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

PURI
https://redirect.ema.europa.eu/resource/46024

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 institution 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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Primary lead investigator

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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 type list

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 data collection

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
100000095780
levonorgestrel and ethinylestradiol
100000125024
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 ?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/30?g EE and 0.15mg LNG/30?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

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