A Comparative Observational Study Evaluating the Incidence Rate of Endometrial Cancer in Women aged 50 Years and Over Who Use Low dose Vaginal Estrogen Unopposed by a Progestogen: A Post-authorization Safety Study in the United States and Sweden (Low dose vaginal estrogen and endometrial cancer)

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Last updated: 11/12/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS45602

Study ID

47017

DARWIN EU® study

No

Study countries

- [ ] Sweden
- [ ] United States

Study description

This study is a retrospective cohort study utilizing a longitudinal US healthcare claims data source (HealthCore Integrated Research Database HIRD) and longitudinal data collected from linked Swedish National Registers. The study includes women aged >=50 years with an intact uterus and no prior use of vaginal estrogens. The three exposed treatment groups are new users of unopposed low-dose vaginal estrogen (LDVE), unopposed moderate-dose vaginal estrogen (MDVE), and unopposed high-dose Premarin VC (HDVC) in US only (regardless of other use of prior hormone therapy). The two comparator groups are non-users of vaginal estrogen who are women over age 50 with at least one gynecological visit without prior or current use of vaginal estrogen at the time of the gynecological visit but, regardless of their prior use of hormone therapy, and E+P HT new users with no prior use of hormone therapy. Diagnosis of endometrial cancer will be identified in the US using codes that have been validated in the HIRD, and in Sweden using records in the Swedish Cancer Register. Covariates will include patient demographics, comorbidities, medications, and healthcare utilization. In the primary analysis, adjusted hazard ratios (HRs) will be calculated using Cox proportional hazards models to compare the hazard of endometrial cancer between 1) unopposed LDVE and non users of vaginal estrogen, 2) unopposed MDVE and non-users of vaginal estrogen, 3) unopposed HDVC with non-users of vaginal estrogen (US only).

Study status

Ongoing

Research institutions and networks

Institutions

HealthCore

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Institution

Carelon Research

Contact details

Study institution contact

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Primary lead investigator

Li Wang

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 01/03/2019

Actual: 16/09/2019

Study start date
Planned: 01/04/2022

Actual: 01/05/2022

Date of final study report
Planned: 31/10/2023

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Pfizer

Study protocol

B2811020_PFI_EST_PVC Protocol Version 7 Final CLEAN sv5 01.04.22.pdf (1.28 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Study design:

This is a non-interventional, retrospective cohort study among women aged ≥50 years using a US
healthcare claims data source (the HIRD) and longitudinal data collected from five Swedish
National Registers. The three exposed groups are new users of vaginal estrogen grouped into 3
dose categories.

Main study objective:

Estimate and compare IR of endometrial cancer in postmenopausal women aged >50 years with a uterus regardless of prior hormone therapy (any estrogen, progestin, E+P HT or opposed estrogen hormone therapy) in the following groups: a. New users of LDVE vs. non-users of vaginal estrogen b. New users of MDVE vs. non-users of vaginal estrogen c. New users of HDVC vs. non-users of vaginal estrogen

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

PREMARIN

ESTRING

VAGIFEM

Medicinal product name, other

Oestring, Yuvafem, Imvexxy

Anatomical Therapeutic Chemical (ATC) code

(G03CA03) estradiol

estradiol

(G03CA57) conjugated estrogens

conjugated estrogens

Medical condition to be studied

Endometrial cancer metastatic

Endometrial cancer recurrent

Endometrial cancer stage 0

Endometrial cancer stage I

Endometrial cancer stage II

Endometrial cancer stage III

Endometrial cancer stage IV

Endometrial cancer

Population studied

Short description of the study population

The study includes women aged >50 years with an intact uterus and no prior use of vaginal estrogens. The exposed group of LDVE will include new users who had ≥1 dispensing of LDVE (daily doses ≤10 mcg/day estradiol or ≤0.3 mg/day conjugated estrogen) unopposed by a progestogen, regardless of prior use of other hormone therapy between 01 January 2007 and 31 December 2020 (or most recent available date) in the HIRD, and between 01 July 2007 to 31 December 2019 (or most recent available date) in the Swedish National Registers (the exposure ascertainment period). Similarly, two additional exposure groups will be created for MDVE (daily doses >10 mcg – 25 mcg/day estradiol or >0.3 mg – 0.45 mg/day conjugated estrogen) and, in the HIRD only, HDVC (daily doses >0.45 mg/day conjugated estrogen). These two additional groups will also include women with ≥1 dispensing of MDVE or HDVC, respectively, regardless of prior use of hormone therapy. The difference in study periods between the HIRD and Swedish databases is due to the difference in lag time for data availability
between the two data sources. The comparator groups are: (1) women with ≥1 gynecological visit on or after age 50 with no prior use of vaginal estrogen at the time of their gynecological visit (i.e., non-users) and (2) new users of E+P HT with no prior use of hormone therapy. Women with less than 12 months of continuous health plan enrollment in the HIRD or less than 24 months of medical history in Sweden prior to the index date, without a uterus, or with a history of endometrial cancer will be excluded.

Age groups

- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)

- Adults (85 years and over)

Estimated number of subjects

152941

Study design details

Setting

The study population consists of women in the HIRD and Sweden who are at least 50 years of age. For subjects using a vaginal estrogen or E+P HT, cohort qualification status will be assessed for the first study drug dispensing (index date) during the exposure ascertainment period (see Table 1) based on the inclusion and exclusion criteria described below. For the purpose of the primary objective, non-users of vaginal estrogen, subjects with at least one gynecological visit after age 50 and without any prior or current use of vaginal estrogens at the time of their gynecological visit (index date for non-users) will be included in this population regardless of their prior use of hormone therapy. Subjects may have multiple qualifying gynecological visits. For the purpose of the secondary
objective, E+P HT new users with no prior use of hormone therapy will be included.

Outcomes

The endpoint is the occurrence of endometrial cancer. In the United States, the cases of endometrial cancer will be identified using a validated algorithm in the United States and using the Swedish Cancer Register in Sweden.

Data analysis plan

Propensity score matching will be applied to each cohort pair (comparison) with a 1:4 exposed:comparator matching ratio. Propensity scores will be estimated

separately for each comparison, using logistic regression and a set of baseline covariates. Descriptive statistics and all additional analyses will be performed on the PS-matched cohorts. Baseline characteristics will be compared across the study cohorts to assess comparability. The IR of endometrial cancer and 95% confidence intervals (CIs) will be computed for each study cohort. Adjusted hazard ratios (HRs) will be calculated using Cox proportional hazards models to compare the hazard of endometrial cancer between 1) unopposed LDVE and non-users, 2) unopposed MDVE and non-users, 3) unopposed HDVC with non-users (US only).

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Sweden National Prescribed Drugs Register / Läkemedelsregistret

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Data source(s), other

HealthCore Ingegrated Research DatabaseSM HIRD United States, Swedish National Register Sweden, Swedish Cancer Registry Sweden, Cause of Death Registry Sweden, Total population register Sweden

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Data sources (types)

Administrative healthcare records (e.g., claims)

Other

Data sources (types), other

The HIRD is a longitudinally integrated research database comprising automated payment claims for healthcare encounters. The Swedish registry data include five large, nationally held registers: the Swedish NPR, the Swedish Prescribed Drug Register (SPDR), the Swedish Cancer Register (SCR), the Cause of Death Registry, and the Total Population Register (TPR).

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No