International Active Surveillance study - Folate and Oral Contraceptive Utilization Study (INAS-FOCUS)

First published: 26/10/2010

Last updated: 30/01/2025

Study Finalised

Administrative details

EU PAS number

EUPAS1597

Study ID

36862

DARWIN EU® study

No

Study countries

- ☐ Canada
- ☐ Russian Federation
- ☐ Ukraine
- ☐ United States

Study description

Oral Contraceptives containing DRSP have been available since 1995. Numerous studies have supported and refuted the hypothesis that DRSP contraceptives have an increased risk of VTE compared with LNG containing OCs. The scientific debate regarding VTE risk is ongoing necessitating an additional PASS study in this field. In addition, whilst there is probably no impact of folate on VTE risk, robust clinical data is not available and therefore an investigation of the VTE risk associated with the combination of DRSP/EE is required.A 15-year follow-up phase was initially planned for INAS-FOCUS to examine the association between DRSP/EE+ and Colorectal cancer (CRC). Because of the rarity of CRC, the recruitments rates and exposure figures observed, strongly suggest that the assessment of the risk of CRC for this study will not have power to draw meaningful conclusions and a decision was made to discontinue the study after the cardiovascular results. An amended protocol and statistical analysis plan (SAP) was approved by Safety Monitoring and Advisory Council on 13th May, 2018. Details regarding Part II (colorectal cancer outcomes) have been removed from both the protocol and SAP. Colorectal cancer and other cancer outcomes will be analyzed as secondary outcomes. In addition, reference to a third cohort (DNG/EE+) was removed from the protocol as this oral contraceptive never came to market.

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

Juergen Dinger

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 01/04/2010

Actual: 14/05/2010

Study start date
Planned: 22/11/2010

Actual: 01/12/2010

Data analysis start date
Actual: 02/10/2019

Date of final study report
Planned: 31/03/2020

Actual: 19/08/2020

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Bayer Schering Pharmaceuticals

Study protocol

Protocol INAS-FOCUS.pdf(130.47 KB)

Protocol INAS-FOCUS_V02-00.pdf(295.78 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 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 assess the risks of short and long-term use of DRSP/EE plus 451mcg of metafolin and of established OCs in a study population that is representative for the actual users of the individual preparations. The main clinical outcomes are:1. Venous thromboemobolic events2. Acute myocardial infaction3.

Cerebrovascular Accidents

Study Design

Non-interventional study design

Cohort

Other

Non-interventional study design, other

Large, transatlantic, prospective, non-interventional, long-term cohort study, intensive monitoring schemes

Study drug and medical condition

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

DROSPIRENONE

DIENOGEST

ETHINYLESTRADIOL

FOLIC ACID

Medical condition to be studied

Thrombosis

Acute myocardial infarction

Ischaemic stroke

Oral contraception

Pregnancy on oral contraceptive

Population studied

Short description of the study population

The study participants are women who

• are new users of an OC (first ever use, recurrent use with and without pill break)

• are willing to participate in this long-term follow-up study Women will be categorized into three different groups depending on OC-user characteristics. These groups have been previously found to be important in assessing cardiovascular risk. The groups are defined as 1) OC starters (firsttime users), 2) recurrent users with a break (re-starters and switchers with a break) and 3) recurrent users without a pill-intake break.

There are no specific medical inclusion or exclusion criteria. However, women

• who are not cooperative/available for follow-up may be excluded from study participation

• with a language barrier will not be eligible for study inclusion

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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

80000

Study design details

Outcomes

The primary variable for inferential statistics is VTE. The null hypothesis to be tested is that the VTE hazard ratio for DRSP/EE/metafolin compared to established OCs is higher or equal to two.The risk of Cerebrovascular accidents will also be assessed and primary outcomes of interest with a similar non-inferiority design. Analyse the drug utilization patterns of OCs under routine medical conditionsCharacterise the baseline risk of users of individual formulationsEstablish risks of OCs in adolescent populationsInvestigate pregnancy related data on discontinuation of OCsCharacterise folate intake of users of OCsColorectal CancerOther Cancer entities

Data analysis plan

The study is designed to analyse rare and very rare events (less than 1/10,000WY). VTE and ATE prevalence estimates are based on the EURAS-OC results. A non-inferiority approach will be used for all hypothesis.Adjusted and Crude Hazard ratios will be provided for all primary outcomes with stratification of women into user categories (new, re-starter or switcher (with or without break). The adjusted model will be based on known risk factors for VTE and ATE.A detailed statistical 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 Monitoring and Advisory Council before the first interim analysis of follow-up data.

Documents

Study results

IFOC_FinalStudyReport_Public Version 20200819.pdf(2.87 MB)

Data management

ENCePP Seal

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

INAS-FOCUS_Conflict of Interest.pdf(11 KB)

Composition of steering group and observers

SMAC Members.pdf(9.7 KB)

Signed code of conduct

2010-0003-declaration_29.10.2010.pdf(39.14 KB)

Signed code of conduct checklist

2010-0003-annex2_29.10.2010.pdf(163.19 KB)

Signed checklist for study protocols

2010-0003-mcklist_29.10.2010.pdf(170.33 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