Estetra Post Authorisation study information

Title	International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)
Protocol version identifier	V04-00
Date of last version of protocol	Not applicable
EU PAS register number	Not yet registered
Active substance	Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens, and estrogens, fixed combinations, Anatomical Therapeutic Chemical Classification System (ATC) code: G03AA18 Active substances: drospirenone and estetrol
Medicinal product	Drospirenone 3 mg/estetrol 14.2 mg film-coated tablets
Product reference	Lydisilka: H0005382 Drovelis: H0005336
Procedure number	Lydisilka: EMEA/H/C/005382 Drovelis: EMEA/H/C/005336
Marketing authorisation holder(s)	Estetra SRL Rue Saint-Georges 5 4000 Liège Belgium Gedeon Richter Plc Gyömrői út 19-21 1103 Budapest Hungary
Joint PASS	Yes
Research question and objectives	The primary objective of the study is to characterize and compare the risks of E4/Drospirenone (DRSP) with levonorgestrel-containing combined oral contraceptives (EE/LNG) in a study population that is representative of the actual users of these

	preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE). Secondary objectives include measuring the occurrence of unintended pregnancy, assessing the risk of arterial thromboembolism (ATE), describing the drug utilization pattern, describing the baseline risk profile for VTE and ATE, and investigating outcomes associated with foetal exposure to E4/DRSP.
Country(-ies) of study	Europe (Germany, Poland, Czech Republic, the United Kingdom, Hungary, Italy, France, Spain, other (TBD)), USA and Brazil. A complete list is available in **Annex 1**
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Marketing authorisation holder(s)

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List of abbreviations

Abbreviation	Definition
ADB	Administrative Database
AE	Adverse Event
AMI	Acute Myocardial Infarction
AT	As Treated
ATC	Anatomical Therapeutic Chemical Classification System
ATE	Arterial Thromboembolism
BfArM	Federal Institute for Drugs and Medical Devices (an acronym for the German term '*Bundesinstitut für Arzneimittel und Medizinprodukte*')
BMI	Body Mass Index
BYOD	Bring Your Own Device
CATI	Computer Assisted Telephone Interview
COC	Combined Oral Contraceptive
CT	Computed Tomography
DRSP	Drospirenone
DVT	Deep Venous Thrombosis
E4	Estetrol
ECG	Electrocardiography
EDC	Electronic Data Capture
EE	Ethinyl Estradiol
eIDAS	Electronic Identification, Authentication and Trust Services
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMIS	Egton Medical Information Systems
EU	European Union
EURAS	European Active Surveillance (study)
EVDB	Event Validation Database
GEP	Good Epidemiological Practices

GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
GXP	Good Practice Guidelines
HC	Hormonal Contraception
HCP	Health Care Professional
HR	Hazard Ratio
ICD-10	International Classification of Diseases, 10th revision
ICF	Informed Consent Form
ICMJE	International Committee on Medical Journal Editors
IME	Important Medical Event
INAS	International Active Surveillance Study
IPTW	Inverse Probability of Treatment Weighting
ITT	Intention To Treat
LNG	Levonorgestrel
LOCF	Last Observation Carried Forward
LTFU	Lost To Follow-Up
MAH	Marketing Authorisation Holder
MRI	Magnetic Resonance Imaging
NEES	Native Estrogen Estetrol (E4) Safety Study
OC	Oral Contraceptive
OPS	Operations and Procedures Classification System (an acronym for the German term '*Operationen- und Prozedurenschlüssel*')
PAS(S)	Post-Authorisation Safety (Study)
PE	Pulmonary Embolism
PS	Propensity Score
PTC	Product Technical Complaint
SAE	Serious Adverse Event
SDB	Study Database
SMAC	Safety Monitoring and Advisory Council

SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TOPFA	Termination of Pregnancy for Foetal Anomaly
VTE	Venous Thromboembolism
WHO	World Health Organization
WY	Woman-years
ZEG	Berlin Center for Epidemiology & Health Research (acronym for the German term '*Zentrum für Epidemiologie & Gesundheitsforschung Berlin*')

Responsible parties

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1. Abstract

Title

International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)

Study protocol outline (Version of 26 April 2022)

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Rationale and background

The combined oral contraceptive (COC) containing estetrol (E4) and drospirenone (DRSP) (E4/DRSP) is a novel oral contraceptive containing a fixed dose of E4 (14.2 mg) and DRSP (3 mg). E4 is a natural oestrogen only produced during pregnancy by the foetal liver. When combined with the progestin DRSP, ovulation is inhibited. The E4/DRSP combination may have less impact on hepatic and haemostasis parameters in comparison to combinations of ethinyl estradiol (EE) and levonorgestrel (LNG) or EE and DRSP. Yet, it is unknown whether this regimen has an impact on the cardiovascular risk associated with the use of hormonal contraceptives.

Research question and objectives

The primary objective of the study is to characterize and compare the risks of E4/DRSP with EE/LNG, in a study population that is representative of the actual users of these preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes. The main clinical outcome of interest is venous thromboembolism (VTE), i.e., deep venous thrombosis (DVT) of the lower extremities and pulmonary embolism (PE). Secondary objectives include measuring the occurrence of unintended pregnancy, assessing the risk of arterial thromboembolism (ATE), describing the drug utilization pattern, describing the baseline risk profile for VTE and ATE, and investigating outcomes associated with foetal exposure to E4/DRSP.

Study design

Multinational, comparative, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[1] and restarters[2]) of two different groups of hormonal

[1] First-ever user of a COC

[2] User who restarts hormonal contraceptive use with a COC (same COC as before or new COC) after an intake break of at least two months.

contraceptives: E4/DRSP and EE/LNG. The study is taking a non-interventional[3] approach to provide comprehensive information on these treatments in a routine clinical practice setting. Study participants will be enrolled via an international network of COC-prescribing health care professionals (HCPs) and then followed up for one to two years. All outcomes of interest will be captured by direct contact with the study participants. Reported outcomes of interest will be validated via attending physicians and relevant source documents. The classification of outcomes of interest into 'confirmed' and 'not confirmed' will be verified by blinded independent adjudication.

Population

Approximately 101,000 study participants (50,500 E4/DRSP and 50,500 EE/LNG new users) will be recruited via a network of COC-prescribing health care professionals in Europe, the USA, and Brazil. All new users (starters and restarters) prescribed E4/DRSP or EE/LNG who are willing to participate may be eligible for enrolment in the study.

Variables

The variable to determine the primary endpoint is the occurrence of a new VTE (DVT of the lower extremities and PE) during follow-up, which will be compared between E4/DRSP and EE/LNG users. Variables to determine the secondary endpoints include the occurrence of unintended pregnancies, ATE, and outcomes associated with foetal exposure to E4/DRSP. Variables to characterize the baseline risk profile of users are baseline population characteristics, socio-economic factors, parameters of reproductive, contraceptive, and medical history, and concomitant medication.

Data sources

This is a field study that entails exposure to COCs and the occurrence of clinical outcomes of interest by completing questionnaires at baseline (study entry) and follow-up (at 6-, 12-, 18-, and 24-months post-baseline), in addition to potential confounding factors and potential effect modifiers. Medical confirmation of the occurrence of a clinical outcome of interest will be sought from the attending HCP and/or study participant (e.g., diagnostic report, discharge letter). All documents exchanged between ZEG and the MAHs will be in English.

Study size

The study is sufficiently powered to show non-inferiority of E4/DRSP compared to EE/LNG assuming that the VTE risk among E4/DRSP users is not higher than among EE/LNG users. For this purpose, a total of 101,000 women (50,500 E4/DRSP users and 50,500 EE/LNG users) will be recruited and followed up taking into account treatment adherence, treatment stopping/switching, and lost to follow-up (LTFU)/dropout. Sample size calculations assuming an incidence of 10 VTEs per 10,000 woman-years (WY) show that approximately 150,000 WY of observation is statistically sufficient (power =80%, α =0.05) to exclude a 1.5-fold VTE risk for E4/DRSP users compared to EE/LNG users.

[3] Specifically, 1) all new users of E4/DRSP or EE/LNG are eligible for enrollment if they give their informed consent; and 2) recruitment of study participants should not influence the physician's prescribing, diagnostic, or therapeutic decisions.

Data analysis

The final analyses will include both an "as-treated" (AT) and an "intention-to-treat" (ITT) analysis. All eligible women will be assigned to the ITT and AT population at baseline. Only women with follow-up information will be considered for longitudinal analysis. Women who never started their prescribed baseline medication will be considered in the ITT analysis but excluded from the AT analysis. Population characteristics, e.g., socio-economic factors, parameters of reproductive, contraceptive history, and medical history, will be summarized descriptively and used to estimate the probability of treatment differences. Inverse probability of treatment weighting combined with time-to-event analysis of VTE will be carried out based on the extended Cox model to calculate hazard ratios (HR) with 95% confidence intervals. The null hypothesis to be tested is HR of VTE ≥ 1.5 (i.e., the VTE HR for E4/DRSP vs. EE/LNG is higher than or equal to 1.5). The alternative hypothesis is HR of VTE <1.5.

Milestones

Data collection is expected to start Q4/2022after EMA approval of protocol and medical drug commercially available and is anticipated to end Q4/2028 after the start of data collection. The final study report will be available in Q2/2029.

2. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
None				

3. Milestones

Milestone	Planned date
Global Ethics Approval	Q4/2022
Registration in the EU PAS register	Q4/2022
Start of study	Q4/2022
Start of data collection (First Patient First Visit)	Q1/2023
Last regular follow-up[1]	Q3/2027
End of data collection (Last Patient Last Follow-Up)	Q3/2028
Annual report(s)[2]	Annually (First report: Q2/2023)
Final report of study results	Q2/2029

EMA=European Medicines Agency, MA=Marketing Authorization, PRAC=Pharmacovigilance Risk Assessment Committee
[1]Assumes last 20% of study participants followed for 12 months only.
[2]To be harmonized with the Periodic Safety Update Reports (PSURs), where applicable

4. Rationale and background

E4/DRSP is a novel oral contraceptive containing a fixed dose of E4 (14.2 mg) and DRSP (3 mg) which is taken for 24 days followed by 4 days of placebo. E4 is a natural estrogen, only produced during pregnancy by the foetal liver. When combined with the progestin DRSP, ovulation is inhibited. The E4/DRSP combination may have less impact on hepatic and haemostasis parameters in comparison to combinations of DRSP with ethinyl estradiol (EE) and ethinyl estradiol/levonorgestrel combination (EE/LNG) [1–3].

Clinical experience suggests that serious clinical outcomes are rare when using COCs. [4, 5] One of the most serious adverse clinical events that have been linked to the use of COCs is VTE. However, the statistical power to detect and observe rare (incidence<0.01%) adverse events (AEs) with a certain precision in clinical trials is limited.

There is preliminary evidence that E4/DRSP has less influence on haemostasis compared to EE/DRSP. [6] Therefore, it is conceivable that E4/DRSP might be associated with a lower risk of VTE compared to an EE-containing COC. However, robust estimates of the risk of VTE associated with E4/DRSP are not available. As part of the Risk Management Plan for the novel

COC containing E4/DRSP, Estetra and Gedeon Richter have committed to conducting a non-imposed, category 3, Post-authorization Safety Study (PASS) according to DIR 2001/83/EU art 107m). The PASS will be conducted to assess the risk of VTE in 'real world' users of E4/DRSP, as well as the risk of ATE and unintended pregnancy.

The European Active Surveillance (EURAS) study and similar studies (such as INAS-SCORE[4], INAS-OC[5] and PRO-E2[6]) have demonstrated that large, comparative, cohort studies are suitable for (1) safety monitoring of contraceptives, (2) reliable identification of relevant clinical outcomes, and (3) providing robust estimates of their incidence. The proposed study has a similar design to the PRO-E2 with few modifications due to country and product-specific characteristics.

5. Research question and objectives

The main research question of the study is to assess the thromboembolic risk associated with the use of E4/DRSP compared to EE/LNG in a study population that is representative of the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes as defined below.

5.1. Primary objective

The primary objective of this study is to assess the risk of VTE among E4/DRSP users compared to users of EE/LNG, specifically:

- Deep Venous Thrombosis (DVT) of the lower extremities (ICD-10 codes: I80.1 and I80.2), and
- Pulmonary Embolism (PE; ICD-10 codes: I26.0 and I26.9)

5.2. Secondary objectives

The secondary objectives of this study are to assess the risk and compare it between E4/DRSP users and EE/LNG users (stratified by age, smoking, and BMI) for:

- All VTE, including thromboses of the renal, mesenteric, portal, cerebral and retinal veins[7] (a sensitivity analysis will be done for the ICD-10 code I80.3),
- ATE, including acute myocardial infarction (AMI) (ICD-10 code I21.* [8]) and cerebrovascular accidents (CVA) (ICD-10 code: I24.9, G45.*, I61.*, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9),

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4 ClinicalTrials.gov identifier: NCT01009684

5 ClinicalTrials.gov identifier: NCT00335257

6 ClinicalTrials.gov identifier: NCT01650168

7 ICD-10 codes: I26.0, I26.9, I63.6, I67.6, I80.1, I80.2, I80.3, I80.8, I80.9, I81, I82.0, I82.2, I82.3, I82.8, I82.9, H34.8, K55.0 and N28.0

8 * For all stars, it means including all codes within this category

- Unintended pregnancy, and
- Neonatal malformations associated with foetal exposure to E4/DRSP and EE/LNG.

- Drug utilization pattern,
- Baseline risk profile for primary and secondary clinical outcomes– in particular for cardiovascular outcomes.

6. Research methods

6.1. Study design

This is a large, multinational, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[9] and restarters[10]) of two different groups of hormonal contraceptives: E4/DRSP and EE/LNG. The study will use a non-interference[11] approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting.

Study participants will be recruited via recruitment centres (health centres, pharmacies, telemedicine/online prescription services, and electronic medical records [see details in Section 6.2]) for the INAS-NEES study. An international network of COC-prescribing HCPs will recruit eligible COC-users over an estimated period of 5 years. After study entry, study participants will be followed for a maximum of 2 years for rare serious safety outcomes. Additional follow-up procedures (see Section 6.4.2) will be used to validate patient-reported events. A non-interventional approach will be used for the INAS-NEES study. Enrolment procedures should not interfere with the prescribing behaviour of the participating HCPs or with the individual needs of their patients. People prescribed a new COC are eligible to join the study provided they are prescribed a COC under investigation, sign an informed consent form (ICF), complete a baseline questionnaire, and understand the language of the ICF and questionnaires. Adolescents (below the age of 18 years) will be eligible to participate based on local legislation.

Through direct contact with the study participants at 6, 12, 18, and 24[12] months after enrolment, relevant clinical outcomes will be captured. However, because laypersons often over-report, or misclassify AEs (e.g., varicose veins as "thrombosis" or pneumonia as "pulmonary embolism"), patient-reported events of interest to the study will undergo careful validation. This will be accomplished by contacting the relevant HCPs (usually the treating physicians) and by reviewing medical documentation. Under routine medical conditions, clinical outcomes are not always

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9 First-ever user of a COC

10 User who restarts hormonal contraceptive use with a COC (same COC as before or new COC) after an intake break of at least two months.

11 I.e., 1) all new users of E4/DRSP or EE/LNG are eligible for enrolment if they give their informed consent; and 2) recruitment of study participants should not influence the physician's prescribing, diagnostic, or therapeutic decisions.

12 Or at the end of the study if the study ends prior to the 24-month follow-up of an individual participant.

confirmed by diagnostic procedures with high specificity. Therefore, reported serious clinical outcomes will be classified as "confirmed" or "not confirmed" according to predefined algorithms. At the end of the study, this classification will be verified by blinded independent adjudication (see. ***Annex 3.2***) by three medical experts (e.g., cardiologists, phlebologists, internists), who are proposed by ZEG and approved by the Safety Monitoring and Advisory Council (SMAC). They will assess the VTE and ATE cases independently from ZEG (see Section 6.4.3).

6.2. Setting

This multinational, prospective, controlled, primary data collection study will be conducted by the Berlin Center for Epidemiology and Health Research GmbH (ZEG Berlin) in Europe, the USA, and Brazil to collect high-quality, real-world data on new users of COCs. In parallel, the recruited users will also be included in an independently conducted ongoing registry.

It is estimated that more than 60% of the study data will be obtained from European Union (EU) countries, with the remaining proportion from non-EU countries. There is no literature evidence to suggest that risk factors in women who take COCs are different between EU and non-EU populations, except for sickle cell trait in women of African descent. Risk factors of VTE are well established and consistent across populations and include age, family disposition, obesity, smoking, immobilization, coagulation disorders, pregnancy, puerperium, and history of cancer. All these factors will be collected during this study and propensity score matching during analyses can correct for potential unbalanced groups, although this is not foreseen. Recruitment will be conducted in a 1:1 ratio on the national level to ensure an even distribution of cohorts on the local level.

The study will be overseen by an independent committee of experts, the SMAC, who will review the selected study data every 6 months and at the request of the Principal Investigator and the MAHs (see ***Annex 3.1***).

The study will be divided into 2 phases: the recruitment phase and the follow-up phase. The recruitment phase starts when the study participant is introduced to the study by the HCP (i.e., after a prescription has already been agreed upon), the signing of an ICF, and the completion of a baseline questionnaire (baseline survey). The follow-up phase includes direct follow-up with the study participant at 6, 12, 18, and 24 months after study entry. The follow-up phase will end approximately one year after enrolment of the last study participant. However, participants who are enrolled within the last year of the recruitment phase will have their last routine follow-up at the end of the follow-up phase (instead of 24 months after study entry). Visits and follow-up contacts are calculated in calendar months and years following the baseline visit. In keeping with German national regulations, the recruitment process will be modified for Germany. The description of the relevant modified passages is displayed in ***Annex 3.3***.

HCPs will act as recruiters, identifying potentially eligible study participants, facilitating the onboarding process, educating study participants regarding the study expectations, and consenting them to participate in the study. There will be limited additional involvement from the recruiting HCP. Importantly, the role of HCPs in this PASS should be to act as a recruiter and point of contact for the collection of the study participant's safety information. The primary method of data collection will be through patient-reported outcome questionnaires. Study participants will be followed up by the ZEG Berlin study team independent of the recruiting

HCPs. In the case a study participant will report an outcome of interest to the study, the recruiting HCP may be re-contacted to clarify health outcomes of interest reported by the study participant.

The following recruitment centres will be used:

1. **Health centres**

A network of HCP recruitment centres will be established. Depending on the individual health care system, HCPs may be family practitioners, general practitioners, obstetricians, women's health doctors, midwives, nurse-practitioners, and/or physician assistants. The HCP may only invite eligible study participants to join the study after the decision to start E4/DRSP or EE/LNG is made. HCPs in Germany will be instructed to recruit only on-label users of the respective COCs. The HCP will explain the nature of the study to the study participant and if they will be interested, provide them with access to an online study portal that will guide them through the consenting and ICF completion process.

2. **Pharmacies**

Pharmacy networks will be used as point-of-sale recruitment centres to enhance study recruitment. This recruitment approach will be started in Germany and rolled out to other countries where technology and network infrastructure allow. In the German pharmacies, there will be a screening process to ensure only COC users are recruited who use the respective COCs on-label.

Pharmacy merchandise management systems will be programmed to alert pharmacies of a potentially eligible study participant at the point of sale. Pharmacists will be considered as recruiting HCPs.

All networked pharmacies will receive basic information about the study. Merchandise software will be programmed to provide basic information about the study at the point of HC sale. Following the sale of the HC, it is assumed that pharmacists will provide study participants with basic information about the study and direct those interested in study participation to the study-portal via a QR-code-based system.

Potential study participants entering the study-portal will be initially guided through a brief screening questionnaire to ensure that subjects meet the specified inclusion criteria. Following the successful screening, subjects will be guided through a consenting process. Subjects will be considered to have been successfully enrolled in the study on completion of the eConsent documentation.

3. **Telemedicine/online prescription services**

Digitalization of the healthcare system is an evolving process. Online consultations and the dispensing of prescriptions in the clear absence of personal doctor-patient contact are regulated and reimbursed in France, Germany, the United Kingdom (UK), and the USA. User acceptance and use of telemedicine and online prescription services have accelerated in light of the Covid-19 pandemic and the enforced social distancing policies it has necessitated.

Study participants will be invited by their telemedicine HCP to participate in the study and will be directed to the study-portal after receiving their prescription of a new HC. Potential study

participants entering the study-portal will be initially guided through a brief screening questionnaire to ensure that subjects meet the specified inclusion criteria. Following the successful screening, subjects will be guided through a consenting process. Study participants will be considered to have been successfully enrolled in the study on completion of the eConsent documentation.

4. Electronic medical records

In the UK, data from the Egton Medical Information Systems (EMIS) health software platform will be used to identify potential study participants with a recent prescription of HCs. The EMIS health software is used by over 40% of all primary and acute care service providers in the UK, and currently contains over 1.9 million people who have consented to be contacted for clinical research. Following identification of people fulfilling the eligibility criteria, study participants will be contacted via their HCP, informed about the study, and consented to study participation using eConsent and electronic signature (eSignature, Electronic Identification, Authentication and Trust Services [eIDAS]-compliant).

The four recruitment strategies aim to contact potential study participants at the time of incident HC prescription and/or purchase. Utilizing several recruitment approaches will increase the speed with which study participants can be enrolled in the study and ensures that a representative group of incident HC users will be enrolled in the study, encompassing both study participants who are early adopters of telemedicine and electronic prescriptions, and HC users who prefer to access healthcare via face-to-face, clinic-based consultations.

6.2.1. Exposure

There will be two main treatment cohorts for this study:

- Cohort 1: E4/DRSP, a COC containing 14.2 mg of E4 and 3 mg DRSP.
- Cohort 2: EE/LNG, containing COCs.

6.2.2. Selection of study population

Approximately 50,500 E4/ DRSP users and 50,500 EE/LNG new users, including adolescents (below the age of 18 years eligible based on local legislation) will be recruited via recruitment centres. Based on experience from previously conducted studies of this type by the investigator team, the proportion of adolescents is expected to range between 4 and 15%, depending on the local prescription behaviour, regulatory framework, and the willingness to participate. Overall, 101,000 study participants are needed to provide approximately 150,000 WY (see Section 6.5), assuming a total drop-out and lost-to-follow-up rate of 15%. More than 60% of study participants will be recruited in Europe and the others will be from the USA and Brazil.

Study participants must meet the following inclusion criteria to be considered eligible for inclusion in this study:

- New users of E4/DRSP

  OR

- New users of EE/LNG

There will be no specific medical inclusion/exclusion criteria, except in Germany where, in accordance with the national recommendations, the protocol describes in section 6.2 how recruitment centres will be instructed to recruit only study participants who are prescribed the COC within on-label use. In summary, recruitment of study participants is conducted via networks of HC-providing HCPs and recruitment centres. Study participants will be considered for enrolment in the study only after the participating HCP has determined that the use of a COC is appropriate. The HCP will explain the nature of the study and facilitate the signing of a study ICF, according to local law. Adolescents (below the age of 18 years) are eligible based on local legislation for study inclusion, provided local regulations regarding co-signature of ICF by a parent or guardian are upheld. All study-related documents are to be approved by the relevant local Ethics Committees and the relevant Data Privacy Office, if applicable.

After enrolment, a study participant may discontinue (and restart) the use of a new COC or may switch to another COC at any time. Participants will be contacted for follow-up until a maximum of two years period is completed, provided they do not withdraw their consent for study participation. Information on the date of study withdrawal during the follow-up phase will be collected.

6.3. Variables

6.3.1. Primary endpoint

The primary endpoint of this study is the incidence rate of VTE, specifically:

- DVT of the lower extremities (ICD-10 codes: I80.1 and I80.2), and
- PE (ICD-10 codes: I26.0 and I26.9)

in E4/DRSP users and users of EE/LNG.

The variable to determine the primary endpoint is:

- The occurrence (or absence) of a new (non-recurrent) confirmed VTE during follow-up.

6.3.2. Secondary endpoints

The secondary endpoints of this study are the incidence rates of:

- All VTEs, including thromboses of the renal, mesenteric, portal, cerebral and retinal veins[13] (a sensitivity analysis will be done for the ICD-10 code I80.3),
- ATE, including acute myocardial infarction (AMI) (ICD-10 code I21.* [13]) and cerebrovascular accidents (CVA) (ICD-10 code: I24.9, G45.*, I61.*, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9),
- Unintended pregnancy, and
- Neonatal malformations associated with foetal exposure to E4/DRSP and EE/LNG

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13 ICD-10 codes: I26.0, I26.9, I63.6, I67.6, I80.1, I80.2, I80.3, I80.8, I80.9, I81, I82.0, I82.2, I82.3, I82.8, I82.9, H34.8, K55.0 and N28.0

13 * For all stars, it means: including all codes within this category

in E4/DRSP users and users of EE/LNG.

Descriptive measures are applied to compare

- Drug utilization pattern and,
- Baseline risk profile primary and secondary clinical outcomes– in particular for cardiovascular outcomes

between users of both cohorts.

The variables to determine the secondary endpoints are:

- The occurrence (or absence) of a new (non-recurrent) confirmed VTE during follow-up, including thromboses of the renal, mesenteric, portal, cerebral and retinal veins,
- The occurrence of unintended pregnancy during follow-up.

The variable to determine the drug utilization pattern is:

- The time-varying exposure to COCs observed from study entry through the follow-up period, with dates and duration of each contraceptive prescription.

The variables to characterize the baseline risk profile of COC users are:

- Baseline population characteristics (e.g., age, BMI, family VTE history, and country)
- Socio-economic factors (e.g., education and smoking)
- Parameters of reproductive, contraceptive, and medical history (e.g., gravidity, parity, number of pregnancies/live births, previous use of HCs, disease history [including VTE history] at study entry)
- Concomitant medication.

The variables to determine foetal health outcomes are:

- Occurrence of major congenital malformations, according to classification by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT), as reported during follow-up among pregnancies observed
- Stillbirth (defined as foetal death with a gestational age ≥20 weeks)
- Neonatal death (defined as deaths occurring among live births during the first 28 completed days of life)
- Spontaneous/elective abortion (defined as a loss of pregnancy at a gestational age <20 weeks)
- Termination of pregnancy for foetal anomaly (TOPFA [where prenatal diagnosis was made of malformation in a live foetus and the pregnancy was then terminated])
- Preterm delivery (defined as delivery strictly before 37 completed weeks of gestation)
- Low birth weight (defined as a birth weight <2,500g)
- Small for gestational age infants

The list of variables in Table 1 are similar to the variables used in previous PASS conducted by ZEG-Berlin.

Table 1: List of variables to be used in INAS-NEES

Category		Variable *X - present; G - present in Germany only; U - present under 18 only; T - present, triggers additional follow up*	Questionnaire		
Participant Characteristics			**Baseline**	**Follow-up**	**Extra Follow-up**
Participant Characteristics	*Screening*	Did you take an oral contraceptive pill or any other hormonal contraceptive in the last 2 months?	**X**		
		Before you were asked whether you want to take part in this study, you and your doctor decided on a new prescription for an oral contraceptive pill. Was the prevention of pregnancy the reason for this prescription?	***G***		
		Do you have (or have you ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE), or other organs?	***G***		
		Are you aware of having a disorder affecting your blood clotting – for instance, protein C deficiency, protein S deficiency, antithrombin-III deficiency, factor V Leiden, or antiphospholipid antibodies?	***G***		
		Do you need an operation or are you off your feet for a long time (e.g., hip/leg surgeries, neurological surgeries, trauma surgeries)?	***G***		
		Have you ever had a heart attack or a stroke?	***G***		
		Do you have (or have you ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary symptoms of stroke)?	***G***		
		Do you have severe diabetes with blood vessel damage?	***G***		
		Do you have very high blood pressure?	***G***		
		Do you have a severely increased blood lipids (cholesterol or triglycerides)?	***G***		
		Do you have a condition known as hyperhomocysteinaemia?	***G***		
		Do you have (or have you ever had) a type of migraine called 'migraine with aura'?	***G***		
		Do you have (or have you ever had) a tumour in the liver (benign or malignant)?	***G***		
		Do you have (or have you ever had) a serious liver disease and your liver function is still not normal?	***G***		
		Are your kidneys not working well (renal insufficiency)?	***G***		
		Do you have (or have you ever had) breast cancer or cancer of the genital organs, or is there a suspicion of such a cancer?	***G***		
		Do you have any unexplained bleeding from the vagina?	***G***		
		Are you allergic to estetrol or drospirenone, or any of the other ingredients (Lactose monohydrate, Sodium starch glycolate, Maize starch, Povidone K30, Magnesium stearate (E470b), Hypromellose (E464), Hydroxypropylcellulose (E463), Talc (E553b), Cottonseed oil (hydrogenated), Titanium dioxide (E171), Iron (III) oxide red (E172))?	***G***		
	Demography	Year of birth	**X**		
		Height	**X**	**U**	
		Weight	**X**	**X**	
		Education level	**X**		

Category		Variable *X - present; G - present in Germany only; U - present under 18 only; T - present, triggers additional follow up*	Questionnaire		
Participant Characteristics			**Baseline**	**Follow-up**	**Extra Follow-up**
	Gynaec. history	Age at first menstrual period	X		
		Problems related to period	X		
		Ever been pregnant before	X		
		Pregnant in the last 3 months	X		
		Number of live births	X		
		Age at first delivery	X		
	Regular Medication	Taking regular medication	X	X	X
		Brand name of regular medication	X	X	X
Risk Factors			**Baseline**	**Follow-up**	**Extra Follow-up**
Risk Factors	*Family History*	Any DVT/PE in close relatives	X		
		Close relatives who experienced DVT/PE	X		
		Any MI/Stroke related death in close relatives	X		
		Close relatives who died as result of MI/Stroke	X		
	Diseases	Participant's knowledge of their own risk-factor diseases/conditions	X		
	Deep Vein Thrombosis	Date of being informed about DVT diagnosis	X		
		Was DVT treated by physician?	X		
		Was DVT treated with blood-thinners?	X		
	Pulmonary Embolism	Date of being informed about PE diagnosis	X		
		Was PE treated by physician?	X		
		Was PE treated with blood-thinners?	X		
	Myocardial Infarction	Date of being informed about MI diagnosis	X		
		Was MI treated by physician?	X		
		Did ECG/laboratory confirm MI?	X		
	Stroke	Date of being informed about Stroke diagnosis	X		
		Was Stroke treated by physician?	X		
	Thrombophilia	Date of being informed about Thrombophilia diagnosis	X		
		Was Thrombophilia treated by physician?	X		
		Type of Thrombophilia	X		
	Cancer	Date of being informed about Cancer diagnosis	X		
		Type of cancer	X		
		Was Cancer treated by physician?	X		
		Was Cancer treated with chemotherapy?	X		
	Diabetes	Date of being informed about Diabetes diagnosis	X		
		Was Diabetes treated by physician?	X		
	High Blood Pressure	Date of being informed about HBP diagnosis	X		
		Was HBP treated by physician?	X		
	Other Severe Disease	Description of Other severe disease	X		
		Date of being informed about Other severe disease diagnosis	X		

Category		Variable *X - present; G - present in Germany only; U - present under 18 only; T - present, triggers additional follow up*	Questionnaire		
Participant Characteristics			**Baseline**	**Follow-up**	**Extra Follow-up**
		Was Other severe disease treated by physician?	X		
	Surgery	Description of surgery	X		
		Date of surgery	X		
	COVID-19	COVID-19 infection	X	X	
	Liver disease	Liver disease	X		
	Renal disease	Severe renal disease/kidney disease	X		
	Migraine	Migraines with neurological symptoms	X		
	Tobacco use	Smoking habit	X	X	X
		Years of regular smoking	X		
		Per day smoking	X	X	X
		Vaping habit	X	X	X
		Years of regular vaping	X		
		Per day vaping	X	X	X
Hormonal Contraceptive Therapy			**Baseline**	**Follow-up**	**Extra Follow-up**
Hormonal Contraceptive Therapy	*Past Therapy*	Any hormonal contraceptive use before study	X		
		Total duration of all hormonal contraceptive use before study	X		
	Change	Change or cessation of hormonal contraceptive therapy since last contact		X	
	Current Therapy	Brand name of current hormonal contraceptive	X	X	
		Indication for current hormonal contraceptive prescription	X		
		Non-contraceptive indications for current hormonal contraceptive prescription	X		
		Date of current therapy start		X	
	Stopped Therapy	Brand name of most recently stopped hormonal contraceptive	X	X	
		Date of therapy stop		X	
	If Multiple Therapies Since Last Contact	Brand name of previous hormonal contraceptive		X	
		Date of previous therapy start		X	
		Date of previous therapy stop		X	
		Treatment gap of min. 1 month when switching to previous therapy		X	
		Duration of treatment gap in months		X	
Events of Interest - Diseases			**Baseline**	**Follow-up**	**Extra Follow-up**
Events of Interest - New Deep Vein Thrombosis Diagnosis	*Diagnoses*	Newly diagnosed disease in study objective scope since last contact		X	
	New Deep Vein Thrombosis Diagnosis	Date of New DVT diagnosis		X	
		Was New DVT treated by physician?		X	
		Exact diagnosis for New DVT		X	
		Symptoms experienced of New DVT		X	
		Body parts affected by New DVT		X	
		Incidental risk factors experienced up to 6 weeks before New DVT		X	

Category	Variable *X - present; G - present in Germany only; U - present under 18 only; T - present, triggers additional follow up*	Questionnaire		
Participant Characteristics		**Baseline**	**Follow-up**	**Extra Follow-up**
	COVID-19 vaccination in the 6 weeks before the New DVT symptoms		X	
	Brand name of COVID-19 vaccine		X	
	Was New DVT treated with blood-thinners?		X	
	Brand name of blood-thinner		X	
	New DVT examinations		X	
	New Genetic Thrombophilia examinations		X	
	Result of New Genetic Thrombophilia Examination		X	
	Type of New Genetic Thrombophilia		X	
New Pulmonary Embolism Diagnosis	Date of New PE diagnosis		X	
	Was New PE treated by physician?		X	
	Exact diagnosis for New PE		X	
	Symptoms experienced of New PE		X	
	Incidental risk factors experienced up to 6 weeks before New PE		X	
	COVID-19 vaccination in the 6 weeks before the New PE symptoms		X	
	Brand name of COVID-19 vaccine		X	
	Was New PE treated with blood-thinners?		X	
	Brand name of blood-thinner		X	
	Hospital admission for New PE		X	
	New PE examinations		X	
	New Genetic Thrombophilia examinations		X	
	Result of New Genetic Thrombophilia Examination		X	
	Type of New Diagnosed Thrombophilia		X	
	Concurrent DVT diagnosis during New PE		X	
	Date of Concurrent DVT diagnosis		X	
	Body parts affected by Concurrent DVT		X	
New Myocardial Infarct Diagnosis	Date of New MI diagnosis		X	
	Was New MI treated by physician?		X	
	Exact diagnosis for New MI		X	
	Symptoms experienced of New MI		X	
	Did ECG/laboratory confirm New MI?		X	
	Hospital admission for New MI		X	
	Surgical intervention for New MI		X	
	Type of surgical intervention for New MI		X	
New Stroke Diagnosis	Date of New Stroke diagnosis		X	
	Was New Stroke treated by physician?		X	
	Type of New Stroke		X	
	Exact diagnosis for New Stroke		X	
	Symptoms experienced of New Stroke		X	
	Duration of New Stroke symptoms		X	

Category		Variable *X - present; G - present in Germany only; U - present under 18 only; T - present, triggers additional follow up*	Questionnaire		
Participant Characteristics			**Baseline**	**Follow-up**	**Extra Follow-up**
		Hospital admission for New Stroke		X	
		New Stroke examinations		X	
		Did examination confirm New Stroke?		X	
		Type of therapeutic intervention for New Stroke		X	
Events of Interest - Pregnancies and Deliveries			**Baseline**	**Follow-up**	**Extra Follow-up**
Events of Interest - Pregnancies and Deliveries	*New Pregnancy*	New Pregnancy since last contact		X	
		Was New Pregnancy planned?		X	
		Duration of trying to get pregnant in months, if planned		X	
		New Pregnancy despite using hormonal contraception		T	
		Hormonal contraceptive used at time of conception of New Pregnancy		X	
		Potential reasons for New Pregnancy despite using hormonal contraception		X	
		New Pregnancy diagnosis by HCP?		X	
		New Pregnancy diagnostic method		X	
		Age of New Pregnancy when diagnosed		X	
		New Pregnancy status at response date		X	X
		Due date of New Pregnancy		X	
		Reason for New Pregnancy end		X	X
		Malformation/chromosomal abnormality of New Pregnancy		X	
		Malformation/chromosomal abnormality diagnostic method		X	
		Frequency of alcohol consumption during New Pregnancy		X	X
		Folic acid taken before New Pregnancy diagnosis		X	X
		Folic acid taken during first 3 months of New Pregnancy		X	X
		Complications related to the New Pregnancy			X
		Infections during New Pregnancy			X
	New Delivery	New Delivery since last contact		X	
		Week of Gestation at New Delivery		X	X
		Date of New Delivery		X	X
		Weight of child born during New Delivery		X	X
		Height of child born during New Delivery		X	X
		Malformation/chromosomal abnormality diagnosed in child born		X	X
		Type of Malformation/chromosomal abnormality diagnosed		X	X
		Malformation/chromosomal abnormality diagnostic method		X	X
		Malformation/chromosomal abnormality family history of biological parents		X	X
		Malformation/chromosomal abnormality diagnosed in biological parents		X	X
		Close family relation between biological father and mother		X	X

6.4. *Data sources*

At study entry (baseline), study participants will sign an ICF and complete a baseline questionnaire designed to capture data on potential confounding factors and potential effect modifiers. Study participants will record personal information such as their age, height, weight, educational level, personal medical history, family medical history of VTE and ATE, concomitant medication, history of hormonal contraceptive use, and smoking status (see Section 6.4.1).

Study participants will complete follow-up questionnaires at 6, 12, 18, and 24 months after entering the study. The follow-up questionnaires will capture information on HC use, the occurrence of specified AEs of interest, and unintended pregnancy (see Section 6.4.2). Data on potential confounding factors (e.g., BMI and smoking status) will also be recorded during the follow-up phase.

6.4.1. *Baseline survey*

Eligible study participants who agree to participate will complete a baseline survey on which they will record demographic data (age, height, and weight), personal medical history (including gynaecological history and medication use), family history of relevant risk factors, previous hormonal contraceptive use, education level, and lifestyle data (e.g., smoking status). The questionnaire will be sent out after successful consenting to the patient via email. The patient can decide if they want to fill out the questionnaire at the HCP via smartphone or tablet or if they want to do it at home on their electronic device.

The baseline questionnaire can be completed at HCP's office or home via the electronic data capture (EDC) system or if EDC is not feasible, through Computer Assisted Telephone Interviews (CATI).

If the study participant does not answer the initial request to answer the baseline questionnaire, two reminders are sent 7 days apart. If these reminders are unsuccessful, 4 attempts will be made by telephone over 14 days. After these contact attempts the baseline questionnaire will be blocked and the patient is not eligible for the study.

6.4.2. *Follow-up phase*

Follow-up will be conducted via direct contact with the participants through EDC or, where EDC is not feasible, CATI. At each pre-defined follow-up time point (i.e., 6, 12, 18, and 24 months after study entry), study participants will be contacted and asked to complete a follow-up web-based questionnaire, accessible via a link sent by SMS or email. The follow-up questionnaire will be designed to capture data on contraceptive use, specific safety outcomes (e.g., VTE, ATE, MI, or stroke), weight, and pregnancy outcomes. If the patient does not complete the questionnaire on the initial contact attempt, two reminders are sent 7 days apart. If these reminders do not lead to success, 4 attempts will be made by telephone during the next 14 days, starting 7 days after the last reminder E-mail. After these contact attempts the follow-up questionnaire will be blocked and the patient will be set to lost to follow-up.

In the case study participants report OC exposure during pregnancy, the women will be followed-up on the outcome of the pregnancy. To obtain the necessary information, an extra follow-up questionnaire will be provided to the respective study participants 3 months after their anticipated date of delivery. The prevalence estimates of major congenital malformation for COC users will be compared with the general population. The total prevalence of major congenital malformations, and live birth prevalence, will be calculated as per EUROCAT definitions.

6.4.3. Validation of self-reported events

If a health outcome of interest (VTE, ATE, or pregnancy) is reported by a study participant by positively answering the respective question in the study questionnaire, it is automatically flagged in the database, and the study participant is immediately asked for more details within the electronic data capture (EDC) system. Flagged follow-up questionnaires are then reviewed by the medical event validation team at ZEG Berlin. Following review, it may be necessary to re-contact the study participant and/or the treating HCP for validation of the information initially received from the study participant. For this purpose, the study participant gives permission to contact the treating physician who has diagnosed the outcome of interest (not necessarily the same as the recruiting HCP) in case the participant cannot provide any valid medical documentation. Necessary information that is unclear or missing will be cross-checked with the study participant and/or HCP for clarification. All additional information received by the medical event validation team is captured in the study database and forms part of the core study dataset.

A self-administered questionnaire used by study participants at short intervals is a sensitive tool that captures almost all serious clinical outcomes and was already used in similar studies [7]. From a methodological point of view, it captures a much higher proportion of these outcomes than methods relying only on the prescribing HCP who may not be involved in the diagnosis and treatment of these outcomes. However, there is a significant difference between the rates of patient-reported and medically confirmed events after validation, as laypersons often misclassify specific AEs, and therefore validation of the self-reported events is of utmost importance.

In this study, a medical confirmation will be sought for self-reported events considered as VTE or ATE captured in the study database. VTE and ATE cases will be classified by ZEG Berlin's medical event validation team according to the following predefined algorithm:

- **Definite Event:**
  Diagnosis confirmed by diagnostic measures with high specificity (DVT: e.g., phlebography, duplex sonography, and magnetic resonance imaging; PE: e.g., pulmonary angiography, ventilation-perfusion scan, magnetic resonance imaging, transesophageal echocardiography, and spiral computed tomography (CT); cerebral magnetic resonance imaging (MRI) for cerebrovascular accidents, electrocardiography (ECG) with typical ST-segment elevation for acute myocardial infarction)) and written proof e.g., medical record.

- **Probable Event:**
  Absence of confirmation by a diagnostic measure with high specificity for the diagnosis, but clinical diagnosis confirmed (verbally or in writing) by an HCP or, supported by diagnostic tests with low specificity (such as ultrasound doppler, plethysmography, D-dimer for VTE or typical ECG/blood gas tests for PE).
  These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician

confirms that the diagnosis is correct, the event will be classified as a VTE, even if specific treatment was not given.

Definite and probable events will be classified as 'confirmed events'

- **Possible Event:**
  Study participant (self-reported) diagnosis of VTE or ATE without a medical confirmation of the event or, no diagnostic measures were performed that could have clarified the diagnosis however, the case history provided (e.g., symptoms, treatment) strongly suggests that this is indeed a VTE/ATE case.

- **Potential Event:**
  Condition considered as VTE or ATE was reported by the study participant only and no further medical confirmation could be obtained, and the case history is not sufficiently clear to allow further clarification.

- **Event disproven:**
  Diagnosis reported by the study participant is excluded by diagnostic procedures or a different medical condition is diagnosed by the attending HCP.

Possible, potential, and disproven events will be classified as a subgroup of 'not confirmed' events.

The classification of VTE and ATE into 'confirmed' and 'not confirmed' will be verified during the blinded adjudication procedure. At least three individual medical specialists (adjudicators) will review available information on the reported outcomes and classify the case as "confirmed" or "not confirmed". For this process, the adjudicator will be blinded to the brand names and composition of the treatments used by the reporting study participant. The adjudicators will perform the reviews independently of each other and without knowing the judgement of the other adjudicators or the investigators. Details of the procedure are given in ***Annex 3.2***.

6.4.4. Lost to follow-up

A low "lost-to-follow-up rate" will be essential for the validity of the study. To minimize lost to follow-up, a multi-faceted follow-up process will be established, which is a four-level follow-up process. Level 1 activities include electronically sending the follow-up questionnaire and – in case of no response – two reminder emails. If Level 1 activities do not lead to a response, multiple attempts are to be made to contact the study participant, and the HCP by phone. In parallel to these Level 2 activities, searches in national and international telephone and address directories, as well as electronic social networks, are started (Level 3 activities). If this is not successful, an official address search via the respective governmental administration and commercial databases will be conducted. This Level 4 activity can provide information on new addresses (or emigration or death). The aim is to keep the total lost to follow-up at the end of the study at less than 15% of the study population. Study participants may want to withdraw from the study, and they are allowed to do so at any time. If possible, the reasons for study withdrawal will be collected.

6.5. *Study size*

The sample size calculation is based on an incidence rate of 10 VTE (DVT of the lower extremities and PE) per 10,000 WY for EE/LNG. It is expected that E4/DRSP is associated with a VTE risk that is not higher than the risk associated with EE/LNG. The study should be powered to test the non-inferiority of E4/DRSP treatment regarding VTE risk in comparison to EE/LNG use.

At an incidence rate of 10 VTE per 10,000 WY, a total of 150 VTE cases could be expected within 150,000 WY. Sample size calculations show that approximately 150,000 WY of observation is statistically sufficient (power = 80%, $\alpha = 0.05$) to exclude a 1.5-fold VTE risk for E4/DRSP users compared to EE/LNG users. Calculations are based on a recruitment phase of 5 years, follow-up of 101,000 women (50,500 E4/DRSP users and 50,500 EE/LNG users) for 2 years, and a total drop-out and lost-to-follow-up rate of 15% (see Table 4).

Subsequent exclusion of users of higher-dose monophasic LNG containing COCs (more than 30µg EE/ more than 150µg LNG), estimated to represent only 0.15% of study participants (equals 230 women-years), will not significantly affect statistical power.

Statistical considerations regarding sample size.

However, observations from COC PASS studies finalized in the last 5 years suggest that the VTE incidence rate in a general population of COC users may be lower than the previously accepted 10 VTE/10,000 WY. The INAS-SCORE (NCT01009684), finalized in February 2017, observed an EE/LNG VTE incidence of 8.8 VTE/10,000 WY in European women and INAS-FOCUS (EUPAS1597), finalized in August 2020, observed an EE/LNG incidence rate of 7.9 VTE/10,000 WY within the USA study population. The recently finalised PRO-E2 study found an overall VTE incidence in LNG/EE users of 5.8 VTE/10,000 WY in the EU population and an incidence of 4.7 VTE/10,000 WY of the lower extremities and PE in the same study population. Anecdotal reports from physicians participating in INAS-SCORE and INAS-FOCUS, and PRO-E2 studies suggest that there is increased awareness regarding the risk of VTE associated with COC use. A change in prescribing practices by physicians due to increased risk awareness may be partially responsible for the change in risk incidence.

Therefore, with the assumption that 150,000 WY is the feasibility limit for a prospective, non-interventional study, it is possible to construct alternative scenarios based on a lower overall VTE incidence rate of 7.0 VTE/10,000 WY (Table 2).

Table 2: Sample size alternatives based on various assumptions.

Inc. COC_{LNG}	Inc. E4/DRSP	HR_0	HR_{ni}	Expected #VTE	WY_{Total}	Power (%)
0.001	0.001	1	1.5	151	150,426	80%
0.0007	0.0007	1	2	105	150,000	97%
0.0007	0.0007	1	1.65	105	150,000	82%

Inc.: incidence of VTE; COC_{LNG}: Levonorgestrel-containing combined oral contraceptive; E4/DRSP: Estetrol/ Drospirenone; HR: Hazard ratio; #VTE: Number of venous thromboembolisms; WY: Women-year

Line 2 and 3 show that with a lower overall incidence of 7.0 VTE/10,000 WY, and pre-specified 150,000 WY of observation, the study would still have 97% power to exclude a 2.0-fold risk, and >80% power to exclude a 1.65-fold risk.

As an additional comment, our current working hypothesis is that E4/DRSP will have a slightly lower risk of VTE compared to currently available COCs, including EE/LNG. This assumption is based on results from clinical trials and comparative studies on coagulation biomarkers:

- The observed VTE incidence from the pooled Phase 2-3 E4 clinical program was 2.8 VTE/10,000 women (95% CI 0.7 - 15.6), with a 95% confidence interval based on Poisson distribution.
- The VTE incidence rate, in view of 2,735 WY of exposure, was 3.7 VTE/10,000 WY (95% CI: 0.9 - 20.4).
- Haemostasis parameters were investigated in Study MIT Es0001-C201 which concluded that E4/DRSP 15/3 mg was associated with -
    - Less resistance to activated Protein C (APC) than EE/LNG (change from baseline: +30% versus +165%)
    - Decreased change from baseline in F1+2 as compared with EE/LNG (+23% versus +71%)
    - No statistically significant changes from baseline in coagulation inhibitors.
    - No effect on soluble E-selectin

  and therefore, a more neutral haemostatic profile.
- Overall haemostasis results indicate that E4/DRSP 15/3 mg has less effect on haemostatic parameters compared with EE/LNG 0.03/0.15 mg, and also less than observed with the COCs containing E2 [8, 9] and E2V. [10, 11]
- The VTE adjusted hazard ratio of E2V versus EE/LNG was observed as 0.4 (95% CI 0.2-1.1) in the INAS-SCORE PASS. [12].

Based on the above argumentation, it is worth considering a scenario with a less conservative margin choice, i.e., that E4/DRSP has a decreased risk of VTE compared to LNG-COC and the subsequent sample size calculations for the proposed PASS study could be modified accordingly (Table 3).

Table 3: Sample size calculations assuming differing incidence rates between cohorts.

Inc. COC_{LNG}	Inc. E4/DRSP	HR_0	HR_{ni}	Expected #VTE	WY_{Total}	Power (%)
0.0007	0.000561	0.8	1.5	95	150,000	92%

Inc.: incidence of VTE; COC_{LNG}: Levonorgestrel-containing combined oral contraceptive; E4/DRSP: Estetrol/ Drospirenone; HR: Hazard ratio; #VTE: Number of venous thromboembolisms; WY: Women-year

For this sample size calculation, the assumption is that the feasibility limit for a prospective non-interventional study of COC is 150,000 WY. Assuming a hazard ratio of 0.8 and an EE/LNG VTE incidence of 7.0 VTE/10,000 WY, the study would have sufficient power to exclude a 1.5-fold risk with 92% power.

The proposed sample size for the investigation of the VTE risk is also sufficient for the evaluation of unintended pregnancy assuming an incidence between 0.5-0.8 per 100 WY (Pearl Index). However, acute myocardial infarction and stroke are very rare in a female population of reproductive age. This study is powered to exclude a 2.5-fold risk of ATE (a secondary outcome). This is sufficient to screen for safety signals.

Table 4 Expected observation time

Assumptions: approx. 101,000 study participants recruited over 60 months (~ 1,684 per month); follow-up of study participants 2 years; drop-out rate of 0.7% per month (e.g., 12 out of 1,684 recruited women will drop-out during the first month after recruitment; therefore, the average number of women during the first month is 1,678 women [(1,684+1,672) x 0.5]); LTFU, end of observation due to treatment stopping or switching, and dropout is expected with approx. 20%.

	Sub-cohorts recruited during the month			
Time after study start [month]	1	2	…	60
	Average number of women in follow-up			
1	1,678			
2	1,666	1,678		
…	…	1,666	…	
24	1,428	…	…	
25		1,428	…	
26			…	
…			…	
60			…	1,678
…			…	…
82			…	1,438
83				1,428
WY	3,099	3,099	3,099	3,099
Total WY (crude)	**185,953**			
Total WY (Corrected regarding treatment adherence, treatment stopping/switching, LTFU/dropout)	**≈150,000**			

6.6. *Data management*

6.6.1. *Databases*

During the study, two different types of data will be collected: (I) administrative data, which includes contact details of the study participants, and (II) study data, which includes all questionnaire data including baseline data, all subsequent follow-up forms, and all event validation forms. All study data will be collected and managed through the EDC System stored on a cloud infrastructure. This EDC system will be annex 11 and part 11 compliant. For data security and privacy reasons, administrative data are stored separately from the study data. Access to administrative data will be restricted and only be accessible for the teams who require contact with the study participants.

Physician/health care professional details are entered and maintained in the EDC System. Study participants' details are connected to a user account and can only be adapted by the study participants.

Study data will be entered directly by the study participants via an ePRO questionnaire following the Bring Your Own Device (BYOD) concept.

Event data collected during the event validation process will be entered in dynamical additional forms. These forms are restricted to the responsible ZEG Berlin employees or the national field organization.

The quality control of entered data will be supported by edit checks which include range, coding, missing and data checks as well cross-reference (consistency) checks between variables. Any inconsistencies or unanticipated answers will be clarified with the study participant in additional contacts. In case of complex data checks, additional checks may be implemented outside of the EDC system and will be sent via queries to the field organizations for further clarification.

All VTE and ATE outcomes will be coded using ICD-10 and all other reported AEs, as well as pregnancy and surgical procedures will be coded only using the MedDRA dictionary (Medical Dictionary for Regulatory Activities). Collected concomitant medication during baseline, follow-up, or event validation will be coded using the World Health Organization Anatomical Therapeutic Chemical Classification System (WHO ATC)-Codes. Where applicable, ZEG Berlin might also use additional codes for the coding of events (e.g., the outcome of unintended pregnancy: induced or spontaneous abortion, delivery of a healthy child, birth defects).

All other relevant information will be coded using a ZEG Berlin-specific, highly standardized coding system (ZEG Coding Dictionary). The ZEG Berlin Coding Dictionary (ZEG-CD) is a proprietary catalogue of different ZEG specific and centrally maintained standardized code lists. ZEG Berlin-specific code lists (e.g., pregnancy wish, fear of side effects, financial reasons, medication not available, etc.) are also developed and employed if international coding classifications such as MedDRA, ICD-10 codes do not exist or prove to be inappropriate.

6.6.2. *Database freeze and lock*

For each interim analysis (see Section 6.7.2) and for the final analysis, the database will be frozen at a predefined time point. The database will be 'cleaned' within 4 weeks of the database freeze.

After the final database lock (approximately 4 months after the last follow-up questionnaires have been sent to the study participants), no additional incoming data will be entered into the database – this database will represent the final data source for all analyses. Safety copies will be made of each database to enable the calculations to be repeated if necessary.

Follow-up of information on pregnancy outcomes will continue after the final database lock. For information gathered after this final database lock, the database will not be reopened, and the information will only be used for pharmacovigilance purposes.

6.7. Data analysis

6.7.1. Statistical analysis

Based on available data and pharmacological considerations, the *a priori* assumption is that the use of E4/DRSP is not associated with an increased risk of VTE compared to EE/LNG. Therefore, a non-inferiority design to investigate the VTE risk of E4/DRSP has been deemed appropriate. The primary analysis will be based on the comparison of the upper confidence limit for the point estimate of the VTE hazard ratio (HRVTE) with a predefined non-inferiority limit. The null hypothesis to be tested is: HRVTE $\geq$ 1.5 (i.e., the VTE hazard ratio for E4/DRSP vs. EE/LNG is higher than or equal to 1.5). The alternative hypothesis is: HRVTE<1.5.

The final analyses will include both an "as-treated" (AT) and an "intention-to-treat" (ITT) analysis. All eligible women will be assigned to the ITT and AT population at baseline. Only women with follow-up information will be considered for longitudinal analysis (e.g., distribution of outcomes over time, incidence rates, time-to-event). Women who never started their prescribed baseline medication will be considered in the ITT analysis but excluded from the AT analysis.

Baseline population characteristics, e.g., socio-economic factors, parameters of reproductive, contraceptive history, and medical history will be described as baseline risk profiles and considered as time-invariant continuous or categorical variables to describe sources of risk and confounding in the analysis. Inverse probability of treatment weighting (IPTW) using propensity scores (PS) will be considered to correct for covariate imbalances between cohorts. Logistic regression will be applied as a common model for the estimation of PS. The adequacy of the PS model will be assessed by comparing absolute standardized differences between IPT-weighted synthetic cohorts. The average treatment effect of E4/DRSP on the risk of VTE compared to EE/LNG will be obtained from time-to-event analysis using an application of the extended (weighted) Cox model. The observed HR_{VTE} between users of E4/DRSP and EE/LNG will be provided with 95% confidence intervals.

Previously proposed classical application of Cox regression on VTE considering a simple exposure-outcome model crude and adjusted for a limited number of a priori defined confounders (e.g., age, BMI, duration of COC use, the concentration of EE/LNG, and family history of VTE) will be provided as sensitivity models. Subsequent analyses of neonatal outcomes stratified by trimester of exposure will be performed based on estimated date of conception.

Missing values for important confounders will be requested through participant recall or imputed by appropriate statistical methods (e.g., last observation carried forward (LOCF), multiple imputations.

A detailed statistical analysis plan addressing descriptive and inferential statistics will be developed during the first year after the study starts for approval by the Safety Monitoring and Advisory Council. The statistical evaluation will be performed with the most current release version (9.4) of the software package SAS®.

6.7.2. Interim analysis

Interim reports are planned to reassess the validity of the assumptions underlying sample size estimation based on the actual study data. As in all similar studies, recruitment and accrual of data are observed on an ongoing basis to ensure the timely conduct of the study. As sample size calculations are based on assumptions (i.e., the prevalence of VTE, prevalence of OC use in women of fertile age, market share of COCs containing E4/DRSP and LNG), these have to be checked based on the actual data on the prevalence of VTE and exposure in the study population.

Data relevant for the steering committee will be made available i.e., the eligibility of women and prevalence of exposure subgroups as well as the distribution of population characteristics. Frequencies and summary statistics for baseline parameters, e.g., age, reproductive history, history of contraception, prior and concomitant diseases will be tabulated and presented to the SMAC. Planned interim reports do not include any statistical modelling of primary outcome variables but will provide incidences and/or prevalence of the so far reported adverse events.

6.8. Quality control

ZEG Berlin is committed to high standards of quality in the conduct of epidemiological studies and, in compliance with Good Clinical Practices, uses Standard Operating Procedures (SOPs) as a quality assurance instrument. Approved SOPs include procedural guidelines relating to Data Management (Section 4), Quality Management (Section 6), and Storage and Archiving (Section 7). The study will be overseen by a Safety Monitoring and Advisory Council comprised of internationally acknowledged experts in the field. This committee will take final decisions in all scientific matters.

6.9. Limitations of the research methods

In non-experimental studies such as this prospective cohort study, the possibility of bias and residual confounding can never be entirely eliminated, and the ability to infer causation is correspondingly limited. [13] Valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology help to reduce the impact of bias and residual confounding. [14] However, the difficulty remains unresolved when all that exists is a weak association. [15, 16] Relative risk estimates that are close to unity may not allow differentiation between causation, bias, and confounding. [17, 18] In general, it is difficult to interpret a relative risk of two or less in observational research. [19, 20]

Within the limitations of non-experimental studies, the proposed study design will minimize bias and residual confounding. To reduce the possibility of selection bias, sites will cover a range of COC prescribers across a broad geographical area; the demographic characteristics of the participants will be representative of typical COC users. HCPs will be expected to enrol all eligible participants, thereby minimizing enrolment bias. Also, misclassification bias is unlikely to have a substantial impact on the results as precise information on exposure and the outcomes of interest will be available. In addition, reliable information on the duration of current COC use

will be available. Accordingly, the study will capture the well-known increased VTE risk during the first months of COC use. [21–23] Since it may be difficult to determine with precision both the date of conception and the stop date of COC use, it will be difficult to accurately assess exposure by trimester. The margin of error will depend on recall bias regarding the date of stopping the COC use, however, the recall bias will not be differential between cohorts.

Patient-reported outcomes are a potent instrument in the context of VTE and ATE because the prescribers of COCs are typically not identical with the HCPs that diagnose and treat these disease entities. The nature of VTE and ATE makes it very likely that the patients will be aware of them when filling in the questionnaire. A weakness of patient-reported outcomes consists in overreporting, e.g., reporting varicose veins as DVTs. This problem is addressed by validation of these reported events. Furthermore, self-reporting by the patients could introduce other limitations, specifically if a participant neglects or forgets to report an event. Failure to self-report can be assumed to be non-differential between cohorts and therefore a small limitation. Regarding the self-reporting of confounding factors, a bias can never be ruled out completely, but may depend on the item (e.g., smoking, unintended pregnancies, and higher BMI may be systematically underreported). Nevertheless, more than one-quarter of USA participants in previous studies were found to be obese. If anything, the tendency would be to report a lower BMI. There is no indication that the reporting of this or any other confounding factor would be differential.

Furthermore, the comprehensive follow-up procedures will ensure a low lost to follow-up rate. In theory, a disproportionately high percentage of SAEs (including VTE and ATE) could occur in those participants who are lost to follow-up, because SAEs could be the reason for the break-in contact with the HCP who prescribed their COC and would be responsible for reporting the SAE in a typical site-based study. An advantage of the study design, however, is that the investigator team will have direct contact with the study participants; contact will not be lost if the women change HCPs, for example (e.g., due to change of residence or dissatisfaction with treatment).

In contrast, it will be impossible to completely exclude diagnostic bias. Clinical symptoms of VTE cover the spectrum from a complete absence or unspecific, slight symptoms to dramatic, acute, life-threatening symptoms. [24–26] A high awareness of potential cardiovascular risks of COC use may lead to more diagnostic procedures and, therefore, to more detected VTE. It is conceivable that this potential bias will lead to an overestimate of the relative risk of a new product cohort (such as E4/DRSP) compared to the LNG cohort. Therefore, diagnostic bias should not result in an underestimate of the VTE risk carried by E4/DRSP.

This study combines several methodological strengths that are substantial for the validity of the results: i) prospective, comparative cohort design; ii) availability of important confounder information (e.g., BMI and family history of VTE); iii) validation of outcomes of interest and the exposure of the relevant cases; iv) comprehensive follow-up procedure and very low lost to follow-up to minimize underreporting; v) independent, blinded adjudication of VTE cases; vi) relevant statistical analyses (e.g., stratified analyses by user status and exposure period; comparison of isochronous, new user cohorts; sensitivity analyses on the impact of the adjudication process and prognostic factor/covariate selection); vii) study population representative of oral contraceptive users under routine clinical conditions; viii) generalizability of results as COC use in this study reflects routine clinical use and study participation is not limited by medical inclusion and exclusion criteria; ix) supervision by an independent Safety

Monitoring and Advisory Council and scientific independence from the study funder and study coordinator.

7. Protection of human subjects

7.1. Ethical conduct of the study and protecting study participant privacy.

This study will be conducted in a manner that is consistent with all relevant European and national guidelines and regulations for conducting studies with human subjects. Specifically, the latest version (2013) of the Helsinki Declaration[14] and the relevant guidelines for "Good Practices" (see Section 7.4) will be observed. All steps will be taken to protect the participant's privacy and all relevant rules on data privacy will be followed. It will be ensured that participants' names and addresses cannot be accessed by the funder or the study coordinator.

7.2. Institutional review

A review of the study protocol will be obtained at ethics committees in the participating countries as required by local law. Non-interventional studies are not within the scope of the European Clinical Trial Directive (2001/20/EC). Accordingly, clinical trial applications to individual European national authorities will not be filed. However, regional regulatory approval within certain European member states will be obtained as required by national regulations. All relevant data protection laws in the participating continents and countries will be followed.

7.3. Informed consent

Participants will be free to sign informed consent forms at baseline after reading a participant information form and discussing the study with the participating physician or health care professional. The HCP will describe the purpose of the study, the non-interventional character of the study, the timing and content of follow-up phase contacts, and the collection of alternative contact information. Consent will include permission to contact any treating physician to follow up on specific safety outcomes. Participants will be informed that ZEG Berlin will contact them during the follow-up phase (i.e., 6, 12, 18, and 24 months after study entry) to ask a predefined set of safety-related questions or to update alternative contact information. Answers to these questions collected by ZEG Berlin will remain anonymous when forwarded to the funder, the study coordinator, or the Safety Monitoring and Advisory Council.

Participants will be asked to provide personal contact information (e.g., telephone number, home, and e-mail address) and information regarding alternative contacts (e.g., primary HCP). If a participant cannot be reached during the follow-up phase, ZEG Berlin via the local field organisation will attempt to reach an alternative contact to re-establish contact with the participant, or, in the event of a participant's death, to confirm the cause of death. Participants may be contacted between two follow-up points to confirm that their personal contact information is correct.

Participants retain the right to withdraw their consent at any time during the study.

[14] Internationally recognized document defining the ethical principles of clinical research; it resulted from a series of meetings of the World Medical Association – a global organization representing physicians – between 1964 and 2013.

7.4. *Confidentiality*

ZEG Berlin (study coordinator), Gedeon Richter, and Estetra SRL (funder) as well as all field organizations and recruiting health care professionals ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to ZEG Berlin, the funder, or the SMAC does not contain any data which, on its account or in conjunction with other freely available data, can be used to re-identify natural persons. The field organizations are obligated to ensure that no documents transferred to ZEG Berlin contain such data. Study participants, as well as health care professional details, are only kept at the local level at the field organizations in all countries except for Germany, where medically trained staff perform the medical evaluation of the reported (adverse) events. Any personal data at ZEG Berlin are kept under restriction and only eligible staff can access these data.

All records identifying the participant will be kept confidential. Study participant names will not be supplied to the study coordinator or the funder. If the study participant's name appears on any document, it must be redacted before a copy of the document is supplied to the study coordinator or the funder. Study findings stored on any computer will be stored following local data protection laws.

Local study teams (field organizations) will contact study participants in case of any query, follow-up, or clarification of an outcome of interest. In the case of a report of an AE, the responsible pharmacovigilance person from Estetra SRL may ask ZEG Berlin for additional clarification. The study coordinator may not contact the study participant directly. All additional information will be provided by the field organization via ZEG Berlin.

7.5. *Study management*

This study will be conducted following:

- 'Guideline on Good Pharmacovigilance Practices (GVP), Module VIII issued by the European Medicines Agency.' - Revision 3: February 3, 2021 (EMA/54854/2021)
- 'Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the European Epidemiology Federation.' – April 2004
- 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology.' - Revision 3: June 2015
- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies (http://www.encepp.eu/code_of_conduct/)
- The ethical principles have their origin in the Declaration of Helsinki. (DoH – October 2013)

8. Management and reporting of adverse events/adverse reactions

This is a non-interventional, post-authorization safety study (PASS) whose main aim is to capture cardiovascular events of interest such as VTE, DVT of the lower extremities and pulmonary embolism (PE) in new-HC users.

The following definitions apply in the context of pharmacovigilance reporting for this study:

- **Adverse event (AE):** Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Serious adverse event (SAE):** An adverse event which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, or is medically significant (e.g., included in the Important Medical Events (IME) List).
    - Disability: A substantial disruption of a person's ability to conduct normal life functions.
    - Life-threatening event: refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
    - Hospitalization only applies, when the patient has to stay overnight and does not apply for patients who are seen in the emergency room and are sent home afterwards.
- **Adverse drug reaction (ADR):** A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from the use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.
- **Study Medicinal Products:** for the purpose of this study, study medicinal product means E4/DRSP [brand names of the country: Drovelis or Lydisilka or Nextstellis (or other future brand names)].

  The other EE/LNG products can be referred to as comparator products which are prescribed according to normal practice with both sets of participants requested to report in the same way.

The study questionnaire is designed to actively seek information on those AEs needed to answer the study objectives and to take appropriate measures to collect and collate all reports of suspected adverse reactions, i.e., those events where a causal relationship is suspected. The study physicians and study participants will be reminded in the physician information and informed consent form of the possibility to report suspected adverse reactions to the marketing authorisation holders or to the national spontaneous reporting system directly.

If, however, an adverse event, which is not actively sought in the study questionnaires is reported within the study data collection scheme, the event will be collected and reported to the competent authorities in accordance with the regulatory reporting requirements.

AEs following the use of the study medicinal products (that is Drovelis / Lydisilka / Nextstellis / other):

- All AEs following the use of the Estetra SRL/Gedeon Richter Plc study medicinal products will be collected and recorded in the study database, irrespective of a causal association.
- All SAEs will be promptly forwarded to the marketing authorization holders (MAH) who will record the cases in their respective Safety Databases. The MAHs will receive these reports translated in English from ZEG as Individual Case Safety Report (ICSR) in form of E2B (XML file) and/or a Council for International Organizations of Medical Sciences (CIOMS)-I form within 7 calendar days of receipt. If new relevant information or a possible causal relationship is found during the validation process at ZEG, this new information will be sent in the same format within 7 calendar days of receipt or identification. The MAHs are responsible for expedited safety reporting to EudraVigilance.
- Reports of congenital anomalies, developmental delay, all pregnancy outcomes, and adverse reactions in the neonate with exposure to a medicinal product either during pregnancy or breastfeeding will be reported to the respective MAH in the same format and within the same timelines as serious ICSRs (within 7 calendar days of receipt).
- All other AEs (non-serious AEs) will be forwarded as monthly line listing to the MAHs.
- Product technical complaints (PTCs) will also be forwarded to the MAHs in form of E2B (XML file) and/or a Council for International Organizations of Medical Sciences (CIOMS)-I form within 7 calendar days of receipt.

The questionnaires with reported AEs in the EDC system will be reviewed by ZEG Berlin's medical event validation team and processed according to the working procedures and the Safety Management Plan (SMP). ZEG will follow-up with the study participants and/or HCP/treating physicians for questions related to the events of interest.

ZEG Berlin will review all AEs reported during study conduct and assess the seriousness of all AEs. The handling of AEs will follow the Guidelines on Good Pharmacovigilance Practices (GVP), especially Module VI and VIII.

The seriousness of an event will be assessed by the medical event validation team based on the available reported information and SAE definition given in ICH-E2A (see GVP Annex I). Medical judgement and/or the IME list will be used to help determining further serious events, in the absence of ICH-E2Aseriousness criteria. The IME list is to be used as a guiding document.

Management and reporting of pregnancies

All study participants reporting exposure to Estetra SRL/Gedeon Richter Plc study medicinal products, i.e, Drovelis, Lydisilka, Nextstellis, other, during pregnancy will be followed-up to the completion or termination of the pregnancy to investigate the pregnancy outcome. To gain this information, an extra follow-up questionnaire will be provided to the participant three months after

the estimated date of birth. All pregnancy reports and follow-up information will be promptly forwarded to MAHs, within the same timelines as SAEs. Regulatory reporting of pregnancies and their outcomes will be further described in the SMP.

Management and reporting of adverse events related to non-study medicinal products marketed by Estetra SRL/Gedeon Richter Plc.

AE and SAE reports following the use of non-study medicinal products marketed by Estetra SRL/Gedeon Richter Plc. will be treated the same way as events under the study drugs, i.e., SAE will be sent directly by ZEG Estetra SRL/Gedeon Richter Plc. within 7 days of receipt and non-serious AEs as monthly line-listing. The cases will be maintained in the study database. Study participants and their prescribing healthcare professionals will be informed about the requirement to report other suspected adverse reactions outside of this protocol scope to the MAH of the suspected medicinal product or to the concerned competent authority via the national spontaneous reporting system referring also to participation in this PASS.

Further information about the reporting of AEs/ADRs can be found in the SMP and supporting appendices.

9. Plans for disseminating and communicating study results.

The final study protocol and the results of this study will be published. Following the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical studies in a public registry as a condition for publication, the study will be registered in the U.S.A. National Institutes of Health's protocol registration database (http://ClinicalTrials.gov), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) database (http://www.encepp.eu/encepp/studySearch.htm), and the European Union (EU) electronic register of post-authorization studies (EU PAS Register) maintained by the European Medicines Agency (EMA). Registration in the EU PAS Register will include both the study protocol and the final study report. The study results will also be published in a peer-reviewed journal.

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	*To be finalized after protocol approval*	*To be finalized after protocol approval*	*Baseline Questionnaire*
2	*To be finalized after protocol approval*	*To be finalized after protocol approval*	*Follow-up Questionnaire*
3	*To be finalized after protocol approval*	*To be finalized after protocol approval*	*Extra Follow-up Questionnaire*
4	*To be finalized after protocol approval*	*To be finalized after protocol approval*	*Milestone Plan*
5	*To be finalized after protocol approval*	*To be finalized after protocol approval*	*List of participating countries*

Annex 2. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked, and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[15]	☒	☐	☐	3
1.1.2 End of data collection[16]	☒	☐	☐	3
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	3
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	3
1.1.6 Final report of study results.	☒	☐	☐	3

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	5
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4
2.1.2 The objective(s) of the study?	☒	☐	☐	5.1, 5.2
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	6.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	6.7.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	6.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	6.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	6.3.1, 6.3.2
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	6.7.1

[15] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[16] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	8

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	6.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	6.1, 6.5
	4.2.2 Age and sex	☒	☐	☐	6.1
	4.2.3 Country of origin	☒	☐	☐	6.1
	4.2.4 Disease/indication	☒	☐	☐	6.1
	4.2.5 Duration of follow-up	☒	☐	☐	6.1, 6.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	6.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	6.2.1

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	6.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	6.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	8

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	6.7.1, 6.9
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	6.9
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	6.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	6.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	6.4.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	6.7.1

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6.4.1/6.4.2
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	6.7.1
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	6.6.1
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	6.6.1
9.3.3 Covariates and other characteristics?	☒	☐	☐	6.7.1
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	6.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	6.5
10.3 Are descriptive analyses included?	☒	☐	☐	6.7.1
10.4 Are stratified analyses included?	☒	☐	☐	6.7.1
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	6.7.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	6.7.1
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	6.7.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	6.7.1

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	6.6.1
11.2 Are methods of quality assurance described?	☒	☐	☐	6.8

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7.4

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	6.9
12.1.2 Information bias?	☒	☐	☐	6.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	6.9
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.2.2

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	7.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	7, 7.4

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	2

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	9

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9

Comments:

Name of the main author of the protocol: Klaas Heinemann

Date: 28/11/22

Signature:

Annex 3. Additional information

Annex 3.1. Safety Monitoring and Advisory Council

This study will maintain scientific independence from the Funder and will be governed by an independent Safety Monitoring and Advisory Council (SMAC). The council will be responsible for regular review and evaluation of safety data during study conduct as well as for review of statistical analysis plan, interim results, study report, and publications. The funder will assure financing of the study. ZEG Berlin and its research team will be accountable to the council in all scientific matters. ZEG Berlin will present all relevant safety data to the council in a timely fashion. The members of the council will be international experts in relevant scientific fields (e.g., epidemiology, drug safety, gynaecology, statistics). The members will receive remuneration of expenses and an honorarium to compensate for the loss of potential earnings during their work for the SMAC. The members will not be involved in or paid for the operational conduct of the study.

Members of the Safety Monitoring and Advisory Council:

Annex 3.2. Blinded adjudication

The following adjudication procedure will be established:

1) Independent adjudication by the individual specialists
2) Documentation of the individual assessments
3) Comparison of the individual assessments
4) Discussion of "split decisions" among the adjudicators without enforcement of a unanimous decision
5) Independent re-adjudication of the discussed cases by the individual adjudicators
6) Documentation of the individual post-discussion assessments

Based on this procedure six different classification strategies will be possible

I. Classification of the reported event as confirmed if all adjudicators classify the event as confirmed before the discussion of "split decisions" took place (i.e., the decision is based on step 2 of the six-step procedure described above)

II. Classification of the reported event as confirmed if all adjudicators classify the event as confirmed after discussion of "split decision" takes place (i.e., the decision is based on step 6 of the six-step procedure described above)

III. Classification of the reported event according to the assessment of the majority of adjudicators before the discussion of "split decision" takes place (i.e., "majority vote" based on step 2 of the six-step procedure described above)

IV. Classification of the reported event according to the assessment of the majority of adjudicators after discussion of "split decision" takes place (i.e., majority classification based on step 6 of the six-step procedure described above)

V. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed before the discussion of split decisions took place (i.e., "worst-case decision" based on step 2 of the six-step procedure described above)

VI. 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 will be based on strategy VI (worst case decision following discussion of split decisions); this provides adjudicators an opportunity to revise their decisions due to misunderstanding or misreading the case. Alternative analyses will be possible at the request of the Safety Monitoring and Advisory Council or regulatory authorities.

Annex 3.3. Amendment to the German study protocol

Rationale

In accordance with the local regulations regarding the observation of off-label use in Germany, study participants with absolute contraindications to the use of any medicinal products should not be included in the study. Thus, the following amendments will be made to the German protocol. Deletions are crossed out and additions/replacements are marked in the text as underlined.

6. Research methods

6.1. Study design

This is a large, multinational, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[17] and restarters[18]) of two different groups of hormonal contraceptives: E4/DRSP and EE/LNG. The study will use a non-interference[19] approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting.

Study participants will be recruited via recruitment centres (health centres, pharmacies, telemedicine/online prescription services, and electronic medical records [see details in Section 6.2]) for the INAS-NEES study. An international network of HC-prescribing HCPs will recruit eligible HC-users over an estimated period of 5 years. After study entry, study participants will be followed for a maximum of 2 years for rare serious safety outcomes. Additional follow-up procedures (see Section 6.4.2) will be used to validate patient-reported events. A non-interventional approach will be used for the INAS-NEES study. Enrolment procedures should not interfere with the prescribing behaviour of the participating HCPs or with the individual needs of their patients. People prescribed a new HC are eligible to join the study provided they are prescribed an HC under investigation, sign an informed consent form (ICF), complete a baseline questionnaire, and understand the language of the ICF and questionnaires. Adolescents (below the age of 18 years) will be eligible to participate based on local legislation. <u>For Germany an additional eligibility criterion is defined: recruitment centres will be instructed to recruit only study participants who are prescribed the COC within on-label use.</u>

Through direct contact with the study participants at 6, 12, 18, and 24[20] months after enrolment, almost all relevant clinical outcomes will be captured. However, because laypersons often over-report, or misclassify AEs (e.g., varicose veins as "thrombosis" or pneumonia as "pulmonary embolism"), patient-reported events of interest to the study will undergo careful validation. This

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17 First-ever user of a COC

18 User who restarts hormonal contraceptive use with a COC (same COC as before or new COC) after an intake break of at least two months.

19 I.e., 1) all new users of E4/DRSP or EE/LNG are eligible for enrollment if they give their informed consent; and 2) recruitment of study participants should not influence the physician's prescribing, diagnostic, or therapeutic decisions.

20 Or at the end of the study if the study ends prior to the 24-month follow-up of an individual participant.

will be accomplished by contacting the relevant HCPs (usually the treating physicians) and by reviewing medical documentation. Under routine medical conditions, clinical outcomes are not always confirmed by diagnostic procedures with high specificity. Therefore, reported serious clinical outcomes will be classified as "confirmed" or "not confirmed" according to predefined algorithms. At the end of the study, this classification will be verified by blinded independent adjudication (see. ***Annex 3.2***) by three medical experts (e.g., cardiologists, phlebologists, internists), who are proposed by ZEG and approved by the SMAC. They will assess the VTE cases independently from ZEG (see Section 6.4.3).

6.2. Setting

The study will be conducted by the Berlin Center for Epidemiology and Health Research GmbH (ZEG Berlin). Data will be sourced from a multinational, prospective, primary data collection for the INAS-NEES study which will be established in Europe, the USA, and Brazil to collect high-quality, real-world data on users of HCs.

More than 60% of the study data will be recruited from European Union (EU) countries, with the remaining will be from non-EU countries. There is no literature evidence to suggest that risk factors in women who take COCs are different between EU and non-EU populations, except for sickle cell trait in women of African descent. Risk factors of VTE are well established and consistent across populations and include age, family disposition, obesity, smoking, immobilization, coagulation disorders, pregnancy, puerperium, and history of cancer. All these factors will be collected during this study and propensity score matching during analyses can correct for potential unbalanced groups, although this is not foreseen.

The study will be overseen by an independent committee of experts, the Safety Monitoring and Advisory Council (SMAC), who will review the study data every 6 months and at the request of the Principal Investigator (see ***Annex 3.1***).

The study will be divided into 2 phases: the recruitment phase and the follow-up phase. The recruitment phase starts when the study participant is introduced to the study by the HCP (i.e., after a prescription has already been agreed upon), the signing of an ICF, and the completion of a baseline questionnaire (baseline survey). The follow-up phase includes direct follow-up with the study participant at 6, 12, 18, and 24 months after study entry. The follow-up phase will end approximately one year after the enrolment of the last study participant. However, participants who are enrolled within the last year of the recruitment phase will have their last follow-up at the end of the follow-up phase (instead of 24 months after study entry). Visits and follow-up contacts are calculated in calendar months and years following the baseline visit. ~~In keeping with German national regulations, off-label use will not be investigated in Germany.~~

HCPs will act as recruiters, identifying potentially eligible study participants, facilitating the onboarding process, educating study participants regarding the study expectations, and consenting them to participate in the study. There will be limited additional involvement from the recruiting HCP. Importantly, HCPs will not act as typical 'investigators', but solely as 'recruiters'. The primary method of data collection will be through patient-reported outcome questionnaires. Study participants will be followed up by the ZEG Berlin study team independent of the recruiting HCPs. In the case a study participant will report an outcome of interest to the study, the recruiting HCP may be re-contacted to clarify health outcomes of interest reported by the study participant.

The following recruitment centres will be used:

1. **Health centres**

A network of HCP recruitment centres will be established. Depending on the individual health care system, HCPs may be family practitioners, general practitioners, obstetricians, women's health doctors, midwives, nurse-practitioners, and/or physician assistants. The HCP may only invite eligible study participants to join the study after the decision to start an HC is made. HCPs in Germany will be instructed to recruit only on-label users of the respective COCs. The HCP will explain the nature of the study to the study participant and if they will be interested, provide them with access to an online study portal that will guide them through the consenting and ICF completion process.

2. **Pharmacies**

Pharmacy networks will be used as point-of-sale recruitment centres to enhance study recruitment. This recruitment approach will be started in Germany and rolled out to other countries where technology and network infrastructure allow. In the German pharmacies, there will be a screening process to ensure only COC users are recruited who use the respective COCs on-label.

Pharmacy merchandise management systems will be programmed to alert pharmacies of a potentially eligible study participant at the point of sale. Pharmacists will be considered as recruiting HCPs, not clinical investigators. Therefore, the requirements for sites to be Good Clinical Practices (GCP)-compliant and dedicated clinical research centres will not be applicable.

All networked pharmacies will receive basic information about the study. Merchandise software will be programmed to provide basic information about the study at the point of HC sale. Following the sale of the HC, it is assumed that pharmacists will provide study participants with basic information about the study and direct those interested in study participation to the study-portal via a QR-code-based system.

Potential study participants entering the study-portal will be initially guided through a brief screening questionnaire to ensure that subjects meet the specified inclusion criteria. Following the successful screening, subjects will be guided through a consenting process. Subjects will be considered to have been successfully enrolled in the study on completion of the eConsent documentation.

Annex 3.4. Signature

Principal Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed-upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practices, Good Epidemiological Practice, Good Pharmacovigilance Practices, the ENCePP code of conduct, and the ethical principles that have their origin in the Declaration of Helsinki. I also agree to report all information or data in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol.

(Sign) 

(Name) Dr. Klaas Heinemann (Date) 28.11.22

Annex 4. Important Medical Events (IMEs)

As a help to prioritize the review of reports of suspected Adverse Drug Reactions (ADRs) in the framework of the day-to-day pharmacovigilance activities the European Medicines Agency has developed the Important Medical Event (IME) list, which will be used in this study to support assessment of seriousness.

IME_List_version_24.x
lsx

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International Active Surveillance Study:
Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)

SIGNATURE PAGE

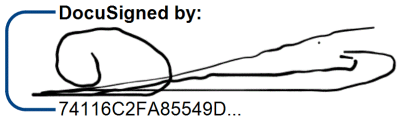
Signature of the qualified person in pharmacovigilance (QPPV) or his/her delegate

Name and function

Delphine Cossard, EU QPPV Estetra SRL

Associate Director, IQVIA Lifecycle Safety

Signature



Date (DD-MMM-YYYY)

21 décembre 2022 | 15:49 CET

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International Active Surveillance Study:
Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)

Signature of the qualified person in pharmacovigilance (QPPV) or his/her delegate

Name and function

Attila Oláh, MD

EU QPPV, Head of Global Patient Safety, Gedeon Richter Plc

Signature

DocuSigned by:
Oláh Attila
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Date (DD-MMM-YYYY)

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