EURAS-LCS12

European Active Surveillance Study of LCS-12

FINAL STUDY PROTOCOL

PASS information

Title	**EURAS-LCS12** European Active Surveillance Study of LCS-12
Protocol version identifier	2
Date of last version of protocol	21 FEB 2014
EU PAS register number	
Active substance	Levonorgestrel
Medicinal product	Jaydess® intrauterine contraceptive system (LCS12)
Product reference	
Procedure number	
Marketing authorisation holder(s)	Bayer Pharma AG 13353 Berlin
Joint PASS	No
Research question and objectives	This study is designed to investigate whether LCS12 is associated with an increased risk of unintended pregnancy compared to Mirena and to copper IUDs. The objective is to assess among new users the risks of certain events (e.g. contraceptive failure rate, ectopic pregnancy and PID) associated with the use of LCS12 compared with the established hormonal IUD Mirena, and compared with established copper IUDs during standard clinical practice. In addition, drug utilization patterns will be described.
Country(-ies) of study	Austria, Germany, Poland, Sweden, United Kingdom, France (tbc)
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2. List of abbreviations

Abbreviation	Definition
ADB	Administrative Database
AE	Adverse Event
AT	As Treated
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CT	Computer Tomography
DIMDI	German Institute for Medical Documentation and Information
ECG	Electrocardiogram
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EURAS	EURopean Active Surveillance (study)
EURAS-LCS12	EURopean Active Surveillance Study of LCS12
GEP	Good Epidemiological Practices
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
GXP	Good Practice Guidelines
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
LCS12	Levonorgestrel intrauterine contraceptive system releasing 12 mcg levonorgestrel/24h in vitro
LNG	Levonorgestrel
MRT	Magnetic Resonance Tomography

OPS	Operations and Procedures Classification System (acronym for the German term ‘Operationen- und Prozedurenschlüssel’)
PID	Pelvic Inflammatory Disease
SAE	Serious Adverse Event
SDB	Study Database
SMAC	Safety Monitoring and Advisory Council
TASC	Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing
VTE	Venous Thromboembolism
WHO	World Health Organization
WY	Women-years
ZEG	Berlin Center for Epidemiology & Health Research (acronym for the German term ‘Zentrum für Epidemiologie & Gesundheitsforschung Berlin’)

3. Responsible parties

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4. Abstract

Title: European Active Surveillance Study of LCS12 (EURAS-LCS12)

Rationale and background: Intrauterine contraceptive methods, such as Mirena and copper IUDs, have a high contraceptive efficacy. LCS12 is a new intrauterine system which, like Mirena, contains levonorgestrel (LNG), but the T-body dimensions and insertion tube diameter of LCS12 are smaller. Because there is a lack of comparative data between LCS12 and other intrauterine contraceptives, it is unclear whether there are differences in contraceptive failure rates between LCS12 and either Mirena or copper IUDs. In addition, any transcervical procedure, including the insertion of an intrauterine device, is potentially associated with the risk of infection/inflammation.

Research question and objectives: The main research question is to assess the effectiveness and safety of LCS12 in real life use in new users as compared to Mirena and to copper IUDs. The primary objective is to investigate whether LCS12 is associated with an increased risk of unintended pregnancy (contraceptive failure) compared to Mirena and compared to copper IUDs. Secondary objectives are the investigation of pelvic inflammatory disease (PID) and ectopic pregnancies. The study also aims to capture the drug utilization pattern of LCS12 and established intrauterine devices during standard clinical practice, outcomes of unintended pregnancies, risk of serious adverse events, difficulties associated with IUD insertion, and cervical conization procedures.

Study design: EURAS-LCS12 is a prospective, controlled, non-interventional, active surveillance cohort study with three user cohorts: LCS12, Mirena and copper IUDs. Study participants will be recruited by a network of health care professionals and will be followed up through active surveillance to collect information regarding the outcomes of interest and major safety outcomes. All self-reported clinical outcomes of interest will be validated by health care professionals. The primary endpoint is unintended pregnancy. Secondary endpoints are ectopic pregnancy and pelvic inflammatory disease (PID).

Population: Study participants will be recruited by health care professionals in at least six European countries over a period of 36 months. Women will be considered for enrollment after the participating physician has determined that LCS12, Mirena or copper IUD use is appropriate. There are no specific medical inclusion/exclusion criteria and no age restrictions. Study participants will contribute follow-up information for 36 months after study entry. In addition, the first 1,000 enrolled LCS12 users who still have the IUD in place at 36 months will be followed up for an additional 12 months (total of 48 months) to determine if there is off-label use of LCS12 beyond 36 months of use.

Variables: The risk of unintended pregnancy (primary clinical outcome), ectopic pregnancy and pelvic inflammatory disease (secondary outcomes) associated with the use of LCS12, Mirena and copper IUD use will be assessed. Potential confounding variables will be limited to well-established risk factors for these outcomes.

Data sources: HCPs and study participants will complete a baseline survey at study entry. Study participants will complete follow-up questionnaires at 6 weeks, 6 months, 12 months, 24 months and 36 months post-baseline. An additional follow-up questionnaire will be completed by the first 1,000 enrolled LCS12 users at 48 months after study entry. Follow-up questionnaires will capture the outcomes of interest and other major safety outcomes.

Study size: Approximately 38,000 study participants will be recruited to contribute approximately 100,000 women years (WY) of observation.

Data analysis: A non-inferiority design will be used to investigate the contraceptive failure rate of LCS12. The primary analysis will be based on the comparison of the upper confidence limit for the point estimate of the contraceptive failure hazard ratio with the predefined non-inferiority limit. Multivariate techniques such as Cox regression will be used to take into consideration the influence of confounding.

Milestones: It is anticipated that data collection will begin during the second quarter of 2014 and end during the fourth quarter of 2020. The final report of study results will be available in the second quarter of 2021.

5. Amendments and updates

None.

6. Milestones

Milestone	Planned date
Start of data collection	Q2/2014
First follow-up	Q2/2014
50% of patients recruited	Q4/2015
Last patient in	Q2/2017
End of data collection	Q4/2020
Blinded Adjudication	Q2/2021
Final report of study results	Q2/2021

7. Rationale and background

Modern intrauterine contraceptive methods were introduced about a century ago. Subsequently, a significant innovation was introduced in the form of hormonally loaded intrauterine systems. In particular, the contraceptive efficacy of these types of devices was higher than that of non-medicated devices. With the very widespread use of the Mirena intrauterine system, both the experiences from the market as well as the results of clinical and epidemiological studies show a favorable benefit/risk balance.

Mirena contains levonorgestrel (LNG) and features a remarkably good contraceptive efficacy. The mode of action is based primarily on local progestogenic effects of LNG. This mechanism is important in pregnancy prevention. In addition, partial ovarian suppression contributes to the high contraceptive effectiveness of Mirena.

LCS12 is a new intrauterine system. Like Mirena, it is a T-shaped device that contains levonorgestrel which is slowly and continuously released into the uterine cavity. LCS12 can remain in situ for up to 3 years. Compared to Mirena, LCS12 has both smaller T-body dimensions and insertion tube diameter. Mirena, copper IUDs and LCS12 are all highly effective methods with low pearl indices. However, there is a lack of comparative data between LCS12 and other intrauterine contraceptives both in clinical studies and routine clinical practice, and therefore it is unclear as to whether there are any differences in contraceptive failure rates between either Mirena or copper IUDs and LCS12. The presented study will compare the risk of contraceptive failure – including ectopic pregnancy rates – associated with use of LCS12, Mirena and copper IUDs.

Any transcervical procedure, including the insertion of an intrauterine device, is potentially associated with the risk of infection/inflammation (1). Therefore, the study will also address the occurrence of Pelvic Inflammatory Disease (PID) in new users of the 3 intrauterine contraceptives as a specific outcome.

The EURAS study (2) and similar studies (such as INAS and TASC), and in particular the EURAS-IUD study (3), have demonstrated that a prospective, controlled, long-term cohort study is suitable for safety monitoring of contraceptives, reliable identification of relevant clinical outcomes and 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 and outcomes of interest.

This study will include European women using intrauterine devices (IUDs). The objective of the study is to assess among new users the risks of certain events (contraceptive failure rate, ectopic pregnancy and PID) associated with use of LCS12 compared with each type of established IUDs (Mirena, copper IUDs) during standard clinical practice. In addition, drug utilization patterns will be described and outcomes of unintended pregnancies, risk of serious adverse events, difficulties associated with IUD insertion, and cervical conization procedures.

8. Research question and objectives

The main research question is to assess the safety profile of LCS12 in real life use in new users as compared to each type of established IUDs (Mirena, copper IUDs). The funder has asked the Berlin Center for Epidemiology and Health Research (ZEG) to conduct a prospective controlled epidemiological study with a robust and efficient study design that investigates the risk of contraceptive failure, ectopic pregnancy and PID associated with the use of LCS12 and established IUDs.

The objective of the study is to assess specific risks of use of LCS12 compared with the use of each type of established intrauterine devices (Mirena and copper IUDs) in a study population that is representative of the actual users of the individual products. This includes an estimate of the absolute risk of rare serious adverse outcomes.

The primary clinical outcome of interest for the short- and long-term follow-up is:

- Unintended pregnancy

Secondary clinical outcomes of interest are:

- Ectopic pregnancy
- Pelvic inflammatory disease (PID)
- Uterine perforations

The study also aims to capture:

- Drug utilization pattern of LCS12 and established intrauterine devices during standard clinical practice

- Outcomes of unintended pregnancies
- Risk of serious adverse events including VTE
- Difficulties associated with IUD insertion
- Cervical conization

The results of the EURAS-IUD study showed a Pearl Index of 0.06 (95% CI: 0.04-0.09) under routine practice. However, for the sample size calculation, a higher pearl index was chosen in order to account for the different age distribution to be expected in this study. The Mirena Pearl Index for women aged between 18 and <30 years in the EURAS IUD study was 0.11 (95% CI: 0.04-0.23), and for women between 30 and <40 it was 0.09 (95% CI: 0.05-0.15).

It is expected that the risk of LCS12 is lower or equal to Mirena and also lower or equal to copper IUDs. The null hypotheses to be tested are: $\mathbf{HR}_{\text{contraceptive failure}} > \mathbf{2}$ (i.e., the contraceptive failure hazard ratio for LCS12 vs. Mirena and for LCS12 vs. copper IUD is higher than or equal to 2). The alternative hypothesis is: $\mathbf{HR}_{\text{contraceptive failure}} < \mathbf{2}$.

In general, unintended pregnancies in IUD users are a rare event. In addition, in the EURAS IUD study, the contraceptive failure rate in Mirena users was found to be substantially lower compared to copper IUD users (Pearl Index for Mirena: 0.06, 95% CI: 0.04-0.09; copper IUD: 0.52, 95% CI:0.42-0.64). Unintended pregnancies as such do not necessarily constitute a serious adverse event. However, the proportion of unintended pregnancies that are ectopic is higher in IUD users compared to other contraceptive methods or non-use of contraception. In the EURAS IUD study, the proportion of unintended pregnancies that were ectopic was 23% in Mirena users and 15% in copper IUD users. However, the absolute risk of ectopic pregnancies in Mirena users was substantially and statistically significantly lower than that of copper IUDs (incidence rate per 100 WY for Mirena: 0.02, 95% CI: 0.01-0.03; for copper IUD: 0.08, 95% CI: 0.04-0.13, hazard ratio after adjustment for age, BMI and parity:0.26, 95% CI: 0.10-0.66).

Given these data, the exclusion of a two-fold risk of contraceptive failure of Jaydess compared to Mirena would confirm the high clinical effectiveness of Jaydess, especially when considering the clearly superior contraceptive efficacy of Mirena relative to copper IUDs.

The decision to aim for the exclusion of a two-fold risk was also based on the fact that in non-experimental studies, the possibility of bias and residual confounding can never be entirely eliminated, and the ability to infer causation is correspondingly limited (5). If an association is of relatively low magnitude (e.g., a relative risk estimate of less than 2.0) it may not be possible to judge whether or not it can be entirely accounted for by bias. Modern epidemiological methodology improved insight into potential sources of bias and confounding (6). However, the difficulty remains unresolved for weak associations (7). In practical terms, a point in the gradient of declining relative risk must be reached at which the amount of bias and residual confounding becomes so small that it cannot realistically be ruled out (8). In general, it is very difficult to interpret a relative risk of two or less in observational research (11).

9. Research methods

9.1 Study design

This will be a multinational, controlled, prospective, non-interventional, active surveillance study that follows three cohorts. The cohorts consist of new users of three different IUDs: LCS12, Mirena and copper IUDs. The study will use a non-interference[1] approach to provide standardized, comprehensive information on these treatments as prescribed in a routine clinical practice setting.

Study participants will be recruited via an international network of about 1,000 gynecologists and other health care professionals who insert IUDs (depending on national practice in the participating countries). After study entry, study participants will be followed for a period of 36 months, or until the discontinuation of the treatment (i.e. the removal of the IUD) is indicated in any follow-up questionnaire or until the consent is withdrawn. 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 9.4.2) will be used to validate self-reported events. The primary endpoint is unintended pregnancy. Secondary endpoints are ectopic pregnancy and pelvic inflammatory disease (PID).

All study participants will be contacted after 6 weeks (to get accurate data on potential PID cases that might occur shortly after IUD insertion), 6 months, 12 months, 24 months, and 36 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., vaginitis as "pelvic inflammatory disease"). This type of inaccuracy in patient reports will require careful validation of the reported events. This will be accomplished by contacting the treating 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 predefined algorithms. At the end of the study this classification will be verified by blinded independent adjudication (cf. Annex 3.3).

Data collection will include data on drug utilization of LCS12, Mirena and copper IUDs. Reasons/indication for IUD use, type of IUD, duration of use, reasons for stopping IUD use as well as tolerance and safety issues will be documented. In order to evaluate if there is off-label use of LCS12 beyond 3 years, the first 1,000 enrolled LCS12 users with the initially inserted IUD still in place at 36-months' follow-up will be followed for a further 12 months (48 months instead of 36 months).

9.2 Setting

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

[1] i.e. 1) all new users of LCS12, Mirena or copper IUDs are eligible for enrolment if they give their informed consent; and 2) recruitment of study participants should not influence the physicians' prescribing, diagnostic or therapeutic decisions.

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 (cf. Annex 3.1).

The study will be conducted in at least 6 European countries. So far, it is planned to include Austria, France, Germany, Poland, Sweden,and the United Kingdom. This plan might be modified depending on the time of market introduction of LCS12 in individual European countries.

9.2.1 Selection of study population

Recruitment of study participants will be conducted over 36 months via existing networks of gynecologists or other health care professionals (depending on national practice) who have participated in similar cohort studies in the past. It is anticipated that 1,000 HCPs will participate. Recruiting sites will be representative of a broad range of practitioners (e.g. gynecologists, general practitioners, university clinics) in both urban and rural areas.

Subjects will be considered for enrollment in this study after the participating physician has determined that LCS12, Mirena or copper IUD use is appropriate. There will be no specific medical inclusion/exclusion criteria and no age restrictions. However, women who are currently enrolled in an interventional trial for IUD use will not be included. 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. For adolescents, local law might require a parent's or guardian's signature, which will then additionally 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 IUDs or may switch to another hormonal contraceptive at any time. Subjects will be contacted for follow-up until the discontinuation of the treatment (i.e. the removal of the IUD) is indicated in any follow-up questionnaire or until the maximum three years' follow-up period is completed, 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 36-month follow-up phase (or 48-month follow-up phase for the first 1,000 enrolled LCS12 users with the first IUD still in place at 36-months' follow-up), subjects will be asked whether they have discontinued IUD use. Information on the date and reason for discontinuation during the follow-up phase will also be collected.

9.3 Variables

The risk of unintended pregnancy (primary clinical outcome) and ectopic pregnancy and pelvic inflammatory disease (secondary outcomes of interest) associated with the use of LCS12, Mirena and copper IUDs will be assessed.

All potential confounders including age (13,14,15), parity (13), history of ectopic pregnancy/PID (13), duration of current use (1,14) and sexual behaviors (1,13,14) will be tested or included in the final model. The final decision on the confounding variables will be made by the Safety Monitoring and Advisory Council at first interim analysis of follow-up data. In addition, to avoid an overload of confounding variables in relation to the actual number of validated outcomes, an alternative model with pre-defined potential prognostic factors will be used. The appropriateness of this decision will be checked by performing an alternative analysis with other potential baseline risks.

9.4 Data sources

The study will be divided into 2 phases: a baseline survey, which includes an initial consultation at baseline with a participating physician and study participant, and a direct to study participant follow-up phase, which includes three follow-up contacts within the first year (6 weeks, 6 and 12 months), and then annual follow-up contacts for up to 3 years post-baseline until study end or until the removal of the respecting IUD was reported during the follow-up phase. Visits and follow-up contacts are calculated in calendar months and years following the baseline visit. In order to evaluate if there is off-label use of LCS12 beyond 3 years, the first 1,000 enrolled LCS12 users with the initially inserted IUD still in place at 36-months' follow-up will be followed for a further 12 months (48 months instead of 36 months). For reported outcomes of interest, the treating physician will be contacted in addition.

9.4.1 Baseline survey

Each physician's office will be provided with simple questionnaires for both physicians and study participants collecting data at baseline. The baseline visit will take place at the participating HCP's office. Only after LCS12, Mirena or a copper IUD 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 have a new IUD placed are to be asked to participate. HCPs will be asked to maintain a log of the number of women asked to participate, recording participating status (yes, no) by IUD type. After discussing the study details (including follow-up procedures and intervals, 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 and take an appropriate period to decide whether to participate. She can complete the baseline questionnaire and informed consent at home, and return the documents to the physician's office. According to the experience in similar studies, about 0.1% of study participants will use this option.

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: Demographic and medical history, (including medication history, gynecologic history including if lactating, history and duration of use of contraceptives, previous IUD use, history of PID and ectopic pregnancies, sexual history, smoking), type of IUD, details of the insertion procedure as well as the addresses, e-mail addresses and phone numbers of the study participant, 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.

9.4.2 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 until the discontinuation of the treatment (i.e. the removal of the IUD) is indicated in any follow-up questionnaire or until the maximum three years' follow-up period is completed.. Subjects who withdraw their consent for follow-up will not be contacted. Subjects with failed insertion attempts will receive one follow-up questionnaire 6 weeks after the insertion attempt to collect AE/SAE information which could potentially be associated with the insertion attempt; after this, they will not be followed-up any further.

Follow-up questionnaires will be mailed to the study participants at 6 weeks, 6, 12, 24 and 36 months after study entry to collect information regarding the outcomes of interest and major safety outcomes.

The specific safety data to be collected during follow-up will focus on unintended pregnancy, ectopic pregnancy and PID, other information of interest and all other serious adverse events[2], as well as changes of risk for outcomes of interest. 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 attended physician is in many 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

[2] 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.

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 any reported pregnancies and the likelihood of a causal relationship to study treatment for each serious or unexpected adverse drug reaction in accordance with a predefined algorithm (cf. Annex 3.2).

9.4.3 Validation of self-reported events

A self-administered questionnaire used by study participants at intervals is a very sensitive tool which captures almost all serious clinical outcomes (2). From a methodological point of view, it captures a higher proportion of these outcomes than methods relying only on the prescribing gynecologist 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.

Self-reported events concerning the study objective will be validated immediately at the international coordinating center (ZEG) after receiving a special report form from the local field organizations.

If a pregnancy or adverse event is reported by a study participant, the subjectively perceived illness and, if possible, the diagnosis as understood by the study participant is 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 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 predefined algorithms.

In order to minimize classification bias - particularly if selectively affecting an individual exposure cohort - classification of ectopic pregnancy and PID into confirmed and not confirmed cases will be adjudicated by two adjudication boards for each outcome of interest (i.e. one adjudication board for ectopic pregnancy and one for PID). The board for ectopic pregnancy will consist of three independent medical experts specializing in gynecology or emergency medicine who are experienced in both, gynecological imaging and laparoscopy. The board for PID will consist of three independent medical experts specializing in gynecology.

The board members will review all available information on the reported outcomes. For this process, the adjudicator 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 Annex 3.3.

9.4.4 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 has demonstrated that the chosen study design is suitable to reach this goal.

9.5 Study size

Approximately 38,000 subjects will be recruited by participating physicians. Overall, 38,000 study participants are needed in order to provide approximately 100,000 women-years (WY) of observation (cf. Section 9.7.2), assuming a drop-out rate of approximately 0.7% per month.

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 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 ICD10 (International Classification of Diseases). ZEG also uses additional codes for the coding of events that are of specific interest (e.g. 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

9.7.1 Statistical Analysis Plan

Based on the similarities between LCS12 and Mirena, the a priori assumption is that use of LCS12 is not associated with an increased risk of unintended pregnancy compared to Mirena. Furthermore, it is expected that the risk is lower or equal to copper IUDs. The Principal Investigator has chosen a non-inferiority design to investigate contraceptive failure rate of LCS12. The primary analysis will be based on the comparison of the upper confidence limit for the point estimate of the contraceptive failure 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.

Crude as well as 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 potential confounding variables will be limited to well-established risk factors for these outcomes based on clinical judgement (e.g., age, parity, history of ectopic pregnancy/PID, duration of current use, sexual behaviors). All potential confounders will be included in the final statistical regression models.

In addition, an alternative analysis will be performed using a limited number of predefined potential prognostic factors. The decision on these selected variables will be made by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data.

The null hypotheses to be tested are: $\mathbf{HR}_{\text{contraceptive failure}} > 2$ (i.e., the contraceptive failure hazard ratio for LCS12 vs. Mirena and for LCS12 vs. copper IUD is higher than or equal to 2). The alternative hypothesis is: $\mathbf{HR}_{\text{contraceptive failure}} < 2$. Similar hypotheses will be tested for the secondary outcomes of interest.

A detailed statistical analysis plan will be developed by the Investigator during the first year after study start. This plan will include methodological details 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.

9.7.2 Power and sample size considerations

The sample size for this study was calculated on the basis of the findings from the EURAS IUD study. The overall contraceptive failure rate for Mirena found in the EURAS IUD study was 0.06 (95% CI: 0.04-0.09). However, for the sample size calculation, a higher pearl index was chosen in order to account for the age distribution to be expected in this study. The Mirena Pearl Index for women aged between 18 and <30 years in the EURAS IUD study was 0.11 (95% CI: 0.04-0.23), and for women between 30 and <40 it was 0.09 (95% CI: 0.05-0.15).

Sample size calculations for a non-inferiority test of two survival curves using Cox's proportional hazard model(4), showed that an exposure of 75,000 woman-years should be sufficient to show non-inferiority when comparing Jaydess and Mirena. The calculations for the primary outcome of interest (contraceptive failure) are based on the following assumptions: 1) one-sided α of 0.025; 2) power (1-β) of 0.80, 3) non-inferiority limit on hazard ratio of 2, 4) a contraceptive failure rate in Mirena users of 0.001, and 5) a proportion of approximately 33% and 67% of LCS12 and Mirena users in this subset of the study population, respectively (see Table 1).

The drop-out rate in similar studies has been approximately 0.7% per month. Assuming 1) a recruitment phase of 36 months, 2) a follow-up phase of 36 months, and 3) a 6 week, 6 , 12, 24 and 36 month follow-up schedule, follow-up of 28,500 women would result in approx. 75,000 WY.

It is expected that 25% of the total study population will be using copper IUD. Therefore, based on the required number of Jaydess and Mirena users, approximately 9,500 women using copper IUD will be included who will contribute approximately 25,000 WYs of exposure. Assuming a Pearl Index of 0.5 for copper IUD, non-inferiority of Jaydess can be assessed with a power of 99% (see Table 2).

Based on the sample size calculation provided, the total study population would include 38,000 IUD users contributing to approximately 100,000 WYs of exposure.

Table 1: Power calculation for the primary outcome of interest (i.e. contraceptive failure Jaydess vs. Mirena) based on the assumption that the true incidence in the LCS12 cohort is not different from the reference cohort.

Test significance level, α (one-sided)	0.025 (=0.05 two-sided)
Incidence of contraceptive failure for reference cohort	10 events/10,000 WY
Non-inferiority margin	10 /10,000 WY (equal to the incidence of contraceptive failure for the reference cohort)
Expected incidence of failure for LCS12 cohort	10 /10,000 WY
Power (%)	80
Proportion of LCS12 users (% of LCS12/Mirena IUD users)	33%
Required women years in LCS12 cohort	25,000
Required women years in reference cohort	50,000
Total women years	75,000

Table 2: Power calculation for the primary outcome of interest (i.e. contraceptive failure Jaydess vs. copper IUD) based on the assumption that the true incidence in the LCS12 cohort is not different from the reference cohort.

Test significance level, α (one-sided)	0.025 (=0.05 two-sided)
Incidence of contraceptive failure for reference cohort	50 events/10,000 WY
Non-inferiority margin	50 /10,000 WY (equal to the incidence of contraceptive failure for the

	reference cohort)
Power (%)	99
Proportion of LCS12 users (% of LCS12/copper IUD users)	50%
Required women years in LCS12 cohort	25,000
Required women years in reference cohort	25,000
Total women years	50,000

Based on these scenarios, the study is sufficiently powered to exclude a 2-fold risk for LCS12 users compared to Mirena users and compared to copper IUD users in the event that the true risk among LCS12 users is not higher than among users of these established products. However, precise power calculations based on actual incidences and drop-out rates will be done on the basis of follow-up data 1) before the end of the recruitment phase and 2) after availability of 20,000 WY of observation. If these calculations do not confirm the assumed incidences and drop-out rates, the patient numbers and/or follow-up times will be adjusted accordingly.

Table 3: Expected observation time
Assumptions: approx. 38,000 patients recruited over 36 months (~ 1,056 per month); individual follow-up for 36 to 60 months; drop-out rate of 0.7% per month

	Sub-cohorts recruited during month				
Time after study start [month]	**1**	**2**	**3**	**…**	**36**
	No. of women in follow-up				
1	1,056				
2	1,049	1,056			
3	1,041	1,049	1,056		
…	…	…	…	...	
24	892	898	905	…	
…	…	…	…	…	
35	826	832	838	…	
36	820	826	832	…	1,056
37		820	826	…	1,049

38			820	…	1,041
…				…	…
72					820
Months	*34,528*	*34,528*	*34,528*	…	*34,528*
WY	*2,877*	*2,877*	*2,877*	…	*2,877*
Total WY	***103,584***				

9.8 Quality control

ZEG 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).

9.9 Limitations of the research methods

The EURAS LCS12 study uses methodology that has been proven in previous investigations (2) and that has earned recognition and very positive international reception (e.g. ACOG-award).

Given the non-experimental, non-interventional, observational study type, the possibility of distorting factors, i.e. bias and residual confounding can never be completely eliminated, and the ability to infer causation is correspondingly limited (5). As in all observational studies, small risk estimates do not allow differentiation between causation on the one hand, and bias and confounding on the other hand. However, valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology help to reduce the impact of bias and residual confounding (6). The difficulty remains unresolved when all that exists is a weak association (7,8). Relative risk estimates that are close to unity may not allow differentiation between causation, bias and confounding (9, 10). In general, it is very difficult to interpret a relative risk of two or less in observational research (11, 12).

Special attention has been paid to typical biases:

- Enrollment bias – Sites will be expected to consecutively enrol eligible subjects and to maintain screening logs of all subjects meeting eligibility criteria, along with reasons for non-enrollment.
- Channeling bias – Factors associated with selection of LCS12 or other IUDs and also with any of the study outcomes of interest will be measured at baseline and accounted for in multivariate analyses, as described further in Section 9.7.
- Follow-up bias – A low loss to follow-up rate of approximately 5% is expected, in part due to the ability of the type of study to follow up directly with subjects even if they

do not return to the enrolling center. A very low rate of loss to follow-up of 2.4% was achieved in our EURAS-OC study of oral contraceptive safety using similar methods of subject contact. This is due to an elaborate stepwise procedure which has to be applied meticulously in order to achieve these results.

In theory, a disproportionately high percentage of SAEs could occur in those patients who are lost to follow-up, because significant events (pregnancy, PID and other SAEs) could be the reason for the break in contact with the investigators. An advantage of the EURAS LCS12 study design, however, is that the investigator team has direct contact with the participants. Contact will not be lost if the women change their gynecologists, for example (e.g., due to change of residence or dissatisfaction with treatment).

- Selection bias - With the approach used in the EURAS LCS12 study, selection bias will probably not be a major issue because gynecological practitioners, as well as clinics and family planning centers, etc., will be participating, leading to a representative mix of the typical institutions prescribing and inserting intrauterine contraceptive devices.
- Recruitment of subjects dependent on market factors – Market uptake of new products such as LCS12 is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets. However, continuous monitoring of subject recruitment at the site and country levels will allow strategies to be modified in response to any such challenges and to reduce or eliminate the potential impact of these factors.
- Misclassification bias – It will have no substantial impact on the results as precise information on the exposure and the outcomes of interest will be obtained. In addition, reliable information on duration of current use is recorded. Knowing that there is wide diagnostic variability with regard to PID, we have provided diagnostic criteria in order to try to minimise misclassification bias.

A major strength of the study is the availability of information on important prognostic factors for the outcomes of interest, e.g., preceding gynecological disease and number of sexual partners.

The EURAS LCS12 study will lead to results that are valid within the general limitations of observational research.

9.10 Other aspects

None.

10. Protection of human subjects

10.1 Ethical conduct of the study and protecting study participant privacy

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[3] and the relevant guidelines for "Good Practices" (cf. Section 10.4) 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.

10.2 Institutional review

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.

10.3 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 (36 months or 48 months for the first 1000 LCS12 users) to ask a predefined set of safety related questions or to update 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, general practitioner). 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.

10.4 Study management

This study will be conducted in accordance with

- 'Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the European Epidemiology Federation in 2007

[3] 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 2008.

- 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2007
- 'Guideline on Good Pharmacovigilance practices (GVP), Module VIII issued by the European Medicines Agency in 2012
- ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, 2010
- The ethical principles that have their origin in the Declaration of Helsinki.

11. Management and reporting of adverse events / adverse reactions

ZEG will capture and review all reported adverse events. Its medical event validation team will assess the seriousness and drug relationship of all adverse events. A physician on the ZEG study team will determine the likelihood of a causal relationship to LCS12, Mirena or copper IUD use for each adverse event in accordance with a predefined algorithm (cf. Annex 3.2) and the relevant summaries of product characteristics (SmPCs). Overall, the handling of adverse events will follow the Guideline on Good Pharmacovigilance Practices (GVP) Module VI and VIII.

Serious adverse drug reactions will be reported to the relevant marketing authorization holder within two working days.

Non-serious adverse drug reactions will be summarized in tabular listings. The listings will be included in the interim reports, and the final study report of EURAS-LCS12.

Expedited reporting of single non-serious adverse drug reactions is not foreseen. This is considered justified for the following reasons: 1. Common, non-serious side effects are well-known for all of the products used in this study and have been characterized in appropriate studies. Expedited reporting of these events will not provide new safety signals or new insights into the products' safety profile. 2. The objectives of this study focus on less common and serious events, which can only be detected in larger numbers of women. The majority of the women will be using products that have been on the market for many years.

ZEG will not monitor whether the marketing authorization holders meet their reporting obligations 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 (http://ClinicalTrials.gov), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) database (http://www.encepp.eu/encepp/studySearch.htm) and the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the European Medicines Agency (EMA).

13. References

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	LCS12B1	February 21th, 2014	Baseline Questionnaire
2	LCS12_FUPAT	February 21th, 2014	Follow-up Questionnaire
3	LCS12_Milestone Plan_1	February 10th, 2014	Milestone Plan
4	LCS12_SizeEstimat_1	February 21th, 2014	Sample Size Calculation

Annex 2. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Checklist of the ENCePP Code of Conduct for ENCePP Studies[1]

The purpose of this checklist is to emphasize the core elements of the ENCePP Code of Conduct that are relevant at the time of study start. The act of completing this checklist confirms that the study for which the status "ENCePP Study" is applied for complies – at the time of submission - with the key requirements of the Code. Of note, completion of the checklist does not release researchers of ENCePP studies from their obligation to adhere to the entirety of the provisions of the Code.

The checklist must be completed by the (primary) lead investigator of the study for which the status "ENCePP study" is applied for. The (primary) lead investigator must:

- Tick all boxes of each section thereby confirming compliance of the study with the core requirements of the Code. In case of sub-sections (e.g. 2.A. and 2.B.), tick all boxes of the sub-section that applies to your study.
- If applicable, provide additional information as requested.
- Sign the checklist.

The undersigned declares upon honour the following answers on behalf of the organisation that he/she represents. Signature should be by the (primary) lead investigator.

1. General	Check
The study has been designed	
➢ in line with the general principles outlined in the Code (see chapter 5 of the Code), and	☑
➢ providing for a maximum level of transparency (see chapter 4 of the Code).	☑
2. Research contract	**Check**
2.A. Studies financed purely from one's own general resources (100% self-funded)	
A declaration on the use of one's own general resources, making clear references to the study and the (primary) lead investigator and being signed by (an) authorised representative(s) of the participating study entity/ies is available.	☐

[1] Complete the Checklist on screen, then print, sign and stamp it (if applicable).

Annex 2
ENCePP Code of Conduct - Checklist

1

2.B. Studies receiving financing from external sources	
A research contract between the (primary) lead investigator and/or the coordinating study entity and the study funder has been concluded prior to study start.	☑
The contract includes the following information:	
➢ The main objectives and a brief description of the intended methods of the research as well as a clear assignment of tasks and responsibilities.	☐
➢ The procedure for achieving agreement on the study protocol as well as the involvement of the funder in the development of the protocol.	☐
➢ The amount of the financial support and the payment scheme.	☐
➢ Conditions for access to the study data.	☐
➢ Ownership of intellectual property rights arising from the study	☐
➢ A communication strategy for the scheduled interim (if applicable) and final results.	☐
2.B.1 Studies financed entirely from public funding schemes	
A reference to the Code is included in relevant parts of the project proposal or equivalent documents[2] in such a way that acceptance of the project proposal or equivalent document by the funding body constitutes agreement to adhere to the provisions of the Code including the requirement for unrestricted freedom of the investigator to publish.	☐
2.B.2 Studies not financed from public sources	
The statement "The parties to this agreement and individuals acting on their behalf hereby commit to adhere to the rules of the ENCePP Code of Conduct in their entirety" is included in the research contract and the latest version of the Code at the time of the signature of the contract is annexed; OR where this is not possible, a separate agreement with the funder has been concluded that clearly references the particular study, includes the above statement on adherence to the Code and states that this adherence with the relevant version of the Code is an additional requirement to those in the (clearly referenced) research contract.	☐
3. Registration of studies	**Check**
The study has been/will be registered[3] in the ENCePP Register of Studies before its start.	☑

[2] Any document that includes a description of the study to be funded and that has been endorsed or is otherwise recognised by the funding body

[3] A study is deemed registered in the ENCePP Register of Studies once the application has been approved by the ENCePP Secretariat.

4. Study protocol	Check
A full study protocol[4] has been developed before study start.	☑
The latest version of the full study protocol is uploaded to the ENCePP Register of Studies[5].	☑
A system is in place to allow for documentation of changes to the original version of the study protocol in a traceable and auditable way.	☑
Information on all parties involved in the writing and adoption of the protocol including a brief description of their contribution is being made publicly available.	☑
A detailed statistical analysis plan is described and included in or annexed to the study protocol.	☑

5. Intellectual property rights and sharing of data	Check
A system has been put in place in order to record the data collected and processed in the study in a way that allows corroboration of published results.	☑
A detailed description of how raw data were transformed into the data set for analysis will be available at the end of the study.	☑
All possible steps to provide for audits by competent authorities will be taken.	☑
Appropriate plans and agreements, if necessary, are being or have been made to respond to requests for data sharing in line with the *Implementation Guidance on Sharing of ENCePP Study Data* (Annex 4).	☑
A procedure for access to the analytical data is described in, or annexed to, the study protocol including the degree to which data can be shared and, if access is restricted, a justification why access is limited. Please indicate the page number in the study protocol:	☑

6. Declaration of interest	Check
Declarations of interests of all parties involved in the conduct of the study are documented and be made public (including members of the study steering group, if such group is being established).	☑
All persons with a financial interest in a particular outcome of the study are excluded from participation from any study activity which could influence the results or interpretation thereof in a particular direction.	☑

[4] For the purpose of the Code of Conduct, a *full* study protocol is a version of the protocol which includes enough detail in order to answer all questions in the *ENCePP checklist for Study Protocols*. The *Checklist* is available at http://www.encepp.eu/encepp_studies/documents/ENCePPChecklistforStudyProtocols.doc.

[5] When uploading the protocol in the Register, it may not be immediately accessible to the public unless the (primary) lead investigator so chooses.

7. Study Steering Group	Check
7.A. Absence of a Study Steering Group	
Please check here if no Steering Group is foreseen for the study.	☐
7.B. Establishment of Study Steering Group foreseen	
No expert with a direct conflict of interest is appointed as a member of the Steering Group	☑
The composition of the Steering Group is being/will be made publicly available.	☑

8. Publication/Reporting of studies	Check
Appropriate plans and agreements, if necessary, have been made (e.g. as part of the dissemination and communication policy) ensuring publication of results	
➢ including results from prematurely terminated studies.	☑
➢ independent of statistical significance and whether the results are positive or negative.	☑
➢ in form of a clear summary of the main results.	☑
➢ in form of an abstract to be provided to the ENCePP Secretariat within 3 months after the final study report. (Note that requests for delays are possible pending response to peer-review comments).	☑
➢ in form of a full report of all results with a scientific or public health impact without delay (taking into account relevant legal provisions in case of a suspected public health impact).	☑
➢ independently by the (principal) lead investigator irrespective of data ownership.	☑
➢ providing for the possibility of review by the study funder prior to submission – but without unjustified delay.	☑
➢ considering comments from the study funder and enabling the study funder to request changes to the presentation of the results to delete confidential information.	☑
➢ making publicly available comments of the funder.	☑
➢ taking into account the provisions for authorship of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (2009).	☑

9. Confidential information	Check
A definition of what constitutes confidential information has been agreed between the parties of the research contract.	☑

The definition of confidential information does not consider data and results as being confidential except in relation to relevant data privacy laws.	☑

Name of the coordinating study entity: ZEG - Berlin Center for Epidemiology and Health Research

Name of (primary) lead investigator: Dr. Klaas Heinemann

Date: 21.2.2014 (dd/mm/yyyy)

Signature: _____

Stamp (if applicable):

Reset Form

ZEG Zentrum für Epidemiologie und Gesundheitsforschung Berlin GmbH
Invalidenstraße 115
10115 Berlin

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 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, 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.

Members of the Safety Monitoring and Advisory Council:

Tbd

Annex 3.2 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.

Annex 3.3 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.

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.

Klaas Heinemann, MD, PhD, MSc, MBA	Date