiologic studies.
2	15 February, 2018	Administrative	**7.3.4**	Covariate updated from "cerebrovascular disease" to "cardiovascular or cerebrovascular disease".	The codes in the appendix indicated both cardiovascular and cerebrovascular disease, which are confounders to secondary outcome – stroke.
3	15 February 2018	Administrative	**7.3.4**	"Antimycobacterials" was removed from and "dermatologicals" was added in the list of covariates.	Variable label update was made to reflect consistency with the analyses.
4	31 March 2018	Administrative	**7.3.3;** **10.1**	Mortality Supplement to Final Report was removed from Milestone table and text references were removed.	Previously, a Mortality Supplement to the Final Report was planned for submission by March 31st, 2021. Because the NDI data lag has shortened substantially since the protocol was written, this supplemental report is no longer necessary.
5	30 April 2019	Substantial	Throughout entire protocol amendment (highlighted in red font)	The inclusion of two additional Research Partners (Healthagen and Optum) has been documented, the study power calculations have been updated, and the methodology and analysis plan have been augmented to describe the aggregation of results across study partners. All codes have been removed from the protocol and will be included in a statistical analysis plan (SAP), which will be co-developed by the three research partners. Sections on National Death Index (NDI) linkage, mortality analyses, and algorithm validation have	Current trends indicate this PASS will not accumulate enough patients to conduct a meaningful assessment of the risk of the primary safety events (endometrial hyperplasia and endometrial cancer) among new users of the study drugs in the near future using only the HIRD. Therefore, the study has been expanded to include two additional databases to accelerate the time needed to achieve an adequate study size.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				been removed. Description of inclusion/exclusion criteria and analyses has been updated to improve clarity and reproducibility between research partners. The study period has been extended to 2014-2019, and the expected date of the final study report has extended. The previous final study report has been changed to be the 4th interim report.	
6	23 August 2019	Substantial	Throughout the entire protocol amendment	The inclusion of two additional databases, to be analyzed by the HealthCore team. Start and end of data collection dates were amended for consistency with definitions in EMA's Guideline on Good Pharmacovigilance Practices (GVP) Module VIII – Post-authorisation safety studies. Further information was provided regarding the proposed meta-analysis. Added updated information on the risk estimates that can be ruled out. Addressed whether women may be included in several databases. Minor edits were made throughout for clarity.	The MarketScan commercial database was included to increase total sample size. The MarketScan Medicaid database was included based on the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) to include patients without commercial health insurance and those who are covered under public programs. The inclusion of these additional databases will increase study size and improve the power to detect differences in endometrial cancer and hyperplasia risk between CE/BZA new users and E+P HT new users. Additional changes were made to address comments in PRAC Response to Third Interim Report.

4. MILESTONES

Milestone	Planned date	Actual date
Date of Institutional Review Board (IRB) approval of protocol	Not Applicable (NA)	20 Feb 2015
Start of data collection[a]	01 November 2015	01 November 2015
End of data collection[b]	01 November 2019	
Registration in the EU PAS register	01 October 2015	01 October 2015
Submission of 1st Annual Interim Report	31 March 2016	31 March 2016
Submission of 2nd Annual Interim Report	31 March 2017	31 March 2017
Submission of 3rd Annual Interim Report	31 March 2018	12 March 2018
Submission of 4th Annual Interim Report	31 March 2019	29 March 2019
Submission of Protocol Amendment for Multi-Database Phase	30 April 2019	30 April 2019
Submission of Protocol Amendment to Include Additional Study Databases	23 August 2019	
Submission of FINAL Study Report	31 March 2021	

a. This is a cohort study and the source data has been accruing since *Duavee* became available in the US in May, 2014. In accordance with EU Pharmacovigilance Guidance (Module VIII), the start of a PASS using secondary data is defined to be when the analytic dataset is extracted.
b. Study Period is from 01 May 2014 through 31 August 2019.

5. RATIONALE AND BACKGROUND

In the EU, CE/BZA (authorized as *Duavive* 0.45 mg/20 mg modified-release tablets) is indicated for the treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.

In the US, CE/BZA (authorized as *Duavee* 0.45 mg/20 mg modified-release tablets) is indicated for use in women with a uterus for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause; and for the prevention of postmenopausal osteoporosis. *Duavee* has been commercially available in the US since May 2014 and was made commercially available in the EU in 2015. Compared to the EU, the US indication for *Duavee* is broader (ie, not restricted to those whom progestin-containing treatment is inappropriate and indicated for osteoporosis prevention). Therefore, it is anticipated that by conducting the PASS in the US, the population of women for whom *Duavive* would be indicated in the EU will be represented. This study will collect real-world data on the risks of various endpoints among populations for which the product is prescribed. Because *Duavee* is an estrogen-containing product, endometrial hyperplasia and endometrial cancer are relevant safety events and have been designated as primary safety endpoints, while selected other safety events are secondary endpoints.

This PASS is designed to provide interim reports at regularly scheduled intervals over the duration of the study. The rationale for conducting the study in a US population is to draw from the broader patient population indicated for *Duavee*, as well as to achieve large study samples sooner than would be possible if the study were to rely on data obtained from the EU. These advantages are based on the earlier launch of the product in the US as compared to the EU, and the large size is due to the greater sample sizes accessible in US healthcare data sources.

During the first four years after introduction of CE/BZA in the US (01 May 2014 through 31 May 2018), the rate of uptake of new users of this medication was lower than projected. As a result, fewer new users of CE/BZA have accrued than had been anticipated during study design. Current trends indicate this PASS will not accumulate enough patients in the HIRD alone, even in the next 5 years, to conduct a meaningful assessment of the risk of the primary safety events (endometrial hyperplasia and endometrial cancer), comparing new users of Duavee and E+P HT. Therefore, the study has been expanded to include additional US databases to minimize the time needed to achieve an adequate study size.

This protocol describes a non-interventional study (NIS) designated as a PASS that will be conducted in the US as a post-authorization commitment to the EMA.

6. RESEARCH QUESTION AND OBJECTIVES

6.1. Research Question

The overall aim of this PASS is to monitor the safety profile of *Duavee* (CE/BZA) in comparison to E+P combination HTs.

6.2. Objectives

- Primary objective: to estimate the incidence and compare the risks of endometrial hyperplasia and endometrial cancer among postmenopausal women initiating *Duavee* and postmenopausal women initiating E+P HT during the first five years of *Duavee* availability in the US (2014-2019).

- Secondary objective: to estimate the incidence and compare the risks of selected safety endpoints listed in Section 7.3.2.2, among postmenopausal women initiating *Duavee* and postmenopausal women initiating E+P HT.

7. RESEARCH METHODS

7.1. Study Design

This PASS is a cohort study utilizing multiple healthcare claims data sources in the US. Two (2) treatment groups (*Duavee* and E+P HT) will be identified, followed, and reported upon using annual database updates. A new-user cohort design will be used for the primary analysis and users with a history of (E+ P) HT will be examined in secondary analyses. This study will accumulate data for an additional one year and three months (31 May 2018 to 31 August 2019), and in four additional databases, as it will follow a dynamic cohort of patients that enter the study at different times, based on when *Duavee* or E+P HT is initiated.

All patients in the selected US healthcare claims databases who initiate *Duavee* or E+P HT in the study period (2014-2019) will be considered for inclusion. This PASS is a cohort study using secondary data. The source data have been accruing since *Duavee* became available in the US in May 2014. In accordance with EMA Pharmacovigilance Guidance (Module VIII),[5] the start of a PASS using secondary data is defined to be when the analytic dataset is extracted. This will not be done for this PASS until the study protocol has been approved by the PRAC.

For the primary analysis, follow-up will continue from the first use of *Duavee* or E+P HT (defined as the index date) through to the earliest of the following censoring events:

- End of continuous health plan eligibility.

- Switch from *Duavee* to an E+P HT medication or vice-versa.

    - (Note: Any use of an estrogen or estrogen-containing product that differs from the HT treatment regimen dispensed on the index date will censor follow-up. This does not include dispensing of a topical estrogen that is a single-unit E+P HT. As described in Section 7.8.4, sensitivity analyses exploring the impact of this criterion will be performed).

- First occurrence of a safety endpoint:
    - Once a patient has had a safety event, they will be censored from the analysis of that event only. For example, a patient for whom an endometrial hyperplasia outcome is identified will remain in follow-up for analysis of endometrial cancer.
- End of the study period.
- Occurrence of any cancer diagnosis:
    - As described in Section 7.8.4, sensitivity analyses exploring the impact of this criterion will be performed.
- Hysterectomy.
- Death.

Discontinuation and/or resumption of *Duavee* or E+P HT treatment will be defined and recorded, but follow-up will not be censored based on treatment discontinuation.

7.2. Study Population

Study subjects are all patients identified in each database with minimal exclusion criteria applied. This broad subject eligibility will ensure that the study is representative of the actual 'real-world' use of the product in a clinical setting.

7.2.1. Inclusion Criteria

All patients who have received a prescription for *Duavee* or E+P HT since May 2014 (date of first commercial availability in the US) and have a baseline period of at least 12 months prior to their first dispensing of a study medicine will be eligible for inclusion.

Primary Analyses

- To be included in the primary analyses, patients need to be new initiators of *Duavee* or E+P HT, as evidenced by a minimum 12 month baseline period with no prior use of either *Duavee* or E+P HT (including non-study estrogens).

Secondary Analyses

- To be included in the secondary analyses, patients will have use of either (1) single-entity estrogens or progestins (non-study drugs) or (2) unopposed estrogen (single-entity estrogen without evidence of any progestin dispensing) in their baseline period.

7.2.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

- Patients with <12 months of continuous enrollment prior to their dispensing of a study medication. This baseline period is necessary to determine if the patient is a new initiator of *Duavee* or E+P HT without a history of unopposed estrogen use, and to ascertain baseline covariates and medical history;
- Patients without a uterus, ie, males, or women for whom evidence of hysterectomy is identified prior to initiation of *Duavee* or comparator E+P HT; or
- Patients with a diagnosis or history of any cancer during their baseline period;
- Patients for whom *Duavee*, comparator E+P HT or unopposed estrogen are identified during the baseline period will be excluded from the primary analyses and will be evaluated in separate secondary analyses;
- Patients for whom cardiovascular outcomes are identified in the six months prior to the index date will be excluded from the analyses of cardiovascular outcomes.

7.3. Variables and Measurement

7.3.1. Exposure

Exposure to *Duavee* or E+P HT treatment is based on pharmacy claims. Patients with any dispensings of progestins at any time in their baseline period will not be categorized as having unopposed estrogen use.

E+P HT comparator products must have been commercially available in the US with an indication for the treatment of moderate to severe VMS associated with menopause or the prevention of postmenopausal osteoporosis.

Exposure to *Duavee* or E+P HT is defined as follows: Person-time will be categorized as having "current use" for *Duavee* or E+P HT from their index date through to 30 days after the date when the supply of their last consecutive prescription is calculated to have been used. Prescriptions will be defined as consecutive if not more than 30 days has passed between the end of days supply and the dispensing date of the next prescription. Otherwise, a new treatment segment will be defined. The 30-day grace periods allow for the possibilities of intermittent inconsistent use. For each patient, duration of exposure will be based upon the summation of recorded supply (in days) across all of their study treatment segments plus the 30 day grace period

Multiple treatment segments due to intermittent HT use will be summed when calculating duration of exposure. The study will measure each exposure segment that occurs during the follow-up period in order to support analyses that consider duration of exposure and time since most recent exposure (defined as time from date of treatment end to censoring).

Patients with long periods of follow-up that contain multiple treatment segments will be reflected in the variables of duration of exposure and time since most recent exposure.

Additionally, total person-time at risk (follow-up time) will be calculated for each patient. Follow-up time will be categorized into the following categories:

- Current use:
    - Follow-up time will be in this category if it occurs between the index date and less than 30 days since the end of days supply for the most recent prescription.
- Recent use:
    - Follow-up time will be in this category if it occurs between 30 and 90 days since the end of days supply for the most recent prescription.
- Past use:
    - Follow-up time will be in this category if it occurs greater than 90 days since the end of days supply for the most recent prescription.

7.3.2. Endpoints

The study will identify non-fatal and fatal events of the following types:

- Primary endpoints:
    - Endometrial cancer;
    - Endometrial hyperplasia.
- Secondary endpoints:
    - Venous thromboembolism;
    - Coronary heart disease (defined as myocardial infarction [MI] and sudden death);
    - Stroke (including transient ischemic attack [TIA]);
    - Breast cancer;
    - Ovarian cancer;
    - Thyroid cancer;
    - Renal cancer and adenoma;
    - Gastrointestinal cancer;
    - Any cancer (any malignant neoplasm, excluding basal cell carcinoma).

All endpoints are included in the EU risk management plan (RMP) for CE/BZA (*Duavive*). Estrogen-associated cancers (breast, ovarian, endometrial cancers) and endometrial hyperplasia are important potential risks in the RMP based on the medical literature for HT and background incidence rates (IRs) in postmenopausal women. An important identified risk potentially associated with *Duavee* use is venous thromboembolism (VTE) because it is a known safety concern for both individual component products of CE/BA (ie, CE and BZA monotherapies). According to the literature,[6] MI and stroke are important potential risks that are associated with the use of HT products in general. Thyroid cancer, renal cancer, renal adenoma, and gastrointestinal tract cancers are considered as important potential risks based on their elevated background incidence in postmenopausal women. All cancers are included because of their inclusion in the EU RMP for CE/BZA.

7.3.2.1. Primary Endpoints

The primary endpoints are endometrial hyperplasia and endometrial cancer. Previously validated algorithms for these two endpoints demonstrated that each outcome was identified in the HIRD with a positive predictive value (PPV) of at least 80%.[7, 8] These algorithms will be updated to include International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes.

7.3.2.2. Secondary Endpoints

Secondary study endpoints include VTE, coronary heart disease (CHD), stroke, breast cancer, ovarian cancer, thyroid cancer, renal cancer, renal adenoma, gastrointestinal tract cancers, all cancers, and all-cause mortality. Algorithms to identify secondary endpoints will be developed based on a targeted literature search to identify automated database studies of the endpoints of interest with a focus on validation studies in claims databases.

7.3.3. Covariates

The study will identify and describe the following variables prior to initiation of *Duavee* or comparator E+P HT treatment. Applicable operational definitions, including International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM diagnosis, ICD-9-CM and ICD-10-CM procedure, Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes will be used to identify each variable.

Patient characteristics:

- Age (ascertained on index date);
- US region of residence (ascertained on index date);
- Calendar year of index date; and
- Duration of health plan eligibility prior to cohort entry (in months).

Medical conditions diagnosed during the 12-month baseline period prior to the start of *Duavee* or E+P HT:

- Vasomotor symptoms;
- Obesity;
- Osteoporosis;
- Cardiovascular or cerebrovascular disease;
- Hyperlipidemia;
- Hypertension;
- Breast pain;
- Benign breast lumps (fibrocystic nodule);
- Diabetes;
- Renal disease;
- Osteoarthritis;
- Major depression;
- History of CHD;
- History of gallbladder disease;
- History of thyroid disease;
- Family history of cancer; and
- At least one diagnosis code indicative of a prior safety event of interest (exclusive of cancers as this is a baseline exclusion criterion) using all available patient data.

Use of prescription medications during the 12-month baseline period prior to the start of *Duavee* or E+P HT:

- Corticosteroids;
- Lipid lowering agents;
- Antihypertensives;

- Antidepressants;
- Sedatives/hypnotics;
- Anticonvulsants;
- Macrolides;
- Antifungals;
- Antivirals;
- Antidiabetics;
- Dermatologicals;
- History of oral contraceptive use;
- History of intrauterine device (IUD) exposure;
- Unopposed estrogen HT;
- Selective estrogen receptor modulators (SERMs);
- Testosterone; and
- Local hormone treatments.

Additionally, the analyses will describe the most frequently occurring diagnoses and medications seen during the baseline period, the reasons that follow-up was censored and characteristics of medication use during the follow-up period, specifically duration of therapy and time since most recent exposure (measured at the time of censoring from study).

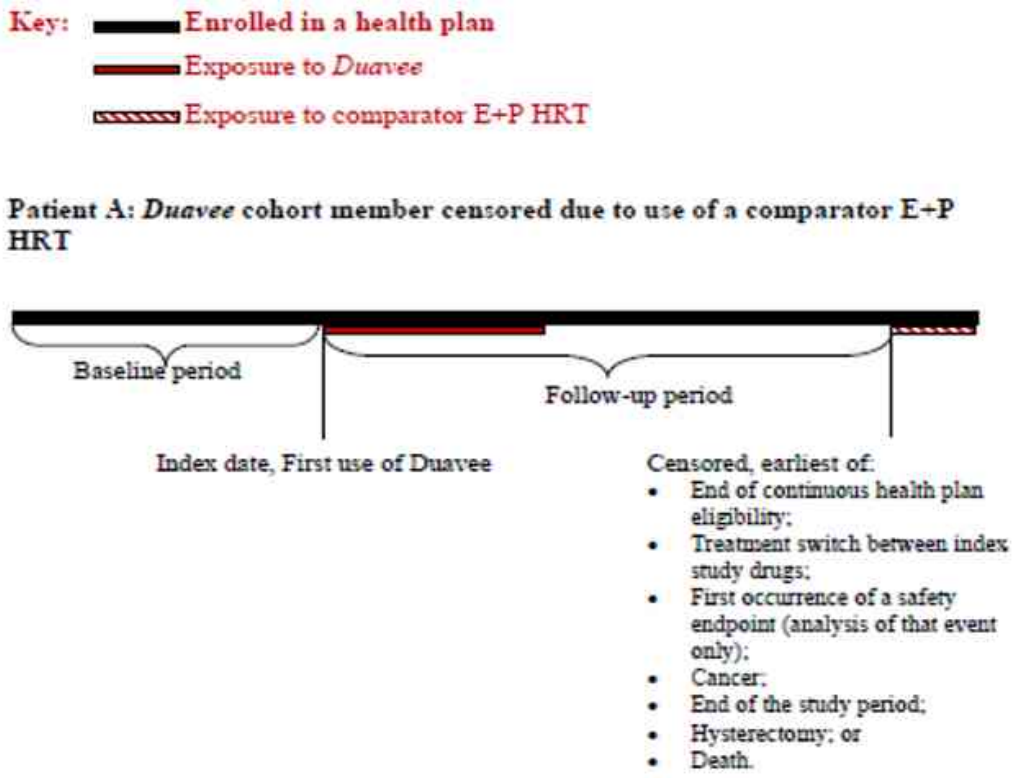
7.4. Time Periods

Each patient will have an index date corresponding to the date of entry into the study cohort, which is their first prescription for *Duavee* or E+P HT treatment between 01 May 2014 and 31 August 2019. Baseline characteristics will be assessed from patient data available 12 months or more prior to index date (baseline period), using all available claims data for each patient.

As described in Section 7.1, follow-up will continue from the first use of *Duavee* or E+P HT through to the earliest occurrence of a censoring event.

Patients will accrue both person-time at risk and person-time on treatment. Analyses will consider patients at risk during the entirety of their follow-up until censoring, regardless of treatment discontinuation. Exploratory analysis will be done on the timing of events in relation to being on treatment. Scenarios illustrating the duration of the follow-up period are presented in Figure 1.

Figure 1. Safety Endpoints



7.5. Data Sources

HealthCore, the data coordinating center (DCC) for this study, will aggregate data from five US databases: the HealthCore Integrated Research Environment, the Healthagen Research Data Source, the Optum Research Database, MarketScan Commercial and Medicare Databases and Marketscan Multistate Medicaid Databases (see Section 7.8.5). HealthCore will develop a common data structure, which will be utilized by other research partners in order to ascertain exposures, outcomes, and confounders consistently across databases and resolve any database specific inconsistencies.

All five databases record the health care experience of persons from across the US who are covered by commercial or public health insurance. The data consist of individuals' insurance claims, demographic information and summary hospitalization records. Because US health insurers use a common file structure for claims processing, their data are already structured similarly across sites. Patient eligibility criteria, covariates for statistical control, and

statistical methods for analysis are all specified in this common protocol and will be applied identically between the sites.

7.5.1. HealthCore Integrated Research Environment

The HealthCore Integrated Research Environment, which includes automated health insurance claims from the HIRD augmented with information obtained from medical records and the NDI. This data source was chosen because of its very large size, its diverse geographical representation, and the high proportion of patients whose medical records were accessible. Medical record access was a key consideration as this will be necessary to accurately identify the primary endpoints of endometrial hyperplasia and endometrial cancer. The HIRD has been previously used in pharmacoepidemiologic research.[1-4] Additionally, data from the HIRD were supplemented with a review of full text medical records, which was used to develop and validate algorithms for endometrial hyperplasia and endometrial cancer.

The HIRD contains healthcare claims integrated across data sources and types (ie, professional claims, facility claims, outpatient pharmacy claims, outpatient laboratory results, and enrollment information) as well as across years (from 2002 onwards). Data are obtained from affiliated health plans in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the US representing members in each of the 50 states of the US. The database represents claims from lines of business such as health maintenance organizations (HMOs), point of service (POS) plans, preferred provider organizations (PPOs), consumer directed health plans (CDHPs), and indemnity plans.

Specific data in the HIRD include enrollment data, medical care, prescription drug use, and health care utilization that can be tracked for everyone throughout the course of their enrollment in the selected health plans. Diagnoses and procedures for both outpatient and inpatient visits/stays are identified by ICD-9-CM and ICD-10-CM diagnostic, ICD-9-CM and ICD-10-CM procedure, CPT, and HCPCS codes. Outpatient pharmacy claims are captured by National Drug Codes (NDCs). Physician, specialist, and emergency room visits, as well as hospital stays, are captured in the database through ICD-9-CM diagnostic, ICD-9-CM procedure, CPT procedures, HCPCS, Uniform Billing Code of 1992 (UB-92) revenue (eg, room and board), and place of service codes. Information on physician specialty and laboratory result data are is also retained in the database. The claims data in the HIRD also contain information necessary for economic analyses for both medical and pharmacy claims, including amounts charged to the provider and facility, amounts paid by the health plan and member (eg, co-payments and deductibles), and coordination of benefits amounts.

7.5.2. Healthagen Research Data Source

The study population will be drawn from the Aetna research database, a database that contains the eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Aetna. Aetna is one of the nation's leading diversified health care benefits companies, serving people with information and resources to help them make better

informed decisions about their health care. Aetna serves people in all 50 states and multiple US territories.

Healthagen, LLC, a subsidiary of Aetna, conducts real world health services research including, but not limited to, observational and prospective studies in distributed research networks, evaluation of health outcomes, utilization and costs through retrospective observational and prospective randomized studies.

The Healthagen data sources include the Aetna enterprise data warehouse and the Aetna Sentinel Common Data Model (SCDM) for research purposes. Healthagen can obtain medical charts from providers or National Death Index Plus data for specific research studies.

The Aetna enterprise data warehouse includes medical and pharmacy health plan membership, medical and pharmacy health plan eligibility, medical claims, outpatient pharmacy claims, outpatient lab test results, and data derived from Aetna's care management processes for Aetna's non-administrative services Commercial members and Medicare Advantage, with service dates from three years plus the current year.

The Aetna SCDM is sourced from the Aetna enrollment and claims data warehouse.

7.5.3. Optum Research Database

The study population will be drawn from the Optum Research Database, a proprietary research database that contains the eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Optum. The population covered by this health plan is geographically diverse across the US and comprises approximately 3% to 4% of the US population. The database contains health insurance claims and enrollment data dating back to 1993. For the year 2015, data relating to approximately 13.5 million individuals, with both medical and pharmacy benefit coverage, were available. The plan provides fully-insured coverage, minus applicable co-pays, for physician, hospital, and prescription drug services. The providers of these services submit their claims for payment directly to the health plan. Optum uses de-identified data derived from these claims on a daily basis for a wide range of safety, utilization, and economic analyses. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. With each update, data through the previous month are loaded, though on average, an additional lag of six months is required to capture over 90% of available medical claims data.

The data include demographics, details from pharmacy claims, all medical and facility claims, including information on the types of services or procedures, and their accompanying diagnoses. The coding of medical claims conforms to insurance industry standards including:

- Use of designated claims forms (eg, physicians use the Centers for Medicare and Medicaid Services [CMS]-1500 format and hospitals use the UB-04 format);
- ICD diagnosis codes and procedure codes (ICD-9 and ICD-10);

- CPT codes;
- CMS HCPCS codes.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. These data allow for longitudinal tracking of medication refill patterns and changes in medications, and include:

- NDC;
- Drug name;
- Dosage form;
- Drug strength;
- Fill date;
- Days of supply;
- Cost information;
- De-identified patient and prescriber codes.

The machine-readable dataset of the Optum Research Database (ORD) can be augmented on an ad hoc basis by further inquiry, including chart review and linkage to the NDI Database. The data are only re-identified following approval by an IRB, and all data access conforms to applicable HIPAA policies.

7.5.4. MarketScan Research Databases

In addition to these three databases, HealthCore will be obtaining and analyzing data from the IBM Truven Health MarketScan Research Databases, a set of data that fully integrates de-identified patient-level health data. These data are contributed by large employers, managed care organizations, hospitals, electronic medical record providers, Medicare and Medicaid.

7.5.4.1. MarketScan Commercial and Medicare Database

The MarketScan Commercial claims and encounters database is a nationwide research database that includes individuals covered by commercial insurance through their employer, and their covered family members. The data are generalizable to the US population covered by employer-sponsored insurance (58.3% of population) and contains eligibility, pharmacy claims and medical claims data.

Truven Health constructs its MarketScan commercial claims databases by collecting data from employers and health plans. Data comprise service-level claims for inpatient and outpatient services and outpatient prescription drugs for employee contractor holders and

their covered family members. Medical claims or encounter data are collected from all available health care sites (inpatient, outpatient, long-term care), for virtually all types of services provided, including specialty, preventive and office-based treatments. Pharmacy data include NDCs, date of service, and days' supply, and are linkable to the Red Book, which includes information such as generic drug name and dosage forms. Claims are linkable based on a unique identification number. All claims have been paid and adjudicated. Financial, clinical, and demographic fields are standardized and then contributor-specific fields are added. Individual level, de-identified data will be used for all analyses.

HealthCore will be obtaining MarketScan Commercial data from May 2014 through July 2019.

7.5.4.2. MarketScan Multi-State Medicaid Database

The MarketScan Multi-State Medicaid Database reflects the healthcare service use of individuals covered by Medicaid programs in numerous geographically dispersed states. The database contains the pooled healthcare experience of Medicaid enrollees, covered under fee-for-service and managed care plans. It includes records of inpatient services, inpatient admissions, outpatient services, and prescription drug claims, as well as information on long-term care. Data on eligibility and service and provider type are also included. In addition to standard demographic variables such as age and gender, the database includes variables of particular value to researchers investigating Medicaid populations, such as federal aid category (income based, disability, Temporary Assistance for Needy Families) and race.

The annual Multi-State Medicaid Database is released in December of each year, with updates released in February and July of each year. The lag time (time between last service date and release date) is 12 months for the annual database release, eight months for the February update, and seven months for the July update. Due to timing of the updates, as well as the lag time, HealthCore will obtain Medicaid data for May 2014 through December 2017.

7.6. Study Size

The purpose of the sample size calculations is to determine the minimum detectable hazard ratio (HR) given estimated study size, durations of follow-up, and event rates of the primary endpoints, endometrial hyperplasia and endometrial cancer.

Table 2. Total Number of CE/BZA and E+P HT New Users by Database

Time Period	MarketScan Commercial		MarketScan Medicaid		Optum		Healthagen		HealthCore		Total	
	(CE/BZA)	(E+P HT)	(CE/BZA)	(E+P HT)	(CE/BZA)	(E+P HT)	(CE/BZA)	(E+P HT)	(CE/BZA)	(E+P HT)	(CE/BZA)	(E+P HT)
05/2014-05/2018	N/A	N/A	N/A	N/A	2,332	13,840	533	3,899	1,502	12,865	4,367	30,604
05/2014-08/2019*	8,929[1]	53,289[1]	104[2]	3,380[2]	2,491	19,708	570	5,552	1,604	18,320	13,698	100,249

*Projected based on rate of accrual of new users of CE/BZA and E+P HT in the HealthCore database between 2017 and 2019.
[1] The MarketScan Commercial counts reflect data from May 1, 2014 through December 31, 2017.
[2]The MarketScan Medicaid counts reflect data from May 1, 2014 through July 31 2019.

7.6.1. Minimum Detectable Risk

In order to calculate the power of a study this size to estimate certain effect sizes for endometrial hyperplasia and endometrial cancer, we assumed a 4:1 matching ratio between new users of E+P HT and CE/BZA, background rates of 81.4 endometrial cancer cases per 100,000 person-years, based on a pilot analyses of the HIRD, and 142.9 endometrial hyperplasia cases per 100,000 person-years,[9] an alpha level of 0.05, and an average duration of follow-up of one year per patient. The one year of follow-up reflects eight months of treatment, estimated from a recent HealthCore report, and four months follow-up post-treatment.

A study size of approximately 13,698 patients who are new users of CE/BZA is estimated to have 80% power to detect a hazard ratio of 1.8 for endometrial hyperplasia (Figure 2) and 2.1 for endometrial cancer (Figure 3).

Figure 2. Power curves for an endometrial hyperplasia study

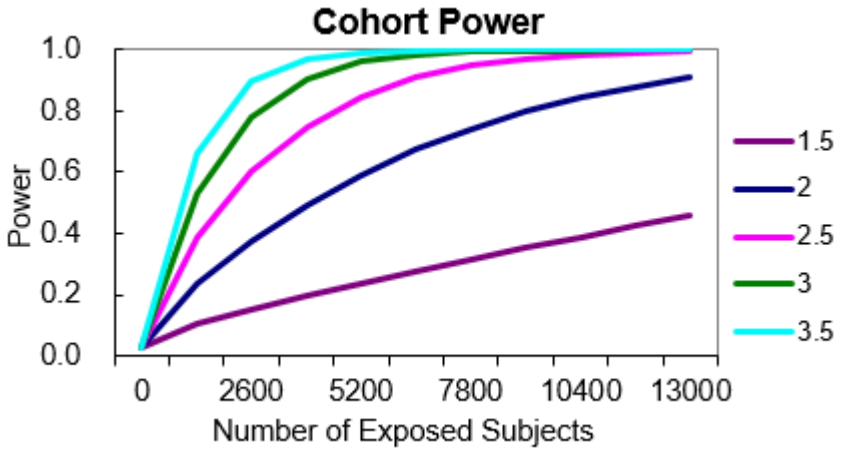
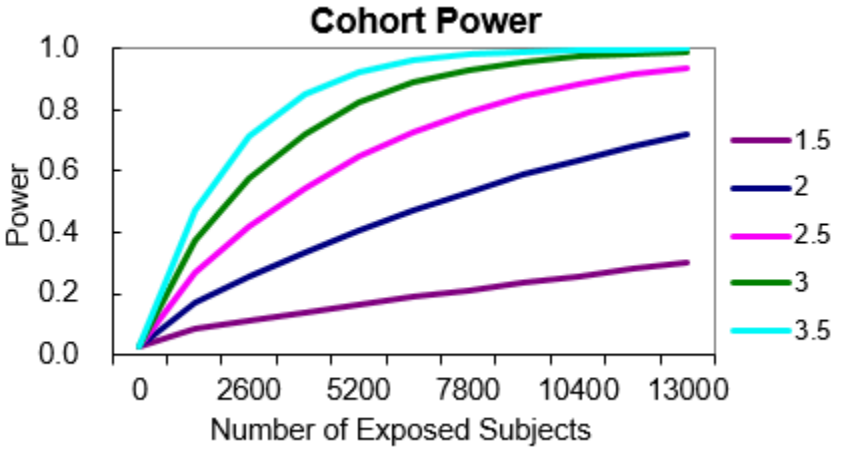


Figure 3. Power curves for an endometrial cancer study



7.6.2. Ruling out Relative Risk

Table 3. Probability of Ruling out Relative Risk

			Probability that Study Size will Estimate 95% Upper Bound Confidence Limits of Relative Risk Less than Specified Value Between CE/BZA and E+P HT				
	Number Exposed	Number Unexposed	RR=2.0	RR=2.5	RR=3.0	RR=3.5	RR=4.0
Endometrial Hyperplasia	13,698	54,792	78.3%	95.2%	99.1%	99.9%	99.9%
Endometrial Cancer	13,698	54,792	54.4%	78.1%	90.7%	96.2%	98.5%

For endometrial cancer, assuming a 4:1 matching ratio, an alpha level of 0.05, an average duration of follow-up of one year per patient, and a background rate of 81.4 events per 100,000 women, a study of this size would have 80% probability of ruling out a relative risk of 2.5.

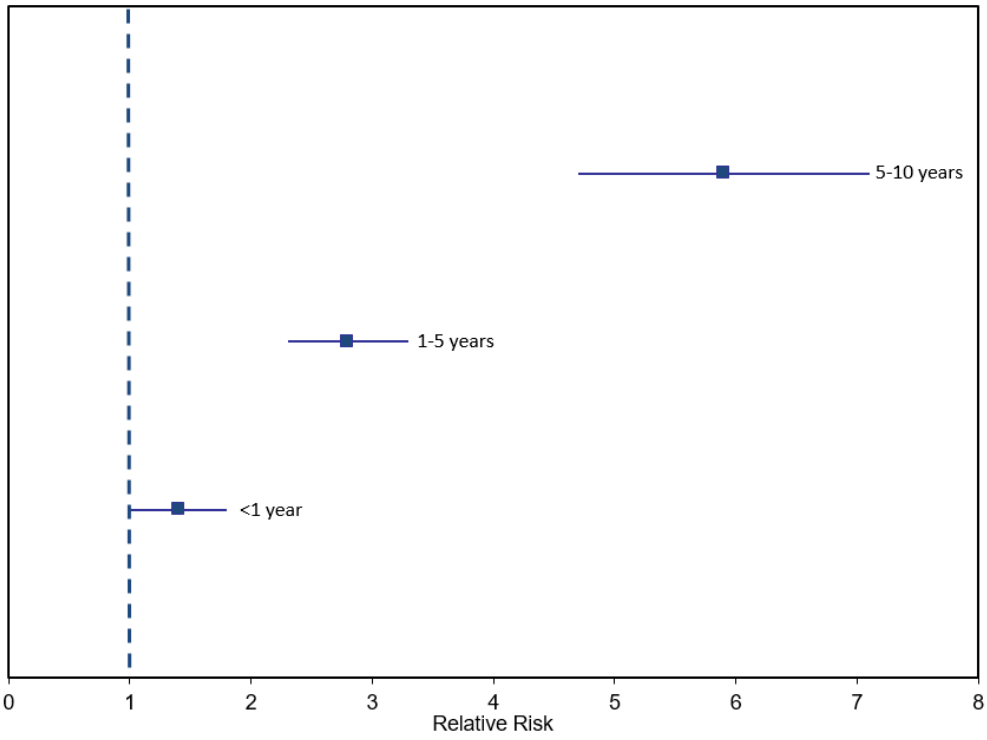
For endometrial hyperplasia, assuming a 4:1 matching ratio, an alpha level of 0.05, an average duration of follow-up of one year per patient, and a background rate of 142.9 events per 100,000 women, a study of this size would have 80% probability of ruling out a relative risk of 2.0.

7.6.3. Contextualizing Study Size

With an expected study size of approximately 13,000 new users of *Duavee*, this study will have 80% power to detect a minimum relative risk of 2.1 for endometrial cancer. Between May 2014 and May 2018, new users of CE/BZA in the HIRD had a median duration of exposure to CE/BZA of about six months and approximately 50% had less than three months since last exposure to CE/BZA. Assuming that the risk of endometrial cancer associated with unopposed estrogen risk represents the upper limit of risk of endometrial cancer associated with *Duavee* use, this risk may vary substantially based on the dose and duration of use.

A meta-analysis pooling results from 37 studies found that the risk of endometrial cancer increased about two-fold in women who had ever used unopposed estrogen therapy, but varied substantially by duration, dose, and type of estrogen used. Short-term unopposed estrogen use, defined as less than one year, was associated 1.4 times the risk of endometrial cancer, while between one and five years of use was associated with a threefold increase in endometrial cancer risk (Figure 4).[10]

Figure 4. Relative Risks from Meta-Analysis of Duration of Unopposed Estrogen Therapy and Risk of Endometrial Cancer



7.7. Data Management

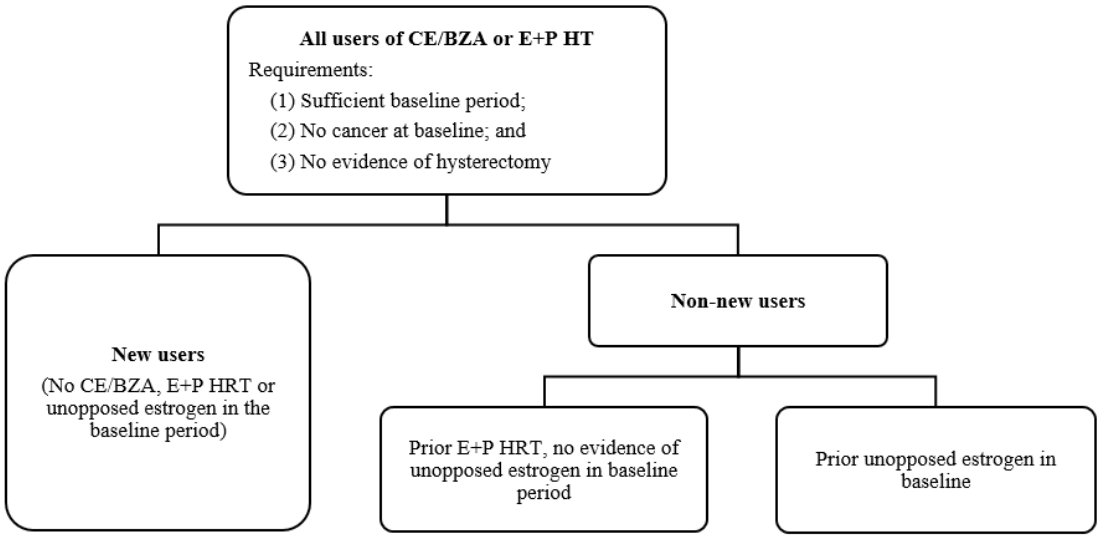
All data management and analyses will be conducted by each Research Partner in accordance with their respective standard operating procedures (SOPs) and guidelines.

7.8. Analysis Plan

The steps to produce the analytic dataset, generate study results, and apply those results to the research objectives will be described in detail in a separate single statistical analysis plan (SAP), approved by all Research Partners, and will be in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on methodological standards in pharmacoepidemiology (Chapter 7-Statistical and Epidemiological Analysis Plans).

Patients will accrue both person-time at risk and person-time on treatment. Analyses will consider patients at risk during the entirety of their follow-up until censoring, regardless of treatment discontinuation. Exploratory analysis will be done on the timing of events in relation to being on treatment. The analytic cohorts to be included in the primary and secondary analyses are described in Figure 5.

Figure 5. Analysis Populations



Analyses will initially be conducted separately within each data source, and then the results will be pooled together. See Section 7.8.5.

7.8.1. Adjustment/Control of Confounding

As with any observational study, an important aspect of study design will be the methods used to ensure comparability of treatment groups and control for any confounding effects due to extraneous risk factors.

Propensity score matching will be used to achieve comparison groups that are balanced on their probability of being prescribed CE/BZA. Propensity scores at the index date will be estimated by logistic regression analyses, incorporating measured potential predictors of exposure group and calendar year of the index date as independent variables in the regression model and will be calculated as the probability of receiving a CE/BZA dispensing. Variables to be considered for propensity score derivation, which include demographic, clinical (medical comorbidities and concomitant medications), and healthcare utilization variables present at or before the index date will be assessed if available in the data source. Separate propensity score models will be developed for cardiovascular and cancer outcomes. Patients with a propensity score outside of the region of overlap of the propensity score ranges in the CE/BZA and E+P HT groups will be excluded. The minimum ratio of the number of patients in the E+P HT group to the number of patients in the CE/BZA group across deciles of propensity score will be identified and patients in the CE/BZA group and the E+P HT group will be frequency matched based on this minimum ratio. We assume a propensity score matching of one CE/BZA patient to four E+P HT comparator patients, based on sample size estimates. The propensity-matched new users of CE/BZA and E+P HT will then be compared in the primary analyses and propensity-matched non-new users will be compared in the secondary analyses.

7.8.2. Primary Analyses

The analyses will describe patients that initiate *Duavee* and the comparator E+P HT cohort with respect to demographic and clinical characteristics as enumerated in Section 7.3.3. Reasons for censoring will also be described by exposure group. Descriptive comparisons of the two cohorts will be done to document their differences at baseline and to identify potential confounders to be addressed in the propensity matching.

For each of the primary endpoints (ie, endometrial hyperplasia and endometrial cancer), an incidence rate (IR) will be calculated as the number of cases of each outcome (first event only) divided by person-time at risk. IRs and their 95% confidence intervals (CIs) will be presented for each treatment group overall and stratified by categorical patient age at cohort entry, duration of *Duavee* or E+P HT treatment, time since last exposure to *Duavee* or E+P HT, exposure to local hormone therapy, and by presence (Y/N) of an osteoporosis diagnosis within the 90 days before or after initiation of *Duavive* or E+P HT, and by current, recent or past use of *Duavive* or E+P HT. Duration of treatment and time since last exposure will be categorized based on observed data distributions. The feasibility of these stratifications and of a possible analysis that stratifies simultaneously by duration of treatment and time since last exposure will be determined based on the number of observed safety events.

HRs and 95% CIs will be estimated using Cox proportional hazards models, comparing initiators of *Duavee* with initiators of E+P HT.

Similarly, to the primary endpoints, the IR and multivariate adjusted HR will be calculated for the following secondary safety endpoints: VTE, stroke, CHD, breast cancer, ovarian cancer, thyroid cancer, renal cancer, renal adenoma, gastrointestinal tract cancers, and all cancers among study subjects initiating *Duavee* or E+P HT.

For all analyses, each endpoint will be identified first in the automated claims data (ie, endpoints that were not fatal prior to the patient reaching the healthcare system).

7.8.3. Secondary Analyses

We will conduct secondary analyses for patients not included in the primary analyses. These patient groups are those with use of either (1) E+P HT (ie, not new initiators), or (2) unopposed estrogen during their baseline period.

Women with a previous history of E+P HT use require special analytic considerations. In a new-user cohort design (as in the main analysis), these types of patients are excluded for several reasons. First, if women with past use of HT incur a study endpoint, it is difficult to determine whether the endpoint is due to previous HT or current HT use. Further, women for whom previous HT use was associated with poor outcomes (eg, adverse effects) are likely to be under represented among those initiating *Duavee* or E+P HT, which would deplete susceptible women and result in a survivorship bias or could lead to channeling of these patients to one study drug over the other. Finally, baseline factors of women with previous use of HT (eg, comorbidities) could include effects of HT (eg, uterine bleeding) that could be intermediate in the causal pathway between exposure and study endpoints (eg, endometrial

hyperplasia, endometrial cancer). Controlling for factors that are intermediate in the causal pathway under study is to be avoided as it can invalidate a given analysis. Because of these limitations, analyses of the primary and secondary endpoints among *Duavee* and E+P HT exposed patients with a previous history of HT use will be limited to estimation of IRs and their associated 95% CI for each cohort overall and stratified IRs by the variables listed in the main analyses (patient age, treatment duration, time since last exposure, and exposure to local hormone therapy). These stratified analyses will only be done once there are at least four events in each of the *Duavee* and E+P HT groups.

7.8.4. Sensitivity Analyses

We propose four sensitivity analyses:

1. Sensitivity analyses will be conducted to examine the impact of censoring based on (i) treatment switch and (ii) cancer diagnosis. These sensitivity analyses are planned to explore the impact of censoring due to treatment switch, censoring from analyses of safety endpoints due to occurrence of any cancer type, and potential misclassification of the primary endpoints based on use of the developed algorithms. Specifically, the primary analyses for the primary and secondary endpoints will be performed including person-time after treatment switch, and the main analysis for the primary endpoints only (endometrial hyperplasia and endometrial cancer) will be performed including patients who had been censored due to cancer occurrence.

2. Sensitivity analyses restricting primary analysis to include only the first new use treatment episode, excluding treatment episodes where patients are re-starting use of *Duavee* or E+P HT. As defined, a patient can discontinue then re-start therapy. If the new episode is the index episode, it is included, but if the new episode is a different therapy, the subject is censored and the new episode is not included. Non-primary episodes, therefore, are informed by experience with prior episodes.

3. Because the PPV's of the algorithm to ascertain the primary outcomes may vary by database, as well as by exposure group, we will adjust the hazard ratios produced by the study, using a range of plausible values of algorithm performance in the exposed and unexposed groups in order to assess the effect and extent of outcome misclassification.[11] Plausible values of algorithm performance will be guided by previous ascertainment and validation of the outcomes in the HIRD.

4. Sensitivity analysis will calculate the incidence of all cancer (any malignant neoplasm), including basal cell carcinoma, as an endpoint.

7.8.5. Pooled Analysis (to be conducted by HealthCore)

Analyses will be undertaken separately in the five databases and hazard ratios for each database will be reported individually. As the study's DCC, HealthCore will use these five risk estimates to perform a random-effects meta-analysis[13] to pool the results from the five different databases. Data source will be included as a variable in the pooled model.

DerSimonian and Laird's approach permits revised variance estimates for studies in which the variance attributable to random variation between sites is added to within-study variance estimates. In addition to the site-specific results, any differences between sites in healthcare administration and insurance plan details, including covariates available for confounder control from the five sites will be carefully considered. The similarities and differences between the settings and the possible reasons for inter-site variation will be considered in the analysis and interpretation of site-specific and pooled estimates. If the sites differ from one another more than expected, the between site variation will be incorporated into the weighting scheme for the pooled estimate as well as the variance estimate.

Important overlap between patients in the HIRD, Optum, Healthagen, and MarketScan Medicaid is unlikely. However, it is estimated that there will be some amount of overlap between the HIRD and the MarketScan Commercial database, as both are comprised of employer-based health insurance claims. It is estimated that approximately 10% of patients captured in the HIRD are also included in the MarketScan Commercial database. Non-independence of these individuals will be accounted for by including a robust sandwich estimator to adjust the variance of the pooled analysis.[14]

7.8.6. Statistical Methods

7.8.6.1. Descriptive Analysis

Baseline characteristics and reasons for censoring will be presented for each exposure group. Counts and percentages for categorical variables, and mean, median, standard deviation and range for continuous variables will be presented. Descriptive characteristics will be presented for the following groups:

1. All new users of *Duavee* and E+P HT included in the cohort;
2. All users of *Duavee* and E+P HT with prior E+P HT exposure; and
3. All users of *Duavee* and E+P HT with prior unopposed estrogen use.

7.8.6.2. Adjusted Analysis

As described in Section 7.8.1 through Section 7.8.3, IRs and their 95% CI overall and stratified by age, duration of treatment, time since most recent exposure and use of topical estrogen products will be presented.

For a given safety endpoint, analyses will not be performed until there is at least one event in both cohorts, and at least four events in total (across cohorts). Until this threshold is reached, analyses will consist of cohort description and IR estimation.

Hazard ratios will be estimated, using Cox proportional hazards models, to estimate the risk of first occurrence of each safety endpoint in women newly exposed to *Duavee* when compared to initiators of E+P HT, using propensity score matching. Models will be tested for the proportional hazards assumption.

7.8.7. Multiplicity Issues

This study will examine a number of end points, which introduces the possibility of incorrectly identifying a significant association between *Duavee* exposure and a given outcome. In order to minimize the effect of multiple endpoints, two primary endpoints, endometrial hyperplasia and endometrial cancer, have been identified.

Therefore, we will not make statistical adjustments for multiple comparisons.

7.8.8. Missing Data

The distribution of all variables will be examined to determine the presence of outliers. Patients with implausible values for age (eg, age >120 years) or multiple values for gender will be regarded as having missing data for these variables and excluded from the analyses; the number of potential individuals excluded due to these data integrity issues will be described and is expected to be small. Imputation or other adjustments for missing values are not planned.

7.9. Quality Control

7.9.1. HealthCore

HealthCore's research team documents the progress and scientific and quality review of all study activities and deliverables (eg, protocol, data management, data analysis, reports, manuscripts, etc) in a Project Log. The Project Log provides documentation of the major study tasks related to a specific study activity performed by HealthCore to develop and execute the requirements of the protocol. In addition, the Project Log documents the quality assurance measures performed for each study activity during the conduct of the study. Any change to study specifications (eg, protocol, study database, variables in the analytic files, etc) is also described in the Project Log. This is necessary to ensure that such communications are appropriately documented, that the most up to date versions of relevant documents are readily identifiable, and that affected documents are clearly tracked in the Project Log.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore SOPs and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not main programmer for the study, internal dataset consistency, and checks to ensure that Protocol criteria were met. If validation checks are not satisfied then an examination of the problem will be performed on the dataset or datasets in question and the problem resolved. All data validation, quality checks, and resolution of issues identified will be documented in the Project Log.

HealthCore will apply these quality control measures for both the HIRD data and MarketScan data, as HealthCore is analyzing both the HIRD and the MarketScan data.

7.9.2. Healthagen

Healthagen, LLC, a subsidiary of Aetna, conducts real world health services research including, but not limited to, observational and prospective studies in distributed research networks, evaluation of health outcomes, utilization and costs through retrospective observational and prospective randomized studies.

Research studies are assigned to a Healthagen research team. The Healthagen Sentinel-Distributed Research Network (DRN) team tracks activities and deliverables, such as protocol, data management, data quality control, data analysis, reports, and manuscripts in Atlassian JIRA project tracking software. Any changes to the study specifications are described in the JIRA with a link to the new version of the study specification are saved on the dedicated, secure shared Window sub-directory.

All study database extraction and analytic dataset creation are performed in accordance with Healthagen Standards. The Standards are rules and guidelines to accurately extract and quality assure the data extractions maintain operational consistency. Data validation and control occurs throughout the data extraction, management, and analysis process. Data quality checks and review include, but are not limited to, the following:

- SAS or other program code;
- Protocol specifications and criteria compared to program code;
- Program execution log;
- Meta data;
- Descriptive statistics on tables and variables;
- Internal data consistency checks;
- External data consistency checks.

If data quality checks reveal data issues, additional investigations and analysis will occur to identify and resolve the problem. All data validation, quality checks, and resolution of issues identified will be documented in JIRA and the SAS Code.

The data quality review is conducted by a team will include at least two people and one senior level programmer. The senior level programmer will determine if the data quality meets Healthagen Standards

7.9.3. Optum

The Optum Research Database contains data derived from claims submitted by providers and pharmacies to obtain payment for health care services rendered, data to track plan membership for premium billing, and provider data to track participating physicians who have contracts with health plans to provide services. The underlying administrative data are

routinely captured, verified, automated, and de-identified. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. Although the health insurance claims data represent financial transactions and are not research records, the financial transactions related to the services provided create financial incentives to record them correctly and fully, so the billable medical services represented in the database are likely to be complete. The validity of this claims research database for epidemiologic research (as compared with data abstracted from medical records) has been widely published.

The study will be carried out according to the Optum Epidemiology group's internal standard operating procedures (SOPs) that are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.[15-18]

Quality control of analytic work typically involves a combination of a review of program logs and lists, independent coding, a review of program processes and documentation to ensure departmental SOPs are followed, and reconciliation of program code to ensure populations and results are consistent with what is needed for the particular study. Individual programs are documented and revised as needed until sign-off by a validation analyst using a validation/programming log.

7.10. Strengths and Limitations of the Research Methods

Strengths:

- This PASS uses population-based data sources of the real-world actual use of *Duavee*. These data will record use in a population anticipated to be broader than the indication for which *Duavive* is authorized in the EU and will complement the existing clinical safety data for CE/BZA. Unlike spontaneous reporting data, the incidence of safety endpoints can be estimated. The HIRD is a well-established resource for conducting pharmacoepidemiologic research and has been shown to be nationally representative with good validity in capturing patient care.[1-4]

- The results of this US PASS will apply to the EU population expected to initiate treatment with *Duavive*. The PASS will provide insight into any possible association of *Duavive* use and the targeted safety events in the EU population. This is true because the internal validity of this study will be optimized, due to careful attention given to designing a study that isolates any true biological relationship between *Duavive* and safety risks, from differences in risk arising from bias due to selection, confounding, or other sources of error. See Section 7.11 for further discussion of the generalizability of this US PASS to the EU.

- Many of the endpoints in this study are well-defined in US healthcare data and have been studied in pharmacoepidemiology studies.[19, 20] Further, MI, and stroke endpoints have been confirmed to have a high PPV in HIRD validation studies.[1]

- The combining of results from five different data sources will be informative not only to increase the sample size of subgroups of interest, but also to increase the number of events for primary and secondary outcomes, and to reduce variances and obtain more precise confidence intervals for the resulting estimates.[21]

Limitations:

- Use of administrative healthcare data for research is associated with outcome misclassification, due to missing codes or coding errors, or to limits in the time period of patient observation available in the data. This study will use well-established sources, but misclassification may still be present. Specifically, women whose hysterectomy is not captured by the claims data and who started either *Duavee* or E+P HT would be misclassified as having an intact uterus. However, this misclassification would be non-differential and would not bias the study comparison.

- There may be uncontrolled residual confounding aspects due to unmeasured prescribing factors that differ between the *Duavee* and E+P HT patient cohorts. Physicians prescribe drugs for specific medical reasons and this may introduce channeling biases whereby one cohort is at higher risk for a particular safety event. This bias could also be due to unrecorded cardiovascular and cancer risk factors such as smoking, body mass index (BMI), and family history. Because the analyses rely on automated claims collected primarily for billing purposes, some desirable data elements are not captured. Lifestyle factors such as smoking and biometric measures like BMI, for example, are systematically unavailable. Likewise, family history of endpoints is unknown. These factors present another source of residual confounding.

- Despite the large size of the claims databases, the identified safety endpoints are rare events so there will be a limit to the precision with which it can estimate elevated risks associated with *Duavee* use. Additionally, the cancer endpoints may have long latency periods from exposure and the ability to follow patients long-term will be limited by duration of enrollment in the database.

- Calculation of HT treatment duration and time since last exposure are based upon assumptions about actual use patterns because drug dispensing is all that can be directly observed using the HIRD.

- The MarketScan Medicaid data are available for May 2014 through December 2017, not the entire study period (May 2014 through August 2019). The MarketScan Commercial data are available for May 2014 through July 2019.

- Secondary analyses of prevalent users of unopposed estrogen may be difficult to interpret due to selection factors and unmeasured covariates. We anticipate that this group will include:

    1. Patients with an intact uterus with past use of unopposed estrogen;

2. Patients without a uterus for whom no hysterectomy was identified in the automated claims data due to timing of the procedure; and

3. Patients who used both estrogen and sporadic progesterone for whom a progesterone dispensing was not observed.

7.11. Generalizability

Whether a finding from a drug safety study in the US that a medication is associated with an adverse event (AE) is relevant for the EU population (and vice versa) is primarily a function of the internal and external validity of the study. For this reason, this study will use a rigorous set of epidemiologic design and analysis methods in an effort to estimate causal effects of *Duavee* with as much control as possible for various sources of error (eg, selection, misclassification, confounding). It follows that if a valid independent drug effect is found in this study, it would be relevant to the *Duavive* EU population. If a result is considered valid, then it is of interest to question to whom the result applies. Allowing that all populations differ from one another in one respect or another, Pfizer is focused upon whether women using *Duavee* in the US will differ from women using *Duavive* in the EU with regard to susceptibility to a particular adverse effect. Although indications for the drug are not identical between US and EU, it is expected that the populations would be largely similar in terms of their risks for these targeted safety endpoints.

Including the MarketScan Commercial databases in the study will improve generalizability due to increased study size and power. Inclusion of the MarketScan Medicaid data will also increase generalizability, as this population will contain patients who are not covered under a commercial insurance plan.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information and Consent

8.1.1. HealthCore

There is no active enrollment or active follow-up of study subjects, and no data are collected directly from individuals. HealthCore maintains Data Sharing Agreements (DSAs) and Business Associate Agreements with all covered entities who provide data to the HIRD. HealthCore's access, use, and disclosure of Protected Health Information (PHI) are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 Code of Federal Regulations (CFR) Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose identifiable PHI unless under a specific waiver of authorization (eg, a HIPAA Waiver of Authorization from an IRB). HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

8.1.2. Healthagen

The proposed retrospective designed study will use medical and pharmacy claims data. The study design has no active enrollment of study subjects, follow-up of study subjects, and/or no data are collected directly from individuals. Healthagen-HealthCore have a Confidentiality Agreement and will enter into a Data Sharing Agreements (DSA) as a part of this study.

Healthagen, a subsidiary of Aetna, uses medical and pharmacy claims data processed by Aetna in its role of administration of health benefits to medical and pharmacy insured members. Healthagen accesses, uses, and disclosures of PHI are in compliance with the HIPAA Privacy Rule [45 CFR Part 160 and Subparts A and E of Part 164].

Healthagen does not access, use, or disclose identifiable PHI unless under a HIPAA Waiver of Authorization from an IRB. The methods/procedures for securing data confidentiality will include appropriate safeguards to prevent use or disclosure of PHI in accordance with 45 C.F.R. 164.412. Aetna has standard operating processes to mitigate, to the extent practicable, any harmful effect that is known of a use or disclosure of PHI; to promptly report to the HIPAA Covered Entity any use or disclosure of PHI not provided for by a Business Associate Agreement; and to report any breach of unsecured PHI without unreasonable delay (in no case later than sixty calendar days after discovery of a breach), including identification of each individual whose unsecured PHI has been, or is reasonably believed by a Business Associate, to have been accessed, acquired, or disclosed. In accordance with 45 CFR 164.502(e)(1)(ii) and 164.308(b)(2), if applicable, any subcontractors that create, receive, maintain, or transmit Protected Health Information on behalf of the Covered Entity and Business Associates agree in writing to the same restrictions and conditions that apply to confidentiality of the data. With respect to Electronic Protected Health Information, data holders will implement and comply with (and ensure that its subcontractors implement and comply with) the administrative safeguards set forth at 45 C.F.R. 164.308, the physical safeguards set forth at 45 C.F.R. 310, the technical safeguards set forth at 45 C.F.R. 164.312, and the policies and procedures set forth at 45 C.F.R. 164.316 to reasonably and appropriately protect the confidentiality, integrity, and availability of the Electronic Protected Health Information that it creates, receives, maintains, or transmits on behalf of the HIPAA-Covered Entity, Aetna.

8.1.3. Optum

This observational study is designed as an analysis of the insurance claims data. There will be no active enrollment or active follow-up of patients, and no data will be directly collected from patients.

8.1.4. MarketScan Commercial/Medicare and Medicaid Databases

There is no active enrollment or active follow-up of study subjects, and no data are collected directly from individuals.

8.2. Patient Withdrawal

Not applicable.

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

8.3.1. HealthCore

The proposed study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US. Though this study does not currently require information from medical records, if necessary HealthCore would seek oversight from an independent IRB. As the IRB is independent, HealthCore cannot control the approval or whether there are conditions for the approval. A copy of the IRB approval letter will be forwarded to Pfizer by HealthCore.

Protected Health Information were accessed from medical records in order to adjudicate the safety endpoints of endometrial hyperplasia and endometrial cancer during the first four years of the study. A HIPAA Waiver of Authorization was applied for from an IRB prior to any PHI being identified.

At no time during the conduct of this study will HealthCore provide to Pfizer information identifying patients or providers.

8.3.2. Healthagen

Healthagen, LLC, a subsidiary of Aetna, conducts real world health services research including, but not limited to, observational and prospective studies in distributed research networks, evaluation of health outcomes, utilization and costs through retrospective observational and prospective randomized studies.

IRB

The proposed retrospective designed study will use medical and pharmacy claims data from a DRN of large insured population in the US. A limited dataset with no Personal Identified Information (PII) will be used to identify and summarize the safety endpoints of endometrial hyperplasia and endometrial cancer. A HIPAA Waiver of Authorization will be applied for from either a single IRB or multiple IRB dependent on the needs of Sponsor and DRN health plan partners. As the IRB is independent, Healthagen cannot promise the approval or whether there are conditions for the approval of the HIPAA Waiver of Authorization. A copy of the IRB approval letter will be forwarded to Sponsor and HealthCore.

Healthagen will not provide data that would identify patients or providers to the Sponsor, HealthCore, or other DRN health plan partners.

8.3.3. Optum

Optum will each seek oversight from an independent IRB. Optum will prepare and submit the appropriate documents to a central IRB, and communicate directly with the IRB to address any questions and/or provide any additional information in connection with the reviews. The Sponsor shall provide any necessary assistance or documents required for the submission to the IRB. Approval from an IRB for this study is not guaranteed. This study will be undertaken only after the protocol and study documents have been approved. The

IRB will be asked to review and re-approve this study on an annual basis (at minimum). Only aggregated results will be provided to the Sponsor.

8.4. Ethical Conduct of the Study

This study will be conducted in accordance with applicable legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and the EMA, ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AE with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the data collection tool (eg, chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. These events will be reported by Pfizer to regulators as single case reports, but no follow-up on these related AEs will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Regulatory Authority Reporting

One final report will be submitted to the EMA covering patients who initiate *Duavee* or E+P HT in 2014-2019. The study protocol and the final report will be published in the EU PAS register under number EUPAS11599.

10.2. Publication

For all peer-reviewed publications relating to this study, Pfizer will follow recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

10.3. Communication of Issues

In the event of any prohibition or restriction imposed (eg, by clinical hold) by an applicable Competent Authority in any region of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

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