STUDY PROTOCOL

PASS Information

Title	EURAS-CORA European Active Surveillance Study Comparing Regimens of Application in combined hormonal contraception
Protocol version identifier	ZEG2014_03
Date of last version of protocol	01 August 2014
EU PAS register number	Study not yet been registered
Active substance	Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens and estrogens, fixed combinations ATC code: G03AA 1 0 gestodene and estrogen Active substances: gestodene and ethinyl estradiol
Medicinal product	apleek[1]: transdermal patch releasing 60 micrograms gestodene/24 hours + 13 micrograms ethinyl estradiol/24 hours
Product reference	
Procedure number	FR/H/0547/001/DC
Marketing authorisation holder(s)	Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany
Joint PASS	No
Research question and objectives	Primary objective: characterization and comparison of the risks of short- and long-term use of FC Patch Low with COC_{LNG}. Main clinical outcomes of interest: venous thromboembolism, specifically deep venous thrombosis of the lower extremities and pulmonary embolism.
Country(-ies) of study	Approximately 6 European countries (tbd)
Author	Klaas Heinemann, MD, PhD, MBA, MSc Invalidenstrasse 115 10115 Berlin Germany Phone: +49 30 945 101 24 Fax: +49 30 945 101 26

[1] Throughout the study protocol, the term „FC Patch Low“ will be used for the product name “apleek”

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany
MAH contact person	Ulrike Wissinger-Gräfenhahn, MD, PhD Senior GMA Physician PASS Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany Phone: +49 30 468 192794 Fax: +49 30 468 16649

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2 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
BMI	Body Mass Index
CHC	Combined Hormonal Contraceptive
CHMP	Committee for Medical Products for Human Use
COC	Combined Oral Contraceptive
COC_{LNG}	Levonorgestrel-containing COC
CT	Computer Tomography
CVA	Cerebrovascular Accidents
DCP	Decentralized Procedure
DIMDI	German Institute for Medical Documentation and Information
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EE	Ethinyl Estradiol
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EURAS	European Active Surveillance (study)
FC	Fertility Control
GEP	Good Epidemiological Practices
GPP	Good Pharmacoepidemiology Practices
GSD	Gestodene
GVP	Good Pharmacovigilance Practice

GXP	Good Practice Guidelines
HC	Hormonal Contraceptive
HR	Hazard Ratio
ICD-10	International Classification of Diseases, 10th revision
ICMJE	International Committee on Medical Journal Editors
INAS	International Active Surveillance Study
ITT	Intention To Treat
LNG	Levonorgestrel
MAH	Marketing Authorization Holder
MRI/MRT	Magnetic Resonance Image/-Tomography
NGMN	Norelgestromin
OC	Oral Contraceptive
OPS	Operations and Procedures Classification System (acronym for the German term 'Operationen- und Prozedurenschlüssel')
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
PIP	Pediatric Investigation Plan
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SAE	Serious Adverse Event
SDB	Study Database
SMAC	Safety Monitoring and Advisory Council
SOP	Standard Operating Procedure
TASC	Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing
TIA	Transient ischemic attack
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’)

3 Responsible Parties

PRINCIPAL INVESTIGATOR:	Dr. Klaas Heinemann Invalidenstrasse 115 10115 Berlin Germany Email: k.heinemann@zeg-berlin.de
STUDY CONDUCT:	ZEG – Berlin Center for Epidemiology and Health Research Invalidenstrasse 115 10115 Berlin Germany
PROJECT MANAGER:	Kristina Bardenheuer, MSc ZEG – Berlin Center for Epidemiology and Health Research Invalidenstrasse 115 10115 Berlin Germany Email: Bardenheuer@zeg-berlin.de
FUNDER:	Bayer HealthCare Pharmaceuticals (hereafter referred to as the FUNDER) Müllerstraße 178 13353 Berlin Germany
FUNDER CONTACT INFORMATION:	Dr. Ulrike Wissinger-Gräfenhahn Senior GMA Physician PASS Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany Phone: +49 30 468 192794 Fax: +49 30 468 16649
SAFETY MONITORING AND ADVISORY COUNCIL:	Members: tbd

4 Abstract

Title

EURAS-CORA
European Active Surveillance Study COmparing Regimens of Application in combined hormonal contraception

Study protocol version of 01 August 2014

Author: Dr. Klaas Heinemann
Principal Investigator
Invalidenstrasse 115
10115 Berlin
Germany

Rationale and background

FC Patch Low uses the transdermal route for contraception. It is applied once a week for three consecutive weeks followed by a break of one week (21/7). One patch contains 2.1mg gestodene and 0.55mg ethinyl estradiol, which is equivalent of releasing 0.06mg gestodene and 0.013mg ethinyl estradiol per 24 hours. VTE and ATE are well-known side effects of COCs. Though the FC Patch Low is not expected to have a negative impact on the risk of VTE and ATE compared to combined oral contraceptives (COC) containing LNG, a prospective, controlled, non-interventional, long-term cohort study to assess the impact of short- and long-term risk was deemed appropriate as data on transdermal use of GSD is limited so far.

Research question and objectives

The primary objective of the study is to characterize and compare the risks of short- and long-term use of FC Patch Low with levonorgestrel-containing combined oral contraceptives (COC_{LNG})[2], in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes. The main clinical outcomes of interest for the short and long-term follow-up are venous thromboembolism, specifically deep venous thrombosis of the lower extremities and pulmonary embolism.

Study design

Multinational, controlled, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[3] and restarters[4]) of two different groups of hormonal contraceptives: FC Patch Low and COC_{LNG}. The study will use a non-interference[5] approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting. Study participants will be enrolled via an international

[2] cf. Section 9.2.1

[3] First ever user of a CHC

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

[5] I.e., 1) all new users of FC Patch Low or COC_{LNG} are eligible for enrollment if they give their informed consent; and 2) the physician's prescribing, diagnostic, or therapeutic decisions take place before study participants are recruited.

network of 2,000 – 3,000 CHC prescribing health care professionals. Study participants will be followed up for 24 months. All outcomes of interest will be captured by direct contacts between the investigator team and 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 FC Patch Low and 50,500 COC_{LNG} users) will be recruited via a network of 2000 – 3000 CHC-prescribing health care professionals (e.g. gynecologists and general practitioners) in approximately 6 European countries. All starters and restarters (see above) of FC Patch Low or COC_{LNG} who are willing to participate in the study are eligible for enrollment into the study[6].

Variables

Primary statistical variable: VTE hazard ratio for FC Patch Low vs. COC_{LNG} adjusted for age, BMI, duration of current use and family history of VTE. Results are based on patient-reported VTE that will be validated via the attending physicians and medical records. Other variables include arterial thromboembolism, cancer, pregnancy related data, application site reactions and serious adverse events.

Data sources

This is a field study. Exposure to hormonal contraceptives, concomitant medication, primary and secondary outcomes, potential confounding factors and potential effect modifiers will be documented by the study participants as well as the recruiting and attending physicians in the questionnaires, and additional documentation sheets, if needed.

***S*tudy size**

The study is sufficiently powered to show non-inferiority of FC Patch Low compared to COC_{LNG} assuming that the true VTE risk among FC Patch Low users is not higher than among COC_{LNG} users. For this purpose a total of 101,000 women (50,500 FC Patch Low and 50,500 COC_{LNG} users) will be followed up for approximately 150,000 woman-years (WY). The power calculations are based on the following parameters: 1) α of 0.05 (one-sided); 2) power (1-β) of 0.80 and 3) non-inferiority limit on hazard ratio of 1.5.

Data analysis

The final analyses will include both an "as treated" (AT) and an intention-to-treat (ITT) analysis using Cox regression models. The safety conclusions of the study, however, will be based on the AT analyses because the ITT approach potentially dilutes differences between treatments. The appropriate confounding variables will be built into the statistical models. Crude as well as adjusted hazard ratios (HRs) will be calculated. The null hypothesis to be tested is: $HR_{VTE} \geq 1.5$ (i.e., the VTE hazard ratio for FC Patch Low vs. COC_{LNG} is higher than or equal to 1.5). The alternative hypothesis is: $HR_{VTE} < 1.5$.

[6] cf. Section 9.2.2

Milestones

Task	Planned date[7]
Start of data collection	June 2015
End of recruitment	June 2020
Last regular follow-up	June 2021
Final report of study results	December 2021

[7] cf. Section 9.9 (“Limitations of the research methods”), last paragraph

5 Amendments and updates

None

6 Milestones

Milestone	**Planned date**[8]
Registration in the EU PAS register	May 2015
Start of data collection	June 2015
Interim Reports	6-monthly until end of study
End of recruitment	June 2020
Last regular follow-up	June 2021
End of data collection[9]	September 2021
Final report of study results	December 2021

[8] cf. Section 9.9 (“Limitations of the research methods”), last paragraph

[9] includes 3 months of loss to follow-up activities after the last regular follow-up

7 Rationale and background

Combined oral contraceptives (COCs) became available in the early 1960s and are - with currently about 100,000,000 users worldwide – the most popular form of effective, reversible contraception available. However, alternative methods for hormone administration have been investigated and are widely used, including injections, implants and intrauterine devices. To broaden the choice of female contraceptive methods, the transdermal route through the use of a patch has been developed because of its potential benefits. With respect to compliance, a patch only has to be applied once per week (three weeks active patch plus one week break, i.e. 21/7 day cycle). This is likely to facilitate its compliant use, especially in women who find it difficult to adhere to a daily intake regimen [1].

From a pharmacological point of view, the development of a patch for hormonal contraception is based on the rationale that active substances given via a transdermal route are not subject to first pass metabolism in the liver; thus, effective serum levels can be achieved with lower total drug exposure, especially with substances of reduced oral bioavailability like ethinyl estradiol (EE). Transdermal formulations provide more stable levels of the active substances in the body, in contrast to oral preparations, which give rise to fluctuations and high peak concentrations. Furthermore, the drug delivery via the transdermal route is unaffected by gastrointestinal complaints such as vomiting and diarrhea. To date, the only contraceptive control patch available on the market is the EE and norelgestromin (NGMN) patch, approved in the US (Ortho Evra) and in Europe (Evra).

The newly developed FC Patch Low consists of a fixed combination of ethinyl estradiol (EE) and gestodene (GSD). The estrogen component, EE, is the standard estrogen used in nearly all combined OCs. It provides acceptable skin permeability and offers efficacious cycle control. The progestin component, GSD, has been extensively used in a wide variety of OCs and products for hormone therapy for over 25 years and has a well-known efficacy and safety profile. GSD was selected based on its high progestogenic potency per weight of the progestin [2] and its good skin permeability, which is unique in comparison to other progestins and renders it specifically suitable to be chosen in a patch application. In comparison to other progestins, GSD also offers particularly good cycle control.

The combination of EE and GSD is well known for many OCs marketed in the European Union (EU) and considerable experience has already been documented for this combination. Worldwide safety data for GSD are based on more than 88,000,000 women-years (WY) of exposure to GSD-containing combined OCs (as of March 2012). However, such experience and epidemiological studies only apply to oral formulations. Although the overall systemic exposure of GSD and EE is almost similar in the patch compared to the oral formulation, daily fluctuation of plasma levels with the oral administration impact the safety profile. Besides, exposure to the respective metabolities of the components may be different with both modalities of administration and this may alter the safety profile. Conclusively, safety data collected with the oral route, could not be reliably extended to the patches. Therefore,

a PASS was chosen to investigate the risk of thromboembolism with this new formulation and compare it to levonorgestrel-containing oral contraceptives. The EURAS-CORA study is part of the Risk Management Plan (RMP).

Since the year 2000 the EURAS [3] study comprehensively investigated the risk of VTE and other serious cardiovascular outcomes which might be associated with OC use. Similar comprehensive data from large, controlled, prospective studies with defined follow-up procedures of rare serious adverse events and low loss to follow-up rates are not available for a patch containing GSD and EE. Data from randomized clinical trials (including 3,570 women) did not show any serious health concerns for FC Patch Low. However, the statistical power to detect rare adverse events is limited in these studies and no firm conclusion could be drawn from the clinical trials regarding the thromboembolism risk. Therefore, it is not yet known, how the risk of FC Patch Low compares with the risk with low dose LNG-containing CHCs. Based on general public concerns about the safety of COCs the study will not only focus on VTE but also on arterial thromboembolism, cancer, pregnancy related data, application site reactions and serious adverse events. The funder has asked ZEG to conduct a large epidemiological study with a robust and efficient study design.

The EURAS study and similar studies (such as INAS-OC[10] and TASC[11]) have demonstrated that a large, prospective, controlled, long-term cohort study is suitable for (1) safety monitoring of contraceptives, (2) reliable identification of relevant clinical outcomes and (3) providing robust estimates of their incidence. The study described in this protocol has a similar design with a few modifications due to country and product-specific characteristics.

This observational study is being conducted as an imposed obligation for a post-authorization safety study described as a condition for market authorization in accordance with an Article 10a of the EU Regulation 726/2004. This study will include European women using specific contraceptives: FC Patch Low and levonorgestrel-containing oral contraceptives (COC_{LNG})[12]. The objective of the study is to assess the cardiovascular and other health risks associated with short and long-term use of FC Patch Low compared with COC_{LNG} during standard clinical practice.

[10] Clinicaltrials.gov identifier: NCT00335257

[11] Clinicaltrials.gov identifier: NCT00524771

[12] cf. Section 9.2.1

8 Research question and objectives

The primary objective of the study is to characterize and compare the risks of short (6 months and less)- and long-term use (more than 6 months) of FC Patch Low with COC_{LNG}, in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.

The main clinical outcomes of interest for the short and long-term follow-up are venous thromboembolism (VTE), specifically:

- Deep Venous Thrombosis (DVT) of the lower extremities (ICD-10 codes: I80.1, I80.2); exluding I80.3
- Pulmonary Embolism (PE); this includes the ICD-10 codes I26.0 and I26.9

Furthermore, sensitivity analyses are planned in order to
1) evaluate the impact of including I80.3 (phlebitis and thrombophlebitis of lower extremities, unspecified), which means that DVT of the lower extremities plus I80.3 plus pulmonary embolisms are analyzed
2) all DVTs and pulmonary embolisms.

Secondary objectives of the study are to measure/describe for FC Patch Low users and compare to users of COC_{LNG} during standard clinical practice;

- All VTE, including thromboses of renal, mesenteric, portal and retinal veins[13]
- Arterial thromboembolism (ATE) incidence rate in short- and long-term users. ATE includes acute myocardial infarction (AMI) and cerebrovascular accidents (CVA)
- Cancer entities
- Application site reactions
- Serious adverse events
- Pregnancy related outcomes

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

9 Research methods

9.1 Study design

This is a large, multinational, controlled, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[14] and restarters[15]) of two different groups of hormonal contraceptives: FC Patch Low and COC_{LNG}. The study will use a non-interference[16] approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting.

Study participants will be recruited via an international network of 2,000 – 3,000 contraceptive-prescribing health care professionals (e.g. gynecologists and general practitioners). It is expected to recruit the 101,000 participating women within 60 months. However, if the actual recruitment is not in line with the recruitment plan, alternatives will be sought to improve recruitment rates. This includes, but is not limited to the expansion to other non-EU countries (e.g. Latin America), contacting of gynecological associations to recommend study participation for physicians or including other prescribing health care professionals. After study entry, study participants will be followed for a period of 12 to 24 months for rare serious safety outcomes. Regular, active contacts with the study participants by the ZEG study team (= active surveillance) will provide the necessary information on health-related events or changes in health status. Additional follow-up procedures (cf. Section 9.2.4) will be used to validate self-reported events.

All study participants will be contacted at 6, 12 and 24[17] months after study entry. By means of these contacts, almost all relevant clinical outcomes will be captured. However, laypersons often misclassify adverse events (e.g., pneumonia as “pulmonary embolism” or migraine attacks as “stroke” even if modern imaging procedures do not provide any indication of the perceived event). This type of inaccuracy in patient reports will require careful validation of the reported events. This will be accomplished by contacting the relevant physicians and by reviewing relevant source documents. Under routine medical conditions, clinical outcomes are not always confirmed by diagnostic procedures with high specificity. Therefore, reported serious clinical outcomes have to be classified as “confirmed” or “not confirmed” by ZEG physician(s) according to a predefined algorithm (cf. Section 9.10.1). At the end of the study this classification will be verified by blinded independent adjudication (cf. Section 9.10.2).

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[14] First ever user of a CHC

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

[16] I.e., 1) all new users of FC Patch Low or COC_{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.

[17] Or at the end of the study if the study ends prior to the 24 month follow-up of an individual patient.

The study will be conducted in approximately 6 European countries.

9.2 Setting

The study will be conducted by the Berlin Center for Epidemiology and Health Research (ZEG).

The study will be divided into 2 phases: a baseline survey, which includes an initial consultation at baseline with a participating physician, and a follow-up phase, which includes two follow-up contacts within the first year, and then a follow-up at 24 months after study entry. The follow-up phase will end approximately one year after enrollment of the last study participant. 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 (between 12 and 24 months after study entry). Follow-up contacts are calculated in calendar months and years following the baseline visit.

Additionally to the baseline questionnaire, a registry will be implemented to document all eligible non-participating women in an anonymized way.

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 on request of the Principal Investigator.

9.2.1 Treatments

Cohort 1: FC Patch low, a transdermal patch containing 2.1mg of gestodene and 0.55mg of ethinyl estradiol

Cohort 2: Levonorgestrel-containing COCs: 1) monophasic preparations containing 20 – 30mcg of ethinylestradiol; 2) multiphasic preparations containing up to 40mcg of ethinylestradiol

9.2.2 Selection of Study Population

Approximately 50,500 FC Patch Low users and 50,500 users of COC_{LNG} (including adolescents) will be recruited by participating physicians. Overall, 101,000 study participants are needed in order to provide approximately 150,000 woman-years (WY) (cf. Section 9.5), assuming a drop-out rate of approximately 0.7% per month.

Recruitment of study participants will be conducted via existing networks of contraceptive-prescribing health care professionals (e.g. gynecologists and general practitioners) who have participated in similar cohort studies in the past. Physicians will recruit FC Patch Low and

COC_{LNG} users in a 1 to 1 ratio. It is expected that this ratio reflects approximately the ratio of starter and restarter prescriptions of FC Patch Low and COC_{LNG} under routine clinical conditions. Only after the decision of the contraceptive prescription has taken place, the physician may ask the woman for study participation. For every FC Patch Low user recruited, the physician has to recruit the next new COC_{LNG} user (starter or restarter) who is willing to participate in the study.

Subjects will be considered for enrollment in this study after the participating physician has determined that FC Patch Low or COC_{LNG} use is appropriate. There will be no specific medical inclusion/exclusion criteria and no age restrictions. However, women who 1) have been pregnant within 3 months before treatment initiation or 2) have a history of cancer/chemotherapy or an increased genetic risk for VTE at baseline will be excluded from the analysis of VTE. All women who are eligible are to be asked by their physician if they are willing to participate. As this is a non-interventional study, the possibility to participate in the study should not be discussed with the study participant before both - physician and study participant - agree upon the prescription. The physician is to explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each woman prior to her entry into the study. Each woman is to have ample opportunity to ask questions and must be informed about her right to withdraw from the study at any time without disadvantage and without having to provide reasons for her decision. This information will be provided on an informed consent and data privacy form, which must be signed by all study participants. This study has no age restrictions and adolescents can be asked for participation in countries where no ethical or regulatory restrictions for that age group exist. As adolescents are a specifically protected group, local law might require a parent's or guardian's signature, which will then additionally to that of the adolescent study participant be provided on the informed consent form. All documents are to be approved by the relevant local Ethics Committees and the relevant Data Privacy Office, if applicable.

Once enrolled, a study participant may discontinue (and restart) use of hormonal contraception or may switch to another hormonal contraceptive at any time. However, subjects will continue to be followed whether or not they remain on the prescribed contraceptive, provided that they do not withdraw their consent. For the primary analysis outcomes of interest/adverse events will be assigned to the treatment at the time the outcome/event occurred. During the follow-up phase, subjects will be asked whether they have discontinued contraceptive use. Information on the date and reason for discontinuation during the follow-up phase will also be collected.

9.2.3 Baseline Survey

Each physician's office will be provided with simple questionnaires for collecting data at baseline. The baseline visit will take place at the participating physician's office. Only after FC Patch Low or a COC_{LNG} has been prescribed will the physician discuss the study with the subject. This ensures that participation in the study is not considered a requirement for treatment. All women who received a new FC Patch Low or COC_{LNG} prescription are to be

asked to participate. After discussing the study details (including content and duration of follow-up contacts, use of data collected, etc.), each subject will be asked to provide written informed consent to participate in the study. If the subject needs time to consider participation, she will be free to leave the physician's office with her prescription and take an appropriate period to decide whether to participate. She can complete the baseline questionnaire and informed consent at home, and multiple ways will be offered to return the documents.

The informed consent will include permission for study data to be collected and analyzed and for contacts to be made by the ZEG study team at intervals during the follow-up phase for collection of study information. Each subject will also be asked to provide information regarding alternative contacts (a close relative or friend, or primary care physician) if ZEG cannot reach the subject after several attempts. Permission for ZEG to contact a subject's primary care physician/attending physician(s) and to review applicable national health databases (where possible and permissible) for relevant subject information will also be sought. Follow-up frequency by ZEG will be explained, and the content of follow-up contacts will be described.

Confidentiality will be maintained throughout the study and no personal information will be shared with alternative contacts. The funder will not have access to names, addresses, or alternative contact information for the subjects and all individual subject data will remain anonymous. Personal and medical information will be recorded on separate documents. ZEG will ensure that access to personal information is restricted in accordance with data privacy rules.

The following information will be recorded at the baseline visit after the study participant has provided written informed consent: prescribed hormonal contraceptive, user status (starter/restarter), risk factors (e.g. personal and family history of VTE and ATE, age, BMI), demographic and medical history, including medication history, history and duration of use of hormonal contraceptives and previous participation in studies (e.g. clinical or observational studies). Additionally, information will be collected on the receipt of the patient information card (study participants will be asked at baseline and follow-up) and the checklist for prescribers (physicians will be asked at baseline). Study participants will also give their contact details like addresses, e-mail addresses and phone numbers, those of their relatives or friends, and the primary care physician. Names, addresses and phone numbers are to be documented on a separate sheet, in compliance with data protection regulations.

9.2.4 Follow-Up Phase

ZEG will perform all follow-up activities during this phase of the study. All subjects who provide written informed consent will be contacted for follow-up regardless of the duration of treatment or whether they discontinue treatment. Subjects who withdraw their consent for follow-up will not be contacted. The funder will not have access to names, addresses, or alternative contact information for the subjects.

Follow-up questionnaires will be mailed to the study participants at 6, 12 and 24[18] months after study entry to collect information regarding major safety outcomes.

The specific safety data to be collected during follow-up will focus on VTE (in particular deep venous thrombosis of the lower extremities and pulmonary embolism), arterial thrombo-embolism (in particular AMI and stroke), the outcomes reflecting the other secondary objectives as well as all other serious adverse events,[19] including cancer and specifically gynecological cancers. Subjects who report any of these outcomes will be asked to provide their primary care physician's/treating physician's name and address information. ZEG will contact the relevant physician (the attending physician is in most cases not the recruiting physician) and inform him/her about the study objectives and will share the subject's informed consent to access her medical information. Follow up by ZEG will include obtaining hospital records and/or discharge summaries, medical history, treatment dates, and concomitant medication use. A qualified medical expert (i.e., pharmacovigilance physician) on the ZEG study team will assess the likelihood of a causal relationship to study treatment for each serious or unexpected adverse drug reaction in accordance with a predefined algorithm (cf. Section 9.10.3).

At each follow-up contact, subjects will be asked about the exact details and timing of their oral contraceptive use, and whether they continue to use the prescribed study medication.

9.2.5 Validation of Self-Reported Events

A self-administered questionnaire used by study participants at short intervals is a sensitive tool which captures almost all serious clinical outcomes [1]. From a methodological point of view, it captures a much higher proportion of these outcomes than methods relying only on the prescribing health care professional who often is not involved in the diagnosis and treatment of these outcomes. However, it must be considered that there is a significant difference between the rates of reported and validated events, because laypersons often misclassify adverse events. Therefore, validation of the self-reported events is of utmost importance.

Validation of self-reported events will start at the level of the local field organizations with a review of all subject-reported "events." This will be followed by a further review at the international coordinating center (ZEG).

If an adverse event is reported by a study participant, the subjectively perceived symptoms, the signs of disease and if possible the diagnosis as understood by the study participant are

[18] Or at the end of the study if the study ends prior to the 24 month follow-up of an individual patient.

[19] Serious adverse event means any AE that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability/incapacity, or requires medical/ surgical intervention to prevent one of said outcomes.

to be recorded on the follow-up questionnaire. The name and address of the relevant physician (attending physician, physician responsible for the follow-up treatment after discharge from hospital, or primary care physician) are also documented.

Follow-up questionnaires containing information on such an event are to be immediately passed on to the medical reviewer group at ZEG. If information is unclear or missing the woman will be contacted by phone, e-mail or other means. For many serious events it will be necessary to contact the diagnosing and/or treating physician for clarification and validation of the information received from the patient.

Under routine medical conditions, diagnosis of an SAE term is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs are classified by the investigators as "confirmed" or "not confirmed" according to a predefined algorithm (cf. Section 9.10.1).

In order to minimize classification bias - particularly if selectively affecting an individual exposure cohort - classification of self-reported serious cardiovascular outcomes, into confirmed and not confirmed cases will be adjudicated by three independent medical experts specializing e.g. in radiology/nuclear medicine, cardiology, and internal medicine/phlebology. They will review all available information on the reported outcomes. For this process, the adjudicators will be blinded to the brand names and composition of the treatments used by the reporting woman. 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 Section 9.10.2.

In addition, the ZEG physician who is responsible for the assessment of individual case reports prior to interim analyses will be blinded to the study drug (i.e. he/she will do his/her assessment based on redacted copies of the available documents). Also individual case reports that are presented to the Safety Monitoring and Advisory Council will be blinded to the study drug.

9.2.6 Loss to follow-up

A low "loss to follow-up rate" will be essential for the validity of the study. In order to minimize loss to follow-up a multi-faceted, four-level follow-up process will be established. Level 1 activities include mailing of the follow-up questionnaire and – in case of no response – up to two reminder letters. If level 1 activities do not lead to a response, multiple attempts are to be made to contact the woman, friends, relatives and the gynecologist/primary care physician per phone. In parallel to these level 2 activities searches in national and international telephone and address directories as well as 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 loss to follow-up at the end of the study at less than 5% of the study

population. The EURAS study [3] has demonstrated that the chosen study design is suitable to reach this goal.

9.3 Variables

9.3.1 Primary Endpoint

Venous Thromboembolism (VTE)

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are the most relevant adverse drug reactions associated with combined hormonal contraceptive use. Based on a request of the European regulatory authorities specific VTEs - DVT of the lower extremities and pulmonary embolism - was chosen as the primary outcome of interest (cf. Section 8). Inferential statistics will be based on the VTE hazard ratio for FC Patch Low vs. COC_{LNG} (cf. Section 9.2.1).

Information about the use of the new FC Patch Low is only available from clinical trials including a limited number of study participants. It consists of a fixed combination of ethinyl estradiol (EE) and gestodene (GSD). The estrogen component, EE, is the standard estrogen used in nearly all combined OCs, and the progestin component, GSD, has been extensively used in a wide variety of OCs and products for hormone therapy for over 25 years with a well-known efficacy and safety profile. The combination of EE and GSD is used for many OCs marketed in the European Union (EU) and considerable experience has already been documented for this combination and oral route of administration.

VTE and ATE are well-known side effects of hormonal contraceptives. No real-life data are available for the effect of the FC Patch Low on VTE and ATE. During the approval process, the MAH received the condition to prove that the FC Patch Low is not expected to have a negative impact on the risk of VTE and ATE compared to combined oral contraceptives (COC) containing LNG. Therefore, a prospective, controlled, non-interventional, long-term cohort study to assess the impact of short- and long-term risk was deemed appropriate. The study proposed in this protocol should provide data that are sufficiently robust to eliminate a 1.5-fold risk in VTE for FC Patch Low compared to COC_{LNG}. The comparator was specifically requested during the DCP of FC Patch Low.

During this study, information on known risk factors for VTE will be collected. This includes age, BMI, family history of VTE and current duration of use. Information on the smoking status (current, ever, never, number of cigarettes and period of smoking) and socio-economic status (highest level of education) will be collected as well although they are believed to have a minor influence. All potential confounding factors will be included in a multivariable model to test whether they change the strength of the association between exposure and outcome.

The main clinical outcomes of interest for the short (FU 1 after 6 months) and long-term follow-up (FU 2 after 12 months and FU 3 after 24 months) are venous thromboembolism (VTE), specifically:

- Deep Venous Thrombosis (DVT) of the lower extremities (ICD-10 codes: I80.1, I80.2); exluding I80.3
- Pulmonary Embolism (PE); this includes the ICD-10 codes I26.0 and I26.9

Furthermore, sensitivity analyses are planned in order to
1) evaluate the impact of including I80.3 (phlebitis and thrombophlebitis of lower extremities, unspecified), which means that DVT of the lower extremities plus I80.3 plus pulmonary embolisms are analyzed
2) all DVTs and pulmonary embolisms.

9.3.2 Secondary Endpoints

For several other clinical outcomes an association to hormonal contraceptive use has been discussed. For some outcomes a causal relationship has to be assumed (e.g., hormonal contraceptive use and myocardial infarction in women with a combination of risk factors - in particular smoking, advanced age and high blood pressure) for other outcomes the existing evidence is weak (e.g. prolonged time to conception after stop of hormonal contraceptive use). The selection of following secondary endpoints will be investigated in this study (cf. Section 8):

- All VTE
- Arterial Thromboembolism (ATE)
- 'Idiopathic' VTE (VTE cases with acute risk factors – such as pregnancy, delivery, trauma, immobilization, long-haul travel, surgery, chemotherapy – excluded)
- Cancer entities
- Application site reactions
- Pregnancy related outcomes
- Serious adverse events

Most of these secondary endpoints were successfully investigated in the EURAS study [1;4;5] and/or similar studies.

9.4 Data sources

This is a field study. Exposure to hormonal contraceptives, concomitant medication, primary and secondary outcomes, potential confounding factors and potential effect modifiers will be documented by the study participants, the recruiting and attending physicians in the

questionnaires and additional documentation sheets, if needed. Baseline data (cf. Section 9.2.3) will be recorded on a self-administered questionnaire containing questions relating to participants' state of health and potential risk factors. Participants will provide their medical history, including medication history and history of OC use. The information given by the study participants will be checked by their physicians.

In addition to the baseline variables described in Section 9.2.3 study participants will provide their addresses and phone numbers, as well as those of relatives or friends – who could serve as reserve contacts – and their primary care physician/gynecologist.

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

Follow-up assessments for each woman in this study are scheduled 6, 12 and 24 months after study entry. Questionnaires will be mailed to the participating women, who often know more about their own personal health-related events than the physician who prescribes their OC. This is especially true for information on SAEs that were treated by other physicians. In some cases, events will be reported by the participant or by relatives, friends or attending physicians between the regular follow-ups. All reports – independent of the source of information – will be validated according to the process given below (cf. Section 9.10.1)

The follow-up questionnaires address the occurrence of adverse events – in particular serious adverse events. Reasons for contraceptive discontinuation or for a switch to another hormonal contraceptive (HC) will be requested if applicable as well as pregnancy related data to gather effectiveness information [4;5]. The variables that are recorded at each follow-up are described in Section 9.2.4.

The questionnaires will be collected in the participating countries by the local collaborators of ZEG, and will be reviewed for completeness and plausibility/consistency of the responses. Missing and inconsistent information will be clarified directly with the women via telephone. The completed questionnaires will be forwarded to ZEG. At ZEG all incoming data will be subjected to comprehensive quality control including electronic and manual plausibility checks. Unclear or inconsistent information will be described in detailed queries which will be forwarded to the local collaborators for clarification with the women. ZEG will monitor and endorse the timely processing of the queries.

The overall results and particularly the results on outcomes of interest will be reviewed by the Safety Monitoring and Advisory Board (cf. Section 10.3). The results of the validation process of reported outcomes of interest will be quality controlled by blinded adjudication (cf. Section 9.10.2).

9.5 Study size

The sample size considerations are based on the expected VTE incidence for COC_{LNG} of 10 VTE per 10,000 WY[20], which was agreed upon recently with CHMP in a comparable PASS that is conducted by ZEG. It is expected that FC Patch Low is associated with a VTE risk that is not higher than the risk associated with COC_{LNG}.

The study should be powered to test non-inferiority of FC Patch Low treatment regarding VTE risk in comparison to COC_{LNG} use. Sample size calculations for a non-inferiority test of two exponential survival curves [6;7] showed that an expected number of 150 VTE cases should be sufficient to reach this goal. These calculations are based on the following assumptions: 1) one-sided α of 0.05; 2) power (1-β) of 0.80 and 3) non-inferiority limit on hazard ratio of 1.5.

At an incidence rate of 10.0/10,000 WY a total of 150 VTE cases could be expected within 150,000 WY. The drop-out rate in similar studies has been approximately 0.7% per month. Assuming 1) a recruitment phase of 60 months, 2) a follow-up phase of 12 - 24 months, and 3) a loss to follow-up rate of about 5%, follow-up of 101,000 study participants (50,500 FC Patch Low users and 50,500 COC_{LNG} users) for up to 24 months would result in approximately 150,000 WY (see table 1).

Based on these scenarios, the study is sufficiently powered to exclude a 1.5-fold VTE risk for FC Patch Low users compared to COC_{LNG} users in the event that the true VTE risk among FC Patch Low users is not higher than among COC_{LNG} users.

However, precise power calculations based on actual incidences and drop-out rates should be done on the basis of follow-up data 1) before the end of the recruitment phase and 2) after availability of 30,000 WY of observation. If these calculations do not confirm the assumed incidence and drop-out rates the Safety Monitoring and Advisory Council will discuss the need to decrease or increase the number of study participants and/or follow-up times.

The sample size needed for the investigation of the VTE risk is also sufficient for the evaluation of secondary outcomes – except ATE. 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. This is sufficient to screen for safety signals and substantial effects.

To monitor the incidence rate and recalculate the study size, if necessary, the incidence rate observed in this study will be provided with each interim report.

[20] 'idiopathic' pulmonary embolism and deep venous thrombosis of the lower extremities

Table 1: Expected observation time[21]

	Sub-cohorts recruited during month						
Time after study start [month]	**1**	**2**	**…**	**24**	**25**	**…**	**60**
	Average number of women in follow-up						
1	1,677						
2	1,665	1,677					
…	…	….	…				
24	1,427	1,437	…	1,677			
25		1,427	…		1,677		
…			…	…	…	…	
60						…	1,677
…						…	…
71							1,563
72							1,552
WY	*3,097*	*3,076*	*…*	*2,635*	*2,617*	*…*	*1,059*
Total WY (crude)	***170,023***						
Total WY *(corrected for loss to follow-up and 'within study switchers' who do not contribute to exposure of starter and restarter)*	***~151,000***						

9.6 Data management

9.6.1 Databases

Two different databases are used for data collection; the administrative database (ADB) and the study database (SDB).

The ADB is provided by ZEG to the national field organizations. Physician details, as well as data from the study participant, can be entered and maintained in this database.

The SDB is validated according to GXP rules. It contains all questionnaire data including baseline data and all subsequent follow-ups. ZEG regularly performs cross-check and

[21] Assumptions: approx. 101,000 study participants recruited over 60 months (~ 1,683 per month); follow-up of study participants for 12 - 24 months; drop-out rate of 0.7% per month (e.g., 12 out of 1,683 recruited women will drop-out during the first month after recruitment; therefore the average number of women during the first month is 1,677 women [(1,683+1,671) x 0.5]); loss to follow-up and loss to 'within study switchers': 11%

verification checks on the data and any inconsistencies or unanticipated answers are mailed to the field organizations for further clarification.

From the questionnaire data, event data is derived from the SDB. All disease diagnoses are coded using the ICD-10 (International Classification of Diseases). ZEG also uses additional codes for the coding of events that are of specific interest (e.g. VTE during pregnancy or delivery, outcome of an unintended pregnancy: induced or spontaneous abortion, delivery of a healthy child, birth defects).

Concomitant medication is coded using WHO ATC-Codes. Surgical procedures are coded using the modified operation and procedure coding list (OPS) provided by DIMDI (German Institute for Medical Documentation and Information). All other relevant information will be coded by a ZEG specific, highly standardized coding system (ZEG Coding Dictionary). All outcomes of interest are additionally described in a case narrative, the “case summary”.

9.6.2 Dataflow

When questionnaires are received from study participants, all pages are counted and the questionnaire is date-stamped. Questionnaires are to be checked for correct subject identification number, missing pages, legibility, and incomplete information on the questionnaires. Missing pages, illegible or missing information are requested from the study participants prior to data entry of the respective questionnaire.

Data is entered by double data entry via formatted entry screens designed to reflect the appearance of the questionnaire. Discrepancies between first and second data entry are identified by comparison of the two entry files within the statistical software SAS. The decision on the true entry is done by the responsible data manager at ZEG. This may require direct contact with the study participant who filled in the questionnaire. Corrections will be made to the questionnaire only after contact with the study participant or her treating physician. All corrections are dated and initialed by the data manager who received the relevant new information (e.g., via direct contact or by a copy of medical reports/documents). The incorrect entry will be crossed out; however, it must remain legible, and the correct entry will be placed next to it. The reason for any correction of medical data on the questionnaire must be documented.

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

9.6.3 Database Freeze/Lock

For each interim analysis and for the final analysis the database is frozen at a predefined time point. The database will be ‘cleaned’ within 4 weeks of the database freeze. After the

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

9.7 Data analysis

Based on available data and pharmacological considerations the *a priori* assumption is that use of FC Patch Low is not associated with an increased risk of VTE compared to COC_{LNG}. That is, a statistical comparison of FC Patch Low and COC_{LNG} is not expected to show a difference. Therefore, a non-inferiority design was chosen to investigate the VTE risk of FC Patch Low. The primary analysis will be based on the comparison of the upper confidence limit for the point estimate of the VTE[22] hazard ratio with the predefined non-inferiority limit (see below).

The final analyses will include both an "as treated" (AT) and an intention-to-treat (ITT) analysis using Cox regression models. The safety conclusions of the study, however, will be based on the AT analyses (outcomes of interest will be assigned to the treatment she used at the time of the event) because the ITT approach (outcomes of interest are assigned to the treatment which was prescribed at study entry) potentially dilutes differences between treatments.

Incidence rates, incidence rate ratios (HRs), excess risks, as well as crude and adjusted hazard ratios will be calculated. The appropriate confounding variables will be built into the model. Based on the expectation of a small absolute number of serious outcomes of interest the number of confounding variables will be limited to well-established risk factors for these outcomes (e.g., age, BMI, duration of current use, and VTE history). The final decision on the confounding variables will be made by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data. In addition, alternative analysis will be performed with other potential baseline risks to check the appropriateness of this decision. Similar analyses will be performed for all VTE (cf. Section 8) and arterial thromboembolism (e.g., acute myocardial infarction and stroke), the other secondary variables and other serious adverse events.

The null hypothesis to be tested is: $\mathbf{HR_{VTE} \geq 1.5}$ (i.e., the VTE hazard ratio for FC Patch Low vs. COC_{LNG} is higher than or equal to 1.5). The alternative hypothesis is: $\mathbf{HR_{VTE} < 1.5}$.

In the case of VTE it is conceivable that the proportional hazard assumption that effect parameters multiply hazard does not hold. Therefore, time-dependent factors will be included in the Cox model. The appropriateness of the model will be checked by comparing results of this analysis with results of an alternative analysis which stratifies by time of

[22] DVT of the lower extremities and pulmonary embolism, cf. Section 8

exposure. This stratification addresses also the potential problem of effect modification by current duration of use.

Real-life field studies frequently face the situation of missing data. The multiple reasons include superficial reading of the questions, misunderstanding of the questionnaire or simply unwillingness to give certain information. The questionnaires of this study have a clear layout and most questions have been tested in several former studies in large populations. The amount of missing information will be minimized by contacting participating women several times. If the missing information can also be collected by the enrolling physician (e.g. any information on prescription, details regarding pregnancies, etc.), he/she will be contacted. If these strategies are unsuccessful, missing variables will be either accepted or, for certain variables, e.g. BMI, the last value will be carried forward. In general, missing data will comprise less than 5% of all data collected based on the experience of comparable studies conducted by ZEG.

In addition to the before mentioned main analysis, an automated selection method will be used to arrive at a more parsimonious model. A backward stepwise approach will be used to reduce the number of covariates in each analysis/sub-analysis. The pre-specified significance level for removal or addition of a covariate will be $p>0.10$ and $p<0.05$, respectively. However, there is no general agreement in the scientific literature about the most appropriate method for covariate selection or whether it should be applied at all. The latter view is based on the general request that the selection of relevant prognostic factors should be content driven (i.e., which factors are potential confounders). Therefore, the backward stepwise approach will only be performed for exploratory purposes.

A detailed statistical analysis plan addressing descriptive and inferential statistics will be developed by the study team during the first year after study start. This plan will include methodological details (e.g., censorship at time of cancer diagnosis, surgery or occurrence of other acute VTE risk factors for the analysis of VTE), a specification of sub-analyses (such as stratification by dose of ethinylestradiol (e.g., HR_{VTE} for FC Patch Low vs. COC_{LNG} with 20mcg of ethinylestradiol) and current duration of use (e.g., HR_{VTE} during the first year of use)) as well as a comprehensive set of mock tables for the presentation of the study results. The final analysis plan will be approved by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data. Changes of this document are to be approved by the Safety Monitoring and Advisory Council.

9.8 Quality control

The organization that is responsible for the conduct of the study (ZEG) has implemented different quality assurance procedures for day-to-day work. Internal audits confirm that ZEG fully complies with GPP ('Guidelines for Good Pharmacoepidemiology Practices' issued by the International Society for Pharmacoepidemiology in 2007), GEP (Good Epidemiological Practice issued by the European Epidemiology Federation in 2007), GVP (Good pharmacovigilance practices issued by the EMA in 2012/2013), the ENCePP Code of Conduct, the Nuremberg Code and the Declaration of Helsinki. Additionally, ZEG has been audited three times by large pharmaceutical companies, without major issues being identified. For this study, as for all other studies conducted by ZEG, site audits in the participating local field organizations will be conducted by ZEG on a regular basis. This includes organizational aspects as well as source data verification.

ZEG's internal standard operating procedures (SOPs) manual describes standardized working procedures to ensure high quality and compliance with all applicable guidelines. The SOPs are reviewed on an annual basis and updated where necessary to ensure that all processes are in line with legal compliance and integrity of data. ZEG also uses standardized working procedures for the Safety Monitoring and Advisory Council (SMAC), the Blinded Adjudication Board and study-specific working procedures for the local organizations.

ZEG assures that the study will be conducted in compliance with the protocol and any applicable regulatory requirements. All processes that are relevant for legal compliance of the study or the integrity of the data are subject to quality control measures. This includes 1) development of study protocol, questionnaires, databases and data entry screens, 2) data entry, 3) plausibility checks, 4) validation of clinical outcomes, 5) adverse outcome reporting, 6) data analysis, 7) report writing, 8) publication of results, 9) archiving of study materials (i.e. all baseline/follow-up questionnaires, other study documents and electronic files). All quality control measures are based on the four-eye principle (i.e., it is not sufficient that someone controls his/her own work). During study conduct the consistency between ZEG's electronic database and the original questionnaire will be audited several times by an external auditor.

The external auditor is also responsible for a systematic review of quality standards implemented at ZEG and the local organizations, as well as proposing suitable measures to ZEG management to improve quality standards.

ZEG's study work will be overseen for the whole study period by the Safety Monitoring and Advisory Council of internationally acknowledged experts in the field (cf. Section 10.3). This committee will take final decisions in all scientific matters.

9.9 Limitations of the research methods

In non-experimental studies like 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 [8]. Valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology help to reduce the impact of bias and residual confounding [9]. However, the difficulty remains unresolved when all that exists is a weak association [10;11]. Relative risk estimates that are close to unity may not allow differentiation between causation, bias and confounding [12;13]. In general, it is difficult to interpret a relative risk of two or less in observational research [14;15].

Within these limitations of non-experimental studies the chosen study design is capable of minimizing bias and residual confounding. In our judgment, selection bias will not be a major issue in this study because study participants from several settings are included, e.g. private practices, family planning centers, hospitals. Although recruitment will be performed only by a sample of physicians, those can be considered the most possible representative network. In several countries where ZEG currently conducts similar observational studies, all possible recruiting physicians have been contacted and asked for participation. Furthermore, the participants' demographic characteristics have been proven to be representative for adult OC users in the EURAS-OC study, which had an almost identical study design. Differences between the study cohorts can be addressed in the statistical analysis (e.g. inbalances of age distribution will be levelled out by age adjustment to assure comparability of results).

Also, misclassification bias will probably have no substantial impact on the results as precise information on the exposure and the outcomes of interest will be available. In addition, reliable information on duration of current hormonal contraceptive use will be available. Accordingly, the study will capture the well-known increased VTE risk during the first months of combined hormonal contraceptive use [16;17;18]. Furthermore, the comprehensive follow-up procedures will ensure a low loss to follow-up rate. In theory, a disproportionately high percentage of SAEs (including VTE and ATE) could occur in those patients who are lost to follow-up, because SAEs could be the reason for the break in contact with the health care professional who prescribed their COC. An advantage of the study design, however, is that the investigator team will have direct contact with the participants; contact will not be lost if the women change health care professionals, for example (e.g., due to change of residence or dissatisfaction with treatment).

In contrast, it will be impossible to exclude diagnostic bias. Clinical symptoms of VTE cover the spectrum from a complete absence or unspecific, slight symptoms to dramatic, acute, life-threatening symptoms [19;20;21]. A high awareness of potential cardiovascular risks of combined oral contraceptive use may lead to more diagnostic procedures and, therefore, to more detected VTE. It is conceivable that this potential bias lead to an overestimate of the relative risk of a new product (such as FC Patch Low) cohorts compared to the LNG-cohort. Therefore, diagnostic bias should not result in an underestimate of the VTE risk carried by FC Patch Low.

Unlike in many other observational studies on hormonal contraceptives, a strength of the study will be the availability of information on many important prognostic factors for the outcomes of interest. Nevertheless, we acknowledge that due to the non-interventional character of the study, information on specific gene mutations will only be available for VTE cases but not for the vast majority of study participants who will not experience a VTE. This limitation will be mitigated through information on family history of VTE which has a higher predictive value for VTE compared to gene mutations [22].

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 loss 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, outcome definition, and prognostic factor/covariate selection); vii) study population representative for oral contraceptive users under routine clinical conditions; viii) generalizability of results as hormonal contraceptive 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.

9.10 Other aspects

9.10.1 Validation of self-reported events

Under routine medical conditions, diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs will be classified by the investigator team as “confirmed” or “not confirmed” according to the following predefined algorithm:

- Definite Event:

Confirmed by diagnostic measures with high specificity (e.g., phlebography for DVT, spiral CT for pulmonary embolism, cerebral MRT for cerebrovascular accidents, ECG with typical ST segment elevation for acute myocardial infarction, histology for gynecological cancer, two-sided blood pressure measurement with diastolic blood pressure of more than 120 mmHG for hypertensive crisis)

- Probable Event:

Absence of confirmation by a diagnostic measure with high specificity, but clinical diagnosis confirmed by a health professional or supported by diagnostic tests with low specificity (such as 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 probable event even if specific treatment was not given.

- Event not confirmed:
  - Diagnosis reported by the patient is excluded by diagnostic procedures
  - A different medical condition is diagnosed by the attending physician
  - The woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

The exposure data reported by the patients will be validated via the prescribing physicians. Definite and probable events will be classified as 'confirmed events'.

For VTE, the definition of "definite", "probable" and "not confirmed" is further specified:

- **Definite VTE:** Confirmed by imaging procedure
  - DVT: phlebography, duplex sonography, magnetic resonance imaging
  - PE: pulmonary angiography, ventilation-perfusion scan, spiral computed tomography, magnetic resonance imaging, transesophageal echocardiography

- **Probable VTE:**

Absence of confirmation by an imaging test, but a clinical diagnosis was confirmed by a health professional or is supported by a non-imaging test (such as ultrasound doppler, plethysmography, D-dimer for VTE or typical 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 confirmed that the diagnosis is correct, the event was classified as a VTE, even if a specific treatment was not given.

- **VTE not confirmed:**
  - VTE excluded by a physician
  - A different medical condition was diagnosed by the attending physician
  - Woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

For the final analysis this classification will be verified by means of an independent blinded adjudication process (cf. Appendix 3).

For ATE, the definition of "definite", "probable" and "not confirmed" is further specified as follows:

- **Definite ATE**: Confirmed by a diagnostic method with high specificity (incl. intraoperative or post-mortem)

- AMI: typical change of cardiac enzymes with high specificity (CK-MB, cardiac troponin, glycogen phosporylase isoenzyme BB), typical ECG changes (e.g., ST-segment elevation), coronary angiography
- Stroke: typical clinical signs persisting for days, confirmation by imaging with high specificity (e.g., CT, MRI, cerebral angiography, PET)
- TIA: typical clinical signs (followed by resolution within 24 hours) and imaging with high specificity and sensitivity (e.g., MRI) does not indicate tissue necrosis
- Other organs and peripheral arteries (e.g. kidney, gut, adrenals, femoral artery): confirmed by imaging with high specificity (e.g., arteriography, CT, MRI)

- **Probable ATE**: No confirmation by a diagnostic method with high specificity, but other evidence pointing in the direction and the clinical diagnosis is confirmed by attending physician
  - AMI: typical clinical symptoms, change of cardiac enzymes with low specificity (e.g., CK, AST, LDH) or indirect ECG signs (e.g., ST-segment depression in case of posterior myocardial infarction), and clinical diagnosis confirmed by attending physician
  - Stroke: clinical signs persisting for days, confirmatory imaging not done or inconclusive, but clinical diagnosis confirmed by attending physician
  - TIA: typical clinical signs, followed by resolution within 24 hours, but no imaging with high specificity; and the clinical diagnosis is confirmed by attending physician
  - Other organs and peripheral arteries (e.g. kidney, gut, adrenals, femoral artery): confirmatory imaging not done or inconclusive, but clinical diagnosis confirmed by attending physician

- **ATE not confirmed:**
  - ATE excluded by a physician
  - A different medical condition was diagnosed by the attending physician
  - Woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

9.10.2 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 V (worst case decision without discussion of split decisions) because it represents the most conservative approach. Alternative analyses will be possible on request of the Safety Monitoring and Advisory Council or regulatory authorities.

9.10.3 Drug relationship

Categories (Code)	Definition
no (1)	The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of the study drug in the occurrence/worsening of the adverse event exists.
unlikely (2)	The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of the study drug or of the substance class provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known and/or regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of the study drug or the substance class, but another cause is much more probable and/or another cause is confirmed and involvement of the study drug in the occurrence/worsening of the adverse event is unlikely.
possible (3)	Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of the study drug or the substance class, but another cause just as likely to be involved is also known or although the pharmacological properties of the study drug or the substance class provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation
probable (4)	The pharmacological properties of the study drug or of the substance class and/or the course of the adverse event after dechallenge and, if applicable, after rechallenge and/or specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.
definite (5)	The pharmacological properties of the study drug or of the substance class and the course of the adverse event after dechallenge and, if applicable, after rechallenge and specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the adverse event and no indication of other causes exists.

10 Protection of human subjects

The 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 (2008) of the Helsinki Declaration[23] and the guidelines for Good Epidemiological Practice (GEP)[24], Good Pharmacoepidemiology Practices[25] Good Pharmacovigilance Practices (GVP)[26] as well as the ENCePP code of conduct[27], will be observed. All steps will be taken to protect subject's privacy and all relevant rules on data privacy will be followed. It will be ensured that subjects' names and addresses cannot be accessed by the funder.

10.1 Institutional Review

Review of the study protocol will be obtained at ethics committees in the appropriate geographies 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.

10.2 Informed Consent

Subjects will sign informed consent forms at baseline after reading a subject information sheet and discussing the study with the participating physician. The physician will describe the purpose of the study, the non-interventional character of the study, timing and content of follow-up phase contacts, and collection of alternative contact information. Consent will include permission to contact any treating physician to follow up on specific safety outcomes. Subjects will be informed that ZEG will contact them during the follow-up phase (up to 24 months) to ask a predefined set of safety related questions or to update

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[23] 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.

[24] 'Good Epidemiologic Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the European Epidemiology Federation in 2007; http://www.ieaweb.org/index.php?option=com_content&view=article&id=15&Itemid=43

[25] 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2007; http://www.pharmacoepi.org/resources/guidelines_08027.cfm

[26] issued by the EMA in 2012/2013

[27] http://www.encepp.eu/documents/encepp_studies/ENCePP%20Code%20of%20Conduct_20100507.pdf

alternative contact information. Answers to these questions collected by ZEG will remain anonymous when forwarded to the funder or the Safety Monitoring and Advisory Council.

Subjects will be asked to provide personal contact information (e.g., telephone number, home and e-mail address) and information regarding alternative contacts (e.g., relative, friend, physician other than the contraceptive-prescribing physician). In the event that a subject cannot be reached during the follow-up phase, ZEG will attempt to reach an alternative contact to re-establish contact with the subject, or, in the event of a subject's death, to confirm the cause of death. Subjects may be contacted between two follow-up points to confirm that their personal contact information is correct.

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

10.3 Safety Monitoring and Advisory Council

This study will maintain scientific independence from the Sponsor 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 and approval of the study protocol, statistical analysis plan, interim results, study report, and publications. The funder will assure financing of the study. ZEG and its research team will be accountable to the council in all scientific matters. ZEG 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, gynecology, cardiology, statistics). The members will receive remuneration of expenses and an honorarium to compensate for 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.

11 Management and reporting of adverse events/adverse reactions

This is a non-interventional study and no medical procedures are required as part of this protocol. All reported Adverse Events – non-serious as well as serious events –will be recorded in the study database and will be reported in the final study report. ZEG's medical event validation team will perform a causality assessment for all serious adverse events. ZEG will report all confirmed serious adverse events related to the use of a product marketed by the funder within 2 business days to the Funder. These serious adverse events include events related to FC Patch Low use. A physician on the ZEG study team will assess the likelihood of a causal relationship to FC Patch Low use for each serious adverse event in accordance with a predefined algorithm (cf. 9.10.3). In addition, ZEG will report all confirmed pregnancies within 2 business days to the Funder. All confirmed pregnancies where fetal hormonal contraceptive exposure may have taken place during a certain period of the pregnancy will be followed up for final outcome and reported.

Although non-serious adverse events are not actively solicited in this study, all validated drug-related non-serious adverse events (see procedure in Section 9.2.5) will be collected for tabulation in interim and/or final study reports, and will be regularly submitted to the Funder using the same method as described for SAEs.

ZEG will not monitor whether the relevant pharmaceutical companies meet their obligation to report these events to the Health Authorities according to (inter)national rules.

12 Plans for disseminating and communicating study results

The final study protocol and the results of this study will be published. In accordance with 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. National Institutes of Health's protocol registration database (www.clinicaltrials.gov) and in ENCePP's electronic register of studies (http://www.encepp.eu/encepp/studiesDatabase.jsp). Interim results of the study will be submitted to all relevant regulatory authorities twice a year. The final results will be published in a peer-reviewed journal.

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

(Revison 2; adopted by the ENCePP Steering Group on 14/01/2013)

Study title:
EURAS-CORA: EUROpean Active Surveillance study - COmparing Regimens of Application in combined hormonal contraception

Study reference number:
ZEG2014_03

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[28]	☒	☐	☐	12
1.1.2 End of data collection[29]	☒	☐	☐	12
1.1.3 Study progress report(s)	☐	☐	☒	- - -
1.1.4 Interim progress report(s)	☒	☐	☐	12
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

None

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	28
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	- - -

Comments:

None

[28] 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.

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22-24
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	28 - 29

Comments:

None

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17 - 18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	16
4.2.4 Disease/indication?	☒	☐	☐	18
4.2.5 Co-morbidity?	☐	☐	☒	- - -
4.2.6 Seasonality?	☐	☐	☒	- - -
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	17

Comments:

None

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	20
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	15
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	- - -
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	- - -

Comments:

None

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	22 - 23
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	20 - 21; 32-35

Comments:

None

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	29
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	29

Comments:

None

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	17 - 18
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	19 - 20
8.1.3 Covariates?	☒	☐	☐	22
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	18 - 19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19 - 20
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	19
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	15; 27
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	27
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	27
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	- - -

Comments:

None

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	25 - 26

Comments:

None

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	28 - 29
10.2 Is the choice of statistical techniques described?	☒	☐	☐	28 - 29
10.3 Are descriptive analyses included?	☒	☐	☐	28
10.4 Are stratified analyses included?	☒	☐	☐	28 - 29
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	29
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	29

Comments:

None

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27 - 28
11.3 Are methods of quality assurance described?	☒	☐	☐	30
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	30
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	30

Comments:

None

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	31
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	31 - 32

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	16
12.3 Does the protocol address other limitations?	☒	☐	☐	31 - 32

Comments:

None

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	37
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	- - -
13.3 Have data protection requirements been described?	☒	☐	☐	19; 37 - 38

Comments:

Ethical review will be applied for after regulatory approval of the protocol.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

None

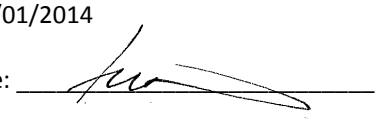
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12; 39
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	39

Comments:

None

Name of the main author of the protocol: Klaas Heinemann

Date: 08/01/2014

Signature: 

Annex 3. Additional information

None