STUDY PROTOCOL

PASS Information

Title	Drug Utilization Study on the Prescribing Indications for CPA/EE[1] in 5 European Countries
Protocol version identifier	ZEG2014_04
Date of last version of protocol	30 October 2014
EU PAS register number	Study has not yet been registered
Active substance	Pharmacotherapeutic group: antiandrogens and estrogens ATC code: G03HB01 Active substances: cyproterone acetate and ethinyl estradiol
Medicinal product	Diane-35: coated tablets 0.035 mg ethinyl estradiol, 2.0 mg cyproterone acetate and its generics
Product reference	EMEA/H/A-107i/1357
Procedure number	NL/H/xxxx/WS/073
Marketing authorisation holder(s)	Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany On behalf of a group of MAHs
Joint PASS	Yes
Research question and objectives	This drug utilization study is designed to compile the reasons and specific indications for the prescription of CPA/EE. The primary objective of the study is to characterize the prescribing behaviors for CPA/EE in 5 European countries (Austria, Czech Republic, France, the Netherlands, and Spain), including: • prescription indications for CPA/EE • use of CPA/EE in accordance with the updated label • concomitant use of CPA/EE and CHCs • second line treatment with CPA/EE for the indication acne
Country(-ies) of study	Austria, Czech Republic, France, the Netherlands, and Spain

[1] Cyproterone Acetate and Ethinyl Estradiol

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Marketing authorization holder(s)

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2 List of abbreviations

Abbreviation	Definition
ADB	Administrative Database
ADR	Adverse Drug Reaction
ANSM	National Agency for the Safety of Medicine and Health Products
ATC	Anatomical Therapeutic Chemical Classification System
CHC	Combined Hormonal Contraceptive
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CPA	Cyproterone Acetate
DUS	Drug Utilization Survey
EE	Ethinyl Estradiol
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FIGO	International Federation of Gynecology and Obstetrics
GEP	Good Epidemiological Practices
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
GXP	Good Practice Guidelines
ICMJE	International Committee on Medical Journal Editors
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
OTC	Over-the-counter
PCOS	Polycystic Ovary Syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
SAE	Serious Adverse Event
SDB	Study Database
SOP	Standard Operating Procedure
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

Drug Utilization Study on the Prescribing Indications for CPA/EE[1] in 5 European Countries

Study protocol version of 30 October 2014

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Rationale and background

Cyproterone acetate (CPA) 2mg, in combination with ethinyl estradiol (EE) 35mcg, is a medicinal product currently indicated for the treatment of moderate to severe acne in women of reproductive age. Due to the combination with EE and the dosing, the preparations also act as effective contraceptives (4).

In 2012 the French health authority conducted a national review of CPA/EE and highlighted serious thromboembolic events and extensive off-label use of these medicines as a contraceptive only (5). This triggered an Urgent Union Procedure at the beginning of 2013. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the benefits of CPA/EE (cyproterone acetate 2mg / ethinyl estradiol 35mcg) outweigh the risks, providing that several measures are taken to minimize the risk of thromboembolism (6). These medicines should be used solely for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age. Since CPA/EE acts as a hormonal contraceptive, women should not take these medicines in combination with hormonal contraceptives. As one of the risk minimization measures, the MAHs were required to conduct a number of studies including the drug utilization survey described in this protocol.

Research question and objectives

This drug utilization study is designed to compile the reasons and specific indications for the prescription of CPA/EE. The study uses a cross-sectional design with a special focus on the clinical decision-making process. The primary objective of the study is to characterize the prescribing behaviors for CPA/EE in 5 European countries (Austria, Czech Republic, France, the Netherlands, and Spain), including:

- prescription indications for CPA/EE
- use of CPA/EE in accordance with the updated label
- concomitant use of CPA/EE and combined hormonal contraceptives (CHCs)
- second line treatment of CPA/EE for the indication acne

Study design

This is a multi-national, cross-sectional study.

The physicians will ask each woman who receives a CPA/EE prescription during the study period if she is willing to participate. The physicians will be requested to provide information

on the prescribed CPA/EE drug, the history of CPA/EE prescription for the individual study participant, use of concomitant hormonal contraceptives, the participant's androgen-sensitive disease characteristics and treatments (including over-the-counter [OTC] medicines), and the reasons for prescribing CPA/EE. This data will be collected in paper form and entered into a database at local field institutes.

Population

A sample of 50 physicians (gynecologists, dermatologists, general practitioners [GPs]) per country in Austria, Czech Republic, France, the Netherlands and Spain will be asked to enroll a total of 5,000 study participants (approximately 1,000 in each country). The selection of physicians aims to obtain a sample that is generally representative of the physician groups that potentially prescribe CPA/EE in the selected countries. Information of non-participating physicians that have been approached for study participation will be compiled and compared to characteristics of participating physicians in order to determine whether there are any differences between the two groups. Physician specialties will be considered when selecting the sample in each country.

Variables

Information about each study participant and prescription will be gathered on a questionnaire filled out by the physician (and from the participant's informed consent form for the date of birth).

The questionnaires include the following:

- name and date of the prescribed CPA/EE-containing drug
- first use, re-use after a break, or continuous use of CPA/EE
- information about androgen-sensitive diseases (duration, previous and concomitant treatment including OTC medicines and information on treatment failure)
- reasons for prescribing CPA/EE
- concomitant hormonal contraceptive use

Data sources

Questionnaires are an established tool for collecting data on drug utilization and are widely used for this purpose. They are able to capture information on OTC medicines as well as prescription medicines, which is of importance to this study. The questionnaires will be filled out by the participating physicians, based on patients' statements and medical records.

***S*tudy size**

It is estimated that each of the at least 50 participating physicians in Austria, Czech Republic, France, the Netherlands and Spain will make at least four CPA/EE prescriptions per month. This will result in a total of 1,000 prescriptions during the estimated 5 months of data collection per country. The following table shows the 95% confidence intervals for four different scenarios of contraceptive off-label use based on 1,000 CPA/EE users on the country level and an intra-class coefficient of 0.02 to adjust for potential cluster effects on the physician level (7,8).

Table 1: Expected precision of the point estimates for off-label use per country

	1%	5%	10%	20%
CPA/EE	0.4 – 2.0	3.5 – 6.8	8.0 – 12.5	17.2 – 23.1

The confidence limits were estimated using a conservative exact method proposed by Clopper and Pearson (9,10). Calculations based on the effective sample size are corrected for variance inflation due to clustering. These results show that information from 1,000 representative prescriptions would be sufficient to estimate the extent of off-label use in each participating country with high precision.

Data analysis

The final report will present point estimates and 95% confidence intervals for the different reasons for prescribing CPA/EE, both in total and stratified by the specialization of the prescribing physicians. The precision of the point estimates will be sufficiently high (see above) to assess the extent of off-label use of CPA/EE in the respective countries. Analyses of this cross-sectional study will be limited to descriptive data and will be performed with the statistical package SAS 9.1.

Milestones

Task	**Planned date**
Study protocol submission	June 2014
Start of data collection (first country)	February 2015
End of data collection (last country)	October 2015
Final report of study results	May 2016

5 Amendments and updates

None

6 Milestones

Milestone	Planned date
Study protocol submission	June 2014
End of variation procedure	December 2014
Registration in the EU PAS register	January 2015
Submission to ethics committees	January 2015
Start of data collection (first country)	February 2015
End of data collection (last country)	October 2015
Final report of study results	May 2016

7 Rationale and background

Cyproterone acetate (CPA) 2mg, in combination with ethinyl estradiol (EE) 35mcg, is a medicinal product currently indicated for the treatment of moderate to severe acne and/or hirsutism in women of reproductive age. Androgen-dependent symptoms such as acne (1), hirsutism (2), seborrhea (3), and alopecia, as well as androgen sensitivity-related symptoms of Polycystic Ovary Syndrome (PCOS), have been considered potential therapeutic targets for CPA. Due to the mode of action and the dose and regimen, these preparations also act as effective contraceptives (4). Market authorization was first granted in 1985.

A review of CPA/EE was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), which on the basis of a national review in France had decided in January 2013 to suspend use of CPA/EE within three months. The review highlighted serious thromboembolic events and extensive off-label use of these medicines as a contraceptive only (5). The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the recommendation by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), which concluded that the benefits of CPA/EE (cyproterone acetate 2mg / ethinyl estradiol 35mcg) outweigh the risks, provided that several measures are taken to minimize the risk of thromboembolism (6). These medicines should be used solely for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age. Furthermore, CPA/EE should only be used for the treatment of acne when alternative treatments, such as topical therapy and antibiotics, have failed.

Since CPA/EE also acts as a hormonal contraceptive, women should not take this medicine in combination with a hormonal contraceptive. Concomitant use of CPA/EE with a hormonal contraceptive would expose women to a higher hormonal dose and therefore potentially increase the risk of thromboembolism.

During the referral procedure, the risk of thromboembolism occurring with CPA/EE was assessed as low and well known. However, to minimize this risk, the respective MAHs were required to take further measures in addition to updating the product information (e.g. educational materials for prescribers and patients). The MAHs were also required to conduct a number of studies including the drug utilization study (DUS) that is described in this protocol. Following discussions with the authorities, Bayer agreed to take the lead in a joint approach to conducting the required studies.

8 Research question and objectives

This drug utilization study is designed to compile the reasons and specific indications for the prescription of CPA/EE. The study uses a cross-sectional design with a special focus on the clinical decision-making process in order to assess prescribing practices for CPA/EE during typical clinical conditions for representative groups of prescribers. Questionnaires are an established tool for data collection on drug utilization and are widely used for this purpose. They are able to capture information on over-the-counter (OTC) medicines as well as on prescription medicines, which is of importance to this study.

The primary objective of the study is to characterize the prescribing behaviors for CPA/EE in 5 European countries, including:

- prescription indications for CPA/EE
- use of CPA/EE in accordance with the updated label
- concomitant use of CPA/EE and combined hormonal contraceptives (CHCs)
- second-line treatment of CPA/EE for the indication acne

9 Research methods

9.1 Study design

This is a multi-national, cross-sectional study that characterizes the reasons for prescribing CPA/EE in 5 European countries: Austria, Czech Republic, France, the Netherlands, and Spain. Information will be collected via paper questionnaires that the physicians fill out.

For this purpose, the physicians will ask each woman who receives a CPA/EE prescription during the study period if she is willing to participate in the study. The physicians will explain the nature of the study, its purpose, and the extent of data collection prior to her study entry. Each potential participant should 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 the study participant. These documents are to be approved by the relevant local ethics committees and data privacy office, if applicable.

The physicians will be asked to provide information on the prescribed CPA/EE drug, use of concomitant hormonal contraceptives, the participant's androgen-sensitive disease characteristics and treatments (including OTC medicines), and the reasons for prescribing CPA/EE. Data will be collected in paper form and forwarded to local field institutes, where it will be entered into a database. From the perspective of the individual study participants, this is a one-time survey with no follow-up.

9.2 Setting

The study will be performed by the Berlin Center for Epidemiology and Health Research (ZEG) in 5 European countries. The countries selected show a high level of diversity with regard to their size (both small and large) and their geographical distribution within Europe. Selection also took into account the fact that an accompanying database study will be performed on CPA/EE prescription data, and therefore this study's countries targeted those, from which no valid information from such databases is available.

The study participants themselves will be recruited via existing networks of contraceptive-prescribing health care professionals (e.g. gynecologists and general practitioners [GPs]) who have participated in similar cohort studies in the past. Additionally, dermatologists will be asked to contribute their prescribing information. The distribution of contacted physicians by specialty will be based on the estimated CPA/EE prescribing patterns in each country:

- Austria: 75% gynecologists, 25% dermatologists
- Czech Republic: 75% gynecologists, 25% dermatologists
- France: 40% gynecologists, 40% GPs, 20% dermatologists
- The Netherlands: 75% GPs, 25% dermatologists
- Spain: 50% GPs, 25% gynecologists, 25% dermatologists

The above-mentioned physicians will be contacted by local field organizations in the respective countries. The primary contact will be via telephone. During the first call, the study background will be explained, verified that the physician prescribes CPA/EE and a short physician initial interview questionnaire will be administered. This questionnaire includes (but is not limited to) information about age, gender, specialty of the physician and the level of experience (defined as number of years work experience). The information on the participating and non-participating physicians will be compared to determine whether the two groups differ in any way as this information will be collected from all physicians that have been approached for study participation.

In case the physician is interested to participate further in the study, the drug utilization questionnaire will be sent to the physician. All women who receive a CPA/EE prescription from participating physicians during the enrollment period should be asked about taking part in the study. There are no specific inclusion or exclusion criteria besides the CPA/EE prescription, and no age restrictions (also not in the label). However, CPA/EE is only indicated for women in childbearing years (i.e. between menarche and menopause). Only after the decision to prescribe CPA/EE is made may the physicians ask the women about study participation. This sequence is important to ensure the non-interventional character of this study.

The physicians are to explain the nature of the study, its purpose and associated procedures before study entry. Each woman is to have ample opportunity to ask questions about the study and the associated use of her medical and personal data. She 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. Personal information about the study participant is needed to perform source data verification audits at the physician's office to compare documented study data with medical record data (see section 9.8). This information will be provided on a data privacy and informed consent form, which must be signed by all study participants. This study has no age restrictions and adolescents can be asked to participate in countries that do not have ethical or regulatory restrictions for that age group. As adolescents are a specifically protected group, local law might require a parent's or guardian's signature, which will then also be provided on the informed consent form. If requested by local law or ethical committees, a patient information and informed consent form that is easy to understand and adapted for adolescents will be provided. All documents are to be approved by the relevant local ethics committees and data privacy office, if applicable.

Each physician will be provided with simple questionnaires for collecting drug utilization data on CPA/EE. Only after CPA/EE has been prescribed will the physicians discuss the documentation of data from this one-time survey with the women. This ensures that study participation will not be considered a requirement for treatment. All women who receive a CPA/EE prescription should be asked for their permission to document the prescription details and for their written informed consent to share medical and personal data.

If potential participants need time to consider whether to participate, they may leave the physician's office with their prescriptions and take an appropriate period to make their decision.

The informed consent will include permission for study data to be collected and analyzed and for source data to be verified at the physician's office. Confidentiality will be maintained throughout the study and no personal information will be shared with any party outside the study team. The funder will not have access to names or addresses of the study participants 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.

9.3 Variables

Information about the study participant and the prescription will be taken from the questionnaire (and from the informed consent form for the date of birth).

The questionnaires include the following:

- name and date of the prescribed CPA/EE-containing drug
- first use, re-use after a break, or continuous use of CPA/EE
- information about androgen-sensitive diseases (duration, previous and concomitant treatment including OTC medicines and information on treatment failure)

- reasons for prescribing CPA/EE
- concomitant hormonal contraceptive use

9.4 Data sources

The questionnaire will be filled out by the participating physician based on the woman's statements and medical records. It documents the use of hormonal contraceptives, the reason for the prescription, the concomitant use of hormonal contraceptives, and status of androgen-sensitive diseases. The 'date of birth' information will be taken from the informed consent form.

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

The questionnaires will be collected in the respective countries by the local field organization of ZEG, and will be reviewed for completeness and plausibility/consistency of the responses. Missing and inconsistent information will be clarified directly with the physicians. 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 field organizations, who will clarify it with the physicians. ZEG will monitor and endorse the timely processing of these queries.

9.5 Study size

It is estimated that each of the at least 50 participating physicians in Austria, Czech Republic, France, the Netherlands and Spain will make at least four CPA/EE prescriptions per month. This will result in a total of 1,000 prescriptions during the estimated 5 months of data collection per country. The following table shows the 95% confidence intervals for four different scenarios of contraceptive off-label use based on 1,000 CPA/EE users on the country level and an intra-class coefficient of 0.02 to adjust for potential cluster effects on the physician level (7,8).

Table 1: Expected precision of the point estimates for off-label use per country

	1%	5%	10%	20%
CPA/EE	0.4 – 2.0	3.5 – 6.8	8.0 – 12.5	17.2 – 23.1

The confidence limits were estimated using a conservative exact method proposed by Clopper and Pearson (9,10). Calculations based on the effective sample size are corrected for variance inflation due to clustering. These results show that the information from 1,000 representative prescriptions would be sufficient to estimate the extent of off-label use in each participating country with high precision.

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 participants, can be entered and maintained in this database.

The SDB is validated according to GXP rules and contains the questionnaire data. ZEG performs cross-checks and verification checks on the data and any inconsistencies or unanticipated answers are sent to the field organizations for further clarification.

9.6.2 Dataflow

When the prescribing physicians send in an informed consent form (signed by the study participant) and the corresponding questionnaire, these documents are checked to make sure they match and are date-stamped. The questionnaires are checked for the correct subject identification number, legibility, completeness and plausibility. Any relevant missing and/or inconsistent data will lead to either logical corrections (where applicable and possible) or to contact with the physician for clarification before data is entered into the database. Any corrections on the questionnaires must be made with indelible pens, and all original entries must remain legible. The initials of the person correcting the data and the date must be added to each change of the data.

Data is entered via formatted entry screens designed to reflect the appearance of the questionnaire. All corrections are dated and initialed by the data manager who received the relevant new information (e.g., via direct contact or a copy of medical reports/documents). Incorrect entries are crossed out but must remain legible, with the correct entries placed beside them. The reasons for any correction of medical data on the questionnaires 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 the (final) analysis the database will be frozen at a predefined point in time. The database will be 'cleaned' within 4 weeks of the database freeze. After freezing, no additional incoming data will be entered in the database – this database will represent the final data source for the analyses. Safety copies will be made of the database, so that all calculations can be repeated if necessary.

9.7 Data analysis

The study focuses on point estimates and 95% confidence intervals for the percentage of off-label use of CPA/EE. The reasons for prescribing CPA/EE will be investigated with respect to concomitant hormonal contraceptive use and androgen-sensitive diseases. Data analysis will be stratified by country and by specialization of the prescribing physicians. Intra-cluster (physician level) correlation of subjects will be considered by adjusting the confidence limits. The precision of the point estimates will be high enough (see above) to assess the extent of off-label use of CPA/EE in the respective countries. The final report will present the patterns of prescription behavior and disease characteristics. Analyses of this cross-sectional study will be limited to descriptive data. No formal hypothesis testing will be performed as part of this study. Descriptive statistical analysis of study data will be performed with the software package SAS 9.1 or higher. A detailed statistical analysis plan will be developed by ZEG before the start of the study. This plan will include methodological details and a set of mock tables for the presentation of results.

Missing data are a common occurrence and can have a significant effect, e.g. in studies where exposure-outcome relations are measured. In this study, missing data for relevant questions will trigger contact with the physician to collect the information. If the data remain missing at the time of analysis, they will be excluded from the analysis of those specific variables and listed in the tables under the category "missing".

All text data on the questionnaires will be coded according to the following dictionaries: the "International Statistical Classifications of Diseases and Related Health Problems" (ICD) will be used for diseases and health problems; a modified version of the "Operationen- und Prozedurenschlüssel" (OPS) for surgery and other medical procedures; and the "Anatomical Therapeutic Chemical Classification System" (ATC) for medications/pharmaceutical products. For questionnaire data for which no (inter)national dictionaries are available, a ZEG-specific coding dictionary will be applied.

9.8 Quality control

The organization that is responsible for conducting the study (ZEG) has established 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 European Medicines Agency (EMA) in 2012/2013), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance's (ENCePP) Code of Conduct, the Nuremberg Code and the Declaration of Helsinki. Additionally, ZEG has been audited three times by large pharmaceutical companies, with no major issues identified. For this study, as for all other studies conducted by ZEG, site audits at the local field organizations will be conducted by ZEG. This includes organizational aspects as well as source data verification.

ZEG's internal manual of standard operating procedures (SOPs) specifies standardized 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 data integrity.

ZEG ensures that the study will be conducted in compliance with the protocol and any applicable regulatory requirements. All processes that are relevant to legal compliance or data integrity are subject to quality control measures. This includes: 1) development of the study protocol, questionnaire, databases and data entry screens; 2) data entry; 3) plausibility checks; 4) data analysis; 5) report writing; 6) publication of results; and 7) archiving of study materials (i.e. questionnaires, other study documents and electronic files). All quality control measures are based on the four-eye principle (i.e., the same person may not do quality control on his/her own work).

Source data verification will be conducted for a subset of the study participants (10% of participating physicians per country with 100% of their recruited participants). The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol, and verification with source documents. This will be performed by monitors who will access medical records on site to verify the data.

9.9 Limitations to the research methods

Because this study is directly prescriber-based, it will provide a realistic view of the reasons underlying the prescription of CPA/EE. However, if the recruitment guidelines are not strictly observed, there is a risk that the selection of cases could lead to a skewed sample and thereby undermine representativeness. Therefore, in order to avoid any pre-selection of participants, *all* those eligible (i.e., all those receiving a prescription for CPA/EE) need to be asked whether they are willing to take part in the study.

The generalizability of such patient data has been questioned in the past, but the comparison of a large women's health study conducted by ZEG and pooled information from National Health Surveys (which were found to be representative for the general population) showed good agreement, indicating an acceptable level of generalizability of cross-sectional results for the general population (11).

Selection bias with regard to the physicians might potentially affect the study results. The network of physicians (including gynecologists and general practitioners) was established earlier in the context of similar studies. Because participation by dermatologists has also been requested for this study, a randomly drawn selection of those specialists will be asked to contribute information as well.

There is no reason to expect deliberate misinformation to be presented by the prescribers. In order to minimize any form of error or misinformation, a dual source method (information recorded by individual physicians *and* information collected from the study participants themselves) might be used in order to increase confidence in the data. However, the resulting confirmatory information would require a very high level of effort without contributing significantly to the results, and will therefore not be collected.

9.10 Other aspects

There are no further aspects that have not already been addressed in other sections of this protocol.

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[2] and the guidelines for Good Epidemiological Practice (GEP)[3], Good Pharmacoepidemiology Practices,[4] and Good Pharmacovigilance Practices (GVP)[5] as well as the ENCePP code of conduct[6] will be observed.

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[2] 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.

[3] '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

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

[5] issued by the EMA in 2012/2013

All steps will be taken to protect the subjects' 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

The study protocol will be reviewed by ethics committees in the appropriate geographical areas as required by local law. Non-interventional studies do not fall 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 countries will be followed.

10.2 Informed consent

The physicians will describe the purpose and the non-interventional character of the study and how the personal and medical source data will be verified. This information is also repeated on the study information sheet and informed consent form. The latter form must be signed by study participants prior to enrollment.

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

11 Management and reporting of adverse events/adverse reactions

This study is not directed at collecting adverse event information. If, however, adverse events or adverse reactions are spontaneously reported during the period of data collection, serious adverse events (SAEs) will be forwarded to the respective MAH within 24 hours, and non-serious ADRs within 10 calendar days.

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.

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

12 Plans for disseminating and communicating study results

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) or the EU-PAS register, if available at study start. With regard to the study results, MAHs and ZEG intend to collaborate on publications. The study results should be published within 12 months after completion of this project. The results might also be communicated to scientific audiences, e.g. at conferences such as the Annual Meeting of the International Society for Pharmacoepidemiology (ISPE) or the upcoming meeting of the International Federation of Gynecology and Obstetrics (FIGO).

13 References

1 Tan J. Hormonal treatment of acne: review of current best evidence. J Cutan Med Surg. 2004;8 Suppl 4:11-5.

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Appendix 1: List of stand-alone documents

None

Appendix 2. ENCePP checklist for study protocols

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

Study title:
Drug Utilization Study on the Prescribing Indications for CPA/EE in 5 European Countries

Study reference number:
ZEG2014_04

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[7]	☒	☐	☐	10
1.1.2 End of data collection[8]	☒	☐	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	- - -
1.1.4 Interim progress report(s)	☐	☐	☒	- - -
1.1.5 Registration in the EU PAS register	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

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)	☒	☐	☐	12
2.1.2 The objective(s) of the study?	☒	☐	☐	12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	15
	☐	☐	☒	- - -

Comments:

None

[7] 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.

[8] 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)	☒	☐	☐	12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12
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)	☐	☐	☒	- - -

Comments:

None

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	13
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	10
4.2.2 Age and sex?	☒	☐	☐	13
4.2.3 Country of origin?	☒	☐	☐	13
4.2.4 Disease/indication?	☒	☐	☐	13
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)	☒	☐	☐	13

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)	☐	☐	☒	- - -
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)	☐	☐	☒	- - -
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	- - -
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?	☐	☐	☒	- - -
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)	☐	☐	☒	- - -

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)	☐	☐	☒	- - -
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	- - -

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.)	☐	☐	☒	- - -
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.)	☐	☐	☒	- - -
8.1.3 Covariates?	☐	☐	☒	- - -
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)	☐	☐	☒	- - -
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	- - -
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	- - -
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	- - -
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	- - -
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Chemical (ATC)Classification System)	☒	☐	☐	- - -
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?	☒	☐	☐	15

Comments:

None

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☐	- - -
10.2 Is the choice of statistical techniques described?	☒	☐	☐	16
10.3 Are descriptive analyses included?	☒	☐	☐	16
10.4 Are stratified analyses included?	☒	☐	☐	16
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	- - -
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	- - -

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?	☒	☐	☐	14; 16
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	14
11.3 Are methods of quality assurance described?	☒	☐	☐	17
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	17
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	- - -

Comments:

None

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	17-18
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)	☒	☐	☐	17-18
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13
12.3 Does the protocol address other limitations?	☒	☐	☐	17-18

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?	☒	☐	☐	18
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	- - -
13.3 Have data protection requirements been described?	☒	☐	☐	18

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?	☒	☐	☐	9

Comments:

None

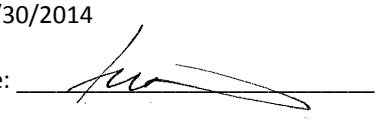
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	19-20

Comments:

None

Name of the main author of the protocol: Klaas Heinemann

Date: 10/30/2014

Signature: 

Appendix 3. Additional information

None