

# 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

### PURI

<https://redirect.ema.europa.eu/resource/36862>

### EU PAS number

EUPAS1597

### Study ID

36862

### DARWIN EU® study

No

### Study countries

☐ Canada

☐ Russian Federation

☐ Ukraine

☐ United States

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## **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.

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## **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

Clare Barnett

**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

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**Study start date**

Planned: 22/11/2010

Actual: 01/12/2010

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**Data analysis start date**

Actual: 02/10/2019

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**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

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## 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

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**Study type:**

Non-interventional study

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**Scope of the study:**

Assessment of risk minimisation measure implementation or effectiveness

Drug utilisation

Effectiveness study (incl. comparative)

**Data collection methods:**

Primary data collection

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**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 thromboembolic events2. Acute myocardial infarction3.

## Study Design

### **Non-interventional study design**

Cohort

Other

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### **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

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### **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)

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## **Special population of interest**

Women of childbearing potential not using contraception

Women of childbearing potential using contraception

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## **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 conditions Characterise the baseline risk of users of individual formulations Establish risks of OCs in adolescent populations Investigate pregnancy related data on discontinuation of OCs Characterise folate intake of users of OCs Colorectal Cancer Other Cancer entities

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## 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)

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## 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)

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### **Composition of steering group and observers**

[SMAC Members.pdf](#)(9.7 KB)

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### **Signed code of conduct**

[2010-0003-declaration\\_29.10.2010.pdf](#)(39.14 KB)

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### **Signed code of conduct checklist**

[2010-0003-annex2\\_29.10.2010.pdf](#)(163.19 KB)

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### **Signed checklist for study protocols**

[2010-0003-mcklist\\_29.10.2010.pdf](#)(170.33 KB)

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## **Data sources**

### **Data sources (types)**

[Other](#)

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### **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

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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