NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Drug Utilization Study of conjugated oestrogens/ bazedoxifene (CE/BZA) in the European Union (EU)
Protocol number	B2311061
Protocol version identifier	Final, Amended
Date of last version of protocol	31 August 2017
EU Post Authorization Study (PAS) register number	ENCEPP/SDPP/11604
Active substance	Conjugated oestrogens/bazedoxifene (CE/BZA)
Medicinal product	*DUAVIVE*® modified-release 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 003**
Marketing Authorization Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	Describe baseline characteristics and utilisation patterns of EU patients initiating *Duavive* or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT).
Country(-ies) of study	All EU countries where CE/BZA is commercially available in 2016-2017 and where adequate data sources are available. • Planned first wave countries are currently Belgium, France, Italy, Netherlands, Spain and UK.

Author	Leo Russo, PhD. Senior Director-Epidemiology P: 001-484-595-4077 E: Leo.Russo@pfizer.com

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT13 9NJ United Kingdom
MAH contact person	Leo Russo, PhD. Senior Director-Epidemiology P: 001-484-595-4077 Email: Leo.Russo@pfizer.com

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
Afssaps	Agence francaise de sécurité sanitaire des produits de santé
BMI	Body Mass Index
CE/BZA	Conjugated oestrogens/bazedoxifene
CHMP	Committee for Medicinal Products for Human Use
COE	Center of Excellence
CSD	Cegedim Strategic Data
CVD	Cardiovascular disease
DUS	Drug Utilisation Study
E+P	Oestrogen +Progestin
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMS	Intercontinental Marketing Services
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LPD	Longitudinal Patient Database
LRx	IMS Longitudinal Prescription Data
MAH	Marketing Authorization Holder
MPI	Midas Prescribing Insights (Data Source)
PASS	Post Authorization Safety Study
PI	Prescribing Insights (Data Source)
PRAC	Pharmacovigilance Risk Assessment Committee
SERM	Selective estrogen receptor modulators
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
THIN	The Health Improvement Network
UK	United Kingdom
VTE	Venous Thromboembolism

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Leo Russo, PhD.	Senior Director-Epidemiology	Pfizer, Inc.	500 Arcola Road Collegeville, PA 19426, USA
Jacco Keja, PhD.	Senior Principal-Health Economics & Outcomes Research, Real-World Evidence Solutions	QuintilesIMS	210 Pentonville Road London, N1 9JY United Kingdom

Country Coordinating Investigators

To be identified

Name, degree(s)	Title	Affiliation	Address
Dorothea von Bredow, PhD	Director RWES	QuintilesIMS IMS Health GmbH & Co OHG	Landshuter Allee 8-10 80637 München Germany

3. ABSTRACT

Title: Drug Utilisation Study of conjugated oestrogens/ bazedoxifene (CE/BZA) in the EU

Protocol: Version 5.0, October 2015; amended Version 6.0 31 August 2017

Main author: Leo Russo, PhD., Pfizer, Inc.

Rationale and background: *Duavive*® (conjugated oestrogens/bazedoxifene [CE/BZA]) was granted an EU marketing authorization on 16 December 2014 for the treatment of oestrogen 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. Since *Duavive* will be new to the market in the EU starting in 2016 it will be important to collect real-world data regarding actual use in the population for which the product is prescribed. Characterizing the patients which are being prescribed *Duavive* in terms of their background risk for safety events (e.g., cardiovascular events and oestrogen-related malignancies) provides essential context for interpreting post-marketing reports and/or safety data. This protocol describes a non-interventional study designed as a drug utilization study (DUS) that will characterize those patients in the EU prescribed *Duavive* in terms of their background risk for safety events (e.g., cardiovascular events and oestrogen-related malignancies) in order to provide essential context for interpreting post-marketing reports and/or safety data. The conduct of this DUS is a component of the pharmacovigilance plan in the EU risk management plan (RMP) for *Duavive* and a post-authorization commitment to the European Medicines Agency (EMA).

Research question: The overall aim of this drug utilization study (DUS) is to describe the baseline characteristics and utilization patterns of EU patients initiating either *Duavive* or oestrogen + progestin hormone replacement therapy (E+P HRT).

Objectives:

For *Duavive* or E+P HRT users, two sets of analyses will be performed: one among those without prior use of any (E+P) HRT during their 12 month baseline period and another among those with prior E+P use. Each analysis will address these objectives:

1. Within each EU country, describe and compare baseline characteristics and medical history between *Duavive* and (E+P) HRT patients.

2. Estimate the proportion of patients that may have been prescribed *Duavive* outside of the specifications of the authorized product information ('off-label use'). See Section 8.5 for the definition of *Duavive* off-label use.

Study design: This is a multi-country, cross-sectional, drug utilization study (DUS) providing data on baseline characteristics and utilization patterns in EU patients prescribed *Duavive* or E+P HRT.

Population: Study subjects are all patients identified in the respective databases, with minimal exclusion criteria applied. For this DUS, the only inclusion criterion is evidence of being newly initiated on *Duavive* or E+P HRT.

Variables:

Variables will be defined and analysed that represent patient characteristics, co-morbidities, concomitant medications, medical history, and drug utilization. The full listing of study variables is provided in **Table 1** of Section 8.3.

Data sources: In this DUS, multiple data sources (e.g., The UK Health Improvement Network [UK THIN] and Intercontinental Marketing Services [IMS] EU databases) will be used. In each of the annual interim and final study reports that will be prepared, results may be pooled across EU countries when feasible and appropriate, and results will be compared descriptively across EU countries.

Study size: For the description of patient characteristics and drug utilization, sample size and power calculations are not applicable. All individual patients identified as new initiators of *Duavive* or E+P HRT in the databases, during the study period, will be included without any sampling procedures. The numbers of patients will depend on the uptake of *Duavive* in those EU countries in which the product is commercially available and appropriate data sources are available.

Data analysis: Among *Duavive* or E+P HRT users with and without prior use of any (E+P) HRT during their 12 month baseline period, analyses will be descriptive in nature, performed annually for 3 years, and use counts and percentages for categorical variables and means ±with standard deviations for continuous variables. Data from each EU country will be analyzed separately, and may be pooled when feasible; and results will be compared descriptively across countries. Once multiple years of data are available, trends over time will also be reported. The demographics (age, body mass index [BMI]) and clinical characteristics (co-morbidities, concomitant medications, medical and drug history) of patients identified to have received a *Duavive* or E+P HRT prescription will be summarized from their 12 month period prior to treatment initiation (pre-index) and compared. Off-label use of *Duavive* has been defined according to the approved SmPC and operationalized within the limitations of the relevant data sources (see Section 8.5). The proportions of *Duavive* patients with possible off-label use will be described.

Milestones: Two (2) annual interim study reports and a final report will be submitted to the EMA which will include patients who initiate *Duavive* or E+P HRT treatment in the first 3 years following the first commercial availability of *Duavive* in the EU (2016-17, 2017-18, and 2018-19). Product availability in the EU is expected in March, 2016.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	31 August 2017	Substantial	Section 8.1, and throughout	Germany, Sweden, and Finland are being removed from the list of countries where this study will be performed.	Duavive is not going to be marketed in those countries.
2	31 August 2017	Substantial	NA	Duavive has become available in Portugal; However, this DUS will not be extended to Portugal.	With the expert assistance of QuintilesIMS, MAH has assessed the availability of adequate data sources to conduct this study in that Portugal. It has been determined there are no data sources available with the required breadth and depth of information.
3	31 August 2017	Substantial	Section 8.6, and throughou	A switch from the originally suggested data sources in France, Italy, and Spain is necessary. (From LRx and DA sources to the Longitudinal Patient Database (LPD	It has been determined that preliminary counts of Duavive users is very low in the originally suggested data sources in those countries and is substantially higher in LPD. Another advantage is that LPD, compared to the LRx databases, are more comprehensive electronic medical record databases (EMR), which include longitudinal patient level information such as date of diagnosis, indication of use, comorbidities and information on medical history and prescription information, all in one data source.
4	31 August	Administrative	Section 8.6.2 and	The global company name was updated to	IMS Health merged with

	2017		throughout.	QuintilesIMS throughout the document as applicable.	Quintiles in 2016.

5. MILESTONES

Milestone	Planned date[a]
Updated FULL Draft Protocol submitted to CHMP/PRAC	13 October 2014
FINAL Draft Protocol Submission to EMA (for PRAC review)	16 February 2015 (two months following product approval)
Update to FINAL Protocol in response to PRAC assessment	23 July 2015
PRAC/CHMP endorsement of the FINAL protocol	08 October 2015
Protocol Registration in the EU PAS register	01 November 2015
First EU Product Launch	31 March 2016
Start of Data Collection	31 March 2016
End of Data Collection[b]	31 March 2019
1st Annual Study Report[c]	31 March 2018
2nd Annual Study Report	31 March 2019
FINAL Study Report	31 March 2020

Milestone	Planned date[a]

a. Milestones are based upon a projected first launch date of the product in the EU of 31 March 2016.
b. Patient Cohorts will be *Duavive* or E+P HT initiators from the first three years post launch (2016-17, 2017-18, and 2018-19).
c. Time from launch to 1st Annual Report is 24 months: 12 months is needed to accumulate one year of observation, plus a database lag phase of 6 months from real-time, and 6 months is needed to extract data, perform analyses, and generate submission ready report.

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

6. RATIONALE AND BACKGROUND

In the EU, conjugated oestrogens/bazedoxifene (*Duavive*® (CE/BZA)) is indicated for 'treatment of oestrogen 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. The experience treating women older than 65 years is limited'.

Since *Duavive* will be new to the market in the EU, it will be important to collect real-world data on its actual use in the population for which the product is authorized and prescribed. Characterizing the patients being prescribed *Duavive* in terms of their background risk for safety events (e.g., cardiovascular events and oestrogen-related malignancies) provides essential context for interpreting post-marketing reports and/or safety data.

Off-label use occurs when a practitioner chooses to prescribe a medicinal product in a manner that is inconsistent with the prescribing information approved by the governing regulatory authority. For medicinal products authorized by the European Commission (or another EU competent authority), the licensed indications are documented in the Summary of Product Characteristics (SmPC). Examples of off-label prescribing may include, but are not limited to, the administration of the product in doses, routes of administration or for reasons outside of the labeled indications, or use in patients in whom the product is contra-indicated or who do not meet age requirements, or other criteria as specified in the product label.

As part of the description of utilization, the proportion of patients being prescribed *Duavive* that is not in accordance with the product information (off-label use) will be estimated as accurately as possible, given the limitations of the available data sources.

This study will utilize multiple population-based healthcare data sources from that are available in the EU. Results will be reported by country and pooled across EU countries, where feasible. This protocol is designed to produce regular reports to satisfy a request from the Pharmacovigilance Risk Assessment Committee (PRAC)/Committee for Medicinal Products for Human Use (CHMP) for an EU DUS for *Duavive*. The intention is to conduct this study for a period of 3 years in all EU countries in which *Duavive* is launched during 2015-2016 and which have adequate data sources available. However, limitations in database availability or validity may preclude some analyses from being performed in a given country. When this occurs, a rationale has been provided.

This study will be collecting 3 years of post-authorization data on *Duavive*. However, if the accrual of *Duavive* patients is found to be lower than anticipated, then the Sponsor will consider extending the duration of the study beyond the currently planned 3 years.

This protocol describes a drug utilization study (DUS) that is designated as a Post Authorization Safety Study (PASS) and is a post-authorization commitment to the EMA/CHMP.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Question

The overall aim of this DUS is to describe the baseline characteristics and utilization patterns of EU patients initiating treatment with either *Duavive* or E+P HRT.

7.2. Objectives

For *Duavive* or E+P HRT users, two sets of analyses will be performed: one among those without prior use of any (E+P) HRT during their 12 month baseline period and another among those with prior use of E+P HRT. Each analysis will address these objectives:

1. Within each EU country, describe and compare baseline characteristics and medical history between *Duavive* and (E+P) HRT patients.

2. Estimate the proportion of patients that may have been prescribed *Duavive* outside of the specifications of the authorized product information ('off-label use'). See Section 8.5 for the definition of *Duavive* off-label use.

8. RESEARCH METHODS

8.1. Study Design

This is a multi-country, cross-sectional, drug utilization study providing data on baseline characteristics and utilization patterns in EU patients initiating treatment with *Duavive* or E+P HRT.

Currently, the planned first wave of EU launch countries are Belgium, France, Italy, Netherlands, Spain, and the UK. Other EU countries may be included in a second or subsequent wave of EU launches.

Drug cohorts will be defined and described using successive database updates. Study duration will be 3 years after the first launch of *Duavive* in the EU. All patients in the countries/databases who initiate *Duavive* or E+P HRT in the first 3 years (2016-17, 2017-18, and 2018-19) following the first EU launch will be enrolled.

In this DUS, multiple data sources (e.g., UK THIN, IMS EU data) will be used. In each of the annual interim and the final study reports, results may be pooled across EU countries when feasible and appropriate; results will also be presented by country and compared

descriptively across EU countries. Some analyses are not feasible in every country due to a lack of sufficient data. Refer to Table 1for information on which data sources/countries contain each study variable and to Section 8.9 for an overview of analyses that will/will not be done in each country.

In summary, this study is designed to monitor and describe the real-world usage of *Duavive* in the EU.

8.2. Setting and Study Population

Study subjects are all patients identified in the respective databases, with minimal inclusion/exclusion criteria applied; except to ensure patients are newly initiated on *Duavive* or E+P HRT. This broad subject eligibility will ensure that the study is representative of 'real-world' use in the EU, including possible off-label use.

The E+P HRT comparator cohort will be comprised of patients prescribed any E+P combination product (oral, patch, or topical) that has an indication for treatment of oestrogen deficiency symptoms, or patients prescribed two E+P products concurrently (e.g., transdermal estrogen and oral progestin). This list of E+P HRT comparator products will vary by EU country based on variations in product availability across different countries (see Appendix 2). E+P HRT products that have indications for treatment of oestrogen deficiency symptoms and prevention of osteoporosis (as per the EU Core SPC for HRT products)[1] are also included, as long as they have the oestrogen deficiency symptoms indication. All E+P HRT products meeting these definitions will be included in the DUS analyses. Codes for specific E+P HRT *combination* products as well separate oestrogen-containing products and progestin-containing products that could be prescribed concurrently, as are listed by country in Appendix 2.

Note: For the purposes of this study, tibolone (Livial®) will also be considered as an (E+P) HRT and included among the comparator drugs in the countries where it is available. The rationale is that tibolone is metabolized to circulating oestrogens, progestins and androgens, and is widely used in those EU countries where it is available.

8.2.1. Inclusion Criteria

Patients must meet both of the following inclusion criteria to be eligible for this study:

- All patients identified in the respective databases who have received at least one prescription for *Duavive* or E+P HRT during the 3 years following the first EU launch of *Duavive* will be included.

- Patients need to be enrolled in the data source for at least 12 months prior to their earliest prescription of either *Duavive* or an (E+P) HRT comparator.

8.2.2. Exclusion Criteria

Patients with less than 12 months of database enrolment prior to their index prescription will be excluded. This period is necessary to determine if the patient is a new initiator and to fully describe the baseline patient characteristics.

8.3. Variables and Measurement

Each study variable to be analysed, their operational definition, and the country/data sources where they are available, are listed in Table 1.

Table 1. Study variables, operational definitions, and availability by country/data source

Variable	Role	Operational definition	BE	FR	IT	NL	SP	UK
Patient Characteristics								
Age	Baseline Characteristic	Age will be analysed as categorical variable (under 40 years, 40-50 years, over 50 years).	Y	Y	Y	Y	Y	Y
Gender	Baseline Characteristic	Gender will be analysed as categorical variable.	Y	Y	Y	Y	Y	Y
Indication	Baseline Characteristic	Determined by presence of diagnostic codes for estrogen deficiency or osteoporosis 90 days before or after drug initiation. Refer to Table 4 in Annex 1 for the full list of specific ICD-10 and READ codes. Four levels for this variable: -Oestrogen deficiency symptoms only -Osteoporosis only -Both -Unknown		Y	Y		Y	Y
BMI (Height and Weight)	CVD Risk Factor	Continuous variables for height and weight, if available; BMI will be analysed as categorical variable (underweight: BMI<18.5; normal range 18.5≤BMI<25; overweight: 25≤BMI<30; obese: BMI≥30); missings expected		Y	Y		Y	Y
Comorbidities		**Co-morbidities will be defined using ICD-10 codes (or READ codes), as appropriate.**						
Osteoporosis/ osteopenia	Baseline Characteristic	ICD-10 codes: M80-M82		Y	Y		Y	Y
Hyperlipidemia	Baseline Characteristic	ICD-10 codes: E78		Y	Y		Y	Y
Hypertension	Baseline Characteristic	ICD-10 codes: I10-I15		Y	Y		Y	Y
Breast Pain	Baseline Characteristic	ICD-10 codes: N64.4		Y	Y		Y	Y
Diabetes	Baseline Characteristic	ICD-10 codes: E10-E14		Y	Y		Y	Y
Renal Disease	Baseline Characteristic	ICD-10 codes: N17-N19		Y	Y		Y	Y

Table 1. Study variables, operational definitions, and availability by country/data source

Variable	Role	Operational definition	BE	FR	IT	NL	SP	UK
Osteoarthritis	Baseline Characteristic	ICD-10 codes: M15-M19, M47		Y	Y		Y	Y
Major Depression	Baseline Characteristic	ICD-10 codes: F32.2; F32.3; F33.2-F33.3		Y	Y		Y	Y
Medications		**Medication will be defined using ATC codes, as appropriate.**						
Corticosteroids	Baseline Characteristic	H02	Y	Y	Y	Y	Y	Y
Lipid lowering agents	Baseline Characteristic	C10	Y	Y	Y	Y	Y	Y
Anti-hypertensives	Baseline Characteristic	C02	Y	Y	Y	Y	Y	Y
Anticoagulants	Baseline Characteristic	B01	Y	Y	Y	Y	Y	Y
Anti-arrhythmics	Baseline Characteristic	C01	Y	Y	Y	Y	Y	Y
Antidepressants	Baseline Characteristic	N06A	Y	Y	Y	Y	Y	Y
Sedatives/ hypnotics	Baseline Characteristic	N05C	Y	Y	Y	Y	Y	Y
Anti-diabetics	Baseline Characteristic	A10	Y	Y	Y	Y	Y	Y
Osteoporosis treatments (biphosphates, SERMs, etc)	Baseline Characteristic	G03, M05B	Y	Y	Y	Y	Y	Y
Local (vaginal) hormone treatments	Baseline Characteristic	G02B; G03C	Y	Y	Y	Y	Y	Y
Oestrogen/ Progestin HRT	Baseline Characteristic	G03C; G03AC	Y	Y	Y	Y	Y	Y

Table 1. Study variables, operational definitions, and availability by country/data source

Variable	Role	Operational definition	BE	FR	IT	NL	SP	UK
Prior Safety Events		**Safety events will be defined using ICD-10 codes (or READ codes), as appropriate.**						
History of VTE/stroke/ CHD/PVD Event	VTE/stroke/CHD Risk Factor	ICD-10 codes: I80-I82, O87.1, O87.3 ; O22.3 ; I26.0, I26.9, I61-I64, I20-I25 cerebral (I63.6, I67.6), I73.9		Y	Y		Y	Y
History of malignancy potentially associated with oestrogen	Malignancy Risk Factor	ICD-10 Codes: C50, C54, C54.1, C56, C57.8, C57.9		Y	Y		Y	Y
History of any Malignancy	Malignancy Risk Factor	ICD-10 codes: C81–C96		Y	Y		Y	Y
Utilization		**More detailed and country specific information will be included in the statistical analysis plan.**						
Duavive or E+P Prescription Date	Rx level characteristic	Prescription date (MPI, LPD) or dispense date (Xponent, LRx)	Y	Y	Y	Y	Y	Y
Duavive or E+P Prescribed Dose	Rx level characteristic	Dose entered , if available directly on prescription; Otherwise, inferred dose based on time period between prescriptions See Section 8.9.2; not available in Italy	Y	Y	Y	Y	Y	Y
Duavive or E+P Prescribed Days Supply	Rx level characteristic	Days supply entered, if available directly on prescription (LRx, Xponent); Otherwise, inferred days supply based on time period between prescriptions (LRx); See Section 8.9.2 not available in Italy; Spain tbd	Y	Y	Y	Y	Y	Y
Switcher from (E+P) HRT (*Duavive* users only)	Rx level characteristic	Prescription for *Duavive* within 30 days following the end of the last filled prescription period of the (E+P) HRT	Y	Y	Y	Y	Y	Y
Off-label Use	Rx level characteristic	See Section 8.5		Y		Y*	Y*	Y

8.4. Time Periods

Each patient will have an index date corresponding to the date of their first prescription for *Duavive* or E+P HRT after the first EU launch of *Duavive*. Baseline characteristics will be assessed from patient enrolment prior to their index date (pre-index period). A minimum of 12 months for this pre-index period will be required. All other data in this study is cross-sectional (i.e., no follow-up data post index date).

8.5. Off-Label Use

In the EU, *Duavive* (conjugated oestrogens/bazedoxifene) is indicated for "*treatment of oestrogen 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 this DUS, possible off-label use of *Duavive* can only be defined by objective factors that are also accurately contained in the data sources. Because of database limitations, the DUS will focus upon the presence of information suggestive of off-label use and not the absence of expected data elements. Once *Duavive* utilization is adequate for conducting stratified analyses, off-label use will be described according to key baseline characteristics (e.g., age, BMI, comorbidities, prescribed dose, etc.) (See Section 8.9.2).

In all data sources, indication for use of *Duavive* is not explicitly recorded, but must be inferred based on diagnoses recorded within a given time frame near the prescription date. This leads to an inability to interpret the intended indication for *Duavive* use when both oestrogen deficiency symptoms and osteoporosis diagnoses are recorded. Therefore, the following 4 groups will be defined and described as part of analyses of off-label use.

1. Those with a recorded diagnosis of oestrogen deficiency symptoms, within 90 days before or after initiation of *Duavive*, and without a diagnosis for prevention and/or treatment of osteoporosis in that same time period.

2. Those with a recorded diagnosis of prevention and/or treatment of osteoporosis, and without a diagnosis of oestrogen deficiency symptoms in that same time period.

3. Those with recorded diagnoses of oestrogen deficiency symptoms and with prevention and/or treatment of osteoporosis in the above time period.

4. Those without recorded diagnoses of oestrogen deficiency symptoms or prevention and/or treatment of osteoporosis in the above time period.

Provided below is a clinical definition of off-label use for *Duavive* based upon the EU SmPC. Annex 1, Table 4 lists the components of this definition by country and describes how each will be operationally defined.

Clinical definition of *Duavive* off-label use

- Patients with a likely indication of osteoporosis only (group 2 above) (note: addition of group 3 will be examined in sensitivity analyses)
- Use in women who are not postmenopausal (e.g., use in pre-menopausal women).
- Use in women without a uterus (hysterectomised women)
- Use in males
- Prescription of non-approved dose or regimen (i.e.. use of more than one tablet per day, divided tablets)
- Use with progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs)
- Use in women with any of the following contraindicated conditions:
    - Known, suspected, or past history of breast cancer. Or use for prevention of breast cancer.
    - Hypersensitivity (e.g., anaphylaxis/anaphylactic reactions, urticaria, drug eruption) to the active substances or to any of the excipients.
    - Known, suspected, or past history of malignancy potentially associated with oestrogen (e.g., endometrial cancer).
    - Undiagnosed genital bleeding.
    - Untreated endometrial hyperplasia.
    - Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis).
    - Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency).
    - Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke).
    - Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal.
    - Women of childbearing potential.

- Porphyria.

*Operational definitions for these criteria are contained in Annex 1, Table 4.

A summary variable indicating *Duavive* off-label use (Y/N) will be created based upon evidence for any of the above criteria for off-label use.

8.6. Data Sources

The initial planned EU launch countries are Belgium, France, Italy, Netherlands, Spain and UK. Other countries may be included in a second or subsequent wave of EU launches.

(Note: Duavive is now available in the UK)In an effort to obtain the most data variables for each country, this DUS will access and analyze more than one database for nearly all of the EU countries The patient-level and prescription-level data sources contain complementary information and will allow the DUS to address as many objectives as possible within each country.

The EU data sources were selected because they are nationally representative of prescribing practice in their respective countries, potentially able to capture *Duavive* and E+P HRT prescriptions in their defined populations, have relatively short data lags, and have established validity for drug utilization research.

Structural differences across the EU data sources exist with respect to the variables included, the medical settings represented, and the duration of historical data. Therefore, by necessity, analyses will differ somewhat across the target EU countries in which the DUS will be conducted based upon database capabilities. The study will attempt to perform all planned analyses in all EU countries where the product becomes available during 2016-2017.

Annex 1 contains Table 3 - Study Variables available by country and data source and Table 4 - Feasibility of Study Objectives/Analyses by Country/Database. These tables lists objectives/analyses, shows which country/data source where they are feasible, and includes a rationale for any analyses not being performed in a specific country/ data source.

When database limitations preclude an analysis from being performed in a given country, a detailed rationale will be provided.

Some of the proposed EU data sources are subject to loss to follow-up due to patients switching to a physician not captured in the data source. Because of the gatekeeper role of the general practitioner (GP) in the UK, and together with the low rate of GP switching in the UK, this is not a concern for the UK THIN database. Based upon the objectives of this DUS, the study is not going to follow patients after their index date (treatment initiation). However, it is possible that for those patients switching to a physician not captured in the data source, the completeness of their pre-index period could be affected. This will be addressed in the DUS by excluding patients without 12 months of uninterrupted database

observation prior to treatment initiation. This exclusion is in place to strengthen the identification of relevant medical history, but it will also address this potential limitation.

8.6.1. UK THIN

The THIN database is comprised of anonymized patient data collected in a non-interventional manner from the daily record keeping of general practices in the UK, which use the Vision practice management software and have agreed to contribute to the scheme. As of January 2014, the THIN database contains primary medical records from over 12 million patients in the UK, of which over 3.6 million are actively registered. Overall, THIN contains data on almost 6% of the UK population.

QuintilesIMS is collaborating with Pfizer on the design, study protocol, interim and final reports, and peer-reviewed publications for this DUS. Pfizer is the Sponsor and IMS is the coordinating center and data holder for most of the sources. Using Pfizer's licensed copy of anonymized THIN data, IMS will perform all analyses of the THIN database and provide Pfizer with tables of results. Neither IMS nor Pfizer will have access to practice or patient identifiers, thereby maintaining patient anonymity.

Data attributes available to researchers consist of demographic, medical and prescription information at the individual patient-level. In addition, there is information on referral to specialists, hospitalization, diagnostics and laboratory results, some lifestyle characteristics and other measurements taken in the GP practice. Clinical information is recorded via the READ disease classification system (http://systems.hscic.gov.uk/data/uktc/readcodes), (also see Chisholm, 1990[2] for further description of READ) and issued prescriptions via the Gemscript drug code system (http://www.resip.co.uk/gemscript).

Research studies using THIN data are approved by a nationally accredited ethics committee, which has also approved the data collection scheme. THIN has been used extensively in medical research since 2003 in the UK, Europe and the US and has been found to be a valid data source for this kind of research.[3]

8.6.2. QuintilesIMS Data Sources

Longitudinal patient level databases held by QuintilesIMSinclude electronic medical records (LPD databases) for France, Spain and Italy, and prescription databases based on pharmacy retail data for Belgium, and the Netherlands. Additional information, from approximately 20 EU countries, reflecting doctor-patient consultations and diagnosis is available in IMS Health® Prescribing Insights (PI), which is a cross-sectional, retrospective medical information database designed and updated by QuintilesIMS.

8.6.2.1. Longitudinal Patient-Level Databases

8.6.2.1.1. IMS (Longitudinal Patient Data) LPD®

France, Italy and Spain –

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in EMR. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in the country.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile.
Data are collected directly and continually during the visits via a patient management software. The LPD databases allows for a longitudinal follow-up of all the different visits of the same patient consulting the same physician in the panel (or even across specialties in Spain). The information allows patients and doctors to be longitudinally monitored in order to analyze the prescriptions' context in real-life situations.

Longitudinal patient records can be searched for presence or absence of specific events in patients exposed to study drug or diagnosed with a condition, and can be used to derive appropriate control groups. Patient records often contain non-prescription data too, which can be used to stratify patient populations for age, sex, diagnosis, risk factors, alongside concomitant therapies and co-morbidities. An update of the database is performed monthly with a lag time of 6 to 12 weeks.

The LPD database contains individual-level data on demographics (age, gender), comorbidities, healthcare contacts (e.g. date, diagnosis, visits), prescribed drugs (ATC-code, strength, daily dose and duration), lab tests (date and result), and clinical measurements (e.g. BMI, blood pressure, pulse) when applicable, and enable longitudinal tracking both for patients and prescribers. Since these data are being collected in a non-interventional way, they reflect real-life clinical practice in the country. The panel of contributing GPs is maintained as a representative sample of the primary care physician population according to three criteria known to influence prescribing: age, sex, and geographical distribution[4] Whenever a GP leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities.[5, 6]

The IMS Health LPD® includes data from 2.6 million active patients in France, 1.2 million patients in Italy and 1.5 million patients in Spain. LPD in France covers 1,200 GPs and 620 specialists (including 120 gynecologists), in Italy 900 GPs and in Spain 1,450 GPs plus 515 specialists (including 177 gynecologists).

In France, repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills is recorded in the database. The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication.

The panel of participating medical doctors is selected from a large number of French physicians who use the Cegedim management software for their daily practice. These office-based, active physicians have agreed to upload to QuintilesIMS servers anonymous and coded excerpts from medical files of patients who have come to see them. The data collected are gathered for each patient within the same doctor's office, thus providing longitudinal data on the same patients. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in France.

In Spain, it is possible to track an individual patient recorded across different specialties, so the history of the patient's treatment at different specialists can be analyzed. The data in LPD database are generated directly from the EMR of the panel physicians' practice via standardized interfaces and provide monthly routine information on patients' diseases and therapies. Please note that in Spain, drug information is only available for reimbursed drugs.

8.6.2.2. Longitudinal Prescription-Level Databases

Longitudinal prescription databases are proposed to provide data for Belgium, and the Netherlands. These sources contain prescription information on a patient level collected from retail pharmacy computers (no hospital based pharmacies). Drug utilization studies based on these longitudinal prescription data have been performed previously throughout the world.[7,8] Depending on the country, information collected in the longitudinal prescription database provides medication dispensed, dose, form, strength, and prescriber specialty. The prescription data is linked to an anonymized patient ID, which tracks the prescriptions by patient over time. An important advantage of the prescription databases is their broad coverage of specialty physicians and pharmacies. Differences between longitudinal prescriptions databases exist with respect to parameters included, and the coverage and the length of historical data.

The current national coverage of pharmacies in the longitudinal prescription databases of each country is shown in Table 2.

Table 2. Longitudinal Prescription Databases and Coverage Per Country

Country	Number of Pharmacies in the Panel	Coverage (% of All Pharmacies)	Historical Data (Up To)	Update
Belgium	≈1200	28%	2008	Monthly
Netherlands	≈ 1400 pharmacies ≈180 dispensing physicians	75%	Three years	Monthly

Table 2. Longitudinal Prescription Databases and Coverage Per Country

Country	Number of Pharmacies in the Panel	Coverage (% of All Pharmacies)	Historical Data (Up To)	Update

8.6.2.2.1. Belgium - IMS LRx (Prescription Dynamics)

In Belgium, the longitudinal prescription data provides information on age, gender, previous and current treatment per patient (for treatments provided the patient shops in pharmacies within the IMS longitudinal prescription level data). Currently, 1,200 pharmacies are captured in Belgium (28% of national coverage). This panel was designed to be representative for distribution channels and physician specialties in the country. All medical specialties and markets are covered. A native patient ID is available and is identical across pharmacies.

8.6.2.2.2. Netherlands - IMS Xponent™

In the Netherlands, longitudinal data will be used from the Xponent™ database.

Xponent™ is a unique source of data capturing local and regional prescription drug dispensing information. Prescriptions by both specialists and GPs are covered. IMS Xponent™ includes prescription data from over 75% of retail pharmacies and dispensing GPs in the Netherlands, collecting data from more than 14.5 million prescriptions per month. From the selected sample pharmacies, IMS collects new and refilled prescriptions for every day of the month. Information on physician specialty, patient age, gender, dose and co-prescriptions is available in Xponent™. The information available in the database allows to extract information on treatment duration and switches and to follow patients over a longer period of time.

8.6.2.3. Cross-sectional Databases

8.6.2.3.1. IMS Health Prescribing Insights Databases

The IMS Health® Prescribing Insights database (PI) is a cross-sectional, retrospective medical information database designed and updated by QuintilesIMS. It provides regular snapshots of doctor-patient consultations and treatment across the world. The data is collected from a representative sample of doctors practicing in the primary care sector from each country that is monitored. MIDAS PI is the international centralized database, which contains over 20 EU countries; the existing data and information are provided by the local PI medical databases.

The means by which information is extrapolated from the sample of doctors in each country is as follows:

- The doctor universe is stratified by physician groups (specialties) and geography.
- Physicians working in both public and in private practices are captured.

- In general, medical data is collected electronically or from diaries that the doctors complete. Each diary gives a full record of consultations over regular sample periods.

- A one week period within 13 weeks (in a quarter) or 26 weeks (in a semester) is documented, which includes all consultations (patients seen), all diagnoses and prescriptions during that week.

- All diaries are then sent to IMS for coding.

- The prescription data collected from the doctor samples is projected upwards to give a total figure that is nationally representative for each country.

- Doctor characteristics are projected with the so-called 'doctor factor', which is doctor universe over doctor sample. The doctor factor is either calculated nationally or regionally by specialty.

- Patient characteristics, diagnosis and prescriptions are projected with the so-called 'patient factor', which is the doctor factor times 13 per quarter or times 26 per semester. The patient factor is either calculated nationally or regionally by specialty.

In both local databases and in the MIDAS PI central database the data collected are based on key figures and variables and represent actual observed behavior, therefore do not rely on doctor's recollection of the event. Each country collects data and information from a sample of prescribers that are registered in a national database and actively participate in the data collection. Prescriber samples are selected to be representative of the countries' clinical practice, allowing extrapolation of the data to the national level and ensuring constancy over time. Even though local PI databases follow the same basic principles as the MIDAS PI, they are autonomous and the availability of the data is dependent on local resources. Medical specialties included in the samples can vary from country to country and data variables available in the MIDAS PI central database may not be present in all countries.

The database collects information for variables related to patient demographics, prescriber characteristics, diagnosis and dose.

Diagnosis variables are based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision – ICD 10.

Data on drug use can be extracted from MIDAS PI both by brand name and by the name of the active compound.

MIDAS PI data and will not be merged or integrated in any way with data from other sources in the country, but rather will be analyzed in parallel.

8.7. Study Size

This DUS will descriptively analyze drug utilization for Duavive and E+P HRT in the EU without any hypotheses to be tested.

For the description of patient characteristics and drug utilization, sample size and power calculations are not applicable. All individual patients identified as new initiators of Duavive or E+P HRT in the database, during the study period, will be included without any sampling procedures. The numbers of patients will depend on the uptake of Duavive in the EU countries in which the product is made available.

8.8. Data Management

QuintilesIMS is the coordinating center for this study and is the data holder for most of the sources. It is collaborating with Pfizer in the design of the study and the writing of protocols, interim and final reports, and peer-reviewed publications. It will be the direct interface with each country database holder. Anonymized data will be extracted by the external data owners and only combined when feasible and appropriate.

The processes for database management differ by country. Generally, the data are stored at the database level and analyzed locally. All data management and analyses will be conducted by QuintilesIMS in accordance with their standard operating procedures (SOPs). Datasets extracted from the databases and dated images of those datasets will be stored at the responsible organizations according to their SOPs. The datasets extracted from the databases will be stored at QuintilesIMS to allow analysis in the future.

The Sponsor will not have access to health records at the level of the individual patient but only to tables with aggregated data.

This study will be conducted in accordance with relevant chapters of European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and International Conference on Harmonisation (ICH) guidelines for data management.

8.9. Data Analysis

Patients will then be divided into the following 4 groups based on their prior use of <u>any</u> E+P HRT during their 12 month baseline period:

- *Duavive* users
    - No E+P HRT in last 12 months
    - E+P HRT in last 12 months
- E+P HRT users
    - No E+P HRT in last 12 months

- E+P HRT in last 12 months

In this DUS, the Sponsor plans to conduct all analyses in all EU countries, without compromising scientific rigor and validity. However, limitations in database availability or validity have precluded some analyses from being performed in a given country (refer to Table 1). In summary:

- The descriptive analyses of patient characteristics are feasible in all countries, with the exception of the BMI variable which is only available in France, Spain, Italy and UK, with missings expected.

- Data sources from Belgium and Netherlands can only detect diagnoses as they occur in the same consultation as prescribing visit. Therefore, the study cannot define variables for indication, comorbidities, or prior safety events in the above two countries.

- In regards to off-label use, because of the limitation to define indication, it will not be possible to define in Belgium and the ability to define it in Netherlands is limited, but feasible.

- For prescription-level data (e.g., co-medications, dose, supply, date) all variables are available in most countries. .

In accordance with ENCePP best practices, a separate statistical analysis plan (SAP) will be developed for this study. The SAP will contain an overview of all major steps to be taken from raw data to final results (including how missing data will be addressed), full details on statistical methods, and the layout of the results tables. This analysis plan will be developed prior to availability of the first year of *Duavive* use (estimate is October 2017), and in accordance with Chapter 7 of the ENCePP Guide on methodological standards in pharmacoepidemiology.

8.9.1. Patient Characteristics

The profile of *Duavive* initiators will be described in several ways.

- When feasible, data from all countries will be pooled and characteristics of all EU *Duavive* patients presented.

- Countries will be analyzed separately, with *Duavive* patients presented across countries.

- Within each country, *Duavive* initiators will be compared to initiators of E+P HRT.

- Once multiple years of data are available, trends over time in *Duavive* patients will also be reported.

These analyses will be descriptive in nature, performed annually for 3 years, and use counts and percentages for categorical variables and means with standard deviations for continuous variables. Demographics and clinical characteristics (ager, indication, comorbidities, concomitant medications, medical and drug history) of patients identified to have initiated *Duavive* will be taken from the pre-index period and summarized. Age at baseline will be analysed into these three categories: under 40 years, 40-50 years, and over 50 years.

Among *Duavive* patients with prior E+P HRT use in their baseline period, those whose prior E+P HRT ended within 30 days from their initiation of *Duavive* will be further categorized as switchers.

In summary, *Duavive* patients will be summarized by all countries combined and by each country separately, and will be compared to E+P HRT patients within each country.

Further details will be provided in the statistical analysis plan which will also contain dummy/ mock tables.

8.9.2. Drug Utilisation and Off-Label Use

The prescribed dose and number of tablets (days supply) at baseline will be summarized for *Duavive* patients within a given country and compared across countries, when feasible. Once multiple years of uptake are available, trends over time will be described by analyzing data stratified by year.

For those data sources where either prescribed dose or prescribed number of tablets (i.e. days supply) is not entered directly (Belgium and UK), these parameters will be estimated based upon the timing of consecutive refills. Prescribed dose will be estimated using the defined daily dose for Duavive and the timing between consecutive refills. For example, if the defined daily dose is one tablet per day containing 0.45 mg CE and 20 mg BZA, and a patient refills their prescription every 90 days, then it will be inferred that the prescribed dose was one 0.45 mg CE and 20 mg BZA tablet per day. Similarly, prescribed number of tablets will be estimated using the approved pack size for Duavive and the timing between consecutive refills. For example, the approved pack size in the EU is 28 tablets, so for a patient who refills their prescription every 90 days, it will be inferred that the prescribed number of tablets was 84 (i.e. 3 monthly packs of 28).

Off-label use of *Duavive* use will be defined according to its product label (SmPC) and operationalized within the limitations of the relevant data source (see Section 8.5). The proportion of patients with possible off-label use of *Duavive* will be described within each country.

In order to fully describe patients potentially using *Duavive* off-label, stratified analyses of off-label use by selected patient characteristics will also be presented once an appropriate sample size is attained (e.g., n=30). For example, potential off-label use by age categories may be described. Additionally, the subgroup of *Duavive* patients with recorded diagnosis of both oestrogen deficiency symptoms and osteoporosis will be identified and described.

8.10. Quality Control

For the UK THIN data, following extraction of patient data from practice software, quality and consistency checks are performed at the primary database owner (Cegedim Strategic Data [CSD]) to ensure that transmission from practices to THIN is complete and accurate. These checks are performed according to CSD's quality management systems. Records which are incomplete or inconsistent are flagged such that they can be excluded from research if desired. The THIN data quality has also been confirmed both externally and internally. Participating THIN practices are given regular feedback reports on the quality of their data, as well as free training sessions that help them to improve data recording. Quality control of programming for the extraction of THIN study variables will be carried out according to QuintilesIMS's standard operating procedures.

For the IMS EU data sources, quality control is conducted at several levels depending on the database. At the database level, the quality unit of the production department of IMS verifies continuously the quality of its sources in terms of representativeness and consistency of collected data. The study will use existing databases which have been widely used for research. At the study level, all aspects of the study from protocol development to the reporting of the results are conducted following SOPs of IMS Center of Excellence (COE) in Retrospective Studies department. SOPs of QuintilesIMS COE in Retrospective Studies HEOR can be consulted on site.

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IMS Quality Management System (QMS) and in accordance to the following policies and procedures:

POL_QA_001 "Quality Management System" policy

POL_QC_001 "Quality Control Strategy" policy

SOP_QC_002 "Quality Control of Project Deliverables"

According to the policies and procedures above, a Quality Control plan for the study will be developed and executed, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.

- The execution of any required corrective action will be documented.
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study.

Also, the Principal in Charge of the study will verify training compliance of IMS employees contributing to the study, as per QuintilesIMS procedure SOP_QA_007 "Training of Quality and Operational Standards".

The Principal in Charge of the study is a senior researcher. Qualification, role and responsibilities of the Principal in Charge of the study are described in OST_OT_014 "Senior Principal RWE- Job Description.

QuintilesIMS is repeatedly being audited by third parties on their QMS, data, technological infrastructure and services. In case there are findings relevant to the concerned study it will be informed. An audit by Pfizer of QuintilesIMS would be considered based on dictating circumstances (for example suspected errors) or could be taken in the frame of broader audit plans for Pfizer's contractors where a risk based approach towards prioritization and selection of contractors is being taken.

8.11. Strengths and Limitations of the Research Methods

Strengths:

- This study will be using population-based data sources of the real-world actual use of *Duavive* and E+P HRT. This will address the limitations of generalizability inherent to the *Duavive* clinical data. The UK THIN database, and QuintilesIMS data sources are well established resources for conducting pharmacoepidemiologic research and have been shown to be nationally representative with good validity in capturing patient care among their defined populations.[3-8]

- By repeating the analyses at the end of every 12 months over a 3 year period, the study will provide real-world data on any changing trends.

Limitations:

- Possible off-label use of *Duavive* can only be defined by objective factors that are also accurately contained in the data sources. The operational definitions of off-label use are subject to limitations of the data sources, and may cause some off-label use to not be identified or to spuriously identify use as off-label when it is not. Data source limitations that impact identifying off-label use include: incomplete recording of postmenopausal status, limited patient history on prior treatments, and a lack of explicit recording of indication for use (i.e., for most sources, this needs to be inferred from proximate diagnoses). In nearly all the data sources being considered, the indication for product usage is not explicitly recorded as such in the electronic data. Therefore, the indication

for use will be inferred from diagnoses of either estrogen deficiency or osteoporosis that are recorded within 90 days before or after product initiation.

- The uptake of *Duavive* may be slower than anticipated following initial EU launches, which may result in relatively small numbers of patients being available for analysis in the first year of the study.

- In those countries where the percentage of pharmacies captured in the prescription-level data sources is low (Belgium) (see Table 2) there could be some selection bias in terms of the patients represented. For the patient-level data sources, those who receive care from a practice or health system not captured in the data will not be included in the DUS. However, the external validity for several of these sources has been established (e.g., THIN, LPD).[3-8]

- *Duavive* patients who are switchers from (E+P) HRT can be defined in most data sources. However, the reason for a switch is not recorded in any of the data sources.

- All analyses are not feasible in every country due to lack of the necessary study variables in a given country/data source. Table 1 shows which data sources/countries contain each study variable and a summary of analyses that will/will not be done in each country is provided in Section 8.9. (Note: Duavive now available in UK)

8.12. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

These are retrospective studies of de-identified data from existing electronic healthcare records databases without any direct enrollment of subjects. Therefore, no informed consent is applicable.

9.2. Patient Withdrawal

Not applicable.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the marketing authorization holder (MAH; Pfizer).

For the proposed study, the following submissions are required:

9.3.1. UK Scientific and Ethical Review Committee

All studies using THIN data must receive scientific or ethical approval to publish or broadcast results into the public domain. Appropriate submissions will be made.

9.4. 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, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual patient. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Regulatory Authority Reporting

Two (2) annual interim study reports and a final study report will be submitted to the EMA. These reports will provide drug utilization data for patients who initiate *Duavive* or E+P HRT in the first 3 years following the initial launches of *Duavive* in the EU (2016-17, 2017-18, and 2018-19). Each annual report will contain both interim and cumulative data. Reports will each contain 12 months of new post-launch data on *Duavive* as well as all prior data. For a given country, the following criteria must be met in order to be included in an annual interim report:

- *Duavive* is commercially available in the given country.
- There are at least 20 new initiators of *Duavive* present in the most recently available data.

For the final report, all countries where *Duavive* is available will be included regardless of the number of initiators.

The structure of the reports will be according to the EMA template:

Reference:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf

Taking into account a current expected first EU launch date by 31 March 2016, the accumulation of 12 months of post-launch data, and a 6 month database lag phase from real-time, the first annual report is expected to be submitted to the EMA by 31 March 2018. Section 5 of the protocol contains key milestones and the planned submission dates for all 3 study reports.

11.2. Publication

Pfizer commits to submitting the key findings of this DUS for peer-reviewed publication.

For all peer-reviewed publications relating to this DUS, 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.

11.3. Communication of Issues

In the event of any prohibition or restriction imposed (e.g., by clinical hold) by an applicable Competent Authority in any region of the world, or if the investigator(s) become aware of any new information which might influence the evaluation of the benefits and risks of *Duavive* , Pfizer Worldwide Safety and Regulatory (WSR) should be informed immediately.

In addition, the investigator(s) will inform Pfizer Worldwide Safety and Regulatory (WSR) immediately of any urgent safety measures taken by them to protect the study patients against any immediate hazard, and of any serious breaches of this Non-Interventional study protocol that the investigator becomes aware of.

12. REFERENCES

[1] EU CMDh Core SPC for Hormone Replacement Therapy Products (CMDh/131/2003, Rev 4, June 2012).

[2] Chisholm J. The Read clinical classification. BMJ 1990;300:1092.

[3] Lewis JD, Schinnar R, Bilker WB, et al. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Safety 2007;16:393-401.

[4] de Bakker DH, Coffie DS, Heerdink ER, van Dijk L, Groenewegen PP. Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis. BMC Health Serv Res. 2007 Aug 22;7:132

[5] Istituto di ricerca della SIMG. VII report Health Search: 2013-2014. Società Italiana di Medicina Generale e delle Cure Primarie. 2014. Available at: http://healthsearch.it/documenti/Archivio/Report/VIIIReport_2013-2014/index.html#p=1

[6] Jouaville SL, Miotti H, Coffin G, Sarfati B, Meilhoc A. Validity and limitations of the Longitudinal Patient Database France for use in pharmacoepidemiological and pharmacoeconomics studies. Value in Health. 2015; 18 (3) A18.

[7] Ziller V, Kostev K, Kyvernitakis I, et al. Persistence and compliance of medications used in the treatment of osteoporosis--analysis using a large scale, representative, longitudinal German database. Persistence and compliance of medications used in the treatment of osteoporosis--analysis using a large scale, representative, longitudinal German database. Int J Clin Pharmacol Ther 2012;50:315-22.

[8] Hamer HM, Dodel R, Strzelczyk A, et al. Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany--a nationwide population-based study in children and adults. Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany--a nationwide population-based study in children and adults. J Neurol 2012;259:2376-84.

APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

- Annex 1: Table 3. Study Variables available by Country and Data Source

  Table 4. Feasibility of Study Objectives/Analyses by Country/Database

  Table 5. ICD-10 to READ Code Translation

APPENDIX 2. DRUG NAMES AND CODES BY COUNTRY

E+P HRT Combination Products

DRUG NAME	ATC CODE
BELGIUM (includes Luxembourg)	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CYCLO PROGYNOVA	G03FB01 / G03FB09
DIVIVA	G03FA12
DUOGESTAN	G03FA12
ENADIOL	G03FA12
ESTALIS	G03FA01 /G03CA53
ESTRAPAK	G03CA03
FEMOSTON	G03FB08
HERIA	G03CX01 / G03DC05
KLIOGEST	G03FA01
MERICOMB	G03FB05
MERIGEST	G03FA01
NAEMIS	G03FB12
PREMPAK	G03FA10
PREMPRO	G03CA57
TOTELLE SEKVENS	G03FB05
TRISEQUENS	G03FB05
TRIVINA	G03FA12
FRANCE	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
AVADENE	G03AA10 / G03AB06 / G03CA03
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CUMORIT	G03CA53 / G03FA04
DIVINA	G03FB06 /G03FA12
DIVISEQ	G03FB06
DUOVA	G03FB06 /G03FA12
FEM7 COMBI	G03FA11 /G03A03 / G03FB09
FEMOSTON	G03FB08
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05

DRUG NAME	**ATC CODE**
NAEMIS	G03FB12
SUCCESSIA	G03AA10 / G03AB06 / G03CA03
SYNERGON	G03CA07 / G03CC04 / G03DA04
TRISEQUENS	G03FB05
ITALY	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
CLIOVELLE	G03FA01
CYCLABIL	G03FB01
DIVINA	G03FB06 /G03FA12
DIVITREN	G03FB06
ESTALIS	G03FA01 /G03CA53
ESTRAPAK	G03CA03
EVOREL PAK	G03CA03
FEMOSTON	G03FB08
FEMSEVEN COMBI	G03FA11 /G03A03 / G03FB09
INDIVINA	G03FA12
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05
MERICOMB	G03FB05
MERIGEST	G03FA01
SEQUIDOT	G03FB05
TOTELLE SEKVENS	G03FB05
TRISEQUENS	G03FB05
NETHERLANDS	
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
CLIMEN	G03HB01
CLIMODIEN	G03FA15
CYCLO PROGYNOVA	G03FB01 / G03FB09
ESTRAPAK	G03CA03
FEM 7 SEQUI	G03FB05
FEMOSTON	G03FB08
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05
PREMPAK	G03F A10
PREMPAK C	G03FA10
PREMPHASE	G03CA57
PREMPRO	G03CA57
TRISEQUENS	G03FB05
SPAIN	
ABSORLENT PLUS	G03CA03 / G03FB05
ACTIVELLE	G03FA01
ANGELIQ	G03FA17
AUROCLIM	G03AA07 / G03AB03 / G03CA53 / G03FA11 / G03FB09
BOLTIN	G03CX01 / G03DC05
CLIMEN	G03HB01

DRUG NAME	ATC CODE
CLIMODIEN	G03FA15
CLISIN	G03HB01
CYCLO PROGYNOVA	G03FB01 / G03FB09
DILENA	G03FB06
DUOFEMME	G03FB05
ESTALIS	G03FA01 /G03CA53
ESTRAPAK	G03CA03
EVIANA	G03FA01
MERIGEST	G03FA01
MERIGEST COMBI	G03FB05
MEVAREN	G03FA15 / G03AB08
NUVELLE	G03CA03
PREMPHASE	G03CA57
PREMPRO	G03CA57
PRIMOSISTON	G03FA01
TRISEQUENS	G03FB05
UK	
ACTIVELLE	G03FA01
ADGYN COMBI	G03CA53 / G03FA01
ANGELIQ	G03FA17
CLIMAGEST	G03FB05
CLIMESSE	G03FA01
CLINORETTE	G03CA53 / G03FA01 / G03FB05
COMBISEVEN	G03AA07 / G03AB03 / G03CA53 / G03FA11 / G03FB09
CONJUGTD OEST/MEDR	G03FB07
CYCLO PROGYNOVA	G03FB01 / G03FB09
DIVITREN	G03FB06
ELLESTE DUET	G03FB05 / G03FA01
ESTRAD/NORETH L.U.	G03AA05
ESTRAPAK	G03CA03
EVOREL PAK	G03CA03
FEMOSTON	G03FB08
FEMSEVEN COMBI	G03FA11 /G03A03 / G03FB09
FEMTAB CONTINUOUS	G03FA01 /G03CA53 / G03CA03
INDIVINA	G03FA12
KLIOGEST	G03FA01
LIVIAL	G03CX01 / G03DC05
NUVELLE	G03CA03
PREMPAK C	G03FA10
PREMPHASE	G03CA57
PREMPRO	G03CA57
TRISEQUENS	G03FB05

Oestrogen-containing Products

DRUG NAME	ATC CODE
BELGIUM (includes Luxembourg)	

DRUG NAME	**ATC CODE**
AACIFEMINE	G03CA04
AERODIOL	G03CA03
CLIMARA	G03CA03
DERMESTRIL	G03CA03
DIMENFORMON	G03CA03
DISTILBENE	G03CB02 / L02AA01
ENADIOL	G03FA01 / G03FA12
ESTRADERM	G03CA03
ESTRADIOL NOVT	G03CA03
ESTRADOT	G03CA03
ESTRAMON	G03CA03
ESTREVA	G03CA03
ESTROFEM	G03CA03
FEMSEVEN	G03FB01
MENO-IMPLANT	G03CA03
MENOREST	G03CA03
OESTROGEL	G03CA03
OVESTIN	G03CA04
PREMARIN	G03CA57
PROGYNOVA	G03CA03
SYSTEN	G03CA03
ZUMENON	G03CA03
FRANCE	
AERODIOL	G03CA03
CLIMARA	G03CA03
DELIDOSE	G03CA03
DEPOFEMIN	G03CA03
DERMESTRIL	G03CA03
ESTRADERM	G03CA03
ESTRADIOL NOVT	G03CA03
ESTRADIOL TEVA	G03CA03
ESTRADOT	G03CA03
ESTRAPATCH THS	G03CA03
ESTREVA	G03CA03
ESTROFEM	G03CA03
ETHINYLESTRAD ITAF	G03CA07
ETHINYLESTRAD SNFI	G03CA07
EVAFILM	G03CA07
MENOREST	G03CA03
OESCLIM	G03CA03
OESTROGEL	G03CA03
OVESTIN	G03CA04
PREMARIN	G03CA57
PROGYNOVA	G03CA03
SYSTEN	G03CA03
THAIS	G03CA03
ZUMENON	G03CA03

DRUG NAME	ATC CODE
ITALY	
AERODIOL	G03CA03
ARMONIL RCDT	G03CA03
CLIMADERM	G03CA03
CLIMARA	G03CA03
DERMESTRIL	G03CA03
DIVIGEL	G03CA03
EPHELIA	G03CA03
EPIESTROL	G03CA03
ESTRADERM	G03CA03
ESTRADIOLO AMSA	G03CA03
ESTRADIOLO ANGELIN	G03CA03
ESTREVA	G03CA03
ESTROCLIM	G03CA03
ESTROFEM	G03CA03
ETINILESTRADIOLO	G03CA01
GELESTRA	G03CA03
MENOREST	G03CA03
OVESTIN	G03CA04
PREMARIN	G03CA57
PROGYNON	G03CA03
PROGYNOVA	G03CA03
RU-EST	G03CA03
SYSTEN	G03CA03
NETHERLANDS	
AACIFEMINE	G03CA04
AERODIOL	G03CA03
CETURA	G03CA03
CLIMARA	G03CA03
DAGYNIL	G03CA57
DERMESTRIL	G03CA03
ESTRADERM	G03CA03
ESTRADIOL MYLA	G03CA03
ESTRADIOL NOVT	G03CA03
ESTRADIOL TEVA	G03CA03
ESTRADIOL-AEN	G03CA03
ESTRADIOL-ATX	G03CA03
ESTRADOT	G03CA03
ESTROFEM	G03CA03
FEMSEVEN	G03FB01
LYNORAL	G03CA01
MENO-IMPLANT	G03CA03
MENOREST	G03CA03
OVESTIN	G03CA04
PREMARIN	G03CA57
PROGYNOVA	G03CA03
SANDRENA	G03CA03
SYSTEN	G03CA03

DRUG NAME	ATC CODE
ZUMENON	G03CA03
SPAIN	
ABSORLENT MATRIX	G03CA03
ALCIS	G03CA03
CLIOGAN	G03CA03
DERMESTRIL	G03CA03
ENDOMINA	G03FA01
EQUIN	G03CA57
ESTRADIOL NOVT	G03CA03
ESTRADOT	G03CA03
MENOREST	G03CA03
MERIMONO	G03CA03
OESTRACLIN	G03CA03
OVESTIN	G03CA04
POSTMENOP	undefined
PREMARIN	G03CA57
PROGYNON	G03CA03
PROGYNOVA	G03CA03
SYSTEN	G03CA03
UK	
ADGYN ESTRO	G03CA03
AERODIOL	G03CA03
BEDOL	G03CA03
CLIMARA	G03CA03
CONJ ESTROGEN L.U.	G03CA57
DERMESTRIL	G03CA03
DIETHYLSTILB L.U.	G03CB02 / L02AA01
DIETHYLSTILB TEVA	G03CB02 / L02AA01
DIETHYLSTILBES HCR	G03CB02 / L02AA01
ELLESTE SOLO	G03CA03
ESTRAD/NORETH L.U.	G03CA53
ESTRADERM	G03CA03
ESTRADIOL L.U.	G03CA03
ESTRADIOL M-CO	G03CA03
ESTRADOT	G03CA03
ESTREVA	G03CA03
ETHINYLESTRAD L.U.	G03CA07
ETHINYLESTRAD TEVA	G03CA07
ETHINYLESTRAD UCB-	G03CA07
FEMSEVEN	G03FB01
HORMONIN	G03CA53
MENOREST	G03CA03
MENORING 50	G03CA03
MERIMONO	G03CA03
OESTROGEL	G03CA03
OGEN	G03CA07/G03CC04
OVESTIN	G03CA04
PREMARIN	G03CA57

DRUG NAME	ATC CODE
PROGYNOVA	G03CA03
SANDRENA	G03CA03
SYSTEN	G03CA03
ZUMENON	G03CA03

Progestin-containing Products

DRUG NAME	ATC CODE
BELGIUM (includes Luxembourg)	
UTROGESTAN	G03DA04
LUTENYL	G03AA14
ORGAMETRIL	G03DC03
DUPHASTON	G03DB01
PRIMOLUT NOR	G03AC01
DEPO PROVERA	G03AC06
VISANNE	G03DB08
CRINONE	G03DA04
COLPRONE	G03DA03
NOGEST	G03DB04
NOMEGESTROL STAD	G03DB04
PROLUTON	G03DA04
FRANCE	
UTROGESTAN	G03DA04
PROGEFFIK	G03DA04
DUPHASTON	G03DB01
PROGESTERONE SERV	G03DA04
NOMEGESTROL MYLAN	G03DB04
CHLORMADINONE MYLA	G03DB06
LUTENYL	G03AA14
CHLORMADINONE TEVA	G03DB06
LUTERAN	G03DB06
PROGESTERONE MYLA	G03DA04
SURGESTONE	G03DB07
CHLORMADINONE SDZ	G03DB06
COLPRONE	G03DA03
PROGESTERONE NOVT	G03DA04
PROGESTERONE TEVA	G03DA04
GEPROMI	G03DA04
VISANNE	G03DB08
HYDROXYPROGES BAYR	G03DA03
NOMEGESTROL BIOG	G03DB04
NOMEGESTROL SANDOZ	G03DB04
NOMEGESTROL STAD	G03DB04
NOMEGESTROL ARROW	G03DB04
NOMEGESTROL TEVA	G03DB04
NOMEGESTROL ZENTIV	G03DB04
EVAPAUSE	G03DA04
GESTORAL	G03AC06

DRUG NAME	**ATC CODE**
ORGAMETRIL	G03DC03
PRECYCLAN	G03DA02/ G03AC06/C03AA01/N05BC51
PRIMOLUT NOR	G03AC01
PROGESTERONE TEVA	G03DA04
TOCOGESTAN	G03DA04
PROGESTERONE DCI	G03DA04
CHLORMADINONE DCI	G03DB06
ITALY	
PROGEFFIK	G03DA04
PRIMOLUT NOR	G03AC01
PROMETRIUM	G03DA04
LUTENYL	G03AA14
DUPHASTON	G03DB01
VISANNE	G03DB08
DEPO PROVERA	G03AC06
PRONTOGEST	G03DA04
LENTOGEST	G03DA03
CRINONE	G03DA04
PROLUTON	G03DA03
LUTOGIN	G03DA04
COLPRONE	G03DA03
NOMEGESTROL FIN	G03DB04
PROGESTOGEL	G03DA04
GESTANON	G03DC01
PROGESTERONE L.U.	G03DA04
NETHERLANDS	
UTROGESTAN	G03DA04
ORGAMETRIL	G03DC03
PRIMOLUT NOR	G03AC01
DEPO PROVERA	G03AC06
DUPHASTON	G03DB01
ULTROGESTAN	G03DA04
PROGESTAN	G03DA04
SPAIN	
PROGEFFIK	G03DA04
UTROGESTAN	G03DA04
PRIMOLUT NOR	G03AC01
DARSTIN	G03DA04
PROGEVERA	G03AC06
VISANNE	G03DB08
ORGAMETRIL	G03DC03
ESOLUT	G03DA04
CRINONE	G03DA04
COLPRONE	G03DA03
DUPHASTON	G03DB01
PROLUTON	G03DA04
UK	
NORETHISTERON L.U.	G03AC01

DRUG NAME	**ATC CODE**
UTOVLAN	G03AC01
DEPO PROVERA	G03AC06
PRIMOLUT NOR	G03AC01
UTROGESTAN	G03DA04
CYCLOGEST	G03DA04
UTROGESTAN VAGINAL	G03DA04
GESTONE	G03DA04
CRINONE	G03DA04
CLIMANOR	G03AC06
DUPHASTON	G03DB01
ADGYN MEDRO	G03AC06
MICRONOR	G03AC01/G03DC02
NORETHISTERONE SDZ	G03AC01
PROGESTERONE L.U.	G03DA04
PROLUTON	G03DA04
NORETHISTERONE WOK	G03AC01
MEDROXYPROGES L.U.	G03AC06
MENZOL	G03AC01
NORETHISTERONE HCR	G03AC01
NORETHISTERONE ATV	G03AC01