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	Final
Date of last version of protocol	22 October 2015
EU Post Authorisation Study (PAS) register number	Pending
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 Limited
Joint PASS	No
Research question and objectives	Compare the incidence of safety endpoints, in patients exposed to CE/BZA compared to estrogen + progestin (E+P) combination hormone replacement therapy (HRT).

Country(-ies) of study	United States
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Marketing Authorization Holder(s)

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APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse Event Monitoring
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
CPT	Current Procedural Terminology
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^{SM}
HMO	Health Maintenance Organization
HR	Hazard Ratio
HRT	Hormone replacement therapy
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IEC	Independent Ethics Committee
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
NIS	Non-interventional study
PASS	Post-Authorization Safety Study
PHI	Protected Health 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
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

Principal Investigator(s) of the Protocol

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2. ABSTRACT

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

Protocol: Version 4.0 (Final), 20 July, 2015

Main author: Leo Russo, PhD., Pfizer, 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 is expected to be commercially available in the EU in 3Q/4Q 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 as much real-world safety data as possible 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).

Research question: The overall aim of this PASS is to monitor the safety profile of *Duavee* in comparison to estrogen + progestin (E+P) combination hormone replacement therapies (HRT) 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 HRT.

- 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 HRT.

Study design: This PASS is a retrospective cohort study utilizing a US healthcare claims data source (HealthCore Integrated Research Database℠ [HIRD]). Two treatment groups of new initiators (*Duavee* and E+P HRT) will be defined and followed for each specified endpoint until the end of the study period or until that endpoint occurs. Other censoring events include hysterectomy, switch of index treatment, and disenrollment from the HIRD, diagnosis of cancer or death. The planned study will be 4 years in duration and will follow new initiators identified in 2014-2018.

Study Population: All patients identified in the HIRD who have received at least one prescription for *Duavee* or E+P HRT since May 2014 (US commercial launch date), and have a baseline period (e.g., 6 or 12 months to be determined by a priori analyses) prior to their first study medicine prescription, will be included in this study. Patients without a uterus and those with an existing cancer diagnosis will be excluded. Only new initiators will be included in the main analysis. To be a new initiator, patients need to have no recorded use of either *Duavee* or E+P HRT products in their baseline period. Patients with prior use of E+P HRT in either the *Duavee* or E+P HRT cohort will be excluded from the main analyses, but will be included in sub analyses. Similarly, patients with a history of unopposed estrogen use in their baseline period will be analyzed in sub analyses but excluded from the main analyses. Figure 4 in Section 7.7 details the analysis populations.

Variables: Variables will be defined and analyzed that represent patient characteristics, comorbidities, utilized medications, medical history, and safety endpoints. A listing of study variables is provided in Section 7.3.1.

Data source: The HIRD is a longitudinally integrated, US research database comprising payment claims for healthcare encounters among included health insurance plans. It is among the largest of its kind in the US and has been extensively used for pharmacoepidemiologic research, including many PASS.[1,2,3,4]

Automated data from the HIRD will be linked to the US National Death Index (NDI) to ascertain mortality endpoints, including all-cause mortality and mortality specific to study endpoints of interest. Medical records (for a random sample of 400 potential cases) will be used to refine and validate algorithms for identification of the primary endpoints (endometrial hyperplasia and endometrial cancer). For development of the endometrial endpoint algorithms, clinical evidence available in the medical record, which includes all results of endometrial biopsies and clinician evaluations, will be considered the gold standard definition of case status against which the claims-based algorithm's performance will be measured.

Study size: Hazard ratios (HRs) and their 95% confidence intervals (CIs) expected to be observed in this study were estimated. Endometrial hyperplasia and endometrial cancer are defined as the primary endpoints and were used for these calculations. The number of *Duavee* users in HIRD during the study period has been projected based on Pfizer commercial forecasts only; no patient data are currently available. Estimates of E+P HRT use were obtained based on pilot analyses of the HIRD from the last three years. For Year 1 of the US PASS, the 95% CI of the HR for the risk of endometrial hyperplasia is projected to lie between 0.44 and 2.26 (assuming the true HR=1.0) indicating that the study would be able to rule out an HR greater than 2.26. For Years 2 and 3, the CIs for endometrial hyperplasia risk in the study is projected to lie between (0.64 and 1.56), and (0.72 and 1.39), respectively. This indicates that the study would be able to rule out an HR greater than 1.56 at two years and greater than 1.39 at three years.

Data analysis: Analyses will focus on the comparison between women initiating either *Duavee* or E+P HRT. 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 HRs will be estimated that compare incidence of the first occurrence of each safety event between *Duavee* and E+P HRT users.

Milestones: Three (3) annual interim study reports and a final report will be submitted to the EMA/Committee for Medicinal Products for Human Use (CHMP) cumulatively covering patients in the HIRD who initiate *Duavee* or E+P HRT in 2014-2015 (interim report 1), 2015-2016 (interim report 2), 2016-2017 (interim report 3) and 2017-2018 (final report). In addition to data on new initiators, each report will also contain cumulative data on the entire cohorts. Due to an 18 to 24-month lag time for availability of mortality data through the NDI, a mortality supplement to the final report will also be provided approximately two years after the final study report, to capture death endpoints over the full study period.

3. AMENDMENTS AND UPDATES

None.

4. MILESTONES

Milestone	**Planned date**
Updated FULL Draft Protocol submitted to CHMP/PRAC	10 October 2014
FINAL Draft Protocol Submission to EMA (for PRAC review)	26 January 2015
Update to FINAL Protocol in response to PRAC assessment	23 July 2015

Protocol Registration in the EU PAS register (upon endorsement from the PRAC/CHMP)	01 October 2015
Start of data collection[a]	01 May 2014
End of data collection[b]	01 May 2018
1st Annual Study Report[c]	31 March 2016
2nd Annual Study Report	31 March 2017
3rd Annual Study Report	31 March 2018
FINAL Study Report	31 March 2019
Mortality Supplement to the FINAL Study Report	31 March 2021[d]

a. This is a retrospective 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. This will not be done until the study protocol has been approved by the PRAC.
b. Study Period is from May 2014 through May 2018.
c. Time from US launch (May 2014) to First Annual Report is 23 months: 12 months is needed to accumulate one year of observation, a database lag of 4 months from real-time, and 7 months needed to extract data, perform analyses, and generate submission ready First Annual Report.
d. National Death Index data lags real-time by 18-24 months and is updated only once annually. Mortality follow-up will end May, 2018. See Figure 2 for further details.

CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; PAS = Post Authorization Studies; PRAC = Pharmacovigilance Risk Assessment Committee.

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*) is indicated for use in women with a uterus for the treatment of moderate to severe VMS associated with menopause; and for the prevention of postmenopausal osteoporosis. *Duavee* has been commercially available in the US since May 2014, and is planned to be made commercially available in the EU during 2015. Compared to the EU, the US indication for *Duavee* is broader (i.e., 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 who would be indicated for *Duavive* in the EU will also be adequately

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 all 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.

This protocol describes a 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 HRTs.

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 HRT during the first four years of *Duavee* availability in the US (2014-2018)

- Secondary objective: to estimate the incidence and compare the risks of selected safety endpoints listed in Section 7.3.2, among postmenopausal women initiating *Duavee* and postmenopausal women initiating E+P HRT.

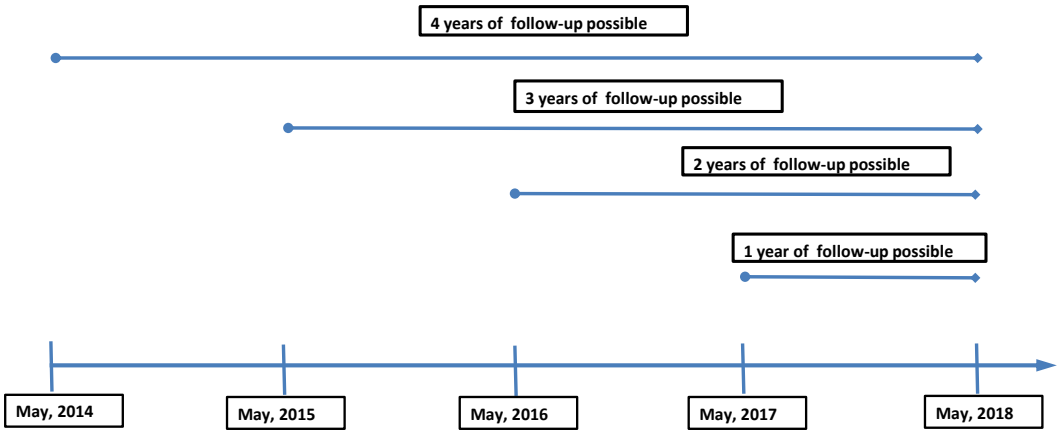
7. RESEARCH METHODS

7.1. Study Design

This PASS is a retrospective cohort study utilizing a healthcare claims data source (HIRD) in the US. Two (2) treatment groups (*Duavee* and E+P HRT) will be identified, followed, and reported upon using annual database updates. A new-user cohort design will be used for the main analysis and users with a history of (E+ P) HRT will be examined in sub-analyses. The study will accumulate data for 4 years (May, 2014-May, 2018) as it follows a dynamic cohort of patients that enter the study at different times, based on when *Duavee* or E+P HRT is initiated.

Figure 1 shows the length of study follow-up according to when new users enter the cohort.

Figure 1. Length of Follow-up Periods by Enrollment Year



The study duration was determined based on sample size calculations, and is the soonest that clinically meaningful HRs for endometrial hyperplasia and endometrial cancer can be detected. Study years and reporting intervals will run from May 1 through April 30 of the next year. Interim (follow-up) and final reports will contain both interval and cumulative data.

All patients in the HIRD who initiate *Duavee* or E+P HRT in the study period (2014-2018) will be considered for inclusion. This PASS is a retrospective cohort study using secondary data. The source data has 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.

Follow-up will continue from the first use of *Duavee* or E+P HRT through to the earliest of the following censoring events:

- End of continuous health plan eligibility;
- Switch from *Duavee* to an E+P HRT medication or vice-versa;
    - (Note: Any use of an estrogen or estrogen-containing product (Appendix 2) that differs from the HRT 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 HRT. As described in Section 7.7.4, 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 breast cancer (and endometrial cancer).
- End of the study period.
    - Patients will be censored by the end of the study period for each interim report and the final study report, however, additional follow-up time for these patients will be added during the subsequent study year.
- Occurrence of any type of cancer diagnosis;
    - As described in Section 7.7.4, sensitivity analyses exploring the impact of this criterion will be performed.
- Hysterectomy;
    - Codes indicating a procedure for hysterectomy will be used to define this censoring criterion.
    - Presence of a code indicating post hysterectomy status (ICD-9-CM V88.01) or a hysterectomy procedure code at any time in the baseline or follow-up period will result in exclusion of the patient. The one exception is, when in the follow-up period, the procedure code precedes the hysterectomy status code (i.e., date of post-index hysterectomy is known); the patient's follow-up will be included, but censored on the procedure date.
- Death.

Discontinuation and/or resumption of *Duavee* or E+P HRT treatment will be defined and recorded, but follow-up will not be censored based on treatment discontinuation. Sensitivity analyses will be conducted to examine the impact of censoring based on (1) treatment switch and (2) cancer diagnosis. The Sponsor will also conduct sub-analyses for patients not included in the main analyses. These patient groups are those with either (1) use of E+P HRT (i.e., not new initiators), or (2) unopposed estrogen in their baseline period.

For each of the 4 study years, the Sponsor will: (1) identify and follow new *Duavee* or E+P HRT users; and (2) extend the follow-up to include newly available data covering any additional follow-up period for patients that were identified during previous study years.

7.2. Study Population

Study subjects are all patients identified in the HIRD 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 identified in the HIRD who have received a prescription for *Duavee* or E+P HRT since May 2014 (date of first commercial availability in the US), and have a baseline period (e.g., 6 or 12 months to be determined by a priori analyses) prior to their first study medicine prescription, will be included in this study. Codes for *Duavee* and specific E+P HRT products are listed in Appendix 2.

- To be included in the main analyses, patients need to be new initiators of *Duavee* or E+P HRT as evidenced by a sufficient baseline period (e.g., 6 or 12 months to be determined using a priori analyses) prior to their first study drug prescription with no prior use of either *Duavee* or E+P HRT.

- The duration of the baseline period will be determined prior to the start of the analysis. The analysis will assess the distribution of continuous enrollment prior to the first dispensing of *Duavee* among the exposed patients. Selection of a threshold will balance inclusion of as many *Duavee* users as is feasible with the need to ensure appropriate capture of baseline covariates among the included patients.

- Sub-analyses will be performed for those with either (1) use of E+P HRT (i.e., not new initiators), or (2) unopposed estrogen in their baseline period. See Figure 4 in Section Section 7.8 for the flow of patients to the separate analyses.

7.2.2. Exclusion Criteria

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

- Patients with an insufficient period of enrollment prior to their index prescription (e.g., 6 or 12 months as determined prior to the start of analysis) will be excluded. This period is necessary to determine if the patient is a new initiator of *Duavee* or E+P HRT without a history of unopposed estrogen use, and also to adequately ascertain baseline covariates/patient history;

- Patients without a uterus, i.e., males, or women for whom evidence of hysterectomy is identified prior to initiation of *Duavee* or comparator E+P HRT; and

- Patients with a history of any type of cancer in their baseline period.

- Patients for whom *Duavee*, comparator E+P HRT or unopposed estrogen are identified during the baseline period will be excluded from the main analyses. They will be evaluated in separate sub-analyses.

7.3. Variables and Measurement

7.3.1. Exposure

The analyses will identify exposure to *Duavee* or E+P HRT treatment based on pharmacy claims with applicable Generic Product Identifier (GPI) codes. A list of included products and the GPI codes is provided in Appendix 2.

E+P HRT comparator products were chosen and 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.

The analyses will define exposure to *Duavee* or E+P HRT as follows: Patients will be categorized as having "current use" for *Duavee* or E+P HRT 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 days supply of two adjacent prescriptions. Otherwise, a new treatment segment will be defined. The 30-day grace periods allow for the possibilities of intermittent inconsistent use and saving of dispensed pills, by which a patient may still be taking the medication even after exhausting the available supply from their most recent dispensing. For each patient, duration of exposure will be based upon the summation of recorded supply (in days) across all of their study treatment segments. Multiple treatment segments due to intermittent HRT 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.

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);
- All-cause mortality.

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 HRT and background incidence rates (IRs) in postmenopausal women. An important identified risk potentially associated with *Duavee* use is VTE because it is a known safety concern for both of the individual component products of CE/BA (i.e., CE and BZA monotherapies). According to the literature,[6] MI and stroke are important potential risks that are associated with the use of HRT 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. All-cause mortality is included to provide context to fatal occurrences of the safety endpoints. For example, if a finding of increased fatal stroke events is observed, it could be assessed if this result coincided with an increase in all-cause mortality.

7.3.2.1. Primary Endpoints

The primary endpoints of endometrial cancer and endometrial hyperplasia are particularly challenging to identify in a claims database as neither endpoint has been extensively studied in this setting. For endometrial cancer, relevant diagnostic codes are nonspecific, including both endometrial cancers and relatively rare non-endometrial uterine cancers. While a claims data-based algorithm for endometrial hyperplasia has not been validated, there has been some suggestion that diagnostics codes alone have low specificity.[7] To reduce outcome misclassification bias, the Sponsor will develop claims-based endpoint algorithms in which information from the medical record will be used as the 'gold standard' to develop predictive models to identify confirmed cases.[1,8] The process for endpoint algorithm development is described in Appendix 3, and will be completed separately for each of the primary endpoints (i.e., endometrial cancer and endometrial hyperplasia).

7.3.2.2. Secondary Endpoints

Secondary study endpoints include VTE, CHD, stroke, breast cancer, ovarian cancer, thyroid cancer, renal cancer, renal adenoma, gastrointestinal tract cancers, all cancers, and all-cause mortality. The major cardiovascular endpoints are well studied in database research, with multiple validation studies in databases, including the HIRD. In addition, certain cancer

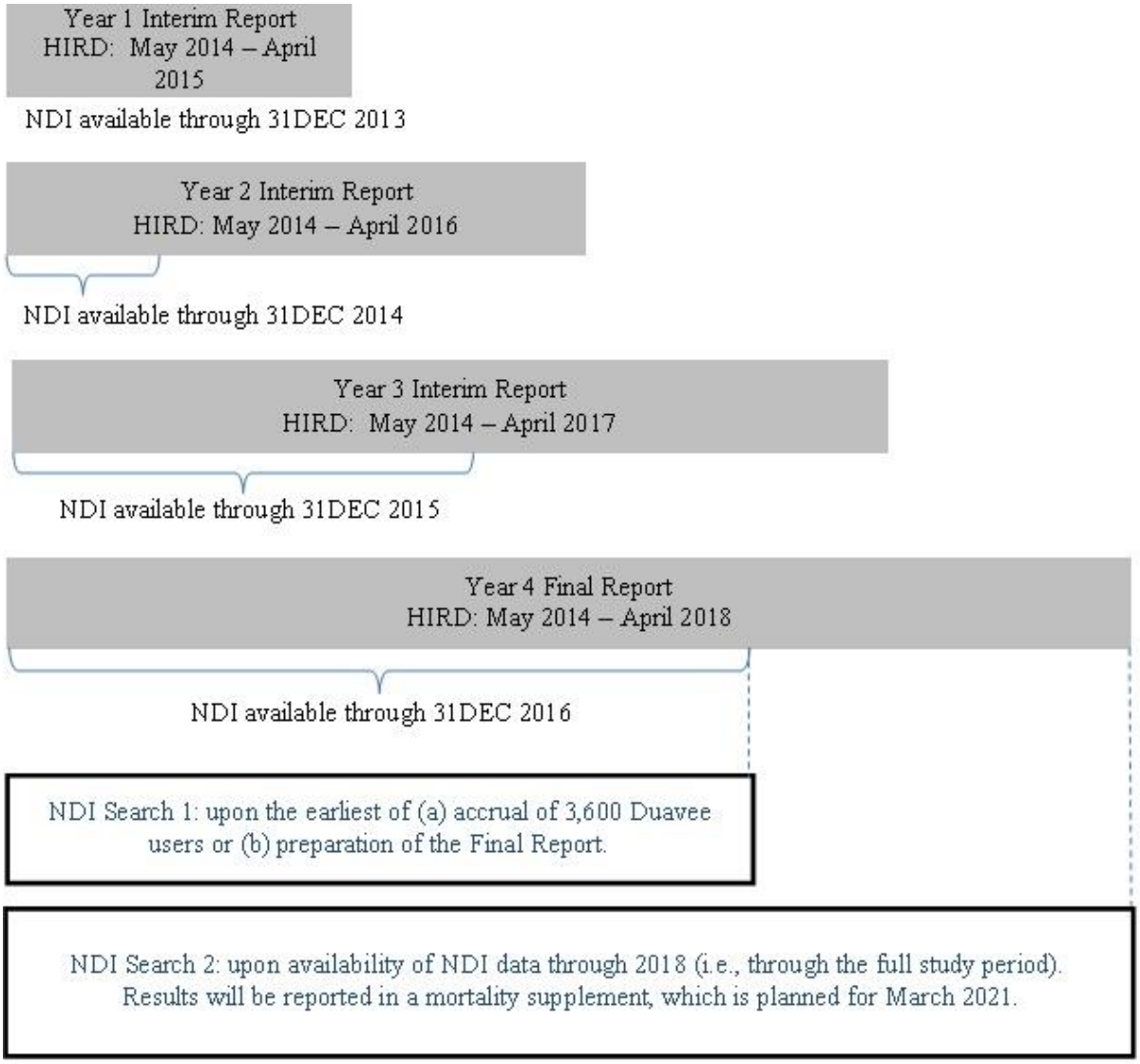
endpoints also have been studied. Based on a targeted literature search to identify automated database studies of the endpoints of interest with a focus on validation studies in claims databases, we have identified validated algorithms for the identification of VTE, CHD, stroke, breast cancer and thyroid cancer, which are described in Appendix 3. For secondary endpoints where validated algorithms were not identified, ie, renal cancer, renal adenoma, gastrointestinal cancer and all cancers, algorithms using diagnostic codes have been developed, as shown in Appendix 3.

7.3.3. Fatal Events

Incident safety events that result in either in-hospital or out-of-hospital death will be analyzed. In-hospital events are recorded in the medical claims, while out-of-hospital deaths, including cause of death, will be identified through linkage of the HIRD to the US NDI using patient characteristics such as full name, gender, date of birth, state of residence and (when available) social security number. Potential matches are assigned a probabilistic score based on the strength of the match, and thresholds will be used to identify decedents. The NDI is a national mortality registry for the US. This centralized database of death record information is maintained by the National Center for Health Statistics (NCHS), and contains information on the date and cause of death in the US dating back to 1979. HealthCore will use this registry to identify decedents among patients who have been censored due to disenrollment from their health plan (ie, those patients that potentially could have died) to identify all-cause mortality and fatal events of each primary and secondary endpoint.

NDI data lags real-time by an average of 18-24 months, and is updated once annually. Therefore, the capture of fatal events will lag behind that for nonfatal events. The HIRD and NDI will be linked to ascertain fatal events at two time points. The first will be the earlier of either (a) accrual of at least 3,600 *Duavee* users for whom NDI data are available, or (b) the last study year (i.e., the Final Report). Based on current projections for the uptake of *Duavee* in the US, it is anticipated that the first search will occur in preparation for the Final Report. The second search will be performed in preparation for the mortality supplement to the Final Report to allow for the inclusion of fatal events upon availability of NDI data spanning the full study period (ie, May 2014-May 2018). This is illustrated in Figure 2.

Figure 2. Timing of Mortality Outcome Ascertainment



It is expected that the majority of chronic and ultimately fatal events, such as cancer, will be captured first in the HIRD and any associated fatality with these will be reported some time later in the NDI. Acute fatal events, such as MI or stroke, which may result in death prior to the patient reaching the healthcare system, will only, be captured in the NDI.

7.3.4. Covariates

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

Procedure Coding System (HCPCS) codes used to identify each variable are shown in Appendix 2.

Patient characteristics:

- Age;
- US region of residence;
- Year of cohort entry (ie, index date); and
- Duration of health plan eligibility prior to cohort entry (in months)

Medical conditions diagnosed during the baseline period:

- Vasomotor symptoms;
- Obesity;
- Osteoporosis;
- 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;

- At least one diagnosis code indicative of a prior safety event of interest (exclusive of cancers as this is a baseline exclusion criterion).

Use of prescription medications during the baseline period prior to the start of *Duavee* or E+P HRT:

- Corticosteroids;
- Lipid lowering agents;
- Antihypertensives;
- Antidepressants;
- Sedatives/hypnotics;
- Anticonvulsants;
- Antimycobacterials;
- Macrolides;
- Antifungals;
- Antivirals;
- Antidiabetics;
- History of oral contraceptive use;
- History of intrauterine device (IUD) exposure; and
- Unopposed estrogen HRT
- Selective estrogen receptor modulators (SERMs)
- Testosterone
- 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

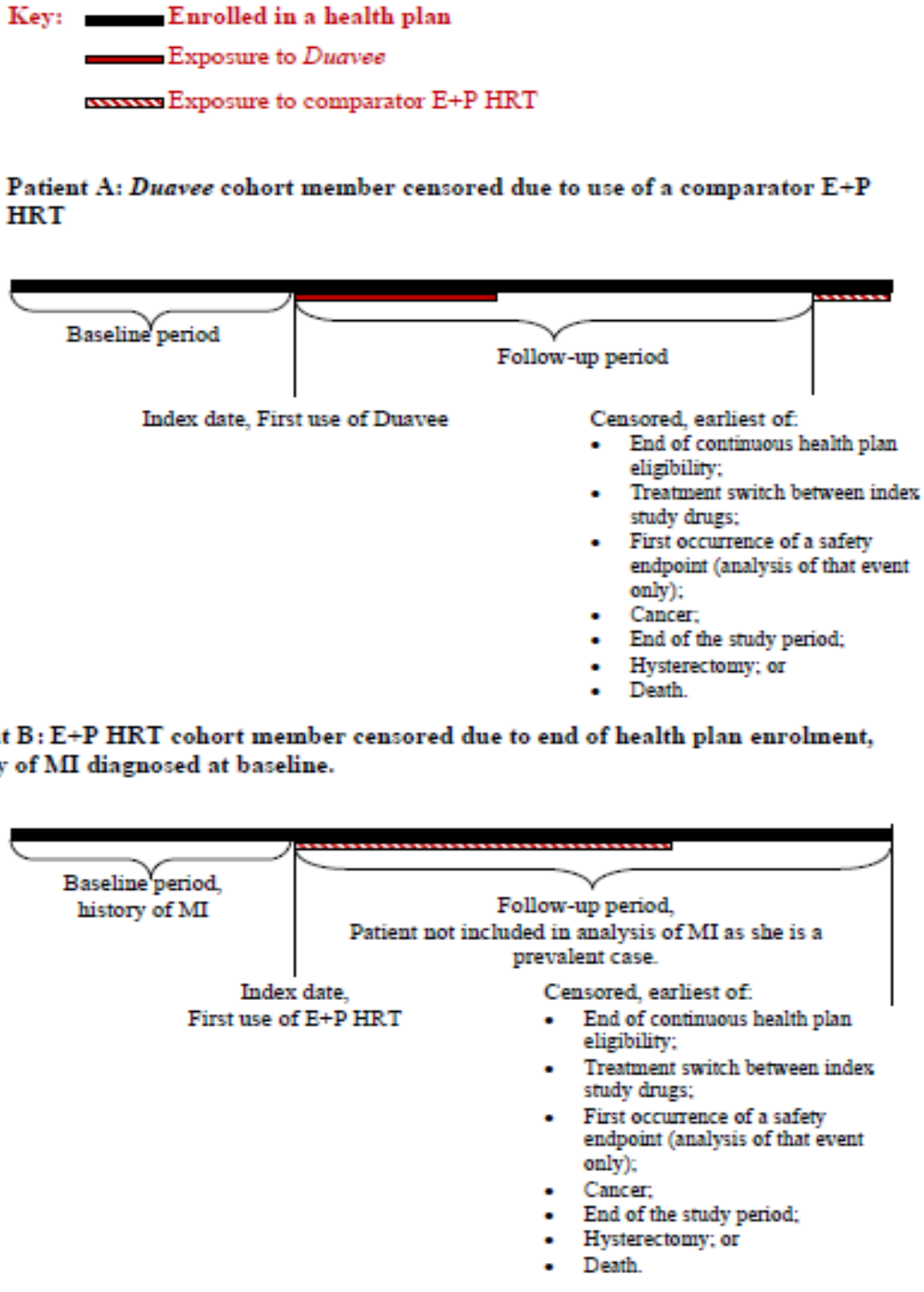
Each patient will have an index date corresponding to the date of their first prescription for *Duavee* or E+P HRT treatment after 01 May 2014. Baseline characteristics will be assessed from patient data collected prior to their index date (baseline period). A baseline period will be specified in a manner that balances inclusion of as many *Duavee* users as is feasible in the cohort with the need to ascertain covariates prior to the start of treatment. The baseline period will be determined prior to conducting analyses based on review of the distribution of prior continuous health plan enrolment among the *Duavee* cohort of patients.

As described in Section 7.1, follow-up will continue from the first use of *Duavee* or E+P HRT 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 3.

Figure 3. Safety endpoints



Data Source

7.4.1. HealthCore Integrated Research Environment

This PASS is a retrospective cohort study, using 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 was chosen over other potential healthcare data sources because it provides both a large patient population and superior access to medical records. The HIRD has been previously used in pharmacoepidemiologic research.[1,2,3,4] Additionally, data from the HIRD will be supplemented with review of full text medical records, which will be used to develop and validate algorithms for endometrial hyperplasia and endometrial cancer, as discussed in Section 7.3.2.

The HIRD is a longitudinally integrated research database comprising payment claims for healthcare encounters among WellPoint, Inc.'s US health benefits insurance plans. WellPoint is one of the largest health benefit companies in terms of total patient enrollment in the US, with current enrollment of approximately 37.3 million members as of 30 June 2014. The HIRD contains approved and denied claims integrated across data sources and types (i.e., professional claims, facility claims, outpatient pharmacy claims, outpatient laboratory results, and enrollment information) as well as across years (from 2006 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 each individual 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 diagnostic, ICD-9-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 (e.g., co-payments and deductibles), and coordination of benefits amounts.

7.5. Study Size

The focus of the sample size calculations is to determine the precision of the estimated HR that can potentially be achieved in the study depending on estimated patient accrual, event rates, and assumed true risk. Because of the CHMP's concerns related to endometrial safety, endometrial hyperplasia and endometrial cancer are the primary endpoints and were used for these sample size calculations.

Precision is a measure inversely related to variance in estimation. For the HRs being estimated in this study, precision is represented by the width of two-sided 95% CI.

Duavee estimates are projections based on Pfizer commercial forecasts of product uptake only; no patient data are yet available. Projections are conservative and assume a reduction of 50% from the original US market forecasts. The estimated number of E+P HRT new users, their total person-time of follow-up, and the expected number of incident endometrial safety events observed in that cohort was obtained based on pilot analyses of the HIRD from the last three years. Therefore, the most recent 3 years of E+P HRT use in the HIRD is being used to project future E+P HRT uptake and use.

In the HIRD pilot analyses, the number of new users of E+P HRT products (i.e., patients with at least 12 months of continuous eligibility prior to the first use of E+P HRT) were identified using a one-, two-, and three-year time frame: 01 January 2011 – 31 December 2011, 01 January 2011 – 31 December 2012, and 01 January 2011 – 31 December 2013. The total person-time of follow-up accrued by the E+P HRT new users was calculated during these periods of interest together with the number of endometrial cancer and endometrial hyperplasia events occurring after the start of E+P HRT use.

All estimates (Table 1) were calculated with two-sided 95% CIs. According to the study plan, there will be a 4-year accrual period and patients will be followed for at least 1 year, with the first two cohorts being followed for a longer duration.

Table 1. Estimated 95% Confidence Intervals for Hazard Ratios of Endometrial Safety

Description	First Annual Report	Second Annual Report	Third Annual Report
Estimated numbers of new users of *Duavee*[a]	1,800	3,600	5,400
Estimated numbers of new users of E+P HRT[b]	36,651	44,122	50,350
Estimated person-years of follow-up for E+P HRT users[b]	27,768	58,399	89,438
Estimated endometrial cancer events after the start of E+P HRT use[b]	29	62	80
HRs (95% CI)			

Table 1. Estimated 95% Confidence Intervals for Hazard Ratios of Endometrial Safety

Description	First Annual Report	Second Annual Report	Third Annual Report
true HR=1.0	(0.18, 5.60)	(0.39, 2.56)	(0.48, 2.10)
true HR=1.5	(0.36, 6.33)	(0.68, 3.33)	(0.80, 2.83)
Estimated endometrial hyperplasia events after the start of E+P HRT use[b]	129	274	399
HRs (95% CI)			
true HR=1.0	(0.44, 2.26)	(0.64, 1.56)	(0.72, 1.39)
true HR=1.5	(0.76, 2.96)	(1.03, 2.19)	(1.13, 1.99)

a. *Duavee* estimates are projections based on Pfizer commercial forecasts of uptake only, no patient data are yet available. Person-time was calculated based on the assumption of 10 month treatment duration per patient[9]. Projections are conservative and assumed a reduction of 50% from actual US market forecasts.
b. E+P HRT users, person-time, and event estimates are derived from pilot analyses of the HIRD from the last three years of data.

Based on the projected numbers of patients initiating *Duavee* and E+P HRT as shown, for Year 1 of the US PASS, the estimated 95% CI of the HRs for the risk of endometrial hyperplasia in Table 1 imply that if the underlying (true) HR comparing *Duavee* users to E+P users is HR=1.0, then the point estimate of HR in the study will lie between 0.44 and 2.26, indicating that the study would be able to rule out the possibility that the true HR is greater than 2.26.

For Years 2 and 3, the estimated 95% CIs of the HRs for the risk of endometrial hyperplasia in Table 1 imply that if the underlying (true) HR comparing *Duavee* users to E+P users is HR=1.0, then the point estimates of HR in the study will lie between (0.64 and 1.56), and (0.72 and 1.39), respectively. This indicates that the study would be able to rule out the possibility that the true HR is greater than 1.56 at two years and 1.39 at three years.

These estimates are dependent on actual future E+P and *Duavee* drug uptake, the speed of patient accrual, safety event rates, and patient follow-up time; if these differ substantially from our estimates, then the precision of the HRs may change.

7.6. Data Management

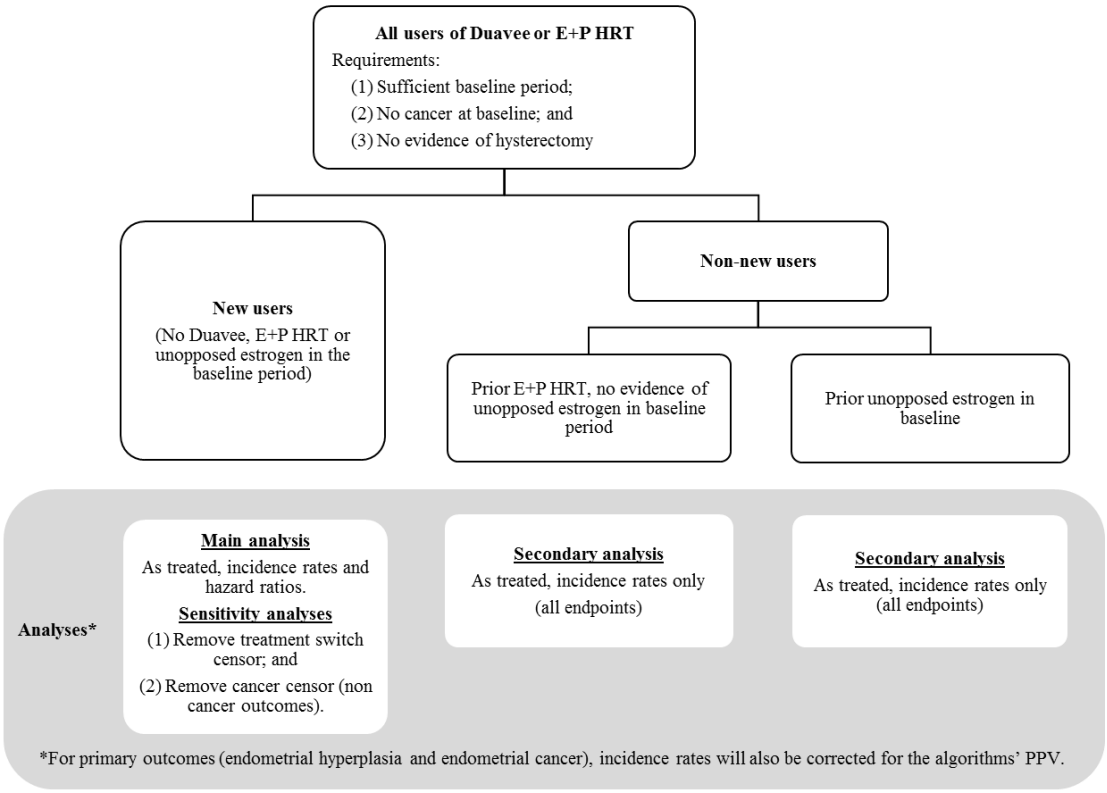
All data management and analyses will be conducted by HealthCore in accordance with their standard operating procedures (SOPs) and guidelines. The study database, analytic files, and statistical programming will be documented in a Project Log, stored electronically, and archived for a period of six years following the delivery of the final study report unless otherwise noted. De-identified and aggregated results will be reported to Pfizer.

7.7. Data Analysis Plan

This overview details the major steps that will be performed to produce the analytic dataset, generate study results, and apply those results to the research objectives 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).[10]

Figure 4. Analysis populations



7.7.1. Main Analyses

The analyses will describe patients that initiate *Duavee* and the comparator E+P HRT cohort with respect to demographic and clinical characteristics as enumerated in Section 7.3.4. 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 (i.e., endometrial hyperplasia and endometrial cancer), an IR will be calculated as the number of women meeting a claims-based algorithm for each outcome (first event only) divided by person-time at risk.

The IR and its associated 95% CI will be presented for each cohort overall and stratified by categorical patient age at cohort entry, total duration of *Duavee* or E+P HRT treatment (long vs. short), time since last exposure to *Duavee* or E+P HRT, exposure to local hormone therapy (See Appendix 2), and by presence (Y/N) of an osteoporosis diagnosis within the 90 days before or after initiation of *Duavive* or E+P HRT. 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.

Further details of the validation process are described in Appendix 3 and will be contained in the separate Endpoint Algorithm Development Report.

Hazard ratios will be estimated that represent the relative risk associated with initiating *Duavee* as compared to E+P HRT. It is planned to conduct both crude (unadjusted) and adjusted analyses to assess the HR for each of the primary endpoints. Adjusted analyses will use propensity score matching to ensure comparability between treatment groups. Further discussion of the methods to be used in computing propensity scores in included in Section 7.7.3.

Similarly to the primary endpoints, the IR and multivariate adjusted HR will be calculated for the following *a priori* defined secondary safety endpoints: VTE, stroke, CHD, breast cancer, ovarian cancer, thyroid cancer, renal cancer, renal adenoma, gastrointestinal tract cancers, all cancers and all-cause mortality among study subjects initiating *Duavee* or E+P HRT. Because only the primary endpoints are being validated as part of this project, positive predictive value (PPV) correction of IR estimates for secondary endpoints will not be performed.

For all analyses, each endpoint will be identified first in the automated claims data (i.e., endpoints that were not fatal prior to the patient reaching the healthcare system) and then, for study reports that include NDI linkage, through either the automated data or the NDI (i.e., a composite of non-fatal and fatal endpoints, such as endometrial cancer and death due to endometrial cancer). Analyses that include NDI linkage will be restricted to the time period that is available in both the HIRD and NDI data sources (i.e., through the end of the 2016 calendar year if the first NDI search is performed in preparation for the Final Study Report).

7.7.2. Sub Analyses

Women with a previous history of E+P HRT use, different from their index drug (i.e., *Duavee* or specific E+P HRT) 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 HRT incur a study endpoint, it is difficult to determine whether the endpoint is due to previous HRT or current HRT use. Further, women for whom previous HRT use was associated with poor outcomes (e.g., adverse effects) are likely to be under represented among those initiating *Duavee* or E+P HRT, 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 HRT (e.g., comorbidities) could include effects of HRT (e.g., uterine bleeding) that could be intermediate in the causal pathway between exposure and study endpoints (e.g., 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 HRT exposed patients with a previous history of HRT 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 4 events in both the *Duavee* and E+P HRT groups.

New initiators of either *Duavee* or (E+P) HRT with evidence of unopposed estrogen therapy (i.e., estrogen HRT use without progestin use) in their baseline period, and no evidence of a hysterectomy, are not included in the main analyses. Patients with evidence of progestin use at anytime in their baseline period will not be categorized as having unopposed estrogen use. This group will be analyzed separately, because of the high likelihood of confounding by indication for the relationship of choice of study drug and the endometrial safety endpoints, and limitations of the data to identify hysterectomies that have occurred prior to a patient's baseline period. This results in an inability to accurately differentiate between patients with and without an intact uterus, both who have used unopposed estrogen. For a given safety endpoint, this analysis will only be done once there are at least four events in both the *Duavee* and E+P HRT groups.

7.7.3. 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. To make full use of the extensive information in the HIRD pertaining to use of prescription medications, diagnoses, procedures, and inpatient as well as outpatient health care encounters, the analyses will use boosted regression to compute propensity scores.[11,12] Boosted regression, a technique common in machine learning that has been more recently applied to propensity scores, provides for a more robust model that better balances treatment groups. Because it is a non-parametric approach, the impact of model assumptions on results and risks of model misspecification are minimized.

E+P HRT comparator subjects will be weighted according to their estimated probability of receiving *Duavee*, and adjusted analyses will use propensity score matching to balance the treatment groups on multiple factors simultaneously at the time of first dispensing of a study drug. The propensity score matched groups will be evaluated for balance and any patient restrictions done as a result of this matching will be described along with impact on generalizability. To avoid issues associated with model misspecification and improve comparability, the analyses will use doubly robust estimation procedures.[11]

7.7.4. Sensitivity Analyses

Three 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 main 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. The IR estimate for each primary outcome (endometrial cancer and endometrial hyperplasia) will be corrected for the PPV of the outcome algorithm as identified through validation. This will be done by multiplying the number of observed cases by the PPV point estimate, and will be presented with a 95% CI.

7.7.5. Additional Analysis Specifications

Since the analyses will employ a time-to-1st event analysis for the safety endpoints, there will not be a discrete risk window; rather the time from index drug exposure to the onset of the safety endpoint will be explored. The risk will be conditional on the duration of exposure to HRT and time since last exposure.

7.7.6. Statistical Methods

7.7.6.1. 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 HRT included in the cohort; and

2. All new users of *Duavee* and E+P HRT with prior E+P HRT exposure.

For those study reports that include data from the NDI where the period of time captured by NDI data is different from the study period available in the automated claims (See Figure), tables showing these characteristics during the interval when NDI data are available will also be included.

7.7.6.2. Univariate/Unadjusted Analysis

As described in Section 7.7.1 through Section 7.7.2, IRs and their associated 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, HRs in either the univariate or multivariate 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.

7.7.6.3. Multivariate/Adjusted Analysis

Hazard ratios will be estimated, using Cox proportion al hazards models, to explore the risk of first occurrence each safety endpoint in women newly exposed to *Duavee* when compared to initiators of E+P HRT, adjusted using propensity score matching.

7.7.7. 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.

Otherwise, multiple comparisons will not be addressed in the analyses. Further, the primary purpose of this study is estimation of IRs and HRs, and not testing of hypotheses.

7.7.8. 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.

7.7.9. Layout of Results Tables

Table shells showing how study results will be presented are contained in Annex 1.

7.8. Quality Control

HealthCore's research team documents the progress and scientific and quality review of all study activities and deliverables (e.g., 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 (e.g., 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.

To help ensure consistency of clinical data collection from medical records, the medical record vendor will be trained on the study's process for medical record acquisition as agreed by HealthCore and Pfizer and approved by an Institutional Review Board (IRB). As part of the training, a pilot phase will be conducted to review a sample of charts (i.e., 5-10 charts) to help ensure that the trained professionals are accurately collecting the data. If any themes are identified across the trained professionals that are resulting in errors in medical record acquisition, re-training may be requested by HealthCore. Throughout the entire medical record acquisition phase, the vendor will keep a question log that will be transferred back and forth with HealthCore. This log will allow the vendor to ask any questions that may not have come up during the training and give HealthCore the opportunity to provide standard answers that will then be shared with the vendor's trained professionals. HealthCore will perform quality checks on the clinical data obtained from the medical records, including any assessments of the clinical data by clinical consultants with expertise in endometrial disease, and resolve any errors or discrepancies. HealthCore will integrate the clinical data with the claims analytical file from and HIRD and perform quality checks to ensure all the variables for analysis are correctly included.

7.9. 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.[1,2,3,4]

- 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 7.10 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,[13,14] some in reference to HRT.[14] Further, MI, and stroke endpoints have been confirmed to have a high PPV in HIRD validation studies.[1]

- HIRD has the capability to conduct linkage with the US NDI, and offers access to medical records for validating algorithms to identify events of endometrial hyperplasia (eg, from biopsy results) and endometrial cancer.

- HIRD is among the very largest longitudinal healthcare databases in the US. The projection of study size indicates that meaningful elevated risks can be both detected and excluded.

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 who have had a hysterectomy before their baseline 12 month period and started either *Duavee* or E+P HRT 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 HRT 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 HIRD, 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 HRT 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 study size is dependent on the rate of uptake of *Duavee* in the US. The study size projections are intentionally conservative (i.e., they are lower than Pfizer marketing forecasts of uptake in the US); to allow for adequate precision even if there is limited uptake in the first year following launch. Uptake will be evaluated at the end of Year 1 and, if needed, additional data sources or extension of study duration will be discussed in the 1st Interim Report.

- Sub 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.

7.10. 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. While the ethnic and racial distribution of postmenopausal women in the US and EU is certain to be different, there is no medical evidence to suggest these factors would modify the relative risk of these safety endpoints between *Duavee* and E+P HRT.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information and Consent

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 (e.g., 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.

8.2. Patient Withdrawal

Not applicable.

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

The proposed study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US augmented with information obtained from medical records. Protected Health Information must be accessed from medical records in order to adjudicate the safety endpoints of endometrial hyperplasia and endometrial cancer. A HIPAA Waiver of Authorization will be applied for from an IRB prior to any PHI being identified. 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.

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

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 HIRD research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* 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

Three (3) annual interim study reports, a final report and a mortality supplement will be submitted to the EMA covering patients in the HIRD who initiate *Duavee* or E+P HRT in 2014-2015, 2015-2016, 2016-2017, and 2017-2018. Each annual report will contain both interim and cumulative data. Reports will each contain 12 months of new post-launch data for *Duavee* as well as all prior data. The first annual report is planned to be submitted to the EMA by 31 March 2016. Section 4 of the protocol contains the planned milestones and submission dates for all annual interim and final study reports.

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.

11. REFERENCES

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Appendix 1. LIST OF STAND ALONE DOCUMENTS

Annex 1. Results Table Shells

Annex 2. ENCePP Protocol Checklist B2311060 *Duavive* US PASS

Appendix 2. Codes and Algorithms

Candidate codes and algorithms for identification of exposures, endpoints and covariates are provided below. Final definitions will be determined based on further review of the literature in preparation for development of the first Annual Interim Report, and updates may be provided in the event that additional codes become available during the course of the study (e.g., new GPI, ICD-9-CM, HCPCS or CPT codes become available, including introduction of ICD-10 in the US).

Cohort defining medications

Product	**GPI Code**
Duavee® (Conjugated estrogens/Bazedoxifene)	24995002100330
Activella® (containing Estradiol, Norethindrone)	2499300212x
Angeliq® (containing Drospirenone, Estradiol)	2499300240x
FemHRT® (containing Ethinyl Estradiol, Norethindrone)	2499300225x
Jinteli™ (containing Ethinyl Estradiol, Norethindrone)	2499300225x
Mimvey™ (containing Estradiol, Norethindrone)	2499300212x
Prefest® (containing Estradiol, Norgestimate)	2499300265x
Premphase® (containing Conjugated Estrogens, Medroxyprogesterone)	2499300204x
Prempro® (containing Conjugated Estrogens, Medroxyprogesterone)	2499300204x

Medications included as covariates

Classification	**GPI code**
Corticosteroids	22x
Lipid lowering agents	39x
Antihypertensives	36x
Antidepressants	58x
Anticonvulsants	72x
Sedatives/ hypnotics	60x
Antimycobacterial agents	90x

Macrolides	35x
Antifungal	11x
Antivirals	12x
Antidiabetics	27x, excluding 2730x and 2757x
Testosterone	23100030x
Local hormone treatments	2600003010x, 2600004000x, 2600004010x 5535001000x, 5535002000x, 5535002010x, 5535002500x, 5535003000x 5537006000x
History of oral conceptive use	2510x
	2599x
History of intrauterine devise (IUD)	2505x
	2520x

Comorbidities

Description	**Diagnosis and Procedure Codes**	
	ICD-9-CM	Procedural
Vasomotor symptoms (VMS)	627.2x, 782.62	
Obesity	278.xx, V77.8x	
Polycystic ovarian syndrome (PCOS)	256.4x, 628.xx, 704.1x,	

CVD (i.e. stroke, transient ischemic attack, sudden cardiac death, myocardial infarction, peripheral vascular disease, coronary artery surgery (CABG), or congestive heart failure)	093.0x, 394.xx-397.xx, 398.91, 401.9x, 402.xx, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 410.xx-414.xx, 424.xx, 425.4x–425.9x, 427.xx, 428.xx, 429.2x, 429.9x, 433.xx-435.xx, 437.3x, 440.xx, 441.xx, 443.1x–443.9x, 447.1x, 557.1x, 557.9x, 798.2x, 798.9x, V43.4x	ICD-9-CM procedure: 36.1x, 36.2x, CPT: 33510-33545 33572
Hyperlipidemia	272.0x-272.4x	
Hypertension	401.xx-405.xx, 437.2x, V81.1x	CPT: 3077F, 3080F
Breast Pain	611.71	
Diabetes	250.xx (Type 1: 250.x1, 250.x3; Type 2: 250.x0, 250.x2)	

Renal Disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.xx, 583.0x–583.7x, 585.xx, 586.xx, 588.0x, V42.0x, V45.1x, V56.xx	
Osteoarthritis	715.xx	
Osteoporosis	733.0x, V82.81	
Major Depression	296.2x, 296.3x, 311.xx, V79.0x	HCPCS: G8959, G8960, G8126, G8127, G9193-G9195, CPT: 3088F-3093F
History of VTE/CVA/CHD Event	415.1x, 451.11, 451.19, 451.2x, 451.81, 453.8, 414.xx, 430.xx-438.xx, V12.51-V12.54	
History of Breast, Ovarian, or Endometrial Malignancy	174.xx, 198.81, V10.3x, 198.6x, 183.0x, 236.2x, 182.0x, 198.82, V10.43, V10.42	19120, 58950-58954, 58956-58958, 58960

Family history of cancer	V16.xx	
Hysterectomy	V88.01, V88.02	ICD-9-CM procedure: 68.4x-68.7x CPT: 58150-58294

Potential Algorithms for Claims-Based Identification of Safety Endpoints*

Event	**Algorithm**
Endometrial Cancer	To be determined via validation
Endometrial Hyperplasia	To be determined via validation
Venous Thromboembolism	Hospitalization with any of the following ICD-9-CM diagnosis codes listed as the principal discharge diagnosis: 415.1x, 451.11, 451.19, 451.2x, 451.81, 453.8x
CHD (i.e. MI, fatal MI, and Sudden Death)	MI defined as a hospitalization with ICD-9-CM code 410.xx (excluding 410.x2) with either (1) a length of stay between 3 and 180 days or (2) discharge status indicating death if length of stay is less than 3 days.
Stroke/TIAs	Hospitalization with ICD-9-CM diagnosis codes 433.x1, 434.x1, 436.x, 437.x1, 437.9x with either (1) a length of stay between 3 and 180 days or (2) death if length of stay is less than 3 days, or hospitalization with a principal discharge diagnosis of 435.xx (TIA)
Breast Cancer	At least two outpatient or one inpatient ICD-9-CM diagnosis code(s) 174.xx.
Ovarian Cancer	At least two outpatient or one inpatient ICD-9-CM diagnosis code(s) 183.0x.

Thyroid Cancer	Thyroidectomy during follow-up and ≥2 ICD-9-CM 193.xx diagnosis codes recorded.
Renal Cancer	At least two outpatient or one inpatient ICD-9-CM diagnosis code(s) 189.x
Renal adenoma	At least two outpatient or one inpatient ICD-9-CM diagnosis code(s) 223.x
Gastrointestinal Tract Cancer	At least two outpatient or one inpatient ICD-9-CM diagnosis code(s) 150.x – 159.x
All Cancers (Malignancies)	At least two outpatient or one inpatient ICD-9-CM diagnosis code(s) in the following range: 140.xx-208.xx

*Endpoints will be identified in the NDI based on the presence of applicable codes listed as cause of death.

Algorithms for Claims-Based Identification of Safety Endpoints Identified in the Literature

Event type	Algorithm	Study Population	Validation
CHD (MI, fatal MI and sudden death)	MI defined as a hospitalization with ICD-9-CM code 410.xx (excluding 410.x2) with either (1) a length of stay between 3 and 180 days or (2) death if length of stay is less than 3 days.	HIRD patients receiving COX-2 inhibitors	In HealthCore data, this had a PPV of 88.4% (83.2% - 92.5%), which was higher in patients receiving COX2-inhibitors (92.3 versus 84.2%). Previously reported PPV of 94% in Medicare data.

CHD (MI, fatal MI and sudden death)	At least one occurrence of any of the following codes: ICD-9 diagnosis codes: 410 - 414, 433 - 438, 440 - 441, 4439. ICD-9 procedure codes: 3601 - 3609, 361, 362, 3812, 3813, 3818, 3925, 3926, 3929, 3950, 3990 CPT codes: 33510 - 33545, 33572, 34101 - 34111, 34201 - 34203, 35301, 35311 - 35381, 35390, 35454 - 35456, 35459, 35470, 35473 - 35474, 35482 - 35483, 35485, 35492 - 35493, 35495, 35533, 35541 - 35571, 35641, 35646, 35654, 92975, 92980 - 92984, 92995 – 92996 *Note - this includes codes for angina, MI, CABG and other procedures not included in the study definition.	HIRD patients receiving statins	Sensitivity of 96%, specificity of 93% and Kappa of 0.82 (PPV not calculated).
Stroke/TIA	An algorithm using primary discharge diagnosis codes for acute ischemic or hemorrhagic stroke (International Classification of Diseases, Ninth Revision, Clinical Modification codes: 430, 431, 433.x1, 434.x1, 436).	Medicare patients	Positive predictive value of 92.6% (95% confidence interval, 88.8%-96.4%), a specificity of 99.8% (99.6%-99.9%), and a sensitivity of 59.5% (53.8%-65.1%). An algorithm using only acute ischemic stroke codes (433.x1, 434.x1, 436) had a positive predictive value of 91.1% (95% confidence interval, 86.6%-95.5%), a specificity of 99.8% (99.7%-99.9%), and a sensitivity of 58.6% (52.4%-64.7%).

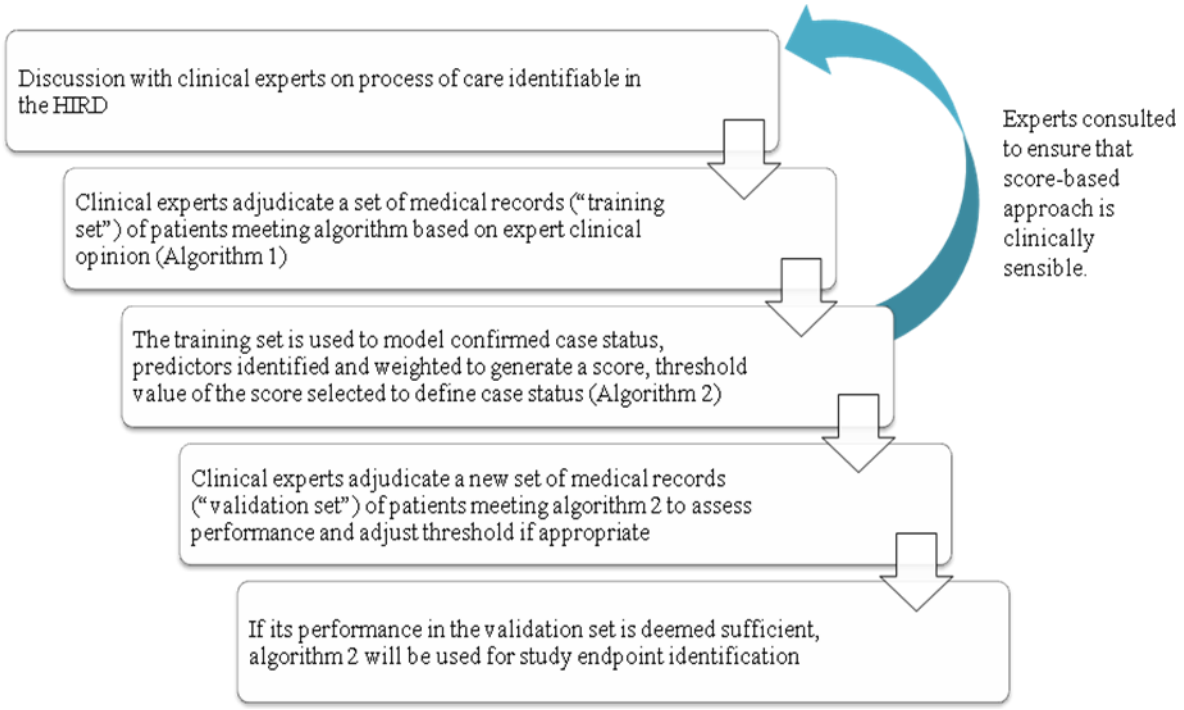
Stroke/TIA	Diagnosis codes for acute ischemic or hemorrhagic stroke (International Classification of Diseases, Ninth Revision, Clinical Modification codes: 430, 431, 433.x1, 434.x1, 436) in any position	Medicare data linked to Women's Health Initiative patients	Specificity was 99.7%, negative predictive value was 99.7%, sensitivity was 82.8%, positive predictive value was 85.8%, and κ=0.84. Whereas specificity and negative predictive value exceeded 99%, sensitivity ranged from 75% to 88% and positive predictive value ranged from 80% to 90% across stroke definitions.
Stroke/TIA	Ischemic stroke without TIA: (1) Hospitalization with ICD-9-CM diagnosis codes 433.x1, 434.x1, 436.x, 437.x1, 437.9x with either (1) a length of stay between 3 and 180 days or (2) death if length of stay is less than 3 days. (2) Hospitalization with ICD-9-CM diagnosis codes 433.x1, 434.x1 with either (1) a length of stay between 3 and 180 days or (2) death if length of stay is less than 3 days.	HIRD patients receiving COX-2 inhibitors	In HealthCore data, algorithm 1 had a PPV of 87.4%, and algorithm 2 95.5% based on review of 175 cases A prior study of Medicare beneficiaries saw a PPV of 96% for algorithm 1.
Breast cancer	At least one inpatient diagnostic or procedure code for breast cancer: Malignant neoplasm of female breast: 174.0-174.9 Any Incisional breast biopsy: 85.12 Excision or destruction of breast tissue: 85.20 - 85.25 Subcutaneous mammectomy: 85.33-85.36 Mastectomy: 85.41-85.48	Piedmont cancer registry	The sensitivity of the algorithm was 76.7%, positive predictive value 87.9%.

Breast cancer	At least one claim with ICD-9-CM code 174.xx, 233.0. 238.3 or 239.3.	HealthCore	Not formally validated, however in this study 766 medical records were reviewed to stage breast cancer. Internal communication was that medical records were not excluded based on lack of evidence of breast cancer. 13.4% of cases were stage zero, and 10.3% could not be staged.
Thyroid cancer	Various, see validation	Optum database	PPV of 53.1% (95% CI 42.8 – 63.1) for the ICD-9 code 193 alone. Additionally requiring a thyroidectomy identified 50 of 52 cases but also captured 16 non-cases (PPV 75.8%; 95% CI 63.4-85.1). Requiring a primary inpatient visit with the ICD9 code removed 41 of the 46 non-cases but only identified 16 of the cases (PPV 76.2%; 95% CI 52.5-90.9). One algorithm yielded a PPV of 91.5% (95% CI 78.7-97.2%). This algorithm required cases to have a thyroidectomy during follow-up and ≥2 ICD9 193 codes ≤ 90 days of this event, identifying 43 cases and 4 non-cases.
Venous thromboembolism	Multiple	Mini-Sentinel evidence review, various algorithms identified.	The highest PPV (65%-95%) was reported for the combined use of ICD-9 codes 415 (pulmonary embolism), 451, and 453 (deep vein thrombosis) as a VTE event.

*****Review of the literature is ongoing; final definitions will be selected using the most current literature and coding available at the start of analyses.

Appendix 3. Endpoint Algorithm Development Plan

Figure 5. Development and Validation of Primary Endpoint Algorithms



In the first phase of the validation study, the Sponsor will develop an initial, proposed claim-based algorithm for each primary endpoint (Algorithm 1). Algorithms will be informed by the published literature and consultation with clinical experts having current experience managing these conditions in clinical practice in order that clinically sensible markers of care may be included. The Sponsor will use the algorithm to identify potential cases among women with at least one prescription of E+P HRT enrolled in the HIRD prior to the start of the study period. From the potential cases identified by applying the algorithm to this population, a random sample of 200 women will be selected for whom medical records will be reviewed for each outcome (ie, endometrial cancer and endometrial hyperplasia). This training dataset will undergo adjudication by the clinical panel, and will then be used to assess the PPV of the preliminary algorithm and to construct an analytic file to be used for predictive modeling. The algorithm (Algorithm 2) will then be optimized by developing a predictive model using machine learning to associate confirmed case status with data in the HIRD.

The Sponsor will use boosted regression techniques that have been used to improve the performance of logistic regression in computing propensity scores for predictive modeling.[11,12] The model will be used to identify predictors in the HIRD and to weight each of the predictors according to their empirical importance. The model will assign to each woman in the population a probability of being a confirmed case. Analyses will be conducted

using Receiver Operating Characteristic (ROC) curves to assign a threshold probability (10). A second set of 200 medical records will then be obtained by randomly selecting 200 women meeting the refined, score-based algorithm from the population of women using E+P HRT prior to the study period. This validation dataset will be used to assess the PPV of Algorithm 2 (1). The PPV will be calculated as the number of algorithm-identified events confirmed as true cases via medical record review divided by the total number of algorithm-identified events that were evaluated, and will be presented with its exact binomial CI. The validated algorithms will then be used in the study analyses to identify the primary endpoints of interest, and sensitivity analyses will be used to assess the impact of misclassification based on algorithm performance characteristics such as PPV. Additional operational details pertaining to the validation process will be described in a separate Endpoint Algorithm Development Plan.