Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17ß-estradiol (1.5mg) (PRO-E2)

First published: 25/01/2012

Last updated: 02/07/2024

Study | Finalised

Administrative details

EU PAS number

EUPAS2196

Study ID

41500

DARWIN EU® study

No

Study countries

- ☐ Australia
- ☐ Austria
- ☐ Colombia

- [ ] France
- [ ] Germany
- [ ] Hungary
- [ ] Italy
- [ ] Mexico
- [ ] Poland
- [ ] Russian Federation
- [ ] Spain
- [ ] Sweden

Study description

NOMAC-E2 (‘Zoely®’) is a monophasic oral contraceptive containing a fixed dose of nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg) which is taken for 24 days followed by 4 days of placebo. The most relevant adverse clinical outcome that has been linked to the use of COCs is venous thromboembolism (VTE). Data from randomized clinical trials did not show any serious health concerns for NOMAC-E2. However, the statistical power to detect rare adverse events is limited in these studies. PRO-E2 is a large, prospective, controlled, long-term active surveillance study to investigate the safety of NOMAC-E2 with regard to venous thromboembolism, arterial thromboembolism, depressive disorders, cholelithiasis, inflammatory bowel disease, effects on short- and long-term fertility and pregnancy outcomes. This study follows the EURAS design methodology with some modifications due to country and product-specific characteristics. The outcomes of interest will be validated via the attending physicians. A multi-faceted follow-up procedure will ensure a low loss to follow-up rate. This study will involve women from Europe, Australia and Latin America who will be followed for up to 2 years. Data analysis will include multivariable techniques such as Cox regression.

Study status

Finalised

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

Planned: 04/04/2011

Actual: 04/04/2011

Study start date
Planned: 01/02/2012

Actual: 18/07/2012

Date of final study report
Planned: 30/04/2021

Actual: 22/04/2021

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Merck Sharp & Dohme Corp. (60%) / Theramex (40%)

Study protocol

PRO-E2_Amendment 1 v 4_redacted.pdf (4.82 MB)

Regulatory

Was the study required by a regulatory body?

Yes

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

EU RMP category 1 (imposed as condition of marketing authorisation)

Methodological aspects

Study type

Study type list

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

Drug utilisation

Effectiveness study (incl. comparative)

Data collection methods:

Primary data collection

Main study objective:

To characterise and compare the risks of short- and long-term use of NOMAC-E2 with levonorgestrel-containing combined oral contraceptives (COC-LNG) in a study population that is representative of the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes (e.g. venous thromboembolism, arterial thromboembolism).

Study Design

Non-interventional study design

Cohort

Other

Non-interventional study design, other

Intensive monitoring schemes, multinational controlled prospective active surveillance study

Study drug and medical condition

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

ESTRADIOL

NOMEGESTROL ACETATE

Medical condition to be studied

Deep vein thrombosis

Pulmonary embolism

Arterial thrombosis

Depression

Cholelithiasis

Inflammatory bowel disease

Weight fluctuation

Hepatobiliary disease

Acne

Population studied

Short description of the study population

All starters and restarters of NOMAC-E2 or COCLNG who are willing to participate in the study are eligible for enrollment into the study.

Subjects were considered for enrollment in the PRO-E2 Study after the participating physician and the woman had determined that NOMAC-E2 or COCLNG use was appropriate. There were no specific medical

inclusion/exclusion criteria and no age restrictions (to fulfill the pediatric investigation plan (PIP) requirement in the EU). However, women who 1) were pregnant within 3 months before treatment initiation or 2) had a history of cancer/chemotherapy or an increased genetic risk for VTE at baseline were excluded from the main analysis of VTE.

Age groups

- Adolescents (12 to < 18 years)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)

Special population of interest

Women of childbearing potential not using contraception

Women of childbearing potential using contraception

Estimated number of subjects

101000

Study design details

Outcomes

The main clinical outcomes of interest for short- and long-term follow-up are venous thromboembolisms (VTEs), specifically: 1. Deep Venous Thrombosis of the lower extremities 2. Pulmonary Embolism, For NOMAC-E2 and COC-LNG users, describe, measure and compare: 1. All VTE 2. Arterial thromboembolism incidence rate (IR) 3. Depressive disorders IR 4. Cholelithiasis IR 5. Inflammatory Bowel Disease IR 6. Effect on short-/long-term fertility 7. Drug utilization patterns and baseline risks for clinical outcomes 8. Pregnancy outcomes 9. Weight change 10. Hepatobiliary disorders 11. Acne

Data analysis plan

Sample size considerations are based on the expected VTE incidence of COC-LNG (10 VTE per 10,000 woman years as requested by CHMP). It is expected that NOMAC-E2 is associated with a VTE risk that is not higher than with COC-LNG. A non-inferiority approach will be used to test hypotheses. Crude and adjusted hazard ratios will be calculated, with stratification of women into user categories (first-ever user, re-starter). The final decision on confounding variables will be made by the Safety Monitoring and Advisory Council. Similar analyses will be performed for all VTE, arterial thromboembolism (which includes acute myocardial infarction and cerebrovascular accidents), other secondary variables and other serious adverse events. A detailed analysis plan will be developed by the Principal Investigator during the first year after study start. The final analysis plan will be approved by the Safety and Monitoring Advisory Council before the first interim analysis of follow-up data.

Documents

Study results

PRO_E2 Final Report_Redacted.pdf (6.89 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.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

DoI_J Dinger_SDPP-2196 24Jul12.pdf (641.88 KB)

Composition of steering group and observers

PRO_E2_SMAC Membership for ENCEPP_Updated.pdf (6.48 KB)

SMAC Membership for ENCEPP registration.pdf (4.27 KB)

Signed code of conduct

CoC Declaration SDPP_2196.pdf (28.35 KB)

Signed code of conduct checklist

CoC Checklist SDPP_2196.pdf (187.42 KB)

Signed checklist for study protocols

Protocol Checklist SDPP_2196.pdf (161.92 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