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

First published: 05/01/2023

Last updated: 23/04/2024

Study Planned

Administrative details

PURI

https://redirect.ema.europa.eu/resource/49985

EU PAS number

EUPAS49984

Study ID

49985

DARWIN EU® study

No

Study countries

☐ Brazil

- [ ] Czechia
- [ ] France
- [ ] Germany
- [ ] Hungary
- [ ] Italy
- [ ] Poland
- [ ] Spain
- [ ] United Kingdom
- [ ] United States

Study description

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.This includes an estimate of the absolute risk of rare serious adverse 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 foetal exposure to E4/DRSP. It is a 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 to provide comprehensive information on these treatments in a routine clinical practice 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) will be recruited via a network of COC-prescribing health care professionals in Europe, the USA, and Brazil. 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.

Study status

Planned

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**

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

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

Date of final study report
Planned: 22/06/2029

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Estetra SRL

Study protocol

INAS-NEES_EMAProtocol_V04-00_20220908.pdf(990.29 KB)

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)

Methodological aspects

Study type

Study type list

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

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

Anatomical Therapeutic Chemical (ATC) code

(G03AA18) drospirenone and estetrol

drospirenone and estetrol

Medical condition to be studied

Atrial thrombosis

Deep vein thrombosis

Pulmonary embolism

Venous thrombosis

Myocardial infarction

Cerebrovascular accident

Unintended pregnancy

Congenital anomaly

Population studied

Age groups

Adolescents (12 to < 18 years)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Estimated number of subjects

101000

Study design details

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 foetal 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

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 sources (types)

Other

Data sources (types), other

Prospective patient-based data collection

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