

# VAG-4602: Vaginal estradiol tablets (Vagifem®) and endometrial cancer risk in the treatment of postmenopausal vaginal atrophy: A register-based cohort study in postmenopausal women

**First published:** 17/01/2022

**Last updated:** 15/01/2025

Study

Finalised

## Administrative details

### EU PAS number

EUPAS44951

### Study ID

50379

### DARWIN EU® study

No

### Study countries

☐ Denmark

☐ United States

## Study description

The study will include data from a nationwide Danish cohort of postmenopausal women and the United States of America (US) cohort of postmenopausal women. The Danish nationwide cohort will be established through linkage of Danish national patient registries. The US cohort will be established based on data from US claims database, Truven. The aim of this study is to evaluate whether exposure to Vagifem® increases the rate of endometrial cancer in postmenopausal women.

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## Study status

Finalised

## Research institutions and networks

### Institutions

[Novo Nordisk](#)

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Institution

[North Zealand hospital Denmark, Truven Health  
MarketScan United States](#)

### Contact details

**Study institution contact**

Clinical Transparency (dept. 2834) Novo Nordisk A/S  
pactadmin@novonordisk.com

Study contact

[pactadmin@novonordisk.com](mailto:pactadmin@novonordisk.com)

**Primary lead investigator**

Clinical Transparency (dept. 2834) Novo Nordisk A/S

Primary lead investigator

## Study timelines

**Date when funding contract was signed**

Planned: 10/12/2021

Actual: 10/12/2021

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**Study start date**

Planned: 31/05/2022

Actual: 15/01/2022

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**Date of final study report**

Planned: 31/12/2023

Actual: 04/03/2024

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## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Novo Nordisk A/S

## Study protocol

[VAG-4602 16-1-01 protocol eu-pas-reg redacted.pdf](#) (616.05 KB)

## Regulatory

### Was the study required by a regulatory body?

No

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

Not applicable

## Methodological aspects

### Study type

### Study type list

#### Study topic:

Human medicinal product

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#### Study type:

Non-interventional study

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**Scope of the study:**

Disease epidemiology

**Main study objective:**

The aim of this study is to evaluate whether exposure to Vagifem® increases the rate of endometrial cancer in postmenopausal women.

## Study Design

**Non-interventional study design**

Cohort

## Study drug and medical condition

**Medicinal product name, other**

Vagifem, Other LDVE product

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**Study drug International non-proprietary name (INN) or common name**

ESTRADIOL

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**Anatomical Therapeutic Chemical (ATC) code**

(G03CA03) estradiol

estradiol

## Population studied

**Age groups**

- Adults (46 to < 65 years)
  - Adults (65 to < 75 years)
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### **Estimated number of subjects**

500000

## **Study design details**

### **Outcomes**

The primary objective is to investigate the hypothesis that there is no difference in risk of endometrial cancer between women using low dose vaginal estrogens (LDVE) (split into Vagifem® and other LDVE products) and women using no hormone replacement therapy to manage symptoms related to the postmenopausal phase. The secondary objective is to compare the rate of endometrial cancer for women exposed to Vagifem® 10 mcg and 25 mcg, respectively, with women that have been exposed to systemic cyclic HRT (defined as estrogen taken daily and progestogen taken in a cyclic pattern for 10 to 14 days of the month) or oral, transdermal and opposed injectable systemic HRT products.

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### **Data analysis plan**

The main statistical analysis will compare patients initiating LDVE (new users), split into Vagifem® and other LDVE, in the study period in a 1:2 ratio with non-users, in an intention to treat fashion, i.e. the patient will be considered at risk after initiation of treatment regardless of treatment discontinuation. Propensity score matching methods will be employed involving the available risk factors, including previous use of HRT. The IR and the 95% confidence intervals will be presented both for the exposure groups and the comparator group. Hazard Ratio and 95% confidence interval will be estimated using a Cox proportion

hazard rate model. For the secondary objective, the same methods will be used, with users of systemic cyclic HRT and oral, transdermal and opposed injectable systemic HRT products in the comparator group rather than non-users. A range of sensitivity analyses will be performed.

## Documents

### Study report

[4602 nsr eu-pas-reg redacted.pdf](#) (1.28 MB)

## 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)

Danish registries (access/analysis)

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### Data source(s), other

Truven health marketscan United States

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### Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Other

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### **Data sources (types), other**

Prescription event monitoring

## Use of a Common Data Model (CDM)

### **CDM mapping**

No

## Data quality specifications

### **Check conformance**

Unknown

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### **Check completeness**

Unknown

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### **Check stability**

Unknown

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### **Check logical consistency**

Unknown

## Data characterisation

### **Data characterisation conducted**



No