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: 05/03/2026

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 chlormadinoe 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

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Last updated: 20/06/2024

Institution | **Laboratory/Research/Testing facility** | **ENCePP partner**

Contact details

Study institution contact

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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 type

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

EURAS/INAS studies are prospective, controlled, non-interventional, long-term cohort studies which followed two or more user cohorts of a hormonal medicine.

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

Short description of the study population

The following inclusion criteria were defined:

• Gender female

• Age 15 to 49 years

• Participation in one of the 4 observational studies conducted between 2000 and 2019

(LASS/EURAS-OC, INAS-OC, INAS-SCORE, INAS-FOCUS)

• COC new users (starters, switchers, and re-starters)

• Applied COCs: CMA/EE or LNG/EE

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 ≤30 µg 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/30µg EE and 0.15mg LNG/30µg 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.

Documents

Study results

RIVET-RCS_FinalStudyReport_V01-00_redacted.pdf (2.04 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

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