International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)

First published: 05/01/2023

Last updated: 20/06/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS49984

Study ID

49985

DARWIN EU® study

No

Study countries

- Czechia
- Germany
- Hungary
- Italy

Poland

Spain

Sweden

United Kingdom

United States

Study description

The primary objective of the study is to characterize and compare the risks of E4/Drospirenone (DRSP) with levonorgestrel-containing combined oral contraceptives (EE/LNG) in a study population that is representative of the actual users of these preparations.

The main clinical outcome of interest is: venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE).

Secondary objectives include measuring the occurrence of unintended pregnancy, assessing the risk of arterial thromboembolism (ATE), describing the drug utilization pattern, describing the baseline risk profile for VTE and ATE, and investigating outcomes associated with fetal exposure to E4/DRSP.

Study status

Ongoing

Research institutions and networks

Institutions

Berlin Center for Epidemiology & Health Research, ZEG Berlin

Germany

First published: 06/08/2019

Last updated: 20/06/2024

Institution | Laboratory/Research/Testing facility | ENCePP partner

Gedeon Richter

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Klaas Heinemann

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 01/07/2022

Study start date
Planned: 31/03/2023

Actual: 29/06/2023

Data analysis start date
Actual: 01/03/2024

Date of interim report, if expected
Planned: 23/06/2023

Actual: 21/06/2024

Date of final study report
Planned: 30/06/2029

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Gedeon Richter Plc

Gyömrői út 19-21

1103 Budapest

Hungary

Study protocol

NEES_EMAProtocol_V04-00_signed.pdf (18.11 MB)

Regulatory

Was the study required by a regulatory body?

Yes

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

EU RMP category 3 (required)

Other study registration identification numbers and links

ClinicalTrials.gov: NCT06028555

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Evaluation of patient-reported outcomes

Data collection methods:

Primary data collection

Study design:

Multinational, comparative, prospective, active surveillance study that follows two cohorts.

The cohorts consist of new users (starters and restarters) of two different groups of hormonal contraceptives: E4/DRSP and EE/LNG.

The study is taking a non-interventional approach.

Main study objective:

The primary objective of the study is to characterize and compare the risks of E4/DRSP with EE/LNG, in a study population that is representative of the actual users of these preparations.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

DROVELIS

LYDISILKA

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

DROSPIRENONE

ESTETROL

Anatomical Therapeutic Chemical (ATC) code

(G03AA18) drospirenone and estetrol

drospirenone and estetrol

(G03AA18) drospirenone and estetrol

drospirenone and estetrol

Medical condition to be studied

Atrial thrombosis

Deep vein thrombosis

Pulmonary embolism

Unintended pregnancy

Congenital anomaly

Pulmonary embolism

Population studied

Short description of the study population

Approximately 101,000 study participants (50,500 estetrol (E4)/drospirenone (DRSP) and 50,500 ethinyl estradiol (EE)/levonorgestrel (LNG) new users) will be recruited via a network of COC-prescribing health care professionals in Europe and the USA.

All new users (starters and restarters) prescribed E4/DRSP or EE/LNG who are willing to participate may be eligible for enrolment in the study.

Age groups

- Adolescents (12 to < 18 years)
- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)

        - Adults (46 to < 65 years)
    - Elderly (≥ 65 years)
        - Adults (65 to < 75 years)
        - Adults (75 to < 85 years)
        - Adults (85 years and over)

Special population of interest

Women of childbearing potential using contraception

Estimated number of subjects

101000

Study design details

Setting

Study participants will be enrolled via an international network of COC-prescribing health care professionals (HCPs) and then followed up for one to two years.

All outcomes of interest will be captured by direct contact with the study participants.

Reported outcomes of interest will be validated via attending physicians and relevant source documents.

The classification of outcomes of interest into ‘confirmed’ and ‘not confirmed’ will be verified by blinded independent adjudication. Approximately 101,000 study participants (50,500 E4/DRSP and 50,500 EE/LNG new users and re-starters) will be recruited via a network of COC-prescribing health care professionals in Europe and the USA.

All new users (starters and restarters) prescribed E4/DRSP or EE/LNG who are willing to participate may be eligible for enrolment in the study.

The variable to determine the primary endpoint is the occurrence of a new VTE (DVT of the lower extremities and PE) during follow-up, which will be compared between E4/DRSP and EE/LNG users.
Variables to determine the secondary endpoints include the occurrence of unintended pregnancies, ATE, and outcomes associated with foetal exposure to E4/DRSP.
Variables to characterize the baseline risk profile of users are baseline population characteristics,
socio-economic factors, parameters of reproductive, contraceptive, and medical history, and concomitant medication.
This is a field study that entails exposure to COCs and the occurrence of clinical outcomes of interest by completing questionnaires at baseline (study entry) and follow-up (at 6-, 12-, 18-, and 24-months post-baseline), in addition to potential confounding factors and potential effect modifiers.
Medical confirmation of the occurrence of a clinical outcome of interest will be sought from the attending HCP and/or study participant (e.g., diagnostic report, discharge letter).

Outcomes

The main clinical outcome of interest is venous thromboembolism (VTE), i.e. deep venous thrombosis (DVT) of the lower extremities and pulmonary embolism (PE).
Secondary objectives include measuring the occurrence of unintended pregnancy, assessing the risk of arterial thromboembolism (ATE), describing the drug utilization pattern, describing the baseline risk profile for VTE and ATE, and investigating outcomes associated with fetal exposure to E4/DRSP.

Data analysis plan

The final analyses will include both an “as-treated” (AT) and an “intention-to-treat” (ITT) analysis.

All eligible women will be assigned to the ITT and AT population at baseline. Only women with follow-up information will be considered for longitudinal analysis.
Women who never started their prescribed baseline medication will be considered in the ITT analysis but excluded from the AT analysis.
Population characteristics, e.g. socio-economic factors, parameters of reproductive, contraceptive history, and medical history, will be summarized descriptively and used to estimate the probability of treatment differences.
Inverse probability of treatment weighting combined with time-to-event analysis of VTE will be carried out based on the extended Cox model to calculate hazard ratios (HR) with 95% confidence intervals.
The null hypothesis to be tested is HR of VTE ≥1.5 (i.e. the VTE HR for E4/DRSP vs. EE/LNG is higher than or equal to 1.5). The alternative hypothesis is HR of VTE<1.5.

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.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

NEES_ENCePP_DeclarationOfInterest_Annex5_signed.pdf (551.93 KB)

Composition of steering group and observers

NEES_SEECS_SMACMembers_V00-01.pdf (23.5 KB)

Data sources

Data source(s)

Other data source

Data source(s), other

Electronic patient-reported outcome questionnaires at baseline and four follow-up questionnaires at 6, 12, 18 and 24 months; electronic medical records

Data sources (types)

Death registry

Electronic healthcare records (EHR)

Non-interventional study

Patient surveys

Spontaneous reports of suspected adverse drug reactions

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after creation of study variables