Retrospective **C**ohort **S**tudy on the **RI**sk of **VE**nous **T**hromboembolism with the Use of Combined Oral Contraceptives Containing Chlormadinone Acetate/Ethinylestradiol and Levonorgestrel/Ethinylestradiol **(RIVET-RCS)**

FINAL REPORT

PASS Information

Title	**R**etrospective **C**ohort **S**tudy on the **RI**sk of **VE**nous **T**hromboembolism Associated with the Use of Combined Oral Contraceptives Containing Chlormadinone Acetate/Ethinylestradiol and Levonorgestrel/Ethinylestradiol (RIVET-RCS)
Version Identifier of the Final Study Report	V01-00
Date of Last Version of the Final Study Report	19 December 2022
EU PAS Register Number	EUPAS12171
Active Substance	chlormadinone acetate (CMA), ethinylestradiol (EE)
Medicinal Product	Combined oral contraceptives (COCs) containing CMA 2 mg and EE 30 µg
Product Reference	N/A
Procedure Number	EMEA/H/A-31/1356
Marketing Authorization Holder(s)	Originator and Lead MAH: Gedeon Richter Plc Budapest, H-1103, Hungary Other MAHs funding the PASS listed in Annex 1.
Joint PASS	Yes
Research Question and Objectives	The main objective of this study was to compare the VTE risk (i.e., deep venous thrombosis and/or pulmonary embolism) associated with COCs containing CMA 2 mg to those containing levonorgestrel (LNG) 0.15 mg, both combined with 30 µg ethinylestradiol (EE) in a study population that is representative for the actual users of the individual preparations.
Country(-ies) of Study	Retrospective pooled analysis including data of four previously conducted large cohort studies following the active surveillance study methodology. An overview of the different studies and countries are listed in Table 1.
Authors	Klaas Heinemann, MD, PhD, MBA ZEG - Berlin Center for Epidemiology and Health Research, Invalidenstrasse 115, 10115 Berlin, Germany

Marketing Authorization Holder(s)

Marketing Authorization holder(s)	Gedeon Richter Plc. H-1103 Budapest Gyömrői út 19-21 Hungary
MAH Contact Person	Name: György Varga MD, PharmD Post-approval Research Lead, Medical and Scientific Evidence Generation, Global Medical Division, Gedeon Richter Plc. Tel.: [redacted] E-mail: [redacted]
Marketing Authorization Holder(s) – Generic Preparation	See Annex 1.

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1 ABSTRACT

Title

Retrospective Cohort Study on the Risk of Venous Thromboembolism Associated with the Use of Combined Oral Contraceptives Containing Chlormadinone Acetate/Ethinylestradiol and Levonorgestrel/Ethinylestradiol (RIVET-RCS).

Keywords

Venous Thromboembolism; Combined Oral Contraceptives; Pooled Analysis; Retrospective Cohort Study

Rationale and Background

The risk of venous thromboembolism (VTE) associated with the use of chlormadinone acetate (CMA) compared to the gold-standard progestin levonorgestrel (LNG) as a component of combined oral contraceptives (COC) is currently unknown. A large prospective case-control study (RIVET-CC) conducted in Germany and Austria was initially proposed in 2014 to compare the VTE risk in CMA 2 mg compared to LNG 0.15 mg users, both combined with ethinylestradiol (EE) 30 µg. Recruitment of both, cases and controls, started in 2016. After four years of recruitment, numbers of both, cases and controls, were still very low and the scientific value of the obtained data remained questionable. Following several unsuccessful attempts to enhance the recruitment in RIVET-CC, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended a retrospective cohort study (RIVET-RCS) instead, using a pooled dataset from four prospective cohort studies previously carried out by the Berlin Center for Epidemiology and Health Research (ZEG Berlin) to clarify whether CMA-containing COCs carry a different VTE risk compared to LNG-containing COCs. The RIVET-CC study was discontinued and instead the pooled RIVET-RCS was conducted.

Research Question and Objectives

The primary objective of the RIVET-RCS study was to compare the VTE risk (i.e., deep venous thrombosis and/or pulmonary embolism) associated with COCs containing CMA 2 mg to those containing LNG 0.15 mg, both combined with EE 30 µg in a study population that is representative for the actual users of the individual preparations. The primary analysis focused on excluding a twofold risk. Accordingly, the null hypothesis prior to the analysis was: HR>2 (i.e., the adjusted VTE hazard ratio for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg is higher than 2).

Comparison of COCs containing CMA and LNG, regardless of dosage, both combined with EE ≤30 µg or EE at any dosage were considered as secondary analysis populations. Stratification by age, body mass index (BMI) and COC user type, and characterization of baseline risk of users of the two formulations (lifetime history of co-morbidity, prognostic factors for VTE, socio-demographic, and lifestyle data) were analysed as secondary objectives. As an exploratory objective, VTE cases derived from RIVET-CC were used to describe population characteristics and to better understand underlying risk factors in comparison to the women diagnosed with a VTE in the pooled RIVET-RCS dataset.

Study Design

The RIVET-RCS study was designed as a retrospective cohort study.

Setting

The RIVET-RCS study included women with prescribed COCs at study entry for any indication.

Inclusion criteria:

- Gender female
- Age 15 to 49 years
- Participation in one of the four 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 (any dosage)

Exclusion criteria:

- Having a personal history of VTE

Variables and Data Sources

Eligible participants were identified retrospectively from a pooled dataset which comprised four large, controlled, prospective, non-interventional active surveillance cohort studies that focused on the risk of VTE associated with the use of combined oral contraceptives:
1) LASS/EURAS-OC, 2) INAS-OC, 3) INAS-SCORE, and 4) INAS-FOCUS. All data included for this pooled analysis were prospectively collected by ZEG Berlin between 2000 and 2019 and followed 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.

The primary outcome variable for the pooled analysis was the occurrence of a new venous thromboembolic event (VTE) during follow-up. The primary exposure variable was the time-varying exposure to COCs containing CMA 2 mg or LNG 0.15 mg, both combined with EE 30 µg, observed from study entry through the follow-up period. Variables used to characterize the baseline risk profile of users were baseline population characteristics, socio-economic factors, parameters of reproductive, contraceptive, and medical history.

Study Size

Power calculations were based on an assumed incidence rate of 9 VTE cases per 10,000 Women-Years (WY) for LNG-containing COCs. It was expected that COCs containing CMA are associated with a VTE risk that is not higher than the risk associated with LNG-containing COCs. The primary hypothesis was restricted to COCs containing CMA 2 mg and LNG 0.15 mg, both combined with EE 30 µg. A non-inferiority logrank test with an overall sample size of 58,000 WY (25,000 WY for CMA 2 mg/EE 30 µg and 33,000 WY for LNG 0.15 mg/EE 30 µg) achieves 80% power assuming: 1) a one-sided α of 0.05 and 2) a non-inferiority limit on a hazard ratio of 2.

Data Analysis

Baseline characteristics, including reproductive, contraceptive, and medical history, were summarized descriptively. The incidence rate of new VTE cases was determined per 10,000 WY during follow-up. Inferential statistics for primary and secondary analysis cohorts were based on the extended Cox model. Crude and adjusted Hazard Ratios (HR) were calculated with the 95%-confidence intervals. Four confounding factors for VTE – age, BMI, current COC duration of use, and family history of VTE – were included as covariates in the Cox model. In a sensitivity analysis, propensity-score (PS) subclassification was applied to balance baseline covariates between comparator cohorts in the stratified Cox model.

Results

In total, 31,379 study participants were identified to be exposed to either CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg and contributed to a total of 59,167 women-years of observation time for the primary exposure cohorts of interest. For the secondary exposure cohorts, a total of 52,890 study participants were exposed to either CMA/EE ≤30 µg or LNG/EE ≤30 µg (secondary exposure cohorts I) and a total of 59,102 were exposed to either CMA/EE or LNG/EE, independent from the specific dosage (secondary exposure cohorts II). The number of identified participants in the secondary cohorts I and II contributed to a total of 108,342 and 125,486 women-years (WY), respectively.

The primary analysis was based on 60 confirmed VTEs (i.e., deep venous thrombosis [DVT] of the lower extremities and pulmonary embolism [PE]): 25 in CMA 2 mg/EE 30 µg users (9.8 per 10,000 WY; 95% CI, 6.4–14.5), 35 in LNG 0.15 mg/EE 30 µg users (10.4 per 10,000 WY; 95% CI, 7.2–14.4). Crude and adjusted Cox models were performed. The crude model resulted in an HR for CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg of 0.93 (95% CI: 0.55–1.55). After adjusting for age, BMI, family history of VTE and current duration of use (expert model), the adjusted HR was 1.25 (95% CI: 0.72–2.14). Similar results were seen in the secondary analysis cohorts and sensitivity analyses.

Discussion

Baseline characteristics and cardiovascular risk factors at study entry were similar between the exposure cohorts.

The primary analysis could not find a statistically significant increased risk of VTE in users of CMA compared to users of LNG-containing COCs, however, a 2.0-fold risk of in users of CMA-containing COCs compared with users of LNG-containing COCs could not be excluded. This result was supported by several sensitivity analyses, including PS subclassification, which were performed to test validity of the model assumptions. The independent Safety Monitoring Advisory Council (SMAC) concluded that COCs containing 2 mg CMA combined with EE 30 µg do not expose users to a clinically important increased risk of VTE compared to users of COCs containing 0.15 mg LNG combined with EE 30 µg.

The RIVET-RCS study benefited from a large comparative study design which optimized the validity of the results within the framework of the inherent limitations of observational studies. Furthermore, data on important potential confounders were captured, outcomes of interest were validated, and VTEs were subjected to blinded adjudication by independent experts and the SMAC maintained scientific oversight for the duration of the study.

Conclusion

The study results could not exclude twofold VTE risk of CMA/EE (2 mg/30 µg) vs LNG/EE (0.15 mg/30 µg), the margin for claiming non-inferiority in this regard, which was determined by the agreement of the study's investigators and PRAC. However, considering all analyses performed on the dataset, the independent SMAC opined, that COCs containing CMA 2 mg combined with EE 30 µg do not expose users to a clinically important increased risk of VTE compared to users of COCs containing LNG 0.15 mg combined with EE 30 µg.

2 LIST OF ABBREVIATIONS

AE	adverse event
AMI	acute myocardial infarction
AS	active surveillance
AT	as treated
ATC	Anatomical Therapeutic Chemical Classification System
ATE	arterial thromboembolism
BMI	body mass index
CI	confidence interval
CMA	chlormadinone acetate
COC	combined oral contraceptives
CRO	clinical/contract research organization
DDD	defined daily dose
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information (German Institute for Medical Documentation and Information)
DRSP	drospirenone
DVT	deep venous thrombosis
ECG	electrocardiogram
EE	ethinylestradiol
EMA	European Medicines Agency
EU	Europe
EU PAS	European Union electronic Register of Post-Authorisation Studies
EURAS-OC	European Active Surveillance Study for Oral Contraceptives
FU	follow-up
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HC	hormonal contraceptive

HCP	healthcare practitioner/professional
HR	hazard ratio
ICD10	International Classification of Diseases
INAS-FOCUS	International Active Surveillance Study – Folate in Oral Contraceptives Utilization Study
INAS-OC	International Active Surveillance Study of Women Taking Oral Contraceptives
INAS-SCORE	International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens
IUD	intrauterine device
IR	incidence rate
LASS	long-term active surveillance study
LNG	levonorgestrel
LTFU	loss-to-follow-up
MAH	market authorization holder
MRI	magnetic resonance imaging
OC	oral contraceptive
OPS	operation and procedure coding list
PE	pulmonary embolism
PS	propensity score
PSA	propensity score analysis
PRAC	Pharmacovigilance Risk Assessment Committee
PV	pharmacovigilance
QPPV	qualified person responsible for pharmacovigilance
RCS	retrospective cohort study
RIVET-CC	Case Control Study on the Risk of Venous Thromboembolism
RIVET-RCS	Retrospective Cohort Study on the Risk of Venous Thromboembolism
RR	relative risk
SAE	serious adverse event

SAS	Statistical Analysis Systems
SMAC	Safety Monitoring and Advisory Council
USA	United States of America
VTE	venous thromboembolism
WHO	World Health Organization
WY	women-years
ZEG	Berlin Center for Epidemiology and Health Research Berlin (acronym for the German term "Zentrum für Epidemiologie und Gesundheitsforschung Berlin")

3 INVESTIGATORS

Klaas Heinemann, MD, PhD, MBA

Berlin Center of Epidemiology and Health Research (ZEG Berlin),
Invalidenstrasse 115,
10115 Berlin,
Germany.

4 OTHER RESPONSIBLE PARTIES

Originator and Lead Marketing Authorization Holder:

Gedeon Richter Plc.,
Gyömrői út 19–21,
Budapest, H-1103,
Hungary.

Other Marketing Authorization Holder(s) – Generic Preparation:

Listed in Annex 1.

Data Preparation and Statistical Analysis:

ZEG – Berlin Center for Epidemiology and Health Research (ZEG Berlin)
Invalidenstrasse 115
10115 Berlin
Germany

5 MILESTONES

The following table summarizes the main milestones since start of the initial planned case-control study (RIVET-CC) in 2014 until its discontinuation in 2022 and includes timelines for the approval and conduct of the pooled RIVET-RCS study, conducted in 2022.

Milestone	Planned date	Actual date	Study
Initial discussions conducting a case-control study to investigate the VTE risk between CMA and LNG between ZEG Berlin, MAHs and PRAC	September 2014	October 09, 2014	RIVET-CC
Final Protocol approval by PRAC	January 2016	January 12, 2016	RIVET-CC
Registration in the EU PAS register	April 2016	April 14, 2016	RIVET-CC
Start of data collection	May 2016	May 25, 2016	RIVET-CC
Interim Report I	January 2019	January 25, 2019	RIVET-CC
Interim Report II	January 2020	January 17, 2020	RIVET-CC
End of data collection	July 2021	April 15, 2022	RIVET-CC
Start of the PRAC protocol amendment procedure (RIVET-CC to RIVET-RCS)	April 2021	April 26, 2021	RIVET-CC/RIVET-RCS
PRAC approval of the RIVET-RCS study protocol	--	February 10, 2022	RIVET-RCS
Discontinuation of the RIVET-CC study	April 2022	April 15, 2022	RIVET-CC
Start of data preparation	Q1 2022	February 16, 2022	RIVET-RCS
End of data preparation	Q1 2022	March 31, 2022	RIVET-RCS
Update in the EU PAS registration	Q2 2022	February 28, 2022	RIVET-RCS
Final report of study results	Q4 2022	December 19, 2022	RIVET-RCS

6 RATIONALE AND BACKGROUND

Combined oral contraceptives (COCs) have evolved over the last 50 years, from a single product containing 10 mg of norethynodrel and 150 µg of mestranol, to a heterogeneous environment where numerous hormonal preparations containing different estrogen and progestin combinations are marketed to women for both contraceptive and non-contraceptive purposes. The general concern regarding the venous thrombotic risk of COCs has been widely discussed and investigated. Deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), is a blood clot either in the deep veins and/or an obstruction of blood vessels in the lung due to a blood clot embolized into the lung. Since the initial findings of very

high VTE risk of COCs with high estrogen doses, a substantial reduction of the dosage of ethinylestradiol (EE) has occurred, progressively leading to the modern low-dose COCs (containing 10–30 µg of estrogen). The common belief is that the estrogenic component displays the main determinant driving the risk of pro-thrombotic mechanisms. However, there have been ongoing intense discussions on whether the progestin component has an additional influence, and if so, whether the latter is varying between different types of progestins. From a research perspective, the progestin levonorgestrel (LNG) is considered to be the gold standard and is recommended as first-line therapy (1). Chlormadinone acetate (CMA) is a synthetic progestin that has been used for medicinal purposes for several decades. It has also been widely used as the progestin component in COCs. The VTE risk associated with the use of CMA compared to the use of other COCs is currently unknown as the available evidence has significant limitations and lacks data on a direct comparison between LNG- and CMA-containing COCs (both combined with EE).

Following the outcome of the Article 31 referral of Directive 2001/83/EC EMEA/H/A-31/1356 for COCs, the market authorization holders (MAH) for CMA-containing COCs were requested to carry out a post-authorization safety study (PASS) to compare the risk of VTE with CMA/EE versus LNG/EE, primarily focusing on CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg. In 2016, the MAHs in cooperation with the CRO ZEG Berlin initiated the RIVET-CC study (Risk of Venous Thromboembolism - The role of oral contraceptives - a case-control study comparing levonorgestrel and chlormadinone acetate. EUPAS12171), a prospective case-control study conducted in Germany and Austria following study participants directly using self-administered study questionnaires. It was aimed to recruit 5,524 VTE cases and approximately 22,000 matched controls (4 controls were matched per case based on gender, year of birth and region of residence) between 2016 and 2020. In a first progress report, published in June 2017, it was first highlighted that the accrual of both cases and controls was too slow to perform any scientifically meaningful analyses. Following several unsuccessful attempts to enhance the recruitment between 2017 and 2020, and after consultation with the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), an alternative retrospective study using a pooled analysis to compare the VTE risk between CMA and LNG users (RIVET-RCS) was approved in February 2022. The RIVET-CC study was discontinued in April 2022.

ZEG Berlin conducted several large prospective cohort studies on the risk of VTE associated with the use of hormonal contraceptives. In the following, four large prospective cohort studies, comprising a substantial number of women using COCs containing CMA or LNG in combination with EE were identified:

- **EURAS-OC** (NCT00302848)/**LASS** (NCT00676065): “European Active [Long-term] Surveillance Study for Oral Contraceptives”
- **INAS-OC** (NCT00335257): “International Active Surveillance Study of Women Taking Oral Contraceptives“
- **INAS-SCORE** (NCT01009684): “International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens”
- **INAS-FOCUS** (NCT01266408): “International Active Surveillance Study – Folate in Oral Contraceptives Utilization Study”

The EURAS-OC/LASS study was conducted in Europe only; the other three studies, INAS-OC, INAS-SCORE and INAS-FOCUS, were transatlantic studies that included participants from both Europe and the United States of America (USA). However, the methodology used in all four studies was similar: all studies were large, controlled, prospective, observational, and active surveillance (AS) studies that focused on the occurrence of self-reported and medically validated VTE associated with the use of hormonal contraceptives. Inclusion and exclusion criteria, the method of patient recruitment and follow-up, as well as data obtained (including prognostic factors for VTE), were similar across all four studies. Therefore, it was methodologically justified to combine the data of these studies for the pooled analysis. The pooled analysis was based on the final datasets of all included studies.

The methodological details of the individual studies and statistical methods used in RIVET-RCS are described in section 9 of this study report.

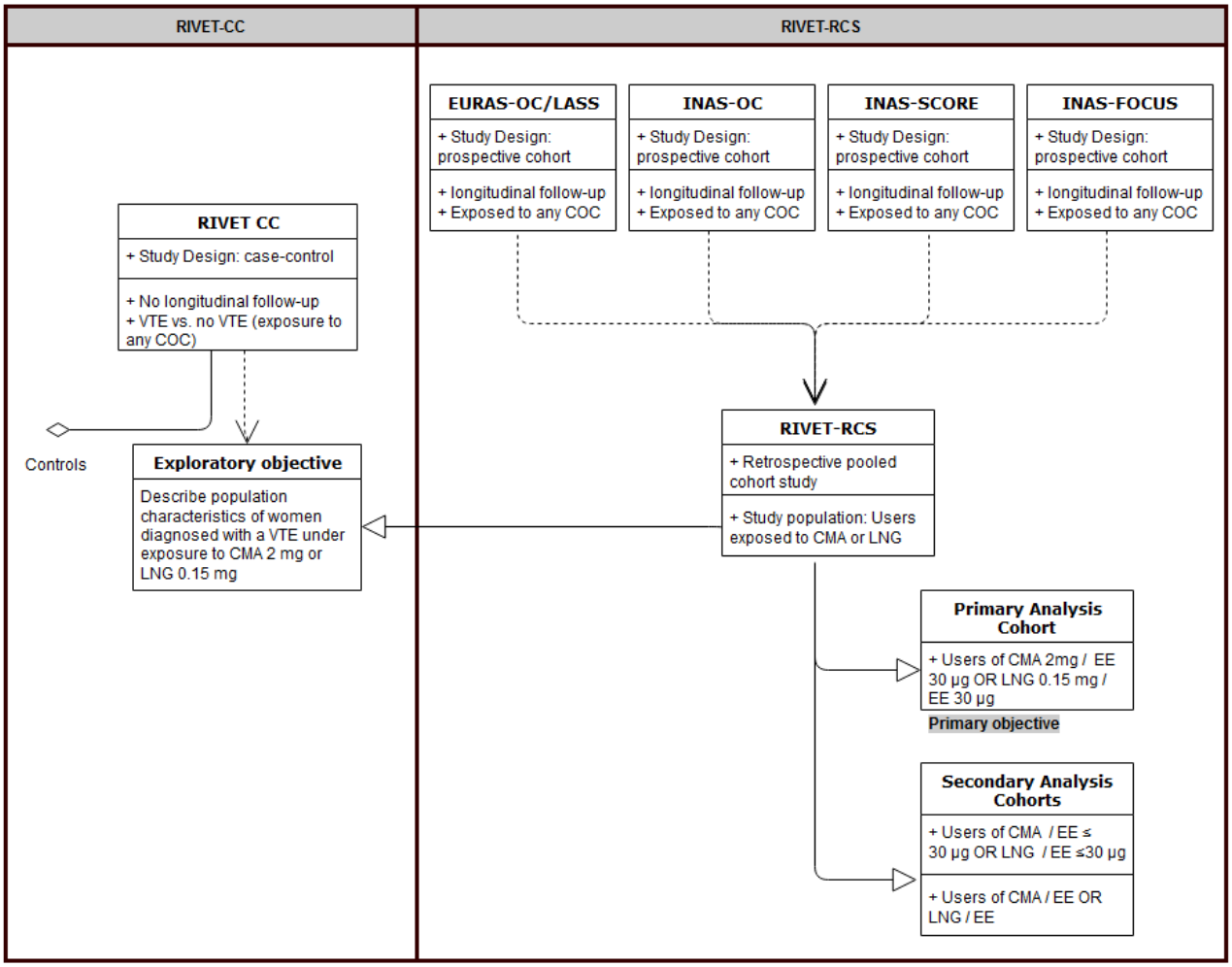
Power calculations showed that the sample of available women and women-years (WY) contributing to CMA or LNG exposure in the four selected studies was sufficient to compare the VTE risk between the treatment cohorts of interest. Similar to the RIVET-CC study design, the RIVET-RCS pooled analysis focused primarily on CMA 2 mg/EE 30 µg versus LNG 0.15 mg/EE 30 µg. Additionally, two secondary analyses were included comparing the VTE risk in users of 1) CMA/EE ≤30 µg vs. LNG/EE ≤30 µg and 2) CMA/EE vs. LNG/EE.

Lastly, the data obtained from the RIVET-CC study could not be used for the pooled analysis due to the different epidemiological nature of the collected data (case-control vs. cohort data). However, since the focus of RIVET-CC was specifically to include women being diagnosed with a VTE under exposure to CMA and LNG, data of a proportionate high number of confirmed VTE cases is available for comparison to the risk profile of VTE cases identified in a longitudinal study setting. Therefore, information of VTE cases derived from RIVET-CC were used to describe population characteristics and to better understand underlying risk factors in comparison to the women diagnosed with a VTE in the pooled dataset. Further details regarding the baseline comparison are outlined in section 9.8.1.

7 RESEARCH QUESTION AND OBJECTIVES

The objective of this study was to compare the VTE risk (i.e., deep venous thrombosis and/or pulmonary embolism) associated with COCs containing CMA to those containing LNG, both combined with EE, in a study population that is representative of the actual users of the individual preparations. Different dosages of CMA, LNG and EE were of interest in the respective primary and secondary objectives and were identified in RIVET-RCS. Additionally, findings from RIVET-CC were considered for exploratory reasons. The figure below provides a detailed overview of the two different studies, RIVET-CC and RIVET-RCS, and which information was used for selection of the analysis cohorts in this final report (Figure 1). More details on the primary, secondary and exploratory objectives can be found in the sections 7.1, 7.2, and 7.3 respectively.

Figure 1. Selection of analysis cohorts.



7.1 Primary Objective

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

The primary analysis focused on excluding a twofold risk. Accordingly, the null hypothesis prior to the analysis was: HR>2 (i.e., the adjusted VTE hazard ratio for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg is higher than 2). The a priori power of the pooled analysis to exclude a twofold VTE risk for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg was approximately 80% based on type-I error of 5% (one-sided).

7.2 Secondary Objectives

The secondary objectives of this study were:

- To assess the risk of venous thromboembolic events stratified by:

  - o COC user type (starter, switcher, re-starter)
  - o Age
  - o BMI

- To assess the risk of VTE in the cohort of users of COCs containing CMA compared to LNG both combined with ≤30 µg EE, and in users of COCs containing CMA compared to LNG both combined with EE at any dosage.
- To characterize the baseline risk of users of the two formulations (lifetime history of co-morbidity, prognostic factors for VTE, socio-demographic, and lifestyle data).

7.3 Exploratory Objective

To better understand the VTE study population exposed to CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg (primary) at time of the VTE diagnosis, population characteristics and distribution of risk factors of VTE cases recruited in the RIVET-CC study to the VTE patients observed in the pooled RIVET-RCS study were compared as an exploratory objective.

8 AMENDMENTS AND UPDATES

Amendment 1 of the RIVET-CC Study Protocol was initiated on 12 March 2018, further refined on 6 July 2018, and subsequently finalized on 14 September 2018 to incorporate feedback provided by the Pharmacovigilance Risk Assessment Committee in their Assessment Report of said Amendment 1 during its amendment procedure (EMEA/H/N/PSA/J/0030.1). The principal amendments to the study protocol included an expansion of recruitment to additional countries (Austria) and modifications to the study timelines. A substantial protocol amendment for change in study methodology for the RIVET-RCS study was initiated on 26 April 2021. A final RIVET-RCS protocol V01.02 was approved by PRAC on 10 February 2022. On 30 June 2022, the MAHs requested PRAC for an extension of timelines for submitting the final RIVET-RCS study report. A V01.03 protocol amendment was submitted which is the current protocol version. This amendment was endorsed by PRAC on 27 October 2022.

9 RESEARCH METHODS

9.1 Study Design

This study was designed as a retrospective cohort study (RCS). Participants were identified retrospectively from a pooled dataset that comprises four large, controlled, prospective, non-interventional active surveillance studies that focused on the risk of VTE associated with the use of COCs: EURAS-OC/LASS, INAS-OC, INAS-FOCUS, and INAS-SCORE. The data were prospectively collected by ZEG Berlin and followed 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. Sections 9.4.1.1 to 9.4.1.8 describe the methodological aspects of the single study designs included in the RIVET-RCS study in detail. An overview of the RIVET-RCS study design is given in the flowchart below (Figure 2).

As an additional exploratory objective, the risk profile of VTE cases exposed to CMA 2 mg or LNG 0.15 mg, both combined with EE 30 µg identified in RIVET-CC, was summarized to better describe the risk profile of women diagnosed with a VTE coming from the pooled dataset. Sections 9.4.2 to 9.4.2.5 provide more details on the RIVET-CC study design and selection of participants for the exploratory objective. Due to the epidemiological difference in nature of the collected data, data from the RIVET-CC study was not used for the pooled analysis and was used for descriptive aims only.

For scientific independence, the study methodology and statistical outputs of the (interim) study data were overseen by an independent committee of experts, the Safety Monitoring Advisory Council (SMAC). The SMAC reviewed the interim progress of the RIVET-CC and consequently progress on the RIVET-RCS pooled analysis every 6 to 12 months. The final results were presented to the SMAC on 9 September 2022.

9.2 Setting

Eligible study participants were identified retrospectively from a pooled dataset that comprised four large, controlled, prospectively maintained active surveillance (AS) studies that focused on the risk of VTE associated with the use of combined oral contraceptives (COCs). All data included for the pooled analysis were prospectively collected by ZEG Berlin and following the EURAS/INAS study design. Inclusion and exclusion criteria defined for the RIVET-RCS study are given in section 9.3.1 and 9.3.2

9.3 Study Population

9.3.1 Inclusion Criteria

The following inclusion criteria were defined:

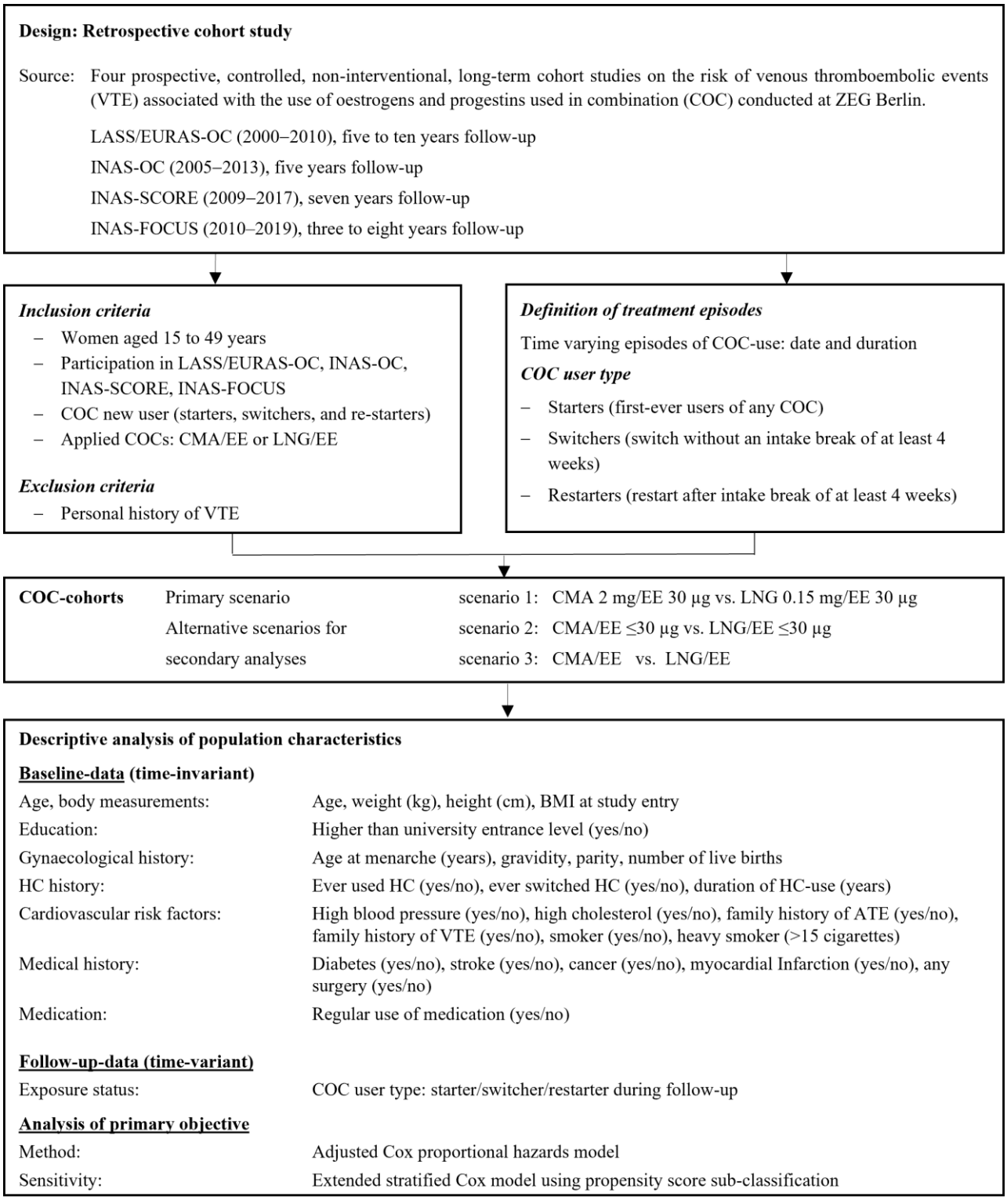
- Gender female
- Age 15 to 49 years
- Participation in one of the 4 observational studies conducted between 2000 and 2019 (LASS/EURAS-OC, INAS-OC, INAS-SCORE, INAS-FOCUS)
- COC new users (starters, switchers, and re-starters)
- Applied COCs: CMA/EE or LNG/EE

9.3.2 Exclusion Criteria

The main exclusion criterion was:

- Having a personal history of VTE.

Figure 2. Study flow chart.



9.4 Data Sources

9.4.1 EURAS-INAS

9.4.1.1 EURAS-INAS: 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. Recruitment and follow-up were based on a "non-interference"[1] approach to provide standardized, comprehensive, and reliable information that characterizes risk associated with hormonal therapies under real-world conditions. Regular, active contacts with the cohort members (active surveillance) provided all necessary information on health-related events or changes in health status during hormone use. The studies relied on self-reported events reported by participants which were subsequently validated by the study team and followed by a blinded adjudication process (Annex 2) through medical boards.

The EURAS/INAS study was designed to have minimal/no impact on the prescribing behaviour of HCPs or the individual needs of the participants. Considerable efforts were made to prevent study participation influencing prescribing practices.

Participants signed an informed consent form at baseline after reading a participant information sheet and discussing the study with the participating Healthcare Professional (HCP). It was the HCP's role to describe the study aims, its non-interventional character and the expected content of follow-up phase. Consent included permission to contact any treating HCP to follow up on specific safety outcomes. Participants were informed that the ZEG Berlin study team would contact them during the follow-up phase to ask a predefined set of safety related questions or to update contact information. Participants were informed in the Informed Consent that the information provided by the participants will serve as the basis for collecting scientific data.

At least two cohorts were defined at baseline, the target hormonal therapy (COC_{XY}) and comparator groups consisting of "other hormonal therapies" (OC_{other}). Recruitment was based on an 'all comer' recruitment process; HCPs may have enrolled any participants prescribed a new OC, regardless of estrogen and progestin composition. This 'non-selective' recruitment approach reduces the possibility of prescriber bias and is considered one of the most robust 'non-interventional' designs available. It results in the comparator group (COC_{other}) typically reflecting the general distribution of progestin and oestrogen OCs available on the market.

Once enrolled, participants may have discontinued or switched their hormonal therapy at any time. However, provided their informed consent was not withdrawn, they remained actively involved in the study. This prospective, observational approach created additional two cohorts during the study's follow-up phase; users who change their hormonal therapy to a non-oral hormonal method (e.g., implant, levonorgestrel releasing intrauterine device [LNG-IUD]) and users who stop using hormonal contraception during the follow-up period (no-use episodes).

[1] All participants who were new users of an OC were eligible for enrolment if they gave their informed consent and the physician's prescribing behavior was not influenced by quotas for specific OCs.

At baseline, participants were categorized into three main user groups; 1) starters defined as first-time users of hormonal medicines, 2) switchers defined as participants changing from one type of hormonal medicine to another and 3) re-starters defined as participants re-commencing hormonal medication after a no-intake period. The precise definition of user groups has shifted slightly over time. Lessons learned from previous EURAS/INAS study results have allowed slight adjustments to be made to the user definitions at baseline.

During follow-up, participants received a short questionnaire designed to capture patient-reported relevant clinical outcomes. Follow-up intervals were typically scheduled every 6–12 months. A self-administered participant questionnaire at short intervals is a very sensitive tool to report serious clinical outcomes. It is able to capture a much higher proportion of these outcomes than methods relying only on the prescribing gynecologists who often are not involved themselves in diagnosis and treatment of respective side effects like VTE. However, self-administered reports have poor specificity: there is a large difference between the rates of reported versus validated events, because laypersons often tend to misinterpret adverse events. Therefore, all patient-reported outcomes of interest were validated by contacting the treating physicians and by reviewing relevant source documents. Primary outcomes of interest were categorized as “confirmed” or “not confirmed” according to a predefined algorithm. At the end of the study this classification was verified by independent, blinded adjudication through specialized medical boards. A study specific overview of the specific features of each EURAS/INAS study design used in this pooled analysis can be found in Table 1.

Table 1. Overview of study details of studies selected for inclusion in RIVET-RCS.

	EURAS-OC/LASS	INAS-OC	INAS-SCORE	INAS-FOCUS
Design	Prospective, non-interventional cohort study	Prospective, non-interventional cohort study	Prospective, non-interventional cohort study	Prospective, non-interventional cohort study
Study Period	Nov 2000–Dec 2010	Aug 2005–Mar 2013	Aug 2009–Feb 2017	Nov 2010–Feb 2019
Cohorts (Baseline)[i]				
Target	DRSP	DRSP24d,	DNG/E2Val,	DRSP/EE+, DRSP-EE-
Comparator	LNG, Other OCs	DRSP21d, non-DRSP OCs	Other COCs	Other COCs

User Groups	First-ever users, switchers without an intake break and recurrent users*	Starters (first-ever users), switchers (users who switch preparations without an intake break of at least 4 weeks) and restarters (participants who restart OC use after an intake break of at least 4 weeks)	Starters (first-ever users), switchers (users who switch preparations with an intake break of less than 4 weeks) and restarters (users who restart COCs after an intake break of at least 4 weeks)	Starters (first-ever users), recurrent users with a break (re-starters and switchers with a pill intake break) and recurrent users without a break. A break is defined as the cessation of OC intake of at least one treatment cycle
Sample Size	47,799	85,100	50,203	82,882
Observation Time (WY)	318,784	206,296	145,224	197,452
Max. Follow-up	10 years	5 years	7 years	8 years
Setting	EURAS-OC: Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom LASS: Germany and Austria	USA, Austria, Germany, Italy, Poland, and Sweden	USA, Austria, France, Germany, Italy, Poland, Sweden, and the UK.	USA, Canada, Russia, Ukraine
Primary Outcomes	VTE, ATE	VTE, ATE	VTE, ATE	VTE, ATE
Secondary Outcomes	Unintended pregnancy, acute renal failure, hepatic diseases breast cancer (LASS)	Return to fertility, drug utilization	Unintended pregnancy, adolescents	Cancer, unintended pregnancy

*The explanations in parentheses (see all other studies) were not yet included in the LASS and EURAS-OC study. Therefore, they have not been included in the table either.[i] DRSP: drospirenone/ethinylestradiol-containing COCs; DRSP24: containing 24 'active' DRSP/EE pills and 3 'sugar' pills; DRSP21d: containing 21 active DRSP/EE pills and 7 'sugar' pills; DRSP/EE^{+}: containing DRSP/EE plus 451 mg of metafolin (L-5-methyltetrahydrofolate); DRSP/EE-: containing DRSP/EE without additional folate; DRSP/E2: containing drospirenone (0.5 or 2 mg) with 1 mg 17β-estradiol (E2); LNG: levonorgestrel-containing OCs; CMA: Chlormadinone-containing OCs.

9.4.1.2 EURAS-INAS: Loss-to-follow-up

A low loss to follow-up (LTFU) rate was essential for the validity of all studies. In order to minimize loss to follow-up a multi-faceted, four-level follow-up process was established.

Level 1 activities included mailing the follow-up questionnaire and, in case of no response, two reminder letters. If level 1 activities did not lead to a response, multiple attempts were made to contact the woman, her friends, relatives, and gynecologist/primary care physician per phone. In parallel to these level 2 activities, searches in national and international telephone and address directories as well as social networks were started (level 3 activities). If this was not successful, an official address search via the respective governmental administration was conducted (in some countries centralized, in others decentralized at community level). This level 4 activity usually provided information on a new address (or information that the respondent moved abroad or died).

Overall, the loss to follow-up rate was low (between 3–16%) in each of the four studies. In theory, a disproportionately high percentage of serious adverse events (SAEs) could have occurred in this segment of the study population, because SAEs could be the reason for the break in contact with the HCPs. This could bias the study results. For all cohort studies (including double-blind, randomized clinical trials), therefore, the loss to follow-up should be kept as low as possible.

However, under real-life study conditions, the loss to follow-up can never be reduced to zero. This is especially true for studies of hormonal therapy where a large share of women participates in such studies during a period of their lives that is marked by frequent major changes in circumstances (e.g., moving to another city as part of the transition from school to university, completing their education, marriage or change of partner). The EURAS/INAS design explicitly addresses this potential methodological weakness. Because the study team had direct contact with the participants, contact was not lost if the participants changed their gynecologists, e.g., due to change of residence or dissatisfaction with treatment and did not rely on the recruiting physician investing time in locating the participants when they did not attend a scheduled follow-up visit.

9.4.1.3 EURAS-INAS: Data Management

Data management procedures were identical for all studies. When questionnaires were received from participants, all pages were counted, and date stamped. Questionnaires were checked for correct subject identification number, missing pages, legibility, and incomplete information on the questionnaires. This information was requested from the participants prior to data entry of the respective questionnaire.

Data were entered by double data entry via formatted entry screens designed to reflect the appearance of the questionnaire.

In compliance with data privacy regulations, two different databases were used for data collection: an administrative database and the study database. Physician details and personal data from the participants were entered and maintained in the administrative database. The study database contained all data from the questionnaires including baseline data and all subsequent follow-ups.

Event data were derived from data entered in the study database. All disease diagnoses were coded using the ICD10 (International Classification of Diseases). Additional codes were used for data/events of specific interest (e.g., reasons for switching/stopping hormonal contraceptive use, VTE during pregnancy or delivery, outcomes of unintended pregnancies). Concomitant medication was coded using WHO ATC codes (World Health Organization Anatomical Therapeutic Chemical Classification System) for the studies INAS-SCORE and INAS-FOCUS and via use of the Rote Liste® for INAS-OC. Concomitant medication was not coded for EURAS-OC/LASS. Surgical procedures were coded using the modified operation and procedure coding list (OPS) provided by DIMDI (German Institute for Medical Documentation and Information).

Exposure data were used to identify the relevant cohorts and sub-cohorts for each exposure period (period of continuous use of one specific hormonal medication) for each participant. Simple data transformations were needed to calculate derived variables such as BMI and to display baseline and follow-up data in age categories or user cohorts, etc.

9.4.1.4 EURAS-INAS: Data Quality Assurance

The EURAS/INAS study design incorporated several quality assurance procedures in its design methodology. All studies complied with the Nuremberg Code, the Declaration of Helsinki, GPP (Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology in 2007) and GEP (Good Epidemiological Practice issued by the European Epidemiology Federation in 2007). Pharmacovigilance reporting processes aligned with either Volume 9A or, for studies running after 2012, GVP (Good Pharmacovigilance Practices).

Routine internal and external audits took place during study conduct. These included organizational aspects as well as source data verification. An additional site monitoring visit at the beginning of the study phase was also mandatory for all local field organizations new to the ZEG Berlin network.

Quality control of entered data was supported by SAS plausibility programs which included range, coding, missing and date checks as well as cross-reference (consistency) checks between variables.

All processes relevant for legal compliance of the study or the integrity of the data were subject to quality control measures. These included 1) development of study protocol, questionnaires, databases, and data entry screens, 2) data entry, 3) plausibility checks, 4) validation of clinical outcomes, 5) adverse outcome reporting, 6) data analysis, 7) report writing, 8) publication of results, 9) archiving of study materials.

9.4.1.5 EURAS-INAS: Inclusion and Exclusion Criteria

An explicit aim of the EURAS/INAS study methodology was the characterization of risk associated with use of medicines in a real-world setting. Therefore, inclusion and exclusion criteria were minimized, and HCPs were encouraged to include all participants seeking a new prescription for an eligible medication. All studies – EURAS-OC/LASS, INAS-OC, INAS-SCORE, and INAS-FOCUS had similar inclusion and exclusion criteria.

Inclusion criteria:

- New users of an OC

AND

- Are willing to participate in a long-term follow-up study.

Exclusion criteria:

- Language barrier that prevents study participation.
- Concurrent participation in another EURAS/INAS study.

Participants could participate in one EURAS/INAS study at any given time. To reduce the possibility of duplicate enrolments, HCPs were actively involved in only one study at any given time. In addition, the administrative databases of each EURAS/INAS study were routinely cross-checked for duplicate entries and cross-checked with other ongoing EURAS/INAS studies.

9.4.1.6 EURAS-INAS: Study Data

9.4.1.6.1 Baseline Data

Baseline data were captured on self-administered questionnaires containing questions related to participants' state of health and potential risk factors. Questionnaires differed little between studies and covered the following topics – administration, demography, general health, gynecological history, oral contraceptive history, cardiovascular risk factors and other (Table 2).

Table 2. Parameters addressed by baseline questionnaires.

Administration	ID-number, date of completion
Demography	Date of birth, education level
General health	Height, weight, smoker, concomitant medications, surgical history
Gynecological history	Age at menarche, parity, gravidity
Oral contraceptive history	Duration of use, number of times switched OC and reasons for stopping, previous AEs during OC-use,
Cardiovascular risk factors	Hypertension, diabetes mellitus, high cholesterol, coronary heart disease, arrhythmias, stroke, blood clots in the lung, thrombosis in a leg, family history of cardiovascular disease
Other	–

In addition, participants provided their postal address, phone number and email address, as well as those of relatives or friends. Relatives' and friends' contact details were used in the case a participant could not be contacted during the follow-up phase. Contact details were also obtained of the particpants' primary care physician/gynecologist. In line with data privacy regulations, these

data were documented on a separate sheet. During study conduct and study evaluation these sheets and the electronic representations of their content were stored separately from the baseline questionnaires and their respective electronic representation. This also applies to the archiving of documents and databases at the end of the study.

9.4.1.6.2 Follow-up Data

Follow-up questionnaires were mailed to participants directly. The EURAS/INAS follow-up approach assumes that otherwise healthy participants are more aware of their personal health-related events than the (recruiting) HCP who prescribed their hormonal therapy. This is particularly true for serious adverse events that are treated by other HCPs (e.g., pulmonary embolism treated by an emergency physician and vascular surgeon). In some situations, events were reported by the participants' relative or the attending physician between regular follow-ups. All reports – independent of the source of information – were validated according to the process described in section 9.4.1.8.

The follow-up questionnaires addressed the occurrence of adverse events, and particularly, serious adverse events. Follow-up questionnaires differed little between studies and covered the following topics: administration, general health, adverse events, hormonal treatment history and ancillary (Table 3). Secondary outcomes of interest differed slightly between EURAS/INAS study designs according to the needs of the study Funder and regulatory bodies.

Table 3. Parameters addressed by follow-up questionnaires.

Administration	ID-number, date of completion, changes in contact details, contact details of treating HCP (AEs)
General health	weight, changes in smoking status, concomitant medications
Adverse event	Acute myocardial infarction (AMI)s, stroke, venous thromboembolism, cancer, hospitalization, other AEs
Hormonal treatment history	changes in treatment (stopped, switched, unchanged), reasons for stopping/switching, extended pill intake, pregnancy despite OC-use
Ancillary	changes in acne, skin/hair problems, folate frequency questionnaire, health problems in a new-born

9.4.1.7 EURAS-INAS: Data Processing

Questionnaires were collected in the participating countries by the local collaborators of ZEG Berlin and reviewed for completeness. Missing and/or inconsistent information was clarified directly by phone with the participants. Complete questionnaires were forwarded to ZEG Berlin. At ZEG Berlin all incoming data were subjected to comprehensive quality control, including electronic and manual plausibility checks. Unclear or inconsistent information were described in detailed queries which were forwarded to the local collaborators for clarification with the participants. ZEG Berlin monitored and endorsed the timely processing of the queries.

As an additional quality control, an independent second data entry was performed at ZEG Berlin. As part of the data verification process, all inconsistent data entries were corrected, and changes documented. A data review was conducted by the Principal Investigator before final analysis.

9.4.1.8 EURAS-INAS: Self-Reported Outcome Processing

The EURAS/INAS self-reported follow-up questionnaire is a sensitive tool that effectively captures serious clinical outcomes of interest. From a methodological perspective it is more sensitive than physician-reported outcome studies, where the prescribing HCPs may be unaware of an adverse event as they were not involved in its diagnosis and treatment. However, laypersons often misclassify adverse events (e.g., varicose veins as thrombosis, differential diagnoses as confirmed events) and as a stand-alone tool, self-reported outcomes have low specificity. Validating self-reported events is a critical step in the EURAS/INAS study methodology ensuring high sensitivity and specificity of diagnostic outcomes and results.

Validation of self-reported events began at the level of the local field organizations with a review of all "events" reported by the participants. Follow-up questionnaires containing potential 'events' were flagged by the field organization and forwarded to the ZEG Berlin medical team for review. All subjectively perceived symptoms, signs and, if possible, the diagnoses as understood by the participants were documented. In addition, the name and address of the relevant physician (attending physician, physician responsible for the follow-up treatment after discharge from hospital, or primary care physician) were documented.

In case of unclear or missing information the participant was contacted by telephone or e-mail for clarification. For many events it was necessary to contact the diagnosing and/or treating physician for further information.

Based on information received during validation, all potential primary and secondary outcomes of interest were classified as "confirmed" or "not confirmed" according to pre-defined algorithms.

Venous thromboembolism (VTE)

Potential VTE events were categorised into three groups 'definite', 'probable' and 'not confirmed' based on information received during the validation process.

Definite VTE: Self-reported VTE confirmed by imaging procedure.

- DVT: phlebography, duplex sonography, magnetic resonance imaging (MRI)
- PE: pulmonary angiography, ventilation-perfusion scan, spiral computed tomography, magnetic resonance imaging, transoesophageal echocardiography

Probable VTE: Self-reported VTE confirmed by HCP (only) or test with low specificity

- Absence of confirmation by an imaging test, but a clinical diagnosis was confirmed by a health professional or is supported by a non-imaging test (such as ultrasound Doppler, plethysmography, D-dimer for VTE or typical electrocardiogram [ECG]/blood gas tests for PE).

- These cases are usually characterized by a specific subsequent therapy (such as fibrinolysis or long-term anticoagulants). However, if the attending physician confirmed that the diagnosis is correct, the event was classified as a VTE, even if a specific treatment was not given.

VTE not confirmed:

- VTE excluded by a physician.
- A different medical condition was diagnosed by the attending physician (e.g., thrombophlebitis).
- The participants did not seek medical help.

All events were included in the primary analysis if, at the end of the validation process, the stated diagnosis was a deep venous thrombosis of the upper or lower extremity[2], pelvic thrombosis, portal vein thrombosis, pulmonary embolism and (non-septic) sinus vein thrombosis. These diagnoses correspond to ICD-10 codes I.26.0, I.26.9, I.63.6, I.67.6, I.80.1, I.80.2, I.80.3, I.80.81, I.80.88, I.80.9, I.81, I.82.2, I.82.3, I.82.8, and I.82.9.

Varicose veins, superficial thrombophlebitis and perianal thrombosis were not counted as VTE because these conditions – unlike deep venous thrombosis – are not associated with a high risk of thrombus detachment and pulmonary embolism.

For the purpose of continuously monitoring safety data during the study, classification of reported VTE was performed by the medical pharmacovigilance (PV) experts. For the final analysis this classification was verified by means of an independent blinded adjudication process to minimize classification bias. Three independent medical experts reviewed all available information on the reported VTE. For this process brand names, dose, regimen, and composition of the OC(s) used by the reporting woman were rendered anonymous. The adjudicators performed the reviews independently of each other and without knowing the judgement of the other adjudicators or the previous classifications by medical experts. The primary analysis was based on the decision of adjudication board. For more details regarding the blinded adjudication process, see Annex 2.

9.4.2 RIVET-CC

9.4.2.1 RIVET-CC: Study Design

The RIVET-CC study was a population-based, non-interventional, case-control study that observed women exposed to any COC, primarily focusing on users of CMA 2 mg and LNG 0.15 mg, both combined with EE 30 µg. Cases have been prospectively included if they were diagnosed with a new venous thrombotic event after study start. Recruited controls, i.e., those without a VTE, have been matched by year of birth, gender, and region of residence.

The primary objective of RIVET-CC study was to compare the VTE risk of new-starting and incident users of COCs containing CMA 2 mg to new-starting and incident users of COCs

[2] Including muscle and brachial vein

containing LNG 0.15 mg, both combined with EE 30 µg. New-starting users were women who have never taken an HC before they started using the currently taken HC (i.e., at time of onset of symptoms of VTE). Incident users were defined as women who have used the same or a different HC before they started the current HC with at least three months intake break of HC.

9.4.2.2 RIVET-CC: Inclusion and Exclusion Criteria

Inclusion criteria (cases):

- Women aged 15 to 49 years with a diagnosis of VTE diagnosed in Germany or Austria during the study period (May 2016 to April 2022). These include the following ICD-10 Codes: I26, I63.6, I67.6, I80.1, I80.2, I80.3, I80.0, I80.9, I82.0, I82.2, I82.3, I82.3, I82.8, I82.9, O22, O87, O00-O07, O08.7.

Exclusion criteria (cases):

- Without consent to study participation.
- Severe language problems (unable to understand consent procedure or to answer the relevant questionnaire).

9.4.2.3 RIVET-CC: Study Data

Cases were prospectively included via recruiting HCPs if they were diagnosed with a new VTE within the study period (May 2016 to April 2022) in the participating countries, Austria and Germany. Controls were matched in a 1:4 ratio to the cases and matching was based on year of birth (±1 year) and region of residence (first 3 digits of the postal code). Both cases and controls received a self-administered baseline questionnaire. There were no follow-up questionnaires.

The HCP who recruited the VTE cases completed a physician baseline questionnaire in which additional information on the event (i.e., diagnosis and treatment of the VTE, laboratory findings, concurrent medication) was collected. HCPs were also asked to provide the medical findings of any relevant diagnostic tests as well as information on the treatment of the VTE (for example hospital discharge letters, laboratory findings or imaging tests) to confirm the final diagnosis.

Data were collected on HC use (current and previous), lifestyle-dependent potential risk factors for VTE (including pregnancy, immobilization, accidents, overweight, smoking etc.), and personal history of VTE via a self-administered questionnaire by the study participants. Medical data on VTE diagnosis and treatment were documented by the reporting HCPs on the physician questionnaire (e.g., abstracted from patients' files).

9.4.2.4 RIVET-CC: Self-Reported Outcome Processing

The collection of VTE reports in the RIVET-CC study relied on initial self-reported events by study participants in the baseline questionnaire. Self-reported VTE events were subsequently validated by the ZEG Berlin study team reviewing medical documentation. The recruiting HCP provided medical documentation for each recruiting VTE case confirming the final diagnosis. Based on information received during validation, all potential primary and secondary outcomes of

interest were classified as "confirmed" or "not confirmed" according to pre-defined algorithms, similarly as prescribed in section 9.4.1.8 for the EURAS/INAS studies. Thereafter, a blinded adjudication process through medical boards was performed. More details regarding the blinded adjudication process are described in Annex 2. As preparation of the data for inclusion in the final RIVET-RCS report as exploratory objective, all VTE cases recruited in RIVET-CC exposed to either CMA/EE or LNG/EE at the time of their first VTE symptoms were adjudicated by 3 independent medical adjudicators. The details of the selected adjudicators for RIVET-CC are given in Annex 2. The medical adjudicators were provided with case summaries blinded to information on exposure. In total, 118 VTE cases were adjudicated. If a case experienced 2 events (e.g., a DVT and a PE), a summarized report was reviewed. Before the adjudication process, 111 VTE cases were classified as "confirmed" and 7 were classified as "not confirmed". After the first review round by the independent adjudicators, 84 VTEs were classified as "confirmed" VTE and 5 were classified as "not confirmed". There was a discordance in VTE classification in 29 cases. After re-adjudication of the remaining cases with a split-decision, the 27 VTE cases were categorized as "confirmed" and 2 VTE cases were classified as "not confirmed". In total, 111 VTE cases and 7 VTE cases exposed to CMA/EE or LNG/EE were classified as "confirmed" and "not confirmed" respectively. There was no discrepancy with the classification of VTE events on a centralized level by ZEG Berlin.

9.4.2.5 RIVET-CC: Data Management

Data management procedures were identical to the EURAS-INAS studies described in section 9.4.1.3.

9.4.3 Variables

9.4.3.1 Variables to Define Primary and Secondary Endpoints

The outcome variables to determine the primary and secondary endpoints were:

- The occurrence (or absence) of a new (non-recurrent) confirmed VTE, including DVT and PE, during follow-up. These diagnoses of interest correspond to ICD-10 codes I.26.0, I.26.9, I.63.6, I.67.6, I.80.1, I.80.2, I.80.3, I.80.81, I.80.88, I.80.9, I.81, I.82.2, I.82.3, I.82.8, and I.82.9.
- Established confounding factors age, BMI, and COC user type (starter/switcher/re-starter) were considered in multivariable Cox regression.

9.4.3.2 Variables to Define Treatment Exposure

The variable to determine exposure to treatment was:

- The time-varying exposure to COCs was observed from study entry through the follow-up period used for cohort assignment.
    - o Primary exposure cohort: CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.
    - o Secondary exposure cohort I: CMA (any dose)/EE ≤30 µg and LNG (any dose)/EE ≤30 µg.

o Secondary exposure cohort II: CMA/EE and LNG/EE, dose independent.

9.4.3.3 Variables to Define Baseline Characteristics (RIVET-RCS)

The variables to characterize the baseline risk profile of users were:

- Baseline population characteristics: country, age, weight (kg), height (cm), BMI (kg/m²).
- Socio-economic factors: education.
- Parameters of reproductive history: age at menarche (years), gravidity, parity, number of live births.
- Parameters of contraceptive history: ever used OC, OC user type (starter/switcher/restarter), duration of OC-use at study entry (years).
- Parameters of medical history: diabetes mellitus, stroke, cancer, myocardial infarction, surgery.
- Cardiovascular risk factors: high blood pressure, high cholesterol, family history of ATE, family history of VTE, currently smoking, heavy smoking (>15 cigarettes).
- Concomitant medication: regular use of medication.

9.4.3.4 Variables to Define the Exploratory Endpoint (RIVET-CC)

The variables to describe population characteristics and distribution of VTE risk factors in the exploratory objective were:

- Baseline population characteristics,
- Socio-economic factors (e.g., education),
- Parameters of reproductive, contraceptive, and medical history,
- Cardiovascular risk factors (e.g., high blood pressure, family history of VTE, smoking),
- Short-term risk factors (e.g., standing occupation, surgery, immobilization),
- Symptoms occurring before diagnosis,
- VTE examination procedures,
- Treatment of VTE.

9.5 Data Transformations

Simple data transformations have been done to calculate derived variables and to compare the variables obtained in the different studies included for the pooled analysis. The data management, data preparation and data pooling were performed with the most current release version (9.4) of the software package SAS® (2).

PRAC requested to include a complete list comparison of baseline variables for both exposure cohorts – including respective information on intake of medication with procoagulatory and

anticoagulatory activity. As specified in section 9.4.1.3 concomitant medication was coded differently across the three studies, INAS-SCORE, INAS-FOCUS and INAS-OC, or not coded for EURAS-OC/LASS. For this specific request, concomitant medication has been coded uniformly by use of ATC WHO. Concomitant medications with procoagulatory and anticoagulatory properties per marketed indication were identified and descriptive results were summarized in the baseline tables. The corresponding WHO ATC codes of medications indicated for either procoagulatory or anticoagulatory mechanism were agents listed under B01 or B02 therapeutic subgroups in the ATC/DDD (defined daily dose) Index of 2022.

9.6 Bias

Potential limitations and types of biases inherent to the study design are discussed in detail in section 11.2.

9.7 Study Size

Power calculations for the RIVET-RCS study were based on an assumed incidence rate of 9 VTE cases per 10,000 WY for LNG containing COCs. It was expected that CMA is associated with a VTE risk that is not higher than the risk associated with LNG. The primary hypothesis was restricted to COCs containing CMA 2 mg or LNG 0.15 mg, both combined with EE 30 µg. A non-inferiority logrank test with an overall sample size of 58,000 WY (25,000 for CMA 2 mg/EE 30 µg and 33,000 WY for LNG 0.15 mg/EE 30 µg) achieves 80% power assuming:

1) A one-sided α of 0.05 and
2) A non-inferiority limit on a hazard ratio of 2.

These calculations suggested that the pooled analysis was sufficiently powered to show non-inferiority of CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg with a non-inferiority hazard ratio of 2.

In secondary analyses, the risk of VTE in the cohort of users of COCs containing CMA/EE ≤30 µg and LNG/EE ≤30 µg (secondary I), and users of COCs containing CMA/EE compared to LNG/EE without dosage restrictions (secondary II) will be assessed and compared to the risk obtained in the primary analysis.

More details on the number of COC treatment cohorts, available women-years, and power for these three scenarios and following the above assumptions are given in Table 4.

Table 4. Power calculations for hypotheses regarding primary and secondary analysis cohorts.

Hypothesis	Primary		Secondary I		Secondary II	
Progestin	CMA 2 mg	LNG 0.15 mg	CMA	LNG	CMA	LNG
Estrogen	EE=30 µg		EE ≤30 µg		EE	
Women years	25,000	33,000	25,000	80,000	29,000	95,000
Power	80%		92%		95%	

9.8 Data Analysis

The statistical analyses were performed retrospectively on a pooled dataset comprised of four prospective cohort studies as described in section 9.5. All analyses were performed using SAS® software, version 9.4 (2).

9.8.1 Cohort Assignment

The primary and secondary analysis cohorts were selected based on the predefined inclusion and exclusion criteria and defined as follows:

- Primary analysis cohorts: CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg
- Secondary analysis cohorts I: CMA/EE ≤30 µg and LNG/EE ≤30 µg
- Secondary analysis cohorts II: CMA/EE vs. LNG/EE

9.8.2 Analysis of Baseline Population Characteristics

Baseline characteristics, including reproductive, contraceptive, and medical history, were summarized descriptively for each exposure cohort. Categorical variables were described by absolute and relative frequencies; continuous variables were summarized by the sample mean and standard deviation.

9.8.3 Analysis of Primary and Secondary Objectives

The incidence of VTE was obtained during follow-up and expressed as incidence rate (IR) based on the occurrence of new cases per 10,000 WY. Inferential statistics for primary and secondary exposure cohorts was based on the extended Cox model. Crude and adjusted Hazard Ratios (HRs) were calculated with the 95%-confidence intervals (CI). Recurrent venous thromboembolic events were excluded from the analysis. Study participants who discontinued prematurely, died during follow-up, or completed without a reported outcome of interest were right censored at the date when they last confirmed they did not experience the event. Four confounding factors for VTE – age, BMI, current duration of use, and family history of VTE – were included as covariates in the Cox model. Analyses were performed for the complete sample and selected subgroups: age, BMI, and OC user group. A further analysis was performed in the European subgroup only.

The analysis focused on the "as-treated" (AT) population. The AT population consists of all study participants who reported at least one episode of contraceptive exposure to study treatment during follow-up. Outcomes of interest were assigned to the product used at the time (month/year) of the event. Information on observed exposure and outcomes was transferred to a monthly time-to-event calendar with treatment episodes defined as time-dependent variables observed from study entry to the follow-up period.

9.8.4 Sensitivity Analysis

Sensitivity Cox regression analyses were performed: 1) on the impact of missing data (BMI imputed by the average value per study and region of origin) and geographic region (stratification by region of origin); 2) on the primary outcome definition (confirmed, validated VTE); and 3) on the inclusion of prognostic factors/covariates. As requested by regulatory authorities, a propensity score (PS)-based approach was applied in addition. Propensity score analysis was evaluated using population sub-classification to balance baseline covariates between cohorts (3, 4). All baseline (time-fixed) population characteristics have been included in the PS model as linear terms, age and BMI have been included as quadratic terms additionally. The adequacy of the PS model was assessed by comparing exposed and non-exposed participants within strata based on the absolute standardized difference of continuous and binary covariates. Absolute standardized differences with a value of lower than 0.1 (10%) have been used to indicate adequate balance between exposure groups and 0.25 served as a threshold for imbalance as suggested by Imbens and Wooldridge (5). The HR was subsequently obtained from the stratified Cox model.

9.8.5 Exploratory Descriptive Comparison with RIVET-CC Interim Data

Despite the different epidemiological nature of the collected data, i.e., cohort versus case-control studies, data from the RIVET-CC study was not included in the RIVET-RCS pooled analysis. However, since the number of VTE cases, exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg, collected in RIVET-CC was relatively high considering the low incidence of VTEs in the population, the obtained interim data from the RIVET-CC study was used to further improve the understanding of potential underlying differences in the distribution of VTE risk factors. As an exploratory objective, ZEG Berlin descriptively represented population characteristics and distribution of risk factors for VTE cases identified in RIVET-CC and RIVET-RCS. Baseline characteristics, including reproductive, contraceptive, and medical history, were summarized descriptively for the exposure cohorts CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.

10 RESULTS

This section describes the results in the following order:

RIVET-RCS

A) Descriptive and baseline characteristics of the identified population in the pooled dataset.
B) Prognostic factors, relative risk, and occurrence of confirmed VTE.
C) Results from the primary, secondary and sensitivity analysis models.

RIVET-CC

D) Results from the exploratory description of baseline characteristics and distribution of VTE risk factors (exploratory objective).

10.1 Part A: Selection and Description of the Study Population Identified from the Pooled Dataset

10.1.1 Selection of the Study Population

Figure 3 shows the selection of the study population included in the RIVET-RCS pooled analysis. Pooling data of the four large INAS/EURAS cohort studies resulted in a total of 276,955 study participants contributing to a total of 870,100 women-years. Of those, 258,161 (93.2%) met the inclusion criteria of the RIVET-RCS study regarding age (between 15 and 49 years) and being prescribed a new COC. Of those, 680 (0.3%) were excluded from the analysis because they had a reported personal history of VTE or did not meet the COC exposures of the study cohorts (77.75%; n=200,607). Among the remaining eligible participants, women were assigned to three different exposure cohort groups depending on the prescribed COC and dosages:

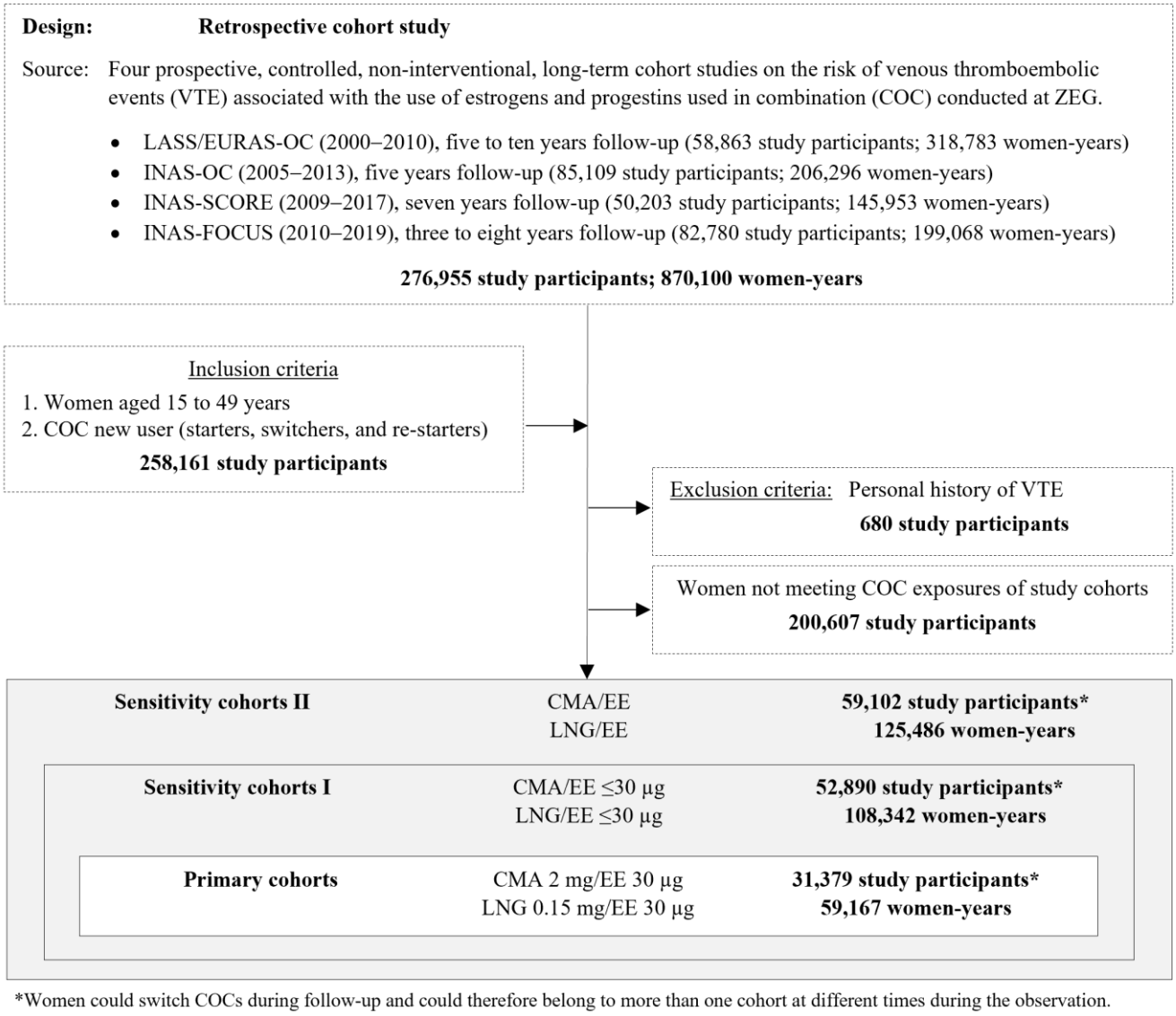
1) Primary exposure cohorts: CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg
2) Secondary exposure cohorts I: CMA/EE ≤30 µg vs. LNG/EE ≤30 µg
3) Secondary exposure cohorts II: CMA/EE vs. LNG/EE

In total, 59,102 women were included in secondary exposure cohorts II, which comprised the entities of secondary exposure cohorts I and the primary exposure cohorts. Since study participants could switch to another COC, including a CMA- or LNG-containing COC, during the follow-up time, women could belong to more than one cohort at different times during the observation.

In total, 31,379 study participants were identified to be exposed to either CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg and contributed to a total of 59,167 women-years of observation time for the primary exposure cohorts of interest. For the secondary exposure cohorts, a total of 52,890 study participants were exposed to either CMA/EE ≤30 µg or LNG/EE ≤30 µg (secondary exposure cohorts I) and a total of 59,102 study participants were exposed to either CMA/EE or LNG/EE, independent from the specific dosage (secondary exposure cohorts II). The number of identified participants in the secondary cohorts I and II contributed to a total of 108,342 and 125,486 women-years (WY), respectively.

The countries where study participants were recruited were Austria, Belgium, Canada, Denmark, France, Germany, Italy, the Netherlands, Poland, Ukraine, United Kingdom, USA, Russia, and Sweden.

Figure 3. Selection of the study population for the RIVET-RCS pooled analysis.



*Women could switch COCs during follow-up and could therefore belong to more than one cohort at different times during the observation.

The table below (Table 5) summarizes the number of women and WY available for CMA or LNG users per user cohort of interest.

Table 5. Number of women and available WY of exposure for all exposure cohorts.

Hypothesis	Primary		Secondary I		Secondary II	
Progestin	CMA 2 mg	LNG 0.15 mg	CMA	LNG	CMA	LNG
Estrogen	EE=30 µg		EE ≤30 µg		EE	
Women years	25,457	33,710	26,215	82,127	30,108	95,378
Number of women	12,710	18,669	13,238	39,652	14,598	44,504

The following sections summarize the results of the primary exposure cohorts of interest, while further descriptive information, tables, and figures of the secondary cohorts I and II can be found in Annex 3.

10.1.2 Population Characteristics of Study Participants

For the primary exposure cohorts, a total of 31,379 participants were identified to be eligible for inclusion in the pooled analysis. Of the total eligible participants, 12,719 (40.5%) were exposed to CMA 2 mg/EE 30 µg and 18,669 (59.5%) were exposed to LNG 0.15 mg/EE 30 µg during the study follow-up period. Since CMA was not marketed in the USA when study participants were recruited, all users exposed to CMA 2 mg/EE 30 µg were residing in Europe only, while for LNG 0.15 mg/EE 30 µg, 10,553 (56.5%) and 8,116 (43.5%) were residing in Europe and the USA respectively.

The mean age at study entry was slightly lower in the CMA 2 mg/EE 30 µg-cohort at 23.8 years (±7.13) compared to 25.8 (±7.61) years in the LNG 0.15 mg/EE 30 µg-cohort. Most participants had used a hormonal contraceptive before (70.0% of CMA 2 mg users and 78.2% of LNG 0.15 mg users). The most common risk factor for VTE identified in both exposure cohorts was smoking (33.6% and 27.6% of the CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg users, respectively). Other risk factors for VTE were less frequent, family history of VTE being the second most common; 5.3% and 3.8% of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg users reported to have a family history (i.e., parents or siblings) of VTE respectively.

Other baseline characteristics, such as age group, history of hormonal contraceptives and cardiovascular risk factors were well balanced between the exposure cohorts, although participants of the LNG 0.15 mg/EE 30 µg cohort had a higher average weight at baseline (66.9 kg vs. 61.7 kg) and comprised more women exposed to LNG 0.15 mg/EE 30 µg had ever been pregnant (44.8% vs. 29.2%) and had given birth before (39.8% vs. 25.8%) (Table 6). Medical history of diabetes mellitus, cancer, stroke, or acute myocardial infarction was generally low (< 1.0%) for both users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.

Furthermore, 28.3% and 32.3% reported to have a history of surgery in the CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg cohort respectively. Of the CMA 2 mg users, 13.5% reported to regularly use medication while for the LNG 0.15 mg/EE 30 µg users, 22.0% took medication at a regular basis at baseline. The number of study participants that were regularly taking a medication indicated for their procoagulatory or anticoagulatory activity was very small (≤0.05%) for both exposure cohorts, which can be explained by various reasons: 1) study participants with a personal history of VTE were excluded from the analysis and 2) contraindications to COC therapy include diseases related to the coagulation system.

Education was well balanced between both exposure cohorts; most study participants had a university degree or higher, with 41.3% and 35.3% having a university level and higher than university level for the CMA 2 mg/EE 30 µg user cohort and 35.6% and 48.7% having a university level and higher than university level for the LNG 0.15 mg/EE 30 µg user cohort.

Table 6. Population characteristics of study participants in cohorts of primary interest.

	Mean (Std) or Relative frequency	
	CMA 2 mg/EE 30 µg (N=12,710)	*LNG 0.15 mg/EE 30 µg (N=18,669)*
Patient characteristics		
Europe	12,710 (100%)	10,553 (56.5%)
USA/Canada	--	8,116 (43.5%)
Age at study entry (years)	23.8 (±7.13)	25.8 (±7.61)
Age <20 years	4,303 (33.9%)	4,196 (22.5%)
20 to <30 years	5,893 (46.4%)	9,475 (50.8%)
30 to <40 years	2,031 (16.0%)	3,724 (19.9%)
40+ years	483 (3.8%)	1,274 (6.8%)
Weight at study entry (kg)	61.7 (±11.47)	66.9 (±15.82)
Height at study entry (cm)	166.7 (±6.30)	165.7 (±6.75)
BMI at study entry (kg/m^2)	22.2 (±3.88)	24.4 (±5.61)
BMI <20 kg/m^2	3,352 (26.4%)	3,163 (16.9%)
20 to <25	6,984 (54.9%)	8,939 (47.9%)
25 to <30	1,760 (13.8%)	3,890 (20.8%)
30 to <35	437 (3.4%)	1,514 (8.1%)
≥35	164 (1.3%)	1,054 (5.6%)
Missing	13 (0.1%)	109 (0.6%)
Gynecological History		
Age at menarche (years)	12.9 (±1.39)	12.9 (±1.55)
Ever been pregnant (gravidity)	3,706 (29.2%)	8,367 (44.8%)
Ever given birth (parity)	3,275 (25.8%)	7,437 (39.8%)
Number of live births	1.5 (±0.67)	1.7 (±0.92)
HC History		
Ever used OC	8,902 (70.0%)	14,606 (78.2%)
Starter	3,808 (30.0%)	4,063 (21.8%)
Switcher	3,362 (26.5%)	5,230 (28.0%)
Restarter	5,540 (43.6%)	9,376 (50.2%)
Duration of HC use (years)	5.1 (±5.38)	6.2 (±5.88)
Cardiovascular Risk Factors		
High blood pressure	191 (1.5%)	467 (2.5%)
High cholesterol	176 (1.4%)	257 (1.4%)
Family history of ATE	161 (1.3%)	345 (1.8%)
Family history of VTE	679 (5.3%)	710 (3.8%)
Current smoker	4,271 (33.6%)	5,148 (27.6%)

	Mean (Std) or Relative frequency	
	CMA 2 mg/EE 30 µg (N=12,710)	*LNG 0.15 mg/EE 30 µg (N=18,669)*
Heavy smoker (>15 cigarettes/day)	664 (5.2%)	893 (4.8%)
Medical History		
Diabetes mellitus	41 (0.3%)	169 (0.9%)
Stroke	3 (0.02%)	13 (0.07%)
Cancer	50 (0.4%)	102 (0.5%)
Acute Myocardial Infarct	2 (0.02%)	11 (0.06%)
Any surgery	3,602 (28.3%)	6,037 (32.3%)
Medication		
Regular use of medication	1,716 (13.5%)	4,114 (22.0%)
Of which, procoagulatory agents	1 (0.01%)	2 (0.01%)
Of which, anticoagulatory agents	6 (0.05%)	5 (0.03%)
Education		
Less than university entrance level	1,360 (10.7%)	1,421 (7.6%)
University entrance level	5,249 (41.3%)	6,651 (35.6%)
Higher than university entrance level	4,492 (35.3%)	9,087 (48.7%)

Women may appear in both cohorts.

In a secondary descriptive analysis, baseline characteristics of the secondary exposure cohorts I (CMA/EE ≤30 µg vs. LNG/EE ≤30 µg) and II (CMA/EE vs. LNG/EE) were summarized. The distribution of baseline characteristics between users exposed to CMA (combined with EE ≤30 µg or EE) and LNG (combined with EE ≤30 µg or EE) show similar results compared to the distribution of baseline characteristics in the primary cohorts of interest. The baseline tables for the secondary exposure cohorts I and II are included in Annex 3.1.1 and Annex 3.1.2 respectively. Similar to users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg, the number of study participants that were regularly taking a medication indicated for their procoagulatory or anticoagulatory activity was very small (≤0.05%) for both CMA/EE and LNG/EE.

10.1.2.1 Average Number and Length of COC Treatment Episodes

The average number and length of COC treatment episodes were summarized for the CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg exposure cohorts. Results are presented in Table 7. The average number of COC treatment episodes was identical between both exposure cohorts of primary interest, 1.2 (±0.52) vs. 1.2 (±0.45) with an average episode length of 19.9 months and 18.6 months for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg, respectively.

Table 7. Average number and length of COC treatment episodes.

	Mean (SD)	
	CMA 2 mg/EE 30 µg (N=12,710)	*LNG 0.15 mg/EE 30 µg (N=18,669)*
Number of COC episodes	1.2 (±0.52)	1.2 (±0.45)
Length of COC episode (months)	19.9 (±18.79)	18.6 (±17.74)

Women may appear in both cohorts.

In addition, the number of treatment episode and length of exposure for the secondary exposure cohorts I and II were summarized in Annex 3.2.1 and Annex 3.2.2. Both the number of treatment episodes as the length of COC episode was comparable to study participants exposed to CMA (either combined with EE ≤30 µg or EE) and LNG (combined with EE ≤30 µg or EE).

10.2 Part B: Prognostic Factors, Relative Risk and Occurrence of Confirmed VTE

10.2.1 Relative Risk of Potential Prognostic Factors on the Occurrence of Venous Thromboembolism (VTE)

The relative risk (RR) for the occurrence of VTE in the LNG 0.15 mg/EE 30 µg-cohort was lower in the USA and Canada in comparison to European participants (RR: 0.77; 95% CI: 0.39–1.52). The relative risk for VTE was increased throughout age groups when using the age group under 20 years of age as reference group, with higher risks in the LNG 0.15 mg/EE 30 µg-cohort as opposed to the CMA 2 mg/EE 30 µg-cohort in each respective age group. Increased risks for the occurrence of VTE were observed for participants with a BMI ≥30 kg/m² in both cohorts (CMA 2 mg/EE 30 µg: 2.75; 95% CI: 0.82–9.15; LNG 0.15 mg/EE 30 µg: 2.17; 95% CI: 1.02–4.63).

With respect to gravidity and parity, both primary exposure cohorts showed different risks for the occurrence of VTE: while the CMA 2 mg/EE 30 µg-cohort showed a slightly reduced risk, both for women who had ever been pregnant (RR: 0.94; 95% CI: 0.39–2.26) and who had ever given birth (RR: 0.91; 95% CI: 0.36–2.28), the risk for VTE was up to twofold higher in the LNG 0.15 mg/EE 30 µg-cohort (Gravidity RR: 1.85; 95% CI: 0.94–3.63; Parity RR: 2.01; 95% CI: 1.03–3.93).

Cardiovascular risk factors contributed to an increased relative risk for VTE. Most prominently, high cholesterol led to a sixfold increase in the CMA 2 mg/EE 30 µg-cohort (RR: 6.19; 95% CI: 1.47–26.07). Additionally, having a high blood pressure led to a fivefold increase in the LNG 0.15 mg/EE 30 µg-cohort (RR: 5.03; 95% CI: 1.78–14.19).

A detailed overview of the relative risks for the occurrence of VTE is given in Table 8.

Table 8. Relative risk (95% CI) of potential prognostic factors on the occurrence of VTE.

	Relative Risk (95% CI)	
	CMA 2 mg/EE 30 µg (N=12,710)	*LNG 0.15 mg/EE 30 µg (N=18,669)*
Patient characteristics		
USA/Canada (ref Europe)	--	0.77 (0.39–1.52)
Age <20 years	*reference*	*reference*
20 to <30 years (ref: Age <20)	1.70 (0.66–4.43)	1.77 (0.59–5.30)
30 to <40 years (ref: Age <20)	1.41 (0.40–5.00)	1.97 (0.58–6.73)
40+ years (ref: Age <20)	1.48 (0.18–12.31)	6.59 (1.99–21.84)
BMI ≥30 kg/m^2 (ref <30)	2.75 (0.82–9.15)	2.17 (1.02–4.63)
Gynecological History		
Ever been pregnant (gravidity)	0.94 (0.39–2.26)	1.85 (0.94–3.63)
Ever given live birth (parity)	0.91 (0.36–2.28)	2.01 (1.03–3.93)
HC History		
Ever used OC (Yes/Otherwise)	2.25 (0.77–6.54)	1.34 (0.56–3.24)
Cardiovascular Risk Factors		
High blood pressure (Yes/Otherwise)	2.73 (0.37–20.08)	5.03 (1.78–14.19)
High cholesterol (Yes/Otherwise)	6.19 (1.47–26.07)	2.11 (0.29–15.33)
Family history of ATE (Yes/Otherwise)	--	6.85 (2.43–19.31)
Family history of VTE (Yes/Otherwise)	3.37 (1.16–9.80)	2.37 (0.73–7.73)
Smoker (Yes/Otherwise)	1.11 (0.49–2.51)	1.55 (0.78–3.08)
Medical History		
MH of diabetes mellitus (Yes/Otherwise)	--	--
MH of stroke (Yes/Otherwise)	--	--
MH of cancer (Yes/Otherwise)	--	5.35 (0.74–38.74)
MH of AMI (Yes/Otherwise)	--	--
Any surgery (Yes/Otherwise)	1.99 (0.90–4.37)	1.39 (0.71–2.74)
Medication		
Regular use of medication (Yes/Otherwise)	2.02 (0.81–5.06)	2.65 (1.36–5.18)
Education		
Higher than university entrance level (Yes/Otherwise)	1.69 (0.77–3.70)	0.89 (0.46–1.73)

Women may appear in both cohorts.

The relative risks of potential prognostic factors on the occurrence of VTE was as well calculated for the secondary exposure cohorts I and II and results are included in Annex 3.3.1 and Annex 3.3.2 respectively. Results of the secondary cohorts I and II are in line with to those for the primary exposure cohorts as listed in Table 8, however, the relative risk of having a VTE when having a medical history of cancer was lower in users of LNG/EE ≤30 µg (RR: 2.89, 95% CI:

0.40–20.69) and users of LNG/EE (RR: 2.62, 95% CI: 0.37–18.74) compared to users of LNG 0.15 mg/EE 30 µg (RR: 5.35, 95% CI: 0.74–38.74).

10.2.2 Absolute Number and Incidence Rates of Venous Thromboembolism (VTE), Deep Venous Thromboembolism (DVT), and Pulmonary Embolism (PE)

Incidence rates of VTE, DVT and PE were calculated per 10,000 women-years (WY); 25,457 WY of observation time for the CMA 2 mg/EE 30 µg-cohort and 33,710 WY for the LNG 0.15 mg/EE 30 µg-cohort were available for analysis.

With 25 and 35 occurrences of VTE, incidence rates were similar between primary exposure cohorts: 9.82 (95% CI: 6.36–14.50) for CMA 2 mg/EE 30 µg and 10.38 (95% CI: 7.23–14.44) for LNG 0.15 mg/EE 30 µg; LNG. There were slightly fewer DVTs in users of CMA 2 mg/EE 30 µg (24 vs. 28), yet the incidence rate was numerically slightly higher than that of the LNG 0.15 mg/EE 30 µg-cohort due to the difference in WY (CMA: 9.43; 95% CI: 6.04–14.03; LNG: 8.31; 95% CI: 5.52–12.00). More PEs occurred in the LNG 0.15 mg/EE 30 µg-cohort (10 vs. 4), which is also reflected in a higher incidence rate, though still with a considerable overlap of confidence intervals between cohorts (CMA 2 mg/EE 30 µg: 1.57; 95% CI: 0.43–4.02; LNG 0.15 mg/EE 30 µg: 2.97; 95% CI: 1.42–5.46). A detailed overview and a visual comparison are given in Table 9 and Figure 4.

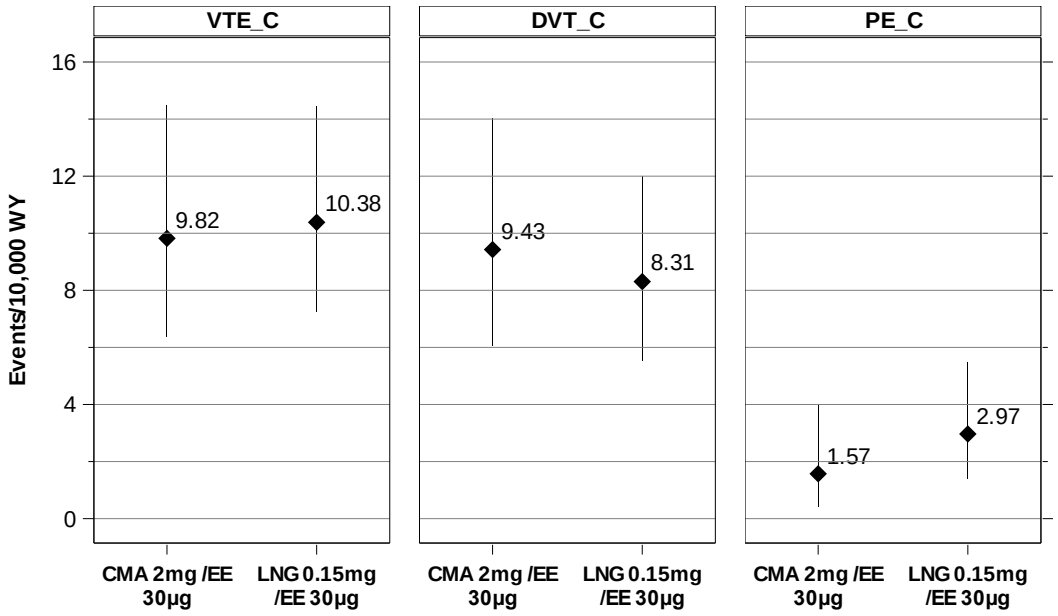
Table 9. Absolute numbers and incidence rates per 10,000 WY of confirmed VTE, DVT and PE events with 95% CI.

	Incidence Rate (95% CI)		*Incidence Rate Ratio (95% CI)*	*Incidence Rate Difference (95% CI)*
	CMA 2 mg/EE 30 µg (N=12,710)	*LNG 0.15 mg/EE 30 µg (N=18,669)*		
Women years	25,457	33,710	--	--
Confirmed VTE				
Number of events	25	35	--	--
IR (95% CI)*	9.82 (6.36–14.50)	10.38 (7.23–14.44)	0.95 (0.57–1.58)	-0.56 (-5.72–4.60)
Confirmed DVT				
Number of events	24	28	--	--
IR (95% CI)*	9.43 (6.04–14.03)	8.31 (5.52–12.00)	1.14 (0.66–1.96)	1.12 (-3.75–5.99)
Confirmed PE				
Number of events	4	10	--	--
IR (95% CI)*	1.57 (0.43–4.02)	2.97 (1.42–5.46)	0.53 (0.17–1.69)	-1.40 (-3.79–1.00)

*IR and 95% CIs are shown per 10,000 WY. Women may appear in both cohorts.

Based on the final SMAC of September 9, 2022, incidence rate ratios and incidence rate differences were as well presented in Table 9 for the primary exposure cohorts. Because of unbalanced primary cohorts with respect to known VTE risk factors, e.g., age and BMI, these crude measures are provided for completeness only.

Figure 4. Incidence rates of VTE, DVT and PE events/10,000 WY.



DVT_C: Deep Venous Thrombosis (confirmed); PE_C: Pulmonary Embolism (confirmed); VTE_C: Venous Thromboembolism (confirmed).

Absolute numbers and incidence rates per 10,000 WY of VTE, DVT and PE for the secondary exposure cohorts I and II are comparable to those of the primary exposure cohorts. Results are summarized in Annex 3.4.1 and Annex 3.4.2. In summary, the absolute numbers of events and available WY for the users exposed to any CMA (independent of dose and combination with EE) did not change substantially between exposure cohorts of interest, while for users exposed to any LNG (independent of dose and combination with EE), the numbers of events and available WY of exposure time increased when broadening the dosage restrictions. For the secondary exposure cohorts I, 25 confirmed VTEs were reported during 26,215 WY of exposure to CMA/EE ≤30 µg resulting in an IR of 9.54 (95% CI: 6.17–14.08). For women exposed to LNG/EE ≤30 µg, 74 confirmed VTEs were reported during 82,127 WY of exposure leading to an IR of 9.01 (95% CI: 7.08–11.31). For the secondary exposure cohorts II, 29 confirmed VTE events were reported during 30,108 WY of exposure to CMA/EE, while 80 VTEs were reported during 95,378 WY exposure to LNG/EE, leading to an IR of 9.63 (95% CI: 6.45–13.83) and 8.39 (95% CI: 6.65–10.44) respectively.

10.3 Part C: Results of the Primary, Sensitivity and Secondary Analysis Models

10.3.1 Primary Analysis Model, Including Sensitivity Checks for Missing Data and Imbalance in Population Baseline Data

In the primary analysis, non-inferiority of VTE risk in users of CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg was assessed.

The primary analysis was based on 60 confirmed VTEs (DVTs of the lower extremities and PEs): 25 in CMA 2 mg/EE 30 µg users (9.8 per 10,000 WY; 95% CI, 6.4–14.5), 35 in LNG 0.15 mg/EE 30 µg users (10.4 per 10,000 WY; 95% CI, 7.2–14.4).

Crude and adjusted Cox models were performed. Results of these analyses are shown in Table 10. The crude model resulted in an HR for CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg of 0.93 (95% CI: 0.55–1.55). After adjusting for age, BMI, family history of VTE and current duration of use (expert model), the adjusted HR was 1.25 (95% CI: 0.72–2.14).

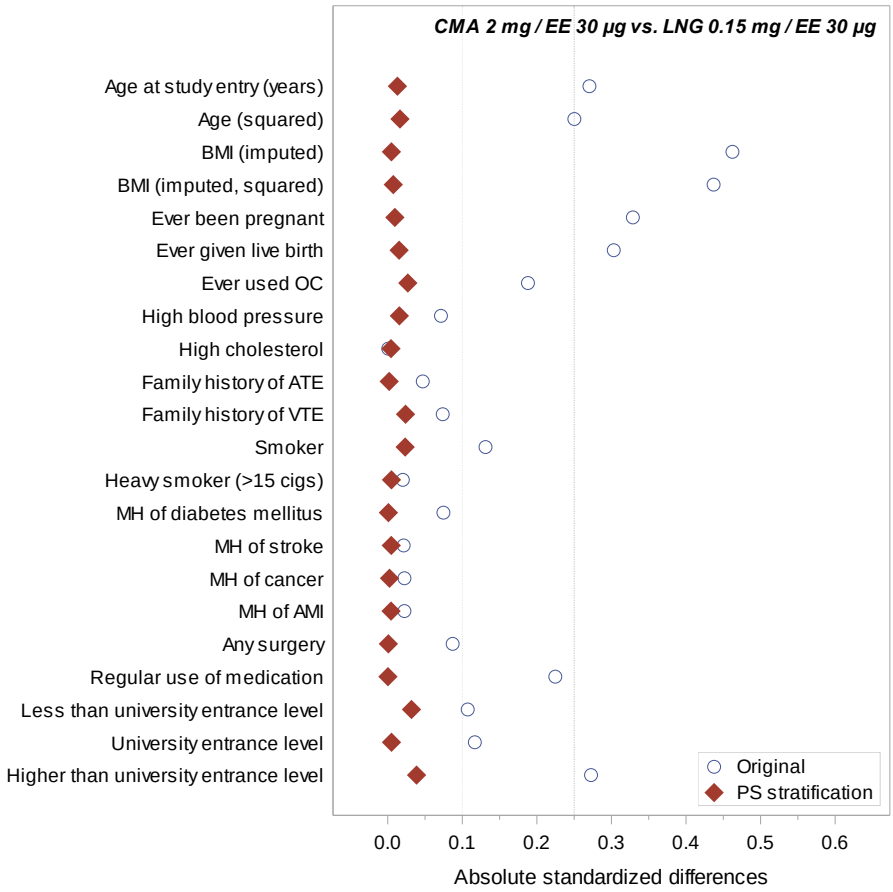
Table 10. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for confirmed VTE.

	Hazard Ratio (95% CI) *CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg*
Confirmed VTE	
Crude	0.93 (0.55–1.55)
Expert	1.25 (0.72–2.14)
Expert, BMI imputed	1.24 (0.72–2.14)
PS stratification	1.22 (0.70–2.11)

Several sensitivity analyses were performed to assess the validity of the primary outcome model. To assess the impact of possible bias due to missing BMI data, BMI was imputed per study and region of origin; there was no change in the adjusted HR (HR: 1.24, 95% CI: 0.72–2.14).

The validity of the model was demonstrated by the standardized differences summarized over strata as weighted average yielded upon PS sub-classification, which were consistently <0.25 and mostly <0.1, indicating an adequate balancing of the cohorts on measured baseline covariates (Figure 5). Propensity scores were estimated based on a logistic model in which the binary exposure status was regressed on baseline population characteristics. The optimized PS model included age, BMI and BMI (imputed) as linear and quadratic terms. Gravidity, parity, ever HC use, high blood pressure, high cholesterol, family history of ATE and VTE, smoking, heavy smoking, medical history of diabetes, stroke, cancer, MI, surgery, regular use of medication, and educational level were included as categorical indicator variables in the PS model. Baseline characteristics between the two exposure cohorts of primary interest were balanced and the resulting PS was included in the Cox model. The PS adjusted model resulted in a HR of 1.22 (95% CI: 0.70–2.11).

Figure 5. Original and PS-Balanced Standardized Differences (SD) of baseline covariates.



The same crude, adjusted and sensitivity analysis models were repeated for confirmed DVTs and PEs separately. Results are shown in Table 11.

For DVT, the crude HR of CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg was 1.11 (95% CI: 0.64–1.91). The expert and BMI adjusted model resulted in the same HR of 1.45 (95% CI: 0.82–2.58); the PS stratified model resulted in a HR of 1.42 (95% CI: 0.79–2.54).

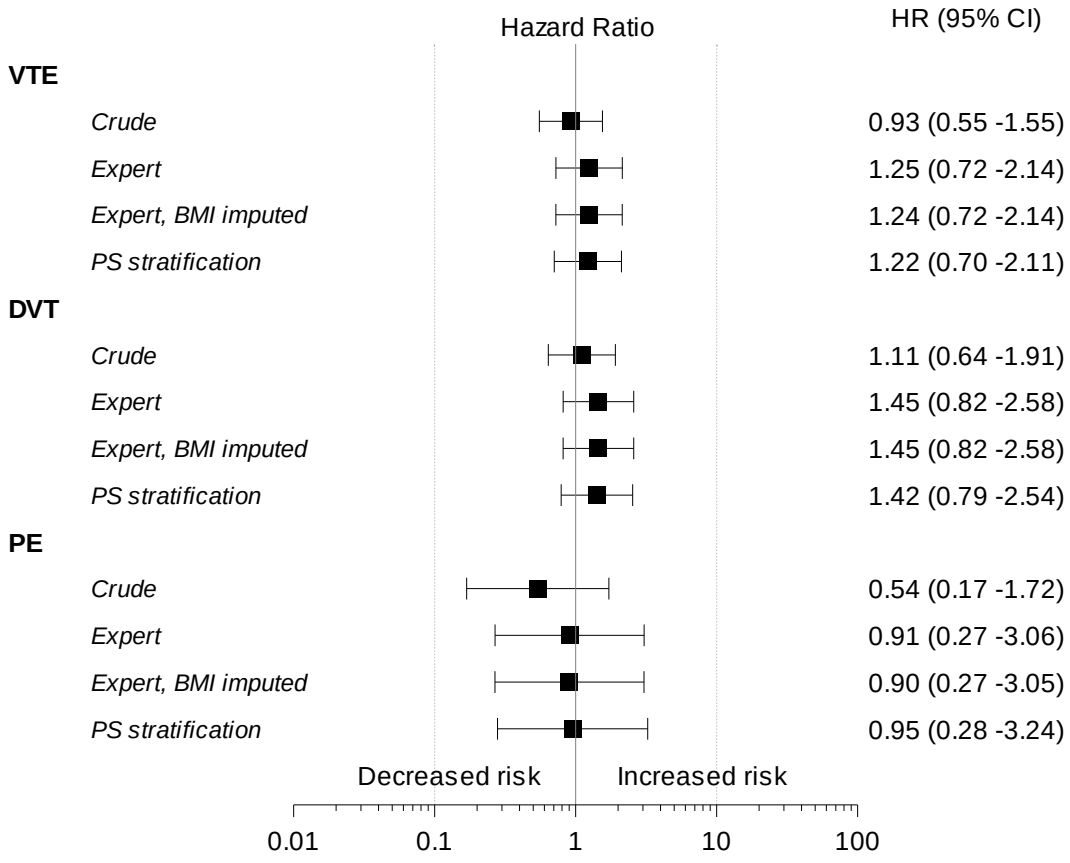
For PE, a crude HR of 0.54 (95% CI: 0.17–1.72) was observed. When adjusting the model, the HR becomes close to 1, with HRs of 0.91 (95% CI: 0.27–3.06), 0.90 (95% CI: 0.27–3.05) and 0.95 (95% CI: 0.28–3.24) for the expert, BMI imputed expert and PS stratified model respectively.

A graphical presentation of the resulting crude, adjusted and PS-adjusted HRs for confirmed VTE, DVT and PE and the 95% CIs is included in Figure 6.

Table 11. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for confirmed DVT and PE.

	Hazard Ratio (95% CI) *CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg*
Confirmed DVT	
Crude	1.11 (0.64–1.91)
Expert	1.45 (0.82–2.58)
Expert, BMI imputed	1.45 (0.82–2.58)
PS stratification	1.42 (0.79–2.54)
Confirmed PE	
Crude	0.54 (0.17–1.72)
Expert	0.91 (0.27–3.06)
Expert, BMI imputed	0.90 (0.27–3.05)
PS stratification	0.95 (0.28–3.24)

Figure 6. Graphical presentation of the crude, adjusted, and PS-adjusted HRs for confirmed VTE, DVT and PE.

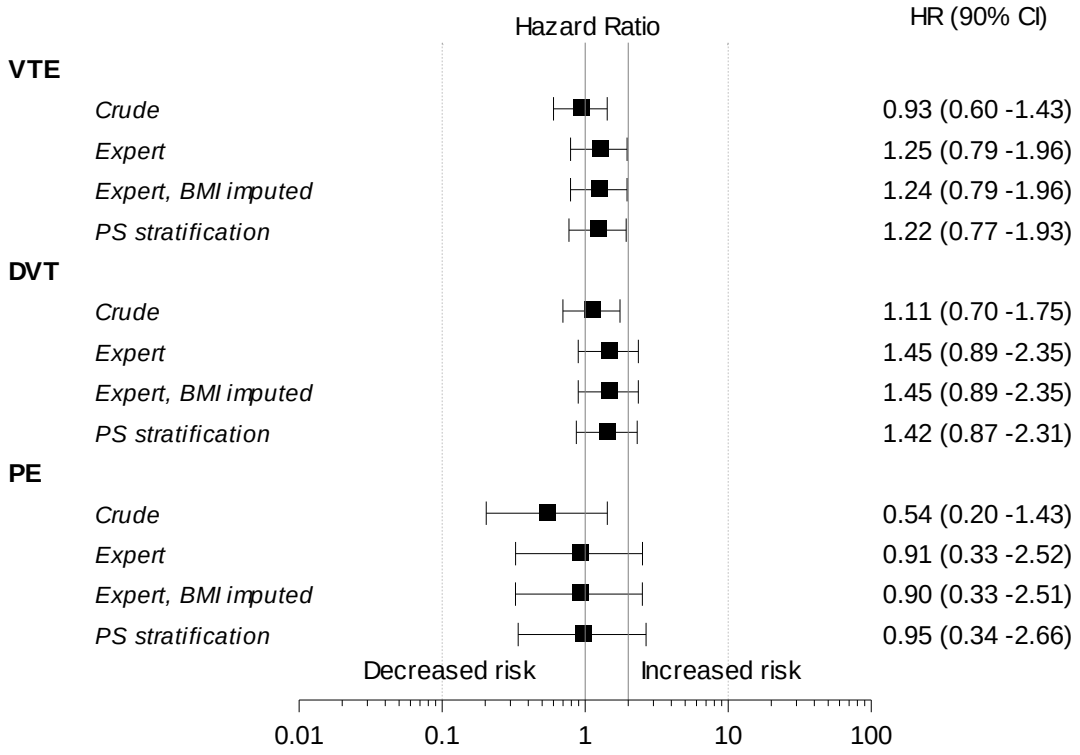


10.3.1.1 Additional Primary Analysis Considerations According to SMAC

Based on discussions during the final SMAC meeting on September 9, 2022, regarding the a priori power calculation based on type-I error of 5% (one-sided) in the context of non-inferiority conclusion, it was decided that an additional analysis should be performed using a two-sided 90% confidence interval for the primary analysis, respectively.

The results of this SMAC request are summarized in Figure 7.

Figure 7. Hazard ratios of VTE, DVT and PE with 90% CI.



Compared with the primary analysis model based on 95% confidence, effect estimates are unchanged, however, the resulting 90% confidence intervals are narrower and could exclude an HR of 2.0 for VTE.

10.3.2 Secondary Objective: VTE Risk Stratified by Age, BMI and COC User Status

As a secondary objective, several stratified analyses were performed for the primary exposure cohorts as further described below:

1) Stratification by age

Crude, adjusted and sensitivity analyses were performed while stratifying by the following age subgroups: 1) lower than 20 years, 2) 20 to lower than 30 years, 3) 30 to lower than 40 years and 4) 40 or higher years.

The age-stratified analysis was based on 6, 14, 4 and 1 confirmed VTEs for users of CMA 2 mg/EE 30 µg and 4, 16, 7 and 8 confirmed VTEs for users of LNG 0.15 mg/EE 30 µg for the age groups 1) lower than 20, 2) 20 to lower than 30, 3) 30 to lower than 40 and 4) 40 or higher years respectively.

Most study participants were aged between 20 and lower than 30 years. Observation times were 9,629 WY, 11,179 WY, 3,693 WY and 956 WY for users of CMA 2 mg/EE 30 µg and 7,588 WY, 16,080 WY, 7,237 WY and 2,805 WY for users of LNG 0.15 mg/EE 30 µg for the age groups 1) lower than 20, 2) 20 to lower than 30, 3) 30 to lower than 40 and 4) 40 or higher years respectively. Incidence Rates and 95% confidence intervals for confirmed VTE, DVT and PE for the different age strata are given in Table 12.

Table 12. Absolute numbers and incidence rates per 10,000 WY of confirmed VTE, DVT and PE events with 95% CI stratified by age.

	Age < 20		Age 20 to < 30		Age 30 to < 40		Age +40	
Number of Women								
CMA 2 mg/EE 30 µg	4,303		5,893		2,031		483	
LNG 0.15 mg/ EE 30 µg	4,196		9,475		3,724		1,274	
Women-years								
CMA 2 mg/ EE 30 µg	9,629		11,179		3,693		956	
LNG 0.15 mg/ EE 30 µg	7,588		16,080		7,237		2,805	
	N	**IR (95% CI)***	**N**	**IR (95% CI)***	**N**	**IR (95% CI)***	**N**	**IR (95% CI)***
VTE								
CMA 2 mg/ EE 30 µg	6	6.23 (2.29–13.56)	14	12.52 (6.85–21.01)	4	10.83 (2.95–27.73)	1	10.46 (0.26–58.27)
LNG 0.15 mg/ EE 30 µg	4	5.27 (1.44–13.50)	16	9.95 (5.69–16.16)	7	9.67 (3.89–19.93)	8	28.52 (12.31–56.20)
DVT								
CMA 2 mg/ EE 30 µg	6	6.23 (2.29–13.56)	13	11.63 (6.19–19.89)	4	10.83 (2.95–27.73)	1	10.46 (0.26–58.27)
LNG 0.15 mg/ EE 30 µg	3	3.95 (0.82–11.55)	13	8.08 (4.30–13.82)	7	9.67 (3.89–19.93)	5	17.83 (5.79–41.60)
PE								
CMA 2 mg/ EE 30 µg	1	1.04 (0.03–5.79)	2	1.79 (0.22–6.46)	1	2.71 (0.07–15.09)	0	--
LNG 0.15 mg/ EE 30 µg	2	2.64 (0.32–9.52)	3	1.87 (0.38–5.45)	1	1.38 (0.03–7.70)	4	14.26 (3.89–36.51)

N: Number of events, * Incidence Rates and 95% CIs are shown per 10,000 WY. Women may appear in both cohorts.

Overall, incidence rates of VTE, DVT and PE increased with increasing age for both users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg. The IR for VTE and DVT was slightly higher for users of CMA 2 mg/EE 30 µg compared to users of LNG 0.15 mg/EE 30 µg for all age strata, except for women older than 40. The IR for PE was higher for users of LNG 0.15 mg/EE 30 µg, except for study participants aged between 30 and lower than 40 years. There were no PE events in users of CMA 2 mg/EE 30 µg aged 40 and higher and therefore, no incidence rates could be calculated.

The resulting HRs of the crude, adjusted and sensitivity models are comparable with the HRs resulting from the unstratified primary model. However, the number of VTE events identified per

age strata, especially for confirmed PE events were generally too low to generate any precise effect estimates. The resulting HRs comparing CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg and their 95% CI are shown per age subgroup below (Table 13).

Table 13. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for confirmed VTE, DVT and PE stratified by age.

	Hazard Ratio (95% CI)			
	Age <20 years	**Age 20 to <30 years**	**Age 30 to <40 years**	**Age 40+ years**
VTE				
Crude	1.16 (0.33–4.14)	1.23 (0.60–2.53)	1.15 (0.33–3.92)	0.28 (0.03–2.32)
Expert	1.44 (0.38–5.41)	1.47 (0.70–3.11)	1.63 (0.46–5.86)	0.27 (0.03–2.29)
Expert, BMI imputed	1.45 (0.38–5.43)	1.47 (0.69–3.10)	1.63 (0.46–5.85)	0.27 (0.03–2.28)
PS stratification	1.45 (0.40–5.25)	1.59 (0.74–3.44)	1.78 (0.49–6.47)	0.42 (0.05–3.47)
DVT				
Crude	1.53 (0.38–6.14)	1.39 (0.64–3.02)	1.15 (0.33–3.92)	0.43 (0.05–3.92)
Expert	1.84 (0.43–7.78)	1.64 (0.73–3.64)	1.63 (0.46–5.86)	0.39 (0.04–3.46)
Expert, BMI imputed	1.84 (0.44–7.82)	1.63 (0.73–3.64)	1.63 (0.46–5.85)	0.38 (0.04–3.44)
PS stratification	1.81 (0.45–7.36)	1.67 (0.73–3.78)	1.78 (0.49–6.47)	0.69 (0.08–6.38)
PE				
Crude	0.43 (0.04–4.71)	0.96 (0.16–5.77)	2.08 (0.13–33.22)	--
Expert	0.75 (0.06–9.10)	1.34 (0.21–8.63)	4.13 (0.22–78.37)	--
Expert, BMI imputed	0.75 (0.06–9.12)	1.34 (0.21–8.64)	4.16 (0.22–78.95)	--
PS stratification	0.71 (0.06–7.92)	2.57 (0.38–17.25)	4.48 (0.28–71.88)	--

2) Stratification by BMI

Crude, adjusted and sensitivity analyses were performed while stratifying by the following BMI subgroups: 1) lower than 30 kg/m^2 and 2) ≥30 kg/m^2.

The BMI-stratified analysis was based on 22 and 3 confirmed VTEs for users of CMA 2 mg/EE 30 µg and 26 and 9 confirmed VTEs for users of LNG 0.15 mg/EE 30 µg for the BMI groups 1) lower than 30 kg/m^2 and 2) ≥30 kg/m^2 respectively.

Most of the study participants had a BMI lower than 30 kg/m^2. Observation times were 24,357 WY and 1,081 WY for users of CMA 2 mg/EE 30 µg and 29,729 WY and 3,922 WY for users of LNG 0.15 mg/EE 30 µg for the BMI groups 1) lower than 30 kg/m^2 and 2) ≥30 kg/m^2 respectively. Incidence rates and 95% confidence intervals for confirmed VTE, DVT and PE for the different BMI strata are given in Table 14.

Overall, incidence rates of VTE, DVT and PE were substantially higher for study participants having a BMI ≥30 kg/m^2 at baseline compared to study participants with a BMI lower than 30 kg/m^2 for both users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg. The IR for VTE, DVT and PE was again slightly higher for users of CMA 2 mg/EE 30 µg compared to users of LNG 0.15 mg/EE 30 µg for all BMI strata, except for study participants with a BMI lower than 30 kg/m^2 being diagnosed with a PE.

Table 14. Unadjusted (crude), adjusted, and propensity score (PS) adjusted incidence rates for confirmed VTE, DVT and PE stratified by BMI.

	BMI <30 kg/m^2	BMI ≥30 kg/m^2
Number of Women		
CMA 2 mg/EE 30 µg	12,096	601
LNG 0.15 mg/EE 30 µg	15,992	2,568
Women-Years		
CMA 2 mg/EE 30 µg	24,357	1,081
LNG 0.15 mg/EE 30 µg	29,729	3,922

	N	IR (95% CI)*	N	IR (95% CI)*
VTE				
CMA 2 mg/EE 30 µg	22	9.03 (5.66–13.68)	3	27.75 (5.72–81.10)
LNG 0.15 mg/EE 30 µg	26	8.75 (5.71–12.81)	9	22.95 (10.49–43.57)
DVT				
CMA 2 mg/EE 30 µg	21	8.62 (5.34–13.18)	3	27.75 (5.72–81.10)
LNG 0.15 mg/EE 30 µg	21	7.06 (4.37–10.80)	7	17.85 (7.18–36.78)
PE				
CMA 2 mg/EE 30 µg	3	1.23 (0.25–3.60)	1	9.25 (0.23–51.54)
LNG 0.15 mg/EE 30 µg	7	2.35 (0.95–4.85)	3	7.65 (1.58–22.36)

N: Number of events; * Incidence Rates and 95% CIs are shown per 10,000 WY. Women may appear in both cohorts.

The resulting HRs comparing CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg and their 95% CI are shown per BMI subgroup below (Table 15).

Table 15. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for confirmed VTE, DVT and PE stratified by BMI.

	Hazard Ratio (95% CI)	
	BMI <30 kg/m2	**BMI ≥30 kg/m2**
VTE		
Crude	1.00 (0.57–1.77)	1.31 (0.35–4.88)
Expert	1.27 (0.70–2.29)	1.55 (0.40–6.05)
Expert, BMI imputed	1.27 (0.70–2.29)	1.55 (0.40–6.03)
PS stratification	1.19 (0.66–2.14)	1.59 (0.39–6.47)
DVT		
Crude	1.18 (0.64–2.17)	1.65 (0.42–6.44)
Expert	1.41 (0.75–2.65)	2.14 (0.53–8.71)
Expert, BMI imputed	1.41 (0.75–2.65)	2.13 (0.52–8.68)
PS stratification	1.32 (0.70–2.47)	2.23 (0.53–9.49)
PE		
Crude	0.52 (0.14–2.03)	1.42 (0.15–13.62)
Expert	0.93 (0.23–3.78)	1.43 (0.14–14.83)
Expert, BMI imputed	0.93 (0.23–3.76)	1.43 (0.14–14.82)
PS stratification	0.84 (0.21–3.43)	1.11 (0.10–12.18)

The resulting HRs of the crude, adjusted and sensitivity models seem to be higher for study participants with a BMI higher or equal to 30 kg/m^2 compared to those with a BMI lower than 30 kg/m^2. However, since the number of VTE events identified per BMI strata is low, the resulting 95% CI are wide and there is a loss in precision in estimating the effect.

3) Stratification by COC user type

Crude, adjusted and sensitivity analyses were performed while stratifying by the following COC user types subgroups: 1) starter, 2) re-starter and 3) switcher.

Most study participants were COC re-starter, followed by COC switcher (Table 16). The number of VTE, DVT and PE is generally low in starters of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg. Starters of LNG 0.15 mg/EE 30 µg having a higher VTE, DVT and PE incidence rate compared to starters of CMA 2 mg/EE 30 µg. However, the absolute number and IR of VTE in starters of CMA 2 mg/EE 30 µg is likely an underrepresentation of starters in the total population since for most CMA users included in the analysis, exposure of interest was be obtained during follow-up of study participants that originally started with other study specific COC.

The VTE, DVT and PE incidence rate in re-starters and switchers is comparable between the primary exposure cohorts, with a slightly higher incidence rate for users of CMA 2 mg/EE 30 µg compared to users of LNG 0.15 mg/EE 30 µg. There were no PE events in re-starters of CMA 2 mg/EE 30 µg and therefore, no incidence rates could be calculated.

Table 16. Unadjusted (crude), adjusted, and propensity score (PS) adjusted incidence rates for confirmed VTE, DVT and PE stratified by COC user type.

	COC starter		COC re-starter		COC switcher	
Number of Women						
CMA 2 mg/EE 30 µg	3,808		5,540		3,362	
LNG 0.15 mg/EE 30 µg	4,063		9,376		5,230	
Women-Years						
CMA 2 mg/EE 30 µg	5,064		10,695		9,697	
LNG 0.15 mg/EE 30 µg	4,397		16,209		13,103	
	N	**IR (95% CI)***	**N**	**IR (95% CI)***	**N**	**IR (95% CI)***
VTE						
CMA 2 mg/EE 30 µg	1	1.97 (0.05–11.00)	12	11.22 (5.80–19.60)	12	12.37 (6.39–21.62)
LNG 0.15 mg/EE 30 µg	5	11.37 (3.69–26.54)	17	10.49 (6.11–16.79)	13	9.92 (5.28–16.97)
DVT						
CMA 2 mg/EE 30 µg	1	1.97 (0.05–11.00)	12	11.22 (5.80–19.60)	11	11.34 (5.66–20.30)
LNG 0.15 mg/EE 30 µg	4	9.10 (2.48–23.29)	14	8.64 (4.72–14.49)	10	7.63 (3.66–14.03)
PE						
CMA 2 mg/EE 30 µg	1	1.97 (0.05–11.00)	0	--	3	3.09 (0.64–9.04)
LNG 0.15 mg/EE 30 µg	3	6.82 (1.41–19.94)	3	1.85 (0.38–5.41)	4	3.05 (0.83–7.82)

N: Number of events; * Incidence Rates and 95% CIs are shown per 10,000 WY. Women may appear in both cohorts.

The resulting HRs comparing CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg and their 95% CI are shown per COC user subgroup below (Table 17). The risk estimate of VTE, DVT and PE seem to be higher in switchers compared to re-starters and starters of COC respectively. However, since the number of events in the different strata is smaller compared to the complete user cohorts, the corresponding 95% confidence intervals are wide and there is loss in precision in estimating the risk estimates in the COC user strata.

Table 17. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for confirmed VTE, DVT and PE stratified by COC user type.

	Hazard Ratio (95% CI)		
	Starter	**Re-starter**	**Switcher**
VTE			
Crude	0.18 (0.02–1.56)	1.03 (0.49–2.16)	1.25 (0.57–2.74)
Expert	0.22 (0.02–1.95)	1.23 (0.56–2.67)	1.91 (0.82–4.43)
Expert, BMI imputed	0.22 (0.02–1.95)	1.23 (0.56–2.67)	1.91 (0.82–4.43)
PS stratification	0.25 (0.03–2.29)	1.14 (0.52–2.50)	2.07 (0.87–4.94)
DVT			
Crude	0.23 (0.03–2.02)	1.24 (0.57–2.69)	1.48 (0.63–3.51)
Expert	0.28 (0.03–2.63)	1.40 (0.62–3.16)	2.29 (0.91–5.78)
Expert, BMI imputed	0.28 (0.03–2.63)	1.40 (0.62–3.16)	2.30 (0.91–5.79)
PS stratification	0.34 (0.03–3.24)	1.28 (0.57–2.90)	2.48 (0.96–6.42)
PE			
Crude	0.30 (0.03–2.85)	--	1.03 (0.23–4.63)
Expert	0.43 (0.04–4.27)	--	1.79 (0.37–8.76)
Expert, BMI imputed	0.43 (0.04–4.28)	--	1.78 (0.36–8.71)
PS stratification	0.45 (0.04–4.68)	--	2.42 (0.48–12.20)

4) European subgroup

Since there might be differences in underlying VTE risk between European and US populations, due to a difference in baseline risk for VTEs (e.g., higher BMI), an additional sensitivity analysis was conducted on a regional level. Since CMA was not marketed in the US when study participants were recruited, crude, adjusted and sensitivity HRs for VTE, DVT and PE could only be calculated for European study participants.

The absolute numbers of confirmed VTE, DVT and PE and the respective IRs and 95% CIs for users of CMA 2 mg/EE 30 µg and users of LNG 0.15 mg/EE 30 µg in Europe and US/Canada are summarized in Table 18.

For Europe only, there were 25 confirmed VTEs for users of CMA 2 mg/EE 30 µg and 22 confirmed VTEs for users of LNG 0.15 mg/EE 30 µg. Observation times were 12,710 WY and 10,553 WY for users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively.

Overall, incidence rates of VTE, DVT and PE were comparable for European study participants in both users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.

For users of LNG 0.15 mg/EE 30 µg, there was a slightly higher IR for VTE in US/Canadian study participants compared with the European user cohort: 11.88 VTEs/10,000 WY (95% CI: 6.33–20.32) versus 9.66 VTEs/10,000 WY (95% CI: 6.05–14.63).

Table 18. Unadjusted (crude), adjusted, and propensity score (PS) adjusted incidence rates for confirmed VTE, DVT and PE stratified by region.

	Europe		US/Canada	
Number of Women				
CMA 2 mg/EE 30 µg	12,710		0	
LNG 0.15 mg/EE 30 µg	10,553		8,116	
Women-Years				
CMA 2 mg/EE 30 µg	25,457		0	
LNG 0.15 mg/EE 30 µg	22,772		10,938	
	N	**IR (95% CI)***	**N**	**IR (95% CI)***
VTE				
CMA 2 mg/EE 30 µg	25	9.82 (6.36–14.50)	--	--
LNG 0.15 mg/EE 30 µg	22	9.66 (6.05–14.63)	13	11.88 (6.33–20.32)
DVT				
CMA 2 mg/EE 30 µg	24	9.43 (6.04–14.03)	--	--
LNG 0.15 mg/EE 30 µg	19	8.34 (5.02–13.03)	9	8.23 (3.76–15.62)
PE				
CMA 2 mg/EE 30 µg	4	1.57 (0.43–4.02)	--	--
LNG 0.15 mg/EE 30 µg	5	2.20 (0.71–5.12)	5	4.57 (1.48–10.67)

N: Number of events; * Incidence Rates and 95% CIs are shown per 10,000 WY.
Women may appear in both cohorts.

The resulting HRs comparing CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg and their 95% CI for European participants are shown in Table 19. In summary, the HRs of the crude, adjusted and sensitivity models are comparable with the HRs resulting from the unstratified primary model.

Table 19. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for confirmed VTE, DVT and PE for Europe only.

	Hazard Ratio (95% CI) **Europe only**
VTE	
Crude	1.02 (0.57–1.81)
Expert	1.19 (0.66–2.15)
Expert, BMI imputed	1.19 (0.66–2.15)
PS stratification	1.13 (0.63–2.03)
DVT	
Crude	1.13 (0.62–2.06)
Expert	1.28 (0.69–2.37)
Expert, BMI imputed	1.28 (0.69–2.37)
PS stratification	1.21 (0.65–2.24)
PE	
Crude	0.72 (0.19–2.70)
Expert	0.99 (0.26–3.82)
Expert, BMI imputed	0.99 (0.26–3.82)
PS stratification	0.98 (0.25–3.74)

10.3.3 Secondary Objective – Risk of VTE in Other CMA and LNG Exposure Cohorts

The crude, adjusted (expert), BMI imputed and PS-adjusted Cox models were as well applied for the secondary exposure cohorts I and II. The resulting HRs for confirmed VTE, DVT and PE are in line with the HRs from the primary analysis model, however, since the number of VTE events identified is proportionally larger as the numbers of CMA- and LNG-containing COC users is larger, the resulting 95% confidence intervals are less wide, thus, the effect estimate is more precise. The resulting HRs and their 95% CIs are included in Table 20 for CMA/EE ≤30 µg vs. LNG/EE ≤30 µg and in Table 21 for users exposed to CMA/EE vs. LNG/EE.

For the secondary exposure cohorts I, the analysis was based on 99 confirmed VTE events: 25 VTEs in users of CMA/EE ≤30 µg and 74 VTEs in users of LNG/EE ≤30 µg. The incidence rate was comparable in both user cohorts: 9.54 VTEs/10,000 WY (95% CI: 6.17–14.08) for CMA/EE ≤30 µg and 9.01 VTEs/10,000 WY (95% CI: 7.08–11.31) for LNG/EE ≤30 µg. More details can be found in Annex 3.4.1.

The crude model resulted in an HR for CMA/EE ≤30 µg vs. LNG/EE ≤30 µg of 1.05 (95% CI: 0.67–1.66). After adjusting for age, BMI, family history of VTE and current duration of use (expert model), the adjusted HR was 1.35 (95% CI: 0.85–2.15). Sensitivity analyses with BMI imputed per study and region of origin and the PS-adjusted analysis, to control for imbalance in baseline characteristics, resulted in HRs of 1.35 (95% CI: 0.85–2.15) and 1.31 (95% CI: 0.82–2.08) respectively.

For DVT, the crude HR of CMA/EE ≤30 µg vs. LNG/EE ≤30 µg was 1.21 (95% CI: 0.75–1.93). The expert and BMI adjusted model resulted in the same HR of 1.50 (95% CI: 0.93–2.43); the PS stratified model resulted in a HR of 1.44 (95% CI: 0.89–2.33).

For PE, a crude HR of 0.63 (95% CI: 0.22–1.85) was observed. When adjusting the model, the HRs were 0.93 (95% CI: 0.31–2.76), 0.92 (95% CI: 0.31–2.76) and 1.07 (95% CI: 0.35–3.22) for the expert, BMI imputed expert and PS stratified model respectively.

Table 20. Crude, adjusted, and PS adjusted HRs for confirmed VTE, DVT and PE for users of CMA/EE ≤30 µg vs. LNG/EE ≤30 µg (secondary exposure cohorts I).

	Hazard Ratio (95% CI)
	CMA/EE ≤30 µg vs. LNG/EE ≤30 µg
VTE	
Crude	1.05 (0.67–1.66)
Expert	1.35 (0.85–2.15)
Expert, BMI imputed	1.35 (0.85–2.15)
PS stratification	1.31 (0.82–2.08)
DVT	
Crude	1.21 (0.75–1.93)
Expert	1.50 (0.93–2.43)
Expert, BMI imputed	1.50 (0.93–2.43)
PS stratification	1.44 (0.89–2.33)
PE	
Crude	0.63 (0.22–1.85)
Expert	0.93 (0.31–2.76)
Expert, BMI imputed	0.92 (0.31–2.76)
PS stratification	1.07 (0.35–3.22)

For the secondary exposure cohorts II, the analysis was based on 109 confirmed VTE events: 29 VTEs in users of CMA/EE and 80 VTEs in users of LNG/EE. The incidence rate was slightly higher for users of CMA/EE vs. LNG/EE: 9.63 VTEs/10,000 WY (95% CI: 6.45–13.83) and 8.39 VTEs/10,000 WY (95% CI: 6.65–10.44) respectively. More details can be found in Annex 3.4.2.

The crude model resulted in an HR for CMA/EE vs. LNG/EE of 1.14 (95% CI: 0.75–1.75). After adjusting for age, BMI, family history of VTE and current duration of use (expert model), the adjusted HR was 1.48 (95% CI: 0.96–2.28). The BMI imputed analysis, to assess the impact of possible bias due to missing BMI data, and the PS-adjusted analysis, to control for imbalance in baseline characteristics, resulted in HRs of 1.48 (95% CI: 0.96–2.28) and 1.43 (95% CI: 0.92–2.21) respectively.

For DVT, the crude HR of CMA/EE vs. LNG/EE was 1.29 (95% CI: 0.83–2.01). The expert and BMI adjusted model resulted in the same HR of 1.62 (95% CI: 1.03–2.55); the PS stratified model resulted in a HR of 1.56 (95% CI: 0.99–2.45).

For PE, a crude HR of 0.58 (95% CI: 0.20–1.69) was observed. When adjusting the model, the HRs were 0.85 (95% CI: 0.29–2.53), 0.85 (95% CI: 0.29–2.52) and 0.99 (95% CI: 0.33–2.97) for the expert, BMI imputed expert and PS stratified model respectively.

Table 21. Crude, adjusted, and PS adjusted HRs for confirmed VTE, DVT and PE for users of CMA/EE vs. LNG/EE (secondary exposure cohorts II).

	Hazard Ratio (95% CI)
	CMA/EE vs. LNG/EE
VTE	
Crude	1.14 (0.75–1.75)
Expert	1.48 (0.96–2.28)
Expert, BMI imputed	1.48 (0.96–2.28)
PS stratification	1.43 (0.92–2.21)
DVT	
Crude	1.29 (0.83–2.01)
Expert	1.62 (1.03–2.55)
Expert, BMI imputed	1.62 (1.03–2.55)
PS stratification	1.56 (0.99–2.45)
PE	
Crude	0.58 (0.20–1.69)
Expert	0.85 (0.29–2.53)
Expert, BMI imputed	0.85 (0.29–2.52)
PS stratification	0.99 (0.33–2.97)

10.3.4 Sensitivity – All VTEs, Confirmed and Not-Confirmed

In a final sensitivity analysis, the outcome was not restricted to "confirmed" VTEs only, and also "not confirmed" VTEs were included. This sensitivity analysis was based on 148 VTEs (confirmed and not confirmed): 64 in CMA 2 mg/EE 30 µg users (25.2 per 10,000 WY; 95% CI, 19.41–32.19), 84 in LNG 0.15 mg/EE 30 µg users (25.0 per 10,000 WY; 95% CI, 19.94–30.95) (Table 22). Of the total reported VTE events, the proportion of confirmed and not confirmed VTEs was similar in both exposure cohorts of primary interest. In users of CMA 2 mg/EE 30 µg, 25 (39.1%) VTEs were confirmed and 39 (60.9%) were not conformed while 35 (41.7%) VTEs were confirmed and 49 (58.3%) were not confirmed in users of LNG 0.15 mg/EE 30 µg.

Table 22. Absolute numbers and incidence rates of all VTE (confirmed and not confirmed) events.

	Incidence Rate (95% CI)	
	CMA 2 mg/EE 30 µg (N=12,697)	*LNG 0.15 mg/EE 30 µg (N=18,649)*
Women years	25,392	33,603
VTE (confirmed and non-confirmed)		
Number of events	64	84
IR (95% CI)*	25.2 (19.41–32.19)	25.0 (19.94–30.95)

Note: All confirmed and non-confirmed VTE events were considered as cases and triggered end of observation at the time of the event date. Recurrent VTE events were excluded; subsequently, the number of women and women-years is lower compared to the primary exposure cohorts. * Incidence Rates and 95% CIs are shown per 10,000 WY. Women may appear in both cohorts.

The results of the crude, adjusted and sensitivity Cox models including all reported VTEs (confirmed and not confirmed) are shown in Table 23. The resulting HRs and their 95% confidence intervals are in line with the HRs from the primary analysis model, however, a two-fold increase in hazard ratio could be excluded for both the crude and the adjusted models. When including all VTEs (confirmed and not confirmed), the crude HR was 1.02 (95% CI: 0.73–1.41), the expert model resulted in an adjusted HR of 1.26 (95% CI: 0.89–1.77). The sensitivity models accounting for missing BMI data and imbalance in baseline data (PS-adjusted) resulted in a HR of 1.26 (95% CI: 0.89–1.77) and 1.28 (0.91–1.81) respectively.

Table 23. Unadjusted (crude), adjusted, and propensity score (PS) adjusted HRs for all VTE (confirmed and not confirmed) events.

	Hazard Ratio (95% CI) *CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg*
VTE (confirmed and non-confirmed)	
Crude	1.02 (0.73–1.41)
Expert	1.26 (0.89–1.77)
Expert, BMI imputed	1.26 (0.89–1.77)
PS stratification	1.28 (0.91–1.81)

10.4 Part D: Results of the Exploratory Objective

As an exploratory objective, population characteristics and distribution of risk factors for VTE cases identified in RIVET-CC and RIVET-RCS were described and compared to further improve the understanding of potential underlying differences of the distribution of risk factors for VTE.

10.4.1 RIVET-CC: Selection of the Analysis Population

Between May 2016 and April 2022, 720 VTE cases were enrolled in the RIVET-CC study. Of these, 33 (4.6%) were exposed to CMA/EE and 119 (16.5%) were exposed to LNG/EE at the time of their first VTE symptoms. In RIVET-CC, 31 (4.3%) VTE cases exposed to CMA 2 mg/EE 30 µg and 53 (7.4%) VTE cases exposed to LNG 0.15 mg/EE 30 µg at time of first VTE symptoms were recruited. Most of the VTE cases were recruited in Germany (93.5% and 96.2% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively), while only few were recruited in Austria (6.5% and 3.8% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively).

Between May 2026 and April 2022, 464 controls were recruited. Of these, 19 (4.1%) were users of CMA/EE and 62 (13.4%) were users of LNG/EE. Only 7 (1.5%) and 9 (1.9%) were exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg respectively. Controls were participants free of the disease and were therefore not included for further descriptive analyses.

The number of recruited VTE cases in RIVET-CC is considerably high considering the low incidence of VTE in the general population: in comparison to RIVET-RCS, 25 and 35 confirmed VTEs were observed in users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively. Data collected on VTE cases in the RIVET-CC study were used to better understand the distribution of VTE and its current management in clinical practice.

10.4.2 Baseline Characteristics and Risk Factors of VTE Cases

Baseline characteristics of VTE cases identified in RIVET-CC exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg were summarized in Table 24. In addition, baseline characteristics of study participants from RIVET-RCS with a VTE diagnosis during follow-up are shown and compared to the VTE cases identified in RIVET-CC.

The VTE cases from RIVET-CC were slightly older at baseline compared to women diagnosed with a VTE in RIVET-RCS for both CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg, which can be explained by the difference in epidemiological design of the selected study population (case-control vs. cohort). In RIVET-CC, the mean age at study entry – which is shortly after the VTE diagnosis – of VTE cases was 31.0 (± 9.71) years and 34.7 (± 9.35) years for CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg users respectively. In RIVET-RCS, the mean age at study entry for women diagnosed with a VTE was 24.9 (±6.63) years and 30.4 (±9.77) years for CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg users respectively. Therefore, the mean age at VTE diagnosis was also presented for the women diagnosed with a VTE in RIVET-RCS (27.8 (±6.76) years and 33.0 (±10.68) years for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg,

respectively). When compared with the age at VTE diagnosis, the difference in age is comparable between study participants from RIVET-CC and RIVET-RCS.

In RIVET-CC, VTE cases exposed to LNG 0.15 mg/EE 30 µg had a slightly higher BMI at baseline (28.0 kg/m^2 vs. 25.6 kg/m^2) and more women had ever been pregnant (58.5% vs. 38.7%) and had given birth before (52.8% vs. 29.0%) compared to VTE cases exposed to CMA 2 mg/EE 30 µg. The difference in distribution for BMI, parity and gravidity between both user cohorts is similar for women diagnosed with a VTE in RIVET-RCS.

In addition, data on cardiovascular risk factors which occurred 6 weeks prior to VTE diagnosis were collected directly from RIVET-CC study participants which were not collected in the RIVET-RCS study. These include pregnancy, delivery, accident, immobility, surgery, long travel, standing occupation and chemotherapy in the 6 weeks prior to VTE diagnosis. Most common risk factors reported by the study participants were standing occupation in the last 6 weeks – 9.7% vs. 24.5% and long travel in the last 6 weeks – 16.1% vs. 9.4% in users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively. The distribution of prior surgery, immobility and pregnancy was 6.5% for CMA 2 mg/EE 30 µg users and 9.4% for LNG 0.15 mg/EE 30 µg users. A higher proportion of users of CMA 2 mg/EE 30 µg (12.9% vs. 1.9%) had an accident 6 weeks prior to their VTE diagnosis, while a higher proportion of users of LNG 0.15 mg/EE 30 µg had a delivery (5.7% vs. 0.0%) and chemotherapy (1.9% vs. 0.0%) 6 weeks prior to VTE diagnosis.

COC history was comparable for both CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg: all (100%) VTE cases had a history of OC use of which most were switchers, 67.7% and 77.4% respectively. For RIVET-RCS, also most women diagnosed with a VTE had used a COC before (84.0% vs. 82.9%), of which most were re-starters: 44.0% and 60.0% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively.

Family history of VTE was higher in VTE cases exposed to LNG 0.15 mg/EE 30 µg compared to CMA 2 mg/EE 30 µg, 28.3% vs. 16.1% respectively. The opposite was seen in the distribution of family history of VTE in study participants diagnosed with a VTE in RIVET-RCS (16.0% vs. 8.6%). Smoking was also higher in VTE cases exposed to LNG 0.15 mg/EE 30 µg compared to CMA 2 mg/EE 30 µg, 26.4% vs. 9.7% respectively, while in RIVET-RCS smoking was more balanced between both user cohorts. The proportion of women who smoke was slightly higher in RIVET-RCS compared to RIVET-CC, which can be explained by the regional differences from where the study participants were recruited (Germany/Austria vs. Eastern European countries).

Similar to baseline distributions in RIVET-RCS, women from RIVET-CC exposed to LNG 0.15 mg/EE 30 µg had a higher regular intake of concomitant medications compared to users of CMA 2 mg/EE 30 µg at baseline: 37.3% vs. 32.3%, respectively. However, differences in distributions were larger in RIVET-RCS (42.9% vs. 24.0%).

Education level was also different between VTE cases exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg. For users of CMA 2 mg/EE 30 µg, most study participants had a university degree or higher, with 51.6% and 19.4% having a university level and higher than university level. For users of LNG 0.15 mg/EE 30 µg, 26.4% and 13.2% had a university level and higher than university level, and most study participants, 60.4%, had an education less than university entrance level. For RIVET-RCS, education level was well balanced between both

exposure cohorts, most of the participants with a VTE diagnosis had a university level degree or higher.

Baseline characteristics of users of CMA/EE and LNG/EE were summarized and included in Annex 3.5. Similarly, to users of CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg, the distribution of baseline characteristics between both CMA/EE and LNG/EE are similar between RIVET-CC and RIVET-RCS as for the primary exposure cohorts of interest.

Table 24. Baseline characteristics of women exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg users having a diagnosed VTE – RIVET-CC vs. RIVET-RCS. ***Continued on next page***

	Mean (Std) or Relative frequency			
	RIVET-CC		**RIVET-RCS**	
	CMA 2 mg/ EE 30 µg	*LNG 0.15 mg/ EE 30 µg*	*CMA 2 mg/ EE 30 µg*	*LNG 0.15 mg/ EE 30 µg*
Number (%) of women	31	53	25	35
Patient characteristics				
Age at study entry (years)	31.0 (±9.71)	34.7 (±9.35)	24.9 (±6.63)	30.4 (±9.77)
Age at diagnosis	31.0 (±9.71)	34.7 (±9.35)	27.8 (±6.76)	33.0 (±10.68)
Age <20 years	4 (12.9%)	3 (5.7%)	6 (24.0%)	4 (11.4%)
20 to <30 years	12 (38.7%)	14 (26.4%)	14 (56.0%)	16 (45.7%)
30 to <40 years	7 (22.6%)	16 (30.2%)	4 (16.0%)	7 (20.0%)
40+ years	7 (22.6%)	20 (37.7%)	1 (4.0%)	8 (22.9%)
Weight at study entry (kg)	72.6 (±17.02)	79.7 (±23.91)	69.3 (±14.72)	74.0 (±17.66)
Height at study entry (cm)	168.1 (±6.54)	168.4 (±7.13)	167.9 (±6.23)	167.5 (±6.99)
BMI at study entry (kg/m^2)	25.6 (±5.67)	28.0 (±8.13)	24.5 (±3.98)	26.4 (±6.39)
BMI <20 kg/m^2	2 (6.5%)	6 (11.3%)	3 (12.0%)	2 (5.7%)
20 to <25	17 (54.8%)	18 (34.0%)	12 (48.0%)	17 (48.6%)
25 to <30	6 (19.4%)	12 (22.6%)	7 (28.0%)	7 (20.0%)
30 to <35	4 (12.9%)	8 (15.1%)	3 (12.0%)	4 (11.4%)
≥35	2 (6.5%)	9 (17.0%)	0 (0.0%)	5 (14.3%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gynecological History				
Ever been pregnant (gravidity)	12 (38.7%)	31 (58.5%)	7 (28.0%)	21 (60.0%)
Ever given birth (parity)	9 (29.0%)	28 (52.8%)	6 (24.0%)	20 (57.1%)
Number of live births	1.4 (±0.53)	1.9 (±0.90)	1.2 (±0.41)	2.0 (±1.17)
HC History				
Ever used OC	31 (100%)	53 (100%)	21 (84.0%)	29 (82.9%)
Duration of HC use (years)	2.0 (±2.14)	6.0 (±7.93)	6.4 (±6.56)	10.6 (±8.73)
Starter	0 (0.0%)	0 (0.0%)	4 (16.0%)	6 (17.1%)

	Mean (Std) or Relative frequency			
	RIVET-CC		**RIVET-RCS**	
	CMA 2 mg/ EE 30 µg	*LNG 0.15 mg/ EE 30 µg*	*CMA 2 mg/ EE 30 µg*	*LNG 0.15 mg/ EE 30 µg*
Switcher	21 (67.7%)	41 (77.4%)	10 (40.0%)	8 (22.9%)
Re-starter	--	--	11 (44.0%)	21 (60.0%)
Incident user*	9 (29.0%)	12 (22.6%)	--	--
Cardiovascular Risk Factors				
Pregnancy in the last 6 weeks	2 (6.5%)	5 (9.4%)	--	--
Delivery in the last 6 weeks	0 (0.0%)	3 (5.7%)	--	--
Accident in the last 6 weeks	4 (12.9%)	1 (1.9%)	--	--
Immobility in the last 6 weeks	2 (6.5%)	5 (9.4%)	--	--
Surgery in the last 6 weeks	2 (6.5%)	5 (9.4%)	--	--
Long travel in the last 6 weeks	5 (16.1%)	5 (9.4%)	--	--
Standing occupation in the last 6 weeks	3 (9.7%)	13 (24.5%)	--	--
Chemotherapy in the last 6 weeks	0 (0.0%)	1 (1.9%)	--	--
Family history of VTE	5 (16.1%)	15 (28.3%)	4 (16.0%)	3 (8.6%)
Current smoker	3 (9.7%)	14 (26.4%)	9 (36.0%)	13 (37.1%)
Heavy smoker (>15 cig)	0 (0.0%)	1 (1.9%)	1 (4.0%)	3 (8.6%)
Medication				
Regular use of medication	10 (32.3%)	20 (37.7%)	6 (24.0%)	15 (42.9%)
Education				
Less than university entrance level	9 (29.0%)	32 (60.4%)	1 (4.0%)	4 (11.4%)
University entrance level	16 (51.6%)	14 (26.4%)	8 (32.0%)	14 (40.0%)
Higher than university entrance level	6 (19.4%)	7 (13.2%)	12 (48.0%)	16 (45.7%)

*Incident users are defined as having a hormonal contraception intake break of at least 3 months. One woman could not be classified as incident user and is considered 'missing' according to COC-user type.

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10.4.3 RIVET-CC: Summary of VTE Characteristics

In RIVET-CC, data was also collected directly from the physician regarding symptoms, examination, and treatment of VTE. The results for VTE cases exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg at time of first symptoms is given in Table 25, Table 26 and Table 27.

Table 25. Symptoms of VTE for CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg.

	Mean (Std) or Relative frequency	
	CMA 2 mg/EE 30 µg	*LNG 0.15 mg/EE 30 µg*
Number (%) of women	31 (100%)	53 (100%)
Symptoms of VTE		
Swelling of leg	13 (41.9%)	33 (62.3%)
Coloring of leg	1 (3.2%)	3 (5.7%)
Heat of leg	2 (6.5%)	9 (17.0%)
Protrusion of leg	0 (0.0%)	2 (3.8%)
Heaviness/tension or weakness of leg	11 (35.5%)	21 (39.6%)
Sensitivity of leg	4 (12.9%)	9 (17.0%)
Shortness of breath	7 (22.6%)	12 (22.6%)
Other symptoms	17 (54.8%)	23 (43.4%)
No symptoms	0 (0.0%)	0 (0.0%)

Note: Women may appear in more than one category.

Of the VTE cases exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg, respectively 54.8% and 43.4% indicated to have other symptoms. These include calf cramps, calf pain, chest pain, dizziness or increased exertional dyspnoea. Study participants having had a DVT mainly reported swelling of leg (41.9% and 62.3% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively), heaviness/tension or weakness of the leg (35.5% and 39.6% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively) or sensitivity in the leg (12.9% and 17.0% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively). Study participants having had a PE mainly reported shortness of breath (22.6% and 22.6% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively).

Table 26 lists the diagnostic procedures used by the HCP to diagnose the VTE. For DVT, doppler ultrasound (38.7% and 47.2%) and duplex sonography (74.2% and 79.2%) were most commonly used for both users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg. For PE, a computerized tomography (CT) scan was the most used diagnostic procedure (25.8% and 26.4% for CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively).

In 16.1% and 13.2% of VTE cases examination for genetic mutation was done for users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg respectively, while in 45.2% and 52.8% hypercoagulation markers were measured to examine blood coagulation disorder(s).

Table 26. Examination of VTE for CMA 2 mg/EE 30 µg vs. LNG 0.15 mg/EE 30 µg

	Mean (Std) or Relative frequency	
	CMA 2 mg/EE 30 µg	*LNG 0.15 mg/EE 30 µg*
Number (%) of women	31 (100%)	53 (100%)
Diagnosis of DVT confirmed with the following examination		
Doppler ultrasound	12 (38.7%)	25 (47.2%)
Duplex sonography	23 (74.2%)	42 (79.2%)
Phlebography	2 (6.5%)	0 (0.0%)
CT or MRT	2 (6.5%)	6 (11.3%)
Other	0 (0.0%)	1 (1.9%)
Diagnosis of PE confirmed with the following examination		
X-ray	0 (0.0%)	0 (0.0%)
Scintigraphy	0 (0.0%)	1 (1.9%)
Angiography	0 (0.0%)	2 (3.8%)
CT of the lung	8 (25.8%)	14 (26.4%)
Pressure check of pulmonary artery	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	1 (1.9%)
Diagnosis of blood clotting confirmed with the following examination		
Genetic mutation	5 (16.1%)	7 (13.2%)
Hypercoagulation markers	14 (45.2%)	28 (52.8%)

Note: Women may appear in more than one category.

Most VTE cases exposed to CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg were treated with anticoagulants (93.5% and 100% respectively), followed by treatment with bandages (80.6% and 83.0% respectively. Other treatments given were bedrest, surgery, referral to a specialist/hospital and other medication/treatment. Observation was only done for 3.2% and 1.9% of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg users respectively. More details can be found in Table 27.

Table 27. Treatment of VTE for CMA 2 mg/EE 30µg vs. LNG 0.15 mg/EE 30µg.

	Mean (Std) or Relative frequency	
	CMA 2 mg/EE 30 µg	*LNG 0.15 mg/EE 30 µg*
Number (%) of women	31 (100%)	53 (100%)
Treatment of VTE		
Observation only	1 (3.2%)	1 (1.9%)
Bed rest	0 (0.0%)	2 (3.8%)
Thrombolysis	0 (0.0%)	1 (1.9%)
Anticoagulation	29 (93.5%)	53 (100%)
Other medication	1 (3.2%)	1 (1.9%)
Bandages	25 (80.6%)	44 (83.0%)
Surgery	1 (3.2%)	1 (1.9%)
Other treatment	0 (0.0%)	1 (1.9%)
Referral to specialist	4 (12.9%)	15 (28.3%)
Referral to hospital	3 (9.7%)	6 (11.3%)
No treatment	0 (0.0%)	0 (0.0%)

Note: Women may appear in more than one category.

Descriptive analyses on VTE symptoms, examination and treatment were repeated for users of CMA/EE and LNG/EE. Results of these analyses are comparable to distribution seen in users of CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg and are included in Annex 3.6.

11 DISCUSSION

This RIVET-RCS pooled analysis aimed to assess the risk of VTE in users of COC with primary focus on users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.

To the investigator's knowledge, this is the first large observational cohort study investigating the risk of VTE in users of CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg. In addition, results included in this report contribute to a better understanding of population characteristics and risk of VTE, its distribution and management in clinical practice in users exposed to CMA-or LNG-containing COCs.

The incidence of VTE is rare amongst healthy women of reproductive age, with rates reported between 5 and 10 per 10,000 WY (6). Therefore, large data sources with qualitative data on rare outcomes such as VTE are warranted. A recent paper compared the risk of VTE in users of CMA-containing versus LNG (EE <50 µg)-containing COCs as a reference using German Claims Data in users ≤19 years of age (7). The researchers found an increased VTE risk for CMA compared to LNG-containing COCs (adjusted Odds Ratio: 2.06, 95% CI: 1.58–2.68). In contrast, while the investigators of the RIVET-RCS study could not exclude a 2.0-fold risk of VTE in users of CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg in the primary Cox model, this model did not prove a definite increased risk either in the investigated age group between 15 and 49 years. The validity of this finding was supported via use of several secondary and sensitivity analyses.

The RIVET-RCS study benefited from a large comparative study design which optimized the validity of the results within the framework of the inherent limitations of observational studies. Furthermore, data on important potential confounders were uniformly captured, outcomes of interest were consistently validated, captured VTEs were subjected to blinded adjudication by independent experts and a SMAC maintained scientific oversight for the duration of the study. Additionally, the investigators of the RIVET-RCS study performed this research in line with the ENCePP Code of Conduct and received the ENCePP Seal (EUPAS12171), indicating scientific independency of the study funder(s) in study conduct and interpretation of the results.

Valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology help reduce the impact of bias and residual confounding (8). Valid information on many relevant prognostic factors were available for RIVET-RCS and the statistical analyses incorporated suggestions by the scientific advisory council as well as the PRAC.

11.1 KEY RESULTS

Results included in this report primarily focus on COC users exposed to CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.

The RIVET-RCS analysis set included data from 257,481 users of COCs containing CMA or LNG, of those 12,710 were exposed to CMA 2 mg/EE 30 µg and 18,669 were exposed to LNG 0.15 mg/EE 30 µg accounting for 25,457 and 33,710 WY, respectively.

Data included in the RIVET-RCS analysis comes from users of CMA and LNG in 14 different countries: Austria, Belgium, Canada, Denmark, France, Germany, Italy, the Netherlands, Poland, Ukraine, United Kingdom, USA, Russia, and Sweden.

Overall, baseline characteristics were similar for the CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg users. The similarities include age, weight, height, BMI, cardiovascular risk factors (e.g., family history of VTE and smoking), medical history, history of hormonal contraceptives and education. Moderate differences were found with respect to parity and gravidity: a higher proportion of LNG 0.15 mg/EE 30 µg users had delivered a child or had been pregnant prior to study entry. The average number of COC treatment episodes and average length of COC episode was found similar in both users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg.

In total, 60 confirmed VTEs were observed of which 25 in users of CMA 2 mg/EE 30 µg and 35 in users of LNG 0.15 mg/EE 30 µg. The incidence rate for VTE was comparable for users of CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg, with incidence rates of 9.82 VTE/10,000 WY (95% CI: 6.36–14.50) and 10.38 VTE/10,000 WY (95% CI: 7.23–14.44) respectively. Breaking down VTE into deep venous thrombosis (DVT) and pulmonary embolism (PE) showed similar results for users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg (DVT IR: 9.43, 95% CI: 6.94–14.03 and 8.31, 95% CI: 5.52–12.00, respectively), although the incidence rate of PE was slightly lower in users of CMA 2 mg/EE 30 µg (PE IR: 1.57, 95% CI: 0.43–4.02 and 2.97, 95% CI: 1.42–5.46, respectively).

The primary Cox model showed an adjusted HR for CMA 2 mg/EE 30 µg versus LNG 0.15 mg/EE 30 µg of 1.24 (95% CI: 0.74–2.14). The corresponding 95% CI did include unity and a 2.0-fold increase in risk for VTE could not be excluded for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg. This result is supported in principle by the results of 1) several sensitivity analyses, including imputation to account for missing data of BMI and PS stratification to account for imbalance in baseline population characteristics, 2) several subgroup analyses, stratifying by age, BMI, COC user status and in European participants only as well as 3) repeating the analyses including all self-reported VTEs. The resulting HRs and their 95% confidence intervals are comparable to the HRs from the primary analysis model.

Descriptive and inferential analyses were repeated for secondary exposure cohorts focusing on COC users of 1) CMA/EE ≤30 µg vs. LNG/EE ≤30 µg (secondary exposure cohorts I) and 2) CMA/EE vs. LNG/EE (secondary exposure cohorts II). Both secondary exposure cohorts I and II had a higher absolute number of VTEs diagnosed during follow-up compared to the primary exposure cohorts of interest, since the number of study participants and available WY of observation increased proportionally when widening the dosage restrictions for CMA, LNG and EE. The descriptive as well as the results from the crude and adjusted Cox models for the secondary exposure cohorts I and II did not differ substantially from the results from the primary exposure cohorts.

Interim baseline data of VTE cases exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg from RIVET-CC, a prospective case-control study, was compared to data from study participants diagnosed with a VTE in RIVET-RCS. In addition, patient and physician collected data from

RIVET-CC was used to better understand the distribution of VTE and its current management in clinical practice. Women having a VTE while exposed to CMA 2 mg/EE 30 µg or LNG 0.15 mg/EE 30 µg are generally aged 30 or older and have used an oral contraceptive before (>82.9%). Common cardiovascular risk factors reported were family history of VTE, standing occupation in the past 6 weeks prior to first symptoms and long travel in the past 6 weeks prior to first symptoms. Most common reported first symptoms of VTE were swelling of leg and heaviness/tension or weakness of the leg for DVT and shortness of breath for PE. In clinical practice, most DVTs were diagnosed via use of doppler ultrasound or duplex sonography, while PEs were mostly diagnosed via a CT scan of the lung(s). VTEs were mostly treated with bandages, anticoagulation or referral to a specialist.

11.2 Limitations

In non-experimental studies like EURAS-OC/LASS, INAS-OC, INAS-FOCUS and INAS-SCORE, the possibility of chance, bias and residual confounding can never be entirely eliminated, and the ability to infer causation is correspondingly limited (9). Valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology helps to reduce the impact of bias and residual confounding (8). However, the difficulty remains unresolved when all that exists is a weak association (10, 11). Relative risk estimates that are close to unity may not allow differentiation between causation, bias, and confounding (12, 13). In general, it is very difficult to interpret a relative risk of two or less in observational research (14, 15).

Within the EURAS-INAS methodology special attention was paid to typical biases of observational studies:

- Enrolment bias – Sites consecutively enrolled eligible participants and maintained screening logs of all participants meeting eligibility criteria, along with reasons for non-enrolment.
- Channelling bias – Factors associated with any of the study outcomes of interest were measured at baseline and were accounted for in the multivariate analyses.
- Follow-up bias – Overall, the loss to follow-up rate was low (between 3–16%) in each of the four studies. A low loss to follow-up rate could be achieved, in part due to the ability of the type of study to follow up directly with participants even if they did not return to the enrolling centre. In theory, a disproportionately high percentage of SAEs could occur in those patients who are lost to follow-up, because significant events (pregnancy, VTE, and other SAEs) could be the reason for the break-in contact with the HCPs. An advantage of the EURAS-INAS study design, however, was that the study team had direct contact with the participants. Contact was not lost if the women change their gynecologists, for example (e.g., due to a change of residence or dissatisfaction with treatment).
- Selection bias – With the approach used in the EURAS-INAS study design, selection bias is not a major issue because gynecological practitioners, as well as clinics and family planning centres, etc., participate, leading to a representative mix of the typical institutions prescribing and inserting intrauterine contraceptive devices.

- Misclassification bias – Since precise information on the exposure and the outcomes of interest were obtained, misclassification bias does not have a substantial impact on the results.
- Depletion of susceptible before study entry can never be fully excluded, but the inclusion of new users and additional stratified analyses by user type was performed to reduce the impact of this bias.
- Neyman bias – The methodology used in the present type of active surveillance study was not prone to the relevant criteria. The participants were healthy when included, and exposure starts with COCs under study. The observation was started simultaneously with a carefully designed follow-up schedule. Furthermore, there was no rationale indicating that any relevant effects would be differential between the two cohorts.

The studies included in this pooled analysis combine several methodological strengths that are substantial for the validity of the results such as: 1) prospective, comparative cohort design; 2) availability of important confounder information (e.g. BMI and family history of VTE); 3) validation of outcomes of interest and exposure for the relevant cases; 4) comprehensive follow-up procedure and low loss to follow-up to minimize underreporting; 5) independent, blinded adjudication of VTE cases; 6) a diverse study population representative for oral contraceptive users under routine clinical conditions; 7) quite different statistical approaches resulting in similar risk estimates and 95% CIs support the validity and robustness of the primary statistical model; and 8) supervision by an independent Safety Monitoring and Advisory Council as well as scientific independence from the study funder. In summary, the RIVET-RCS study led to results that are valid within the general limitations of observational research.

11.3 Interpretation

The primary analysis focused on excluding a twofold risk. Accordingly, the null hypothesis prior to the analysis was: HR>2 (i.e., the adjusted VTE hazard ratio for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg is higher than 2). The a priori power of the pooled analysis to exclude a twofold VTE risk for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg was approximately 80% based on type-I error of 5% (one-sided).

The primary statistical analysis, as well the several sensitivity analyses could not exclude a two-fold risk of VTE for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg based on 95% CIs. The same results were seen when comparing the risk of VTE, DVT and PE in the other CMA and LNG secondary exposure cohorts analyzed in this study.

Several secondary and sensitivity analyses were performed showing high external validity of the estimated effects and its 95% CIs.

In order to reduce the potential of observed differences in the distribution of established risk factors for cardiovascular events, a propensity score sub-classification was carried out, which successfully balanced baseline characteristics between sub-cohorts, as expressed by standardized differences consistently below 0.25. This approach equally accounted for confounding variables in both sub-cohorts, rendering them comparable with regards to the occurrence of treatment-related events.

A comparative analysis of VTE events in women taking different hormonal treatments is generally complicated by the rare occurrence of these events and by the influencing risk factors other than the treatment itself, such as age, smoking, personal and family history of certain diseases. The nature of observational, non-interventional study design cannot completely account for differences in these variables, nor can they be completely balanced by use of propensity scores. Any confounding variable not considered in the propensity score model, e.g., due to the fact that it is unknown/unmeasured, might lead to a residual risk of hidden bias which is a methodological limitation of any observational study.

Since the investigators used a type-I error of 5% (one-sided) for power calculation it was discussed in the final SMAC meeting whether the 5% error margin should be considered exclusively on the upper limit. However, the principal investigator and the SMAC decided that the analyses based on the two-sided 95% confidence intervals should serve as primary analyses (16).

11.4 Generalisability

The RIVET-RCS study was designed as a retrospective pooled analysis to reflect routine clinical use of CMA and LNG containing COCs, primarily focusing on users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg. Data of four large prospective cohorts studies were pooled to assess the risk of VTE between different COC exposure cohorts The selected study participants in the original studies were recruited by COC-prescribing healthcare professionals (e.g., gynecologists, general practitioners, midwives) and all new users of a COC could participate. Study participation to the selected studies was not limited by medical inclusion and exclusion criteria. The RIVET-RCS selected study population covers women coming from a wide geographical range including 12 European countries and the USA/Canada. Therefore, the generalizability of the results is high.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

This is the first large observational cohort study assessing the risk of VTE in a large group of COC users exposed to CMA and LNG, primarily focusing on users exposed to CMA 2 mg/EE 30 µg and to LNG 0.15 mg/EE 30 µg.

The RIVET-RCS pooled analysis, based on four prospective, non-interventional cohort studies comprising 257,481 users of COCs containing CMA or LNG, including 12,710 women exposed to CMA 2 mg/EE 30 µg and 18,669 women exposed to LNG 0.15 mg/EE 30 µg, who were followed up for a total of 25,457 WY and 33,710 WY, respectively.

Within the general limitations of observational research, we conclude that the RIVET-RCS pooled analysis, as well as the primary design of the included studies, are methodologically valid to compare the risk of VTE in users of CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg.

As all included studies did not interfere with prescription behavior of treating healthcare practitioners and reflected routine contraceptive use in over 200,000 women of reproductive age in a wide geographical range covering 12 European countries and the US/Canada, the investigators believe that the generalizability of these results is high. These data provide a comprehensive insight into the risk profile of as components of CMA 2 mg and LNG 0.15 mg, both combined hormonal treatments with EE 30 µg and permits a solid estimation of risk of VTE in these user exposure cohorts.

Given the methodological strengths of the individual studies, the similarity of their study designs, and the quantitative consistency of the analysis results, the investigator could not exclude a 2.0-fold increased risk of CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg. However, a significantly increased risk for CMA 2 mg/EE 30 µg compared to LNG 0.15 mg/EE 30 µg could also not be found.

As an exploratory objective, interim data of VTE cases from a prospective case-control study were used to describe characteristics, distribution, and management of VTE in users of CMA 2 mg/EE 30 µg and LNG 0.15 mg/EE 30 µg in clinical practice.

The SMAC reviewed the final results on the final SMAC meeting on 09 September 2022 and issued following executive summary as the clinical interpretation of the results:

ZEG presented final results of the RIVET-RCS Study to the SMAC. The RIVET-RCS Study is a retrospective analysis of pooled data from four earlier large cohort studies on VTE incidence in users of different combined oral contraceptives (COC).

Data on VTE occurrence among 25,457 women years (WY) of use of CMA 2 mg and 33,710 WY of use of LNG 0.15 mg, both combined with EE 30 mg, was analysed. Twenty-five episodes (9.8 per 10,000 WY) of VTE occurred in CMA/EE users and 35 episodes (10.4 per 10,000 WY) of VTE in LNG/EE users.

As pre-specified by PRAC, the primary analysis was performed including age, body mass index, current duration of use, and family history of VTE as co-variables in the statistical model. The primary analysis model shows a slightly increased risk of VTE in CMA/EE users, which was not statistically significant (hazard ratio [HR] = 1.25, 95% confidence interval 0.72 to 2.14). Multiple sensitivity analyses and stratified analyses of sub-groups supported this result.

However, the upper bound of the 95% confidence interval (CI) was 2.14, exceeding the pre-specified threshold of 2.0 by a small margin. The probability that the true hazard ratio exceeds 2.14 is 2.5% (one-sided alpha error). An analysis using the same statistical model with a 90% confidence interval (i.e., one-sided alpha error of 5%) resulted in HR=1.25 (90% CI: 0,79 to 1.96). The SMAC had asked ZEG to also calculate the absolute risks and risk difference of VTE using the adjusted statistical model. According to ZEG this is not feasible due to the time-dependent nature of the exposure to either CMA or LNG containing COCs.

The SMAC concluded that COCs containing 2 mg CMA do not expose users to a clinically important increased risk of VTE compared to users of COCs containing 0.15 mg LNG.

The SMAC concluded that the study has been performed with great expertise. The SMAC congratulates the investigators for generating these important insights into the risk of VTE in users of CMA/EE compared to users of LNG/EE.

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15 ANNEX

Annex 1. List of Marketing Authorization Holders

Marketing Authorization Holder	Contact person for this protocol	QPPV
Aristo Pharma GmbH Wallenroder Straße 8–10 13435 Berlin Germany	[redacted]	[redacted]
Dr. Kade Pharmazeutische Fabrik GmbH Rigistr. 2 12277 Berlin Germany	[redacted]	[redacted]
Ceres Pharma nv Kortrijksesteenweg 1091 bus b B-9051 Sint-Denijs Westrem Belgium	[redacted]	[redacted]
Gedeon Richter Plc. 1103 Budapest Gyömrői út 19-21 Hungary	[redacted]	[redacted]
Gedeon Richter Polska Sp. z o.o. 5 ks.J. Poniatowskiego 05-825 Grodzisk Maz. Poland	See Gedeon Richter Plc	See Gedeon Richter Plc

Gedeon Richter România S.A. Str. Cuza-Vodă, nr. 99-105 540306 Târgu Mureş România	See Gedeon Richter Plc	See Gedeon Richter Plc
Gynial GmbH Ungargasse 37/4 A-1030 Vienna, Austria	[redacted]	[redacted]
Heaton k.s Na Pankráci 332/14 Prague 4 140 00 Czech Republic	[redacted]	[redacted]
Hormosan Pharma GmbH Hanauer Landstraße 139-143 60314 Frankfurt am Main Germany	[redacted]	[redacted]
ITF Farmahealth, Produtos Farmaceuticos Lda Rua Dom António Ribeiro, nº 9 1495-049 Algés Portugal	[redacted]	[redacted]
Jenapharm GmbH & Co. KG D-07745 Jena Otto-Schott-Str. 15 Germany	[redacted]	[redacted]

Kwizda Pharma GmbH Effingergasse 21 1160 Vienna Austria	[redacted]	[redacted]
Meda Pharma GmbH Benzstrasse 1 D-61362 Bad Homburg Germany	[redacted]	[redacted]
mibe GmbH Arzneimittel Münchener Str. 15 06796 Brehna Germany acis GmbH Arzneimittel Lil-Dagover-Ring 7 82031 Grünwald Germany Dermapharm GmbH Kleeblattgasse 4/13 1010 Vienna Austria Sun-Farm SP.zo.o. ul. Dolna 21 05-092 Lomianki Poland	[redacted]	[redacted]
Mylan dura gmbH Wittstichstr. 6 64295 Darmstadt Germany Mylan S.p.A. Via Vittor Pisani 20 20124 Milano Italy	[redacted]	[redacted]

	[redacted]	[redacted]
Puren Pharma GmbH & Co. KG Willy-Brandt-Allee 2 81829 Munich Germany	[redacted]	[redacted]
Sandoz Spa Largo Umberto Boccioni 1 21040 Origgio Italy Hexal Aktiengesellschaft Industriestr. 25 83607 Holzkirchen Germany	[redacted]	[redacted]
STADA Arzneimittel AG Stadastr. 2–18 61118 Bad Vilbel Germany	[redacted]	[redacted]

Annex 2. Blinded Adjudication Process

BLINDED ADJUDICATION

The following adjudication procedure was established in all four studies included in RIVET-RCS as well as for RIVET-CC:

- Independent adjudication by the individual specialists
- Documentation of the individual assessments
- Comparison of the individual assessments
- Discussion of "split decisions" among the adjudicators without enforcement of a unanimous decision
- Independent re-adjudication of the discussed cases by the individual adjudicators
- Documentation of the individual assessments

Based on this procedure four different classification strategies were established:

1) Classification of the reported event according to the assessment of the majority of adjudicators prior to the discussion of "split decision" took place (i.e., "majority vote" based on step 2 of the six-step procedure described above)
2) Classification of the reported event according to the assessment of the majority of adjudicators after discussion of "split decision" took place (i.e., majority classification based on step 6 of the six-step procedure described above)
3) Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed prior to the discussion of split decisions took place (i.e., "worst case decision" based on step 2 of the six-step procedure described above)
4) Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed after the discussion of split decisions took place (i.e., "worst case decision" based on step 6 of the six-step procedure described above)

The final analysis was always based on strategy 3) (worst case decision without discussion of split decisions) because it represents the most conservative approach. Alternative analyses were used for sensitivity analyses. However, the impact of the used strategy on the results was minimal.

Annex 2.1. Details of the selected adjudicators RIVET-CC

Dr. med. Heinrich Cremer
Internist and Cardiologist

Privatdozent Dr. med. Rufus Baretti
Cardiac Surgery and experience in General Practice

Dr. med. Theodor Krais

Internist, experience in Clinical Research in CV Medicine, including Peripheral Vascular Disease

Annex 3. Tables, Listings and Figures

Annex 3.1 Baseline Population Characteristics

Annex 3.1.1 Baseline Population Characteristics in Users of CMA/EE ≤30 µg vs. LNG/EE ≤30 µg – (Secondary Exposure Cohorts I)

	Mean (Std) or Relative frequency	
	CMA/EE ≤30 µg (N=13,238)	*LNG/EE ≤30 µg (N=39,652)*
Patient characteristics		
Europe	13,238 (100%)	25,931 (65.4%)
USA/Canada	--	13,721 (34.6%)
Age at study entry (years)	23.9 (±7.08)	25.3 (±7.84)
Age <20 years	4,387 (33.1%)	10,889 (27.5%)
20 to <30 years	6,221 (47.0%)	18,635 (47.0%)
30 to <40 years	2,138 (16.2%)	7,358 (18.6%)
40+ years	492 (3.7%)	2,770 (7.0%)
Weight at study entry (kg)	61.7 (±11.41)	65.4 (±14.87)
Height at study entry (cm)	166.8 (±6.30)	165.7 (±6.72)
BMI at study entry (kg/m^2)	22.1 (±3.85)	23.8 (±5.24)
BMI <20 kg/m^2	3,494 (26.4%)	7,374 (18.6%)
20 to <25	7,307 (55.2%)	19,893 (50.2%)
25 to <30	1,807 (13.7%)	7,710 (19.4%)
30 to <35	451 (3.4%)	2,737 (6.9%)
≥35	166 (1.3%)	1,778 (4.5%)
Missing	13 (0.10%)	160 (0.4%)
Gynecological History		
Age at menarche (years)	13.0 (±1.41)	12.9 (±1.50)
Ever been pregnant (gravidity)	3,870 (29.2%)	15,982 (40.3%)
Ever given birth (parity)	3,415 (25.8%)	14,021 (35.4%)
Number of live births	1.5 (±0.69)	1.7 (±0.87)
HC History		
Ever used OC	9,203 (69.5%)	30,030 (75.7%)
Starter	4,035 (30.5%)	9,622 (24.3%)
Switcher	3,398 (25.7%)	10,672 (26.9%)
Restarter	5,805 (43.9%)	19,358 (48.8%)
Duration of HC use (years)	5.0 (±5.33)	5.9 (±6.04)
Cardiovascular Risk Factors		
High blood pressure	194 (1.5%)	986 (2.5%)
High cholesterol	179 (1.4%)	534 (1.3%)

	Mean (Std) or Relative frequency	
	CMA/EE ≤30 µg (N=13,238)	*LNG/EE ≤30 µg (N=39,652)*
Family history of ATE	175 (1.3%)	635 (1.6%)
Family history of VTE	693 (5.2%)	1,804 (4.5%)
Current smoker	4,478 (33.8%)	11,911 (30.0%)
Heavy smoker (>15 cigarettes/day)	695 (5.3%)	1,975 (5.0%)
Medical History		
Diabetes mellitus	44 (0.3%)	290 (0.7%)
Stroke	3 (0.02%)	19 (0.05%)
Cancer	55 (0.4%)	187 (0.5%)
AMI	2 (0.02%)	15 (0.04%)
Any surgery	3,725 (28.1%)	12,505 (31.5%)
Medication		
Regular use of medication	1,749 (13.2%)	7,877 (19.9%)
Of which, procoagulatory agents	1 (0.01%)	4 (0.01%)
Of which, anticoagulatory agents	6 (0.05%)	8 (0.02%)
Education		
Less than university entrance level	1,368 (10.3%)	2,962 (7.5%)
University entrance level	5,454 (41.2%)	14,735 (37.2%)
Higher than university entrance level	4,805 (36.3%)	17,620 (44.4%)

Women may appear in both cohorts.

Annex 3.1.2 Baseline Population Characteristics in Users of CMA/EE vs. LNG/EE – (Secondary Exposure Cohorts II)

	Mean (Std) or Relative frequency	
	CMA/EE (N=14,598)	*LNG/EE (N=44,504)*
Patient characteristics		
Europe	14,598 (100%)	29,905 (67.2%)
USA/Canada	--	14,599 (32.8%)
Age at study entry (years)	24.0 (±7.16)	25.7 (±7.98)
Age <20 years	4,679 (32.1%)	11,547 (25.9%)
20 to <30 years	6,913 (47.4%)	20,583 (46.2%)
30 to <40 years	2,422 (16.6%)	8,970 (20.2%)
40+ years	584 (4.0%)	3,404 (7.6%)
Weight at study entry (kg)	61.7 (±11.36)	65.4 (±14.73)
Height at study entry (cm)	166.9 (±6.31)	165.8 (±6.71)

	Mean (Std) or Relative frequency	
	CMA/EE (N=14,598)	*LNG/EE (N=44,504)*
BMI at study entry (kg/m^2)	22.1 (±3.83)	23.8 (±5.19)
BMI <20 kg/m^2	3,786 (25.9%)	8,137 (18.3%)
20 to <25	8,140 (55.8%)	22,484 (50.5%)
25 to <30	1,987 (13.6%)	8,697 (19.5%)
30 to <35	491 (3.4%)	3,079 (6.9%)
≥35	181 (1.2%)	1,933 (4.3%)
Missing	13 (0.09%)	174 (0.4%)
Gynecological History		
Age at menarche (years)	13.0 (±1.42)	12.9 (±1.49)
Ever been pregnant (gravidity)	4,353 (29.8%)	18,702 (42.0%)
Ever given birth (parity)	3,854 (26.4%)	16,500 (37.1%)
Number of live births	1.5 (±0.69)	1.7 (±0.85)
HC History		
Ever used OC	10,433 (71.5%)	34,179 (76.8%)
Starter	4,165 (28.5%)	10,325 (23.2%)
Switcher	3,811 (26.1%)	11,922 (26.8%)
Restarter	6,622 (45.4%)	22,257 (50.0%)
Duration of HC use (years)	5.3 (±5.49)	6.3 (±6.26)
Cardiovascular Risk Factors		
High blood pressure	229 (1.6%)	1,148 (2.6%)
High cholesterol	203 (1.4%)	629 (1.4%)
Family history of ATE	193 (1.3%)	716 (1.6%)
Family history of VTE	815 (5.6%)	2,084 (4.7%)
Current smoker	4,974 (34.1%)	13,465 (30.3%)
Heavy smoker (>15 cigarettes/day)	796 (5.5%)	2,281 (5.1%)
Medical History		
Diabetes mellitus	50 (0.3%)	322 (0.7%)
Stroke	3 (0.02%)	20 (0.04%)
Cancer	63 (0.4%)	214 (0.5%)
AMI	2 (0.01%)	15 (0.03%)
Any surgery	4,131 (28.3%)	13,991 (31.4%)
Medication		
Regular use of medication	1,979 (13.6%)	8,727 (19.6%)
Of which, procoagulatory agents	1 (0.01%)	4 (0.01%)
Of which, anticoagulatory agents	8 (0.05%)	11 (0.02%)

	Mean (Std) or Relative frequency	
	CMA/EE (N=14,598)	*LNG/EE (N=44,504)*
Education		
Less than university entrance level	1,409 (9.7%)	3,166 (7.1%)
University entrance level	5,970 (40.9%)	16,504 (37.1%)
Higher than university entrance level	5,308 (36.4%)	19,647 (44.1%)

Women may appear in both cohorts.

Annex 3.2 Average Number and Length of COC Treatment Episodes

Annex 3.2.1 Average Number and Length of COC Treatment Episodes in Users of CMA/EE ≤30 µg vs. LNG/EE ≤30 µg – (Secondary Exposure Cohorts I)

	Mean (SD)	
	CMA/EE ≤30 µg (N=13,238)	***LNG/EE ≤30 µg (N=39,652)***
Number of COC episodes	1.2 (±0.51)	1.2 (±0.51)
Length of COC episode (months)	19.7 (±18.54)	20.4 (±19.57)

Women may appear in both cohorts.

Annex 3.2.2 Average Number and Length of COC Treatment Episodes in Users of CMA/EE vs. LNG/EE – (Secondary Exposure Cohorts II)

	Mean (SD)	
	CMA/EE (N=14,598)	***LNG/EE (N=44,504)***
Number of COC episodes	1.3 (±0.53)	1.2 (±0.52)
Length of COC episode (months)	20.2 (±18.84)	21.0 (±20.09)

Women may appear in both cohorts.

Annex 3.3 Relative Risk (95% CI) of Potential Prognostic Factors on the Occurrence of VTE

Annex 3.3.1 Relative risk (95% CI) of Potential Prognostic Factors on the Occurrence of VTE in Users of CMA/EE ≤30 µg vs. LNG/EE ≤30 µg – (Secondary Exposure Cohorts I)

	Relative Risk (95% CI)	
	CMA/EE ≤30 µg (N=13,238)	*LNG/EE ≤30 µg (N=39,652)*
Patient characteristics		
USA/Canada (ref Europe)		0.61 (0.36–1.03)
Age <20 years	*reference*	*reference*
20 to <30 years (ref: Age <20)	1.65 (0.63–4.28)	1.38 (0.68 -2.79)
30 to <40 years (ref: Age <20)	1.37 (0.39–4.84)	2.29 (1.07 -4.88)
40+ years (ref: Age <20)	1.49 (0.18–12.32)	7.15 (3.43 -14.90)
BMI ≥30 kg/m^2 (ref <30)	2.79 (0.84–9.29)	1.82 (1.02 -3.25)
Gynecological History		
Ever been pregnant (gravidity)	0.94 (0.39–2.25)	2.05 (1.30–3.26)
Ever given live birth (parity)	0.91 (0.36–2.27)	2.27 (1.44–3.59)
HC History		
Ever used OC (Yes/Otherwise)	2.30 (0.79–6.70)	1.66 (0.89–3.07)
Cardiovascular Risk Factors		
High blood pressure (Yes/Otherwise)	2.80 (0.38–20.60)	4.10 (1.89 -8.90)
High cholesterol (Yes/Otherwise)	6.34 (1.51–26.71)	2.03 (0.50 -8.27)
Family history of ATE (Yes/Otherwise)	--	4.45 (1.80 -11.00)
Family history of VTE (Yes/Otherwise)	3.45 (1.19–10.02)	4.06 (2.19 -7.52)
Smoker (Yes/Otherwise)	1.10 (0.49–2.49)	1.12 (0.69 -1.82)
Medical History		
MH of diabetes mellitus (Yes/Otherwise)	--	--
MH of stroke (Yes/Otherwise)	--	--
MH of cancer (Yes/Otherwise)	--	2.89 (0.40–20.69)
MH of AMI (Yes/Otherwise)	--	--
Any surgery (Yes/Otherwise)	2.01 (0.91–4.42)	1.18 (0.73–1.89)
Medication		
Regular use of medication (Yes/Otherwise)	2.07 (0.83–5.19)	1.49 (0.89–2.49)
Education		
Higher than university entrance level (Yes/Otherwise)	1.62 (0.74–3.55)	1.06 (0.67–1.68)

Women may appear in both cohorts.

Annex 3.3.2 Relative Risk (95% CI) of Potential Prognostic Factors on the Occurrence of VTE in Users of CMA/EE vs. LNG/EE – (Secondary Exposure Cohorts II)

	Relative Risk (95% CI)	
	CMA/EE (N=14,598)	*LNG/EE (N=44,504)*
Patient characteristics		
USA/Canada (ref Europe)	--	0.59 (0.35–1.00)
Age <20 years	--	--
20 to <30 years (ref: Age <20)	1.69 (0.66–4.36)	1.43 (0.71–2.87)
30 to <40 years (ref: Age <20)	1.93 (0.62–5.98)	2.22 (1.06–4.67)
40+ years (ref: Age <20)	2.67 (0.54–13.20)	6.78 (3.29–13.98)
BMI ≥30 kg/m^2 (ref <30)	2.39 (0.73–7.88)	1.97 (1.14–3.40)
Gynecological History		
Ever been pregnant (gravidity)	1.06 (0.48–2.32)	2.07 (1.32–3.24)
Ever given live birth (parity)	1.06 (0.47–2.40)	2.30 (1.47–3.58)
HC History		
Ever used OC (Yes/Otherwise)	2.50 (0.87–7.16)	1.56 (0.86–2.82)
Cardiovascular Risk Factors		
High blood pressure (Yes/Otherwise)	2.24 (0.31–16.40)	4.20 (2.03–8.69)
High cholesterol (Yes/Otherwise)	5.25 (1.26–21.94)	1.79 (0.44–7.26)
Family history of ATE (Yes/Otherwise)	--	4.08 (1.65–10.05)
Family history of VTE (Yes/Otherwise)	3.52 (1.35–9.21)	3.95 (2.18–7.14)
Smoker (Yes/Otherwise)	1.02 (0.47–2.19)	1.17 (0.74–1.87)
Medical History		
MH of diabetes mellitus (Yes/Otherwise)	--	--
MH of stroke (Yes/Otherwise)	--	--
MH of cancer (Yes/Otherwise)	--	2.62 (0.37–18.74)
MH of AMI (Yes/Otherwise)	--	--
Any surgery (Yes/Otherwise)	1.79 (0.85–3.74)	1.11 (0.70–1.77)
Medication		
Regular use of medication (Yes/Otherwise)	2.03 (0.87–4.74)	1.37 (0.82–2.27)
Education		
Higher than university entrance level (Yes/Otherwise)	1.63 (0.79–3.38)	1.09 (0.70–1.69)

Women may appear in both cohorts.

Annex 3.4 Absolute and Incidence Rates per 10,000 WY of Confirmed VTE, DVT and PE Events (95% CI)

Annex 3.4.1 Absolute Numbers and Incidence Rates per 10,000 WY of Confirmed VTE, DVT and PE Events (95% CI) in Users of CMA/EE ≤30 µg vs. LNG/EE ≤30 µg – (Secondary Exposure Cohorts I)

	Incidence Rate (95% CI)	
	CMA/EE ≤30 µg (N=13,238)	*LNG/EE ≤30 µg (N=39,652)*
Women years	26,215	82,127
VTE		
Number of events	25	74
IR (95% CI)*	9.54 (6.17–14.08)	9.01 (7.08–11.31)
DVT		
Number of events	24	62
IR (95% CI)*	9.16 (5.87–13.62)	7.55 (5.79–9.68)
PE		
Number of events	4	20
IR (95% CI)*	1.53 (0.42–3.91)	2.44 (1.49–3.76)

*IR and 95% CIs are presented per 10,000 WYs. Women may appear in both cohorts.

Annex 3.4.2 Absolute Numbers and Incidence Rates per 10,000 WY of Confirmed VTE, DVT and PE Events (95% CI) in Users of CMA/EE vs. LNG – (Secondary Exposure Cohorts II)

	Incidence Rate (95% CI)	
	CMA/EE (N=14,598)	*LNG/EE (N=44,504)*
Women years	30,108	95,378
VTE		
Number of events	29	80
IR (95% CI)*	9.63 (6.45–13.83)	8.39 (6.65–10.44)
DVT		
Number of events	28	68
IR (95% CI)*	9.30 (6.18–13.44)	7.13 (5.54–9.04)
PE		
Number of events	4	22
IR (95% CI)*	1.33 (0.36–3.40)	2.31 (1.45–3.49)

*IR and 95% CIs are presented per 10,000 WYs. Women may appear in both cohorts.

Annex 3.5 Baseline characteristics for VTE in users of CMA/EE vs. LNG/EE: RIVET-CC vs. RIVET-RCS

	Mean (Std) or Relative frequency			
	RIVET-CC		**RIVET-RCS**	
	CMA/EE	*LNG/EE*	*CMA/EE*	*LNG/EE*
Number (%) of women	33	118	29	80
Patient characteristics				
Age at study entry (years)	31.0 (±9.71)	34.7 (±9.35)	26.1 (±7.06)	31.2 (±9.82)
Age at diagnosis	31.7 (±9.96)	34.8 (±10.06)	29.2 (±7.49)	33.6 (±10.49)
Age <20 years	4 (12.1%)	8 (6.8%)	6 (20.7%)	11 (13.8%)
20 to <30 years	12 (36.4%)	31 (26.3%)	15 (51.7%)	28 (35.0%)
30 to <40 years	8 (24.2%)	36 (30.5%)	6 (20.7%)	19 (23.8%)
40+ years	8 (24.2%)	43 (36.4%)	2 (6.9%)	22 (27.5%)
Weight at study entry (kg)	73.1 (±16.90)	79.1 (±23.00)	68.4 (±13.93)	71.6 (±14.65)
Height at study entry (cm)	168.5 (±6.53)	167.9 (±6.57)	168.6 (±6.26)	167.7 (±6.73)
BMI at study entry (kg/m^2)	25.7 (±5.58)	28.1 (±8.11)	24.0 (±3.93)	25.5 (±5.14)
BMI <20 kg/m^2	2 (6.1%)	8 (6.8%)	4 (13.8%)	5 (6.3%)
20 to <25	18 (54.5%)	43 (36.4%)	15 (51.7%)	38 (47.5%)
25 to <30	6 (18.2%)	31 (26.3%)	7 (24.1%)	21 (26.3%)
30 to <35	5 (15.2%)	17 (14.4%)	3 (10.3%)	11 (13.8%)
≥35	2 (6.1%)	19 (16.1%)	--	5 (6.3%)
Missing	0 (0.0%)	0 (0.0%)	--	--
Gynecological History				
Ever been pregnant (gravidity)	13 (39.4%)	70 (59.3%)	9 (31.0%)	48 (60.0%)
Ever given birth (parity)	10 (30.3%)	63 (53.4%)	8 (27.6%)	46 (57.5%)
Number of live births	1.6 (±0.70)	1.9 (±0.93)	1.1 (±0.35)	1.8 (±0.97)
HC History				
Ever used OC	33 (100%)	118 (100%)	25 (86.2%)	67 (83.8%)
Duration of HC use (years)	2.0 (±2.14)	5.2 (±6.65)	6.8 (±6.10)	11.1 (±8.72)
Starter	0 (0.0%)	0 (0.0%)	4 (13.8%)	13 (16.3%)
Switcher	23 (69.7%)	85 (72.0%)	10 (34.5%)	18 (22.5%)
Re-starter	--	--	15 (51.7%)	49 (61.3%)
Incident user*	9 (27.3%)	25 (21.2%)	--	--
Cardiovascular Risk Factors				
Pregnancy in the last 6 weeks	2 (6.1%)	14 (11.9%)	--	--
Delivery in the last 6 weeks	0 (0.0%)	5 (4.2%)	--	--
Accident in the last 6 weeks	5 (15.2%)	4 (3.4%)	--	--

	Mean (Std) or Relative frequency			
	RIVET-CC		**RIVET-RCS**	
	CMA/EE	*LNG/EE*	*CMA/EE*	*LNG/EE*
Immobility in the last 6 weeks	3 (9.1%)	10 (8.5%)	--	--
Surgery in the last 6 weeks	2 (6.1%)	10 (8.5%)	--	--
Long travel in the last 6 weeks	5 (15.2%)	12 (10.2%)	--	--
Standing occupation in the last 6 weeks	3 (9.1%)	20 (16.9%)	--	--
Chemotherapy in the last 6 weeks	0 (0.0%)	2 (1.7%)	--	--
Family history of VTE	5 (15.2%)	21 (17.8%)	5 (17.2%)	13 (16.3%)
Current smoker	7 (21.2%)	30 (25.4%)	10 (34.5%)	27 (33.8%)
Heavy smoker (>15 cig)	3 (9.1%)	22 (18.6%)	1 (3.4%)	4 (5.0%)
Medication				
Regular use of medication	11 (33.3%)	50 (42.4%)	7 (24.1%)	20 (25.0%)
Education				
Less than university entrance level	10 (30.3%)	64 (54.2%)	1 (3.4%)	5 (6.3%)
University entrance level	17 (51.5%)	32 (27.1%)	9 (31.0%)	28 (35.0%)
Higher than university entrance level	6 (18.2%)	20 (16.9%)	14 (48.3%)	37 (46.3%)

Note: * Incident users are defined as having a hormonal contraception intake break of at least 3 months.

Annex 3.6 Descriptive comparison of VTE symptoms, examination and treatment from VTE cases exposed to CMA/EE or LNG/EE (RIVET-CC)

Annex 3.6.1 Descriptive comparison of VTE symptoms in VTE cases exposed to CMA/EE or LNG/EE

	Mean (Std) or Relative frequency	
	CMA/EE	*LNG/EE*
Number (%) of women	33 (100%)	118 (100%)
Symptoms of VTE		
Swelling of leg	14 (42.4%)	68 (57.6%)
Coloring of leg	1 (3.0%)	9 (7.6%)
Heat of leg	2 (6.1%)	12 (10.2%)
Protrusion of leg	1 (3.0%)	11 (9.3%)
Heaviness/tension or weakness of leg	13 (39.4%)	49 (41.5%)
Sensitivity of leg	5 (15.2%)	16 (13.6%)
Shortness of breath	7 (21.2%)	23 (19.5%)
Other symptoms	17 (51.5%)	51 (43.2%)
No symptoms	0 (0.0%)	1 (0.8%)

Note: Women may appear in more than one category.

Annex 3.6.2 Descriptive comparison of VTE examination in VTE cases exposed to CMA/EE or LNG/EE

	Mean (Std) or Relative frequency	
	CMA/EE	*LNG/EE*
Number (%) of women	33 (100%)	118 (100%)
Diagnosis of DVT confirmed with the following examination		
Doppler ultrasound	14 (42.4%)	55 (46.6%)
Duplex sonography	25 (75.8%)	97 (82.2%)
Phlebography	2 (6.1%)	1 (0.8%)
CT or MRT	2 (6.1%)	15 (12.7%)
Other	0 (0.0%)	4 (3.4%)
Diagnosis of PE confirmed with the following examination		
X-ray	0 (0.0%)	0 (0.0%)
Scintigraphy	0 (0.0%)	3 (2.5%)
Angiography	0 (0.0%)	2 (1.7%)
CT of the lung	8 (24.2%)	28 (23.7%)

	Mean (Std) or Relative frequency	
	CMA/EE	*LNG/EE*
Pressure check of pulmonary atery	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	2 (1.7%)
Diagnosis of Blood clotting confirmed with the following examination		
Genetic mutation	5 (15.2%)	11 (9.3%)
Hypercoagulation markers	16 (48.5%)	61 (51.7%)

Note: Women may appear in more than one category.

Annex 3.6.3 Descriptive comparison of VTE treatment in VTE cases exposed to CMA/EE or LNG/EE

	Mean (Std) or Relative frequency	
	CMA/EE	*LNG/EE*
Number (%) of women	33 (100%)	118 (100%)
Treatment of VTE		
Observation only	1 (3.0%)	2 (1.7%)
Bed rest	0 (0.0%)	9 (7.6%)
Thrombolysis	0 (0.0%)	3 (2.5%)
Anticoagulation	31 (93.9%)	113 (95.8%)
Other medication	1 (3.0%)	4 (3.4%)
Bandages	26 (78.8%)	101 (85.6%)
Surgery	1 (3.0%)	6 (5.1%)
Other treatment	0 (0.0%)	4 (3.4%)
Referral to specialist	4 (12.1%)	28 (23.7%)
Referral to hospital	3 (9.1%)	11 (9.3%)
No treatment	0 (0.0%)	0 (0.0%)

Note: Women may appear in more than one category.

END OF REPORT