

# Retrospective Cohort Study on the Risk of Venous Thromboembolism with the use of combined oral contraceptives containing Chlormadinone Acetate/Ethinylestradiol and Levonorgestrel/Ethinylestradiol (RIVET-RCS)

**First published:** 14/04/2016

**Last updated:** 10/06/2024

Study

Finalised

## Administrative details

### EU PAS number

EUPAS12171

---

### Study ID

46024

---

### DARWIN EU® study

No

---

### Study countries

☐ Germany

---

## **Study description**

Rationale and background: The risk of venous thromboembolism (VTE) associated with the use of chlormadinone acetate (CMA) is currently unknown as the available data have significant limitations and lack data on direct comparison between levonorgestrel- (LNG) and CMA-containing combined oral contraceptives (COCs).

Study design: this is a retrospective cohort study and will be conducted as substitute for the RIVET-Case Control study, which was discontinued due to slow recruitment of both cases and controls. Following several attempts to enhance the recruitment in RIVET-CC, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency recommended a pooled analysis of 4 prospective cohort studies in order to clarify whether CMA/EE-containing COCs carry a different VTE risk compared to LNG/EE-containing COCs. Participants will be identified retrospectively from a pooled dataset which comprises four large, controlled, prospective, non-interventional active surveillance studies that focused on the risk of VTE associated with the use of combined oral contraceptives (LASS/EURAS-OC, INAS-OC, INAS-SCORE, INAS-FOCUS). All data were prospectively collected by ZEG Berlin and follow the EURAS/INAS study design. Inclusion and exclusion criteria, the method of patient recruitment and follow-up as well as research methods were similar across studies.

Gedeon Richter and its Collaborators requested this Study in agreement with the competent European regulatory authority and supports it by an unconditional grant to ZEG. Gedeon Richter and its Collaborators are not actively involved in the conduct of the Study.

---

## **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

Pauline De Corte [p.de-corte@zeg-berlin.de](mailto:p.de-corte@zeg-berlin.de)

**Study contact**

[p.de-corte@zeg-berlin.de](mailto:p.de-corte@zeg-berlin.de)

### Primary lead investigator

Klaas Heinemann

**Primary lead investigator**

## Study timelines

### Date when funding contract was signed

Planned: 21/07/2021

Actual: 09/05/2016

---

**Study start date**

Planned: 26/06/2009

Actual: 27/06/2016

---

**Data analysis start date**

Planned: 21/03/2022

Actual: 31/03/2022

---

**Date of final study report**

Planned: 30/09/2021

Actual: 19/12/2022

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Aristo Pharma, Dr.Kade, Gynial, Hormosan Pharma, Jenapharm, Kwizda Pharma, Meda Pharma, Mibe, Acis, Dermapharm, Sun-Farm, Mithra, Mylan, Gedeon Richter, Pfizer Austria, STADA,WH-Pharma, Zentiva Ph, Actavis, ITF Farmahealth, Sandoz, 1APharma, Hexal, Heaton

## 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 topic:**

Disease /health condition

---

**Study type:**

Non-interventional study

---

**Scope of the study:**

Assessment of risk minimisation measure implementation or effectiveness

**Data collection methods:**

Secondary use of data

---

**Main study objective:**

The objective of this study is to compare the VTE risk (i.e. deep venous thrombosis and/or pulmonary embolism) of users of COCs containing CMA 2mg to users of COCs containing LNG 0.15mg, both combined with EE 30µg.

## Study Design

**Non-interventional study design**

Cohort

## Study drug and medical condition

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

CHLORMADINONE

ETHINYLESTRADIOL

LEVONORGESTREL

---

## **Anatomical Therapeutic Chemical (ATC) code**

(G03AA07) levonorgestrel and ethinylestradiol

levonorgestrel and ethinylestradiol

(G03AA15) chlormadinone and ethinylestradiol

chlormadinone and ethinylestradiol

---

## **Medical condition to be studied**

Venous thrombosis

Embolism venous

## Population studied

### **Age groups**

Adolescents (12 to < 18 years)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

---

## **Estimated number of subjects**

124000

## Study design details

### **Outcomes**

The primary objective of this study is to assess the risk of venous thromboembolic events in the cohort of users of COCs containing 2 mg CMA/30 µg EE compared to 0.15 mg LNG/30 µg EE. The secondary objectives of this study are:

- to assess the risk of venous thromboembolic events stratified by COC user type, age, BMI
- to assess the risk of VTE in the sub-cohort of users of COCs

containing CMA compared to LNG both combined with  $\leq 30$   $\mu\text{g}$  EE.

- to characterize the baseline risk of users of the two formulations.

---

### **Data analysis plan**

Baseline characteristics, including reproductive, contraceptive, and medical history, will be summarized using descriptive statistics. Inferential statistics will be based on the Cox proportional hazards models. Crude and adjusted HRs between the two cohorts of interest – 2mg CMA/30 $\mu\text{g}$  EE and 0.15mg LNG/30 $\mu\text{g}$  EE – will be calculated with 95%-confidence intervals. Four prognostic factors for VTE – age, BMI, current duration of use, and family history of VTE – will be included as covariates in the Cox model.

## **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**

[Annex5\\_Declaration of interest \\_RivetCC\\_2016.pdf](#)(921.51 KB)

---

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

[SMAC\\_RIVET-CC\\_2016-04-14.pdf](#)(220.04 KB)

---

## **Signed code of conduct**

[2016-0039-DoC CoC-SDPP-12171.pdf](#)(65.32 KB)

---

## **Signed code of conduct checklist**

[2016-0039-Checklist CoC-SDPP-12171.pdf](#)(279.16 KB)

---

## **Signed checklist for study protocols**

[2016-0039-Checklist Protocol-SDPP-12171.pdf](#)(399.88 KB)

---

# Data sources

## **Data sources (types)**

[Other](#)

---

## **Data sources (types), other**

This study is designed as a retrospective cohort study. ZEG Berlin conducted several large prospective cohort studies on the risk of VTE associated with the use of hormonal contraceptives. Four of these studies included a substantial number of women using CMA/EE or LNG/EE-containing COCs: LASS/EURAS-OC, INAS-OC, INAS-FOCUS, INAS-SCORE.

# 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