Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study

Protocol Version 2.0

20 April 2015

Prepared for
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RTI-HS Project No. 0303864

PASS Information

Title	Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study
Protocol version identifier	Version 2.0
Date of last version of protocol	3 June, 2014
EU PAS register number	ENCEPP/SDPP/9312
Active substance	INN: cyproterone acetate 2 mg/ethinylestradiol 35 µg; ATC code: G03HB
Medicinal product	Diane-35 and its generics
Product reference	Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study
Procedure number	Referral: EMEA/H/A-107i/1357
Marketing authorisation holder(s)	Bayer Pharma AG on behalf of a group of MAHs
Joint PASS	Yes
Research question and objectives	The primary objective of this study is to measure physician knowledge and understanding of the key information included in the educational material for Diane-35 developed by Bayer. Specifically, the following objectives will be addressed: ▪ Investigate whether physicians have received any educational material related to Diane-35 or its generics ▪ Assess physicians' knowledge and understanding of key safety information pertaining to the following areas: – Contraindications relevant to thromboembolism – Risk factors for thromboembolism – Signs and symptoms of thromboembolism
Country(-ies) of study	Austria, the Czech Republic, the Netherlands, Spain, and France

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Project Title: Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study

Protocol ID Number:17195

Effective Date: 20 April 2015

Authors: Elizabeth Andrews, PhD, MPH; Susana Perez-Gutthann, MD, PhD; Kimberly Davis, MS, BS in Pharmacy; Laurie Zografos BS (RTI Health Solutions)

Version Date: 20 April 2015

The following people have reviewed the protocol and give their approval:

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2 List of Abbreviations

AE	adverse event
ATE	arterial thromboembolism
CPA/EE	cyproterone acetate 2 mg/ethinylestradiol 35 µg
EC	ethics committee
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
IRB	institutional review board
MAH	marketing authorisation holder
MEB	Medicines Evaluation Board
OQA	RTI-HS Office of Quality Assurance
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
RTI-HS	RTI Health Solutions
US	United States
VTE	venous thromboembolism

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4 Abstract

Title

Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and its Generics in Europe: An Observational Post-Authorisation Safety Study

Rationale and Background

Diane-35 (cyproterone acetate 2 mg/ethinylestradiol 35 µg) (CPA/EE) was first authorised in a European Union (EU) country in 1985, and generic versions are available. The new indication for these medicines is for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age. For the treatment of acne, Diane-35 and its generics should only be used after topical therapy or systemic antibiotic treatments have failed. Diane-35 and its generics should not be used in combination with other hormonal contraceptives.

A review of Diane-35 and its generics was initiated in February 2013 at the request of France. The review was conducted by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC reviewed data related to the risks of thromboembolic events and concluded that the risk of venous thromboembolism (VTE) with Diane-35 and its generics is 1.5 to 2 times higher than for combined oral contraceptives containing levonorgestrel and may be similar to the risk associated with contraceptives containing gestodene, desogestrel, or drospirenone. Based on the review, the Coordination Group for Mutual Recognition and Decentralised Procedures—Human endorsed the recommendation of the PRAC, which concluded that the benefits of Diane-35 and its generics outweigh the risks, provided that several measures are taken to minimise the risk of VTE and arterial thromboembolism (ATE).

The PRAC recommended that educational material for health care professionals should focus on thromboembolism and its risks factors, signs, and symptoms and contraindications relevant to thromboembolism. In addition, sponsors were asked to evaluate the effectiveness of this risk-minimisation communication. As part of the risk management plan, Bayer has developed educational material for prescribers.

This protocol is for a joint, observational post-authorisation safety study (PASS). The objective is to assess physician knowledge and understanding of the key safety information outlined by the PRAC and included in the Diane-35 educational material. The Dutch Medicines Evaluation Board (MEB) will be the regulatory lead and will communicate with the PRAC as needed. Bayer will be responsible for liaising with the generic companies on all tasks except for the reporting of adverse events (AEs) to marketing authorisation holders (MAHs) for non-Bayer drugs. If any AEs are reported for non-Bayer drugs, RTI-HS will send the AE report form to the respective MAH. The study will share this common core protocol.

Research Question and Objectives

The primary objective of this study is to measure physician knowledge and understanding of the key information included in the educational material. Specifically, the following objectives will be addressed:

- Investigate whether physicians have received any educational material related to Diane-35 or its generics
- Assess physicians' knowledge and understanding of key safety information pertaining to the patient information card
- Assess physicians' knowledge and understanding of key safety information pertaining to the following areas:
  - Contraindications relevant to thromboembolism
  - Risk factors for thromboembolism
  - Signs and symptoms of thromboembolism

Study Design

- The study will be an observational (non-interventional), cross-sectional study of knowledge and understanding among a representative sample of physicians who have recently prescribed (e.g., within previous 6 months) Diane-35 or its generics in Austria, the Czech Republic, the Netherlands, Spain, and France.
- Physicians will be selected and recruited from a physician panel, with the aim of obtaining a sample generally representative of the physicians in the selected countries. Physician specialty will be considered when selecting the sample in each country based on the Diane-35 prescribing patterns in each country. As a consequence of the revised Diane-35 indication, the study will target recruitment of up to 25% dermatologists in each country. The following physician specialties will be recruited in each country:
  - Austria and the Czech Republic: gynaecologists and dermatologists
  - The Netherlands: general practitioners and dermatologists
  - France: general practitioners, gynaecologists and dermatologists
  - Spain: general practitioners, gynaecologists, and dermatologists
- An invitation will be sent via e-mail or made by phone to the selected sample of physicians. Physicians will be given the option to complete the survey via the Internet or a telephone interview.
- Data from the questionnaire responses will be analysed to ascertain the level of physician knowledge and understanding stratified by country and other relevant characteristics (e.g., physician specialty).

Population

Physicians eligible to participate will have recently prescribed (e.g., within previous 6 months) Diane-35 or its generics. The sampling frame will be constructed from a physician panel. The final list will be determined with the objective of achieving a generally representative sample of physicians prescribing Diane-35 or its generics. Geographic location, specialty, and potentially other factors will be considered when selecting the sample in each country.

Variables

A questionnaire will be developed to elicit responses measuring physician knowledge and understanding of the key information included in the Diane-35 educational material. The physician questionnaire will include items in the following content areas:

- The approved indication of Diane-35 and its generics
- Contraindications relevant to thromboembolism
- Risk factors associated with thromboembolism
- Signs and symptoms of a thrombus

The questionnaire will include additional items to characterise the physicians and their practices and investigate physician receipt and use of any educational materials related to Diane-35 or its generics, including the patient information card.

Data Sources

The source of information for the study will be self-reported data collected from physicians using a standard questionnaire with closed-ended response choices.

Study Size

The study will target recruitment of 60 to 120 physicians each in Austria, Czech Republic, and the Netherlands and 100 to 200 physicians each in France and Spain, for a total of at least 500 participating physicians to allow reasonable precision around estimates of knowledge and understanding of the key safety information.

Data Analysis

Data analyses will be descriptive and will focus on summarising the questionnaire responses in participants who provided informed consent. Results across all countries will be presented as well as stratified by country and possibly other variables, such as physician specialty and experience with Diane-35 or its generics. A detailed analysis plan describing the planned analysis of the physician questionnaire and data presentation, including table shells, will be developed prior to starting the study. In addition to a description of the questionnaire data analysis, the analysis plan will include plans for comparing participants with non-participants (including physicians from other sources outside the survey data collection efforts) based on the data available for these non-participants) and the approach for handling missing data.

5 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	20 April 2015	4, 6, 9, 10, 11, and 12	Amendment	Revisions were made to update the AE reporting process, to increase the time for data storage, and to communicate the planned comparisons of participants and non-participants based on data available on non-participants. Minor editorial revisions were also made for clarity of text, and the timeline was updated

6 Milestones and Timeline

Milestone	Anticipated Timeline
Regulatory approval of protocol and physician questionnaire	August 2014
Completion of cognitive pretesting of questionnaire	February 2015
Submission for institutional review board (IRB) review and approval, ethics committee (EC) review and approval (if required), and Commission Nationale de l'Informatique et des Libertés (CNIL) review and approval	IRB review and approval: April 2015 EC reviews not required CNIL approval: July 2015
Registration in the EU PAS register	April 2015
Start of physician recruitment and data collection	After IRB and CNIL approval[a]
End of physician recruitment and data collection	3 months from CNIL approval
Completion of data analysis	3 months from end of data collection
Final report of study results	2 months from completion of data analysis (Targeted 29 May 2016)
Study progress reports	Every 6 months to Bayer throughout the study

[a] Physician recruitment and data collection will begin in Austria, the Czech Republic, and the Netherlands after IRB approval. Physician recruitment and data collection will begin in France upon CNIL approval. Physician recruitment and data collection will begin in Spain at the same time as data collection in France.

7 Rationale and Background

Diane-35 (cyproterone acetate 2 mg/ethinylestradiol 35 µg) (CPA/EE) was first authorised in a European Union (EU) country in 1985. Generic versions of Diane-35 have been approved via national procedures and are available under several different trade names in all EU Member States except Cyprus (European Medicines Agency [EMA], 2013a). The new indication for these medicines is treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age (EMA, 2013d). For the treatment of acne, Diane-35 and its generics should only be used after topical therapy or systemic antibiotic treatments have failed (EMA, 2013d). Diane-35 and its generics should not be used in combination with other hormonal contraceptives (EMA, 2013d).

The new indication resulted from a review of combination medications containing CPA/EE that was initiated in February 2013 at the request of France, under Article 107i of Directive 2001/83/EC, (EMA, 2013c). The review was conducted by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC reviewed data related to the risks of thromboembolic events based on results from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of these medications, and submissions from stakeholders (EMA, 2013d). The review concluded that the risk of venous thromboembolism (VTE) with these medications is 1.5 to 2.0 times higher than for combined oral contraceptives containing levonorgestrel and may be similar to the risk associated with contraceptives containing gestodene, desogestrel, or drospirenone (EMA, 2013a). Information on the risks of arterial thromboembolism (ATE) associated with these medications is sparse but indicates that this risk is lower than the risk of VTE (EMA, 2013a). Based on the review, the Coordination Group for Mutual Recognition and Decentralised Procedures—Human endorsed the recommendation of the PRAC, which concluded that the benefits of Diane-35 and its generics outweigh the risks, provided that several measures are taken to minimise the risk of VTE and ATE (EMA, 2013e).

The PRAC recommended additional risk minimisation measures to encourage safe use of the product and to promote early diagnosis, treatment, and prevention of complications from VTE and ATE. Educational material for health care professionals would focus on thromboembolism (i.e., deep vein thrombosis, VTE, pulmonary embolism, heart attack, and stroke) and its risks factors, signs, and symptoms and contraindications relevant to thromboembolism. In addition, sponsors were asked to evaluate the effectiveness of this risk-minimisation communication.

As part of the risk management plan for Diane-35, Bayer has developed educational material for prescribers that includes the following key safety information:

- A patient information card, which includes information related to the risks of developing blood clots, describes the signs and symptoms of a blood clot, and informs when a patient should seek medical attention
- A prescriber checklist of risk factors associated with thromboembolism (i.e., deep vein thrombosis, VTE, pulmonary embolism, heart attack, and stroke)
- A prescriber checklist of contraindications for the use of Diane-35 in the context of thromboembolism

The educational material is being distributed to health care professionals who are expected to prescribe Diane-35 or its generics. Distribution started in July 2014. Specific timing may vary by country based on regulatory approvals of the educational materials in local language versions.

In collaboration with Bayer, we have developed this protocol for a joint, observational post-authorisation safety study (PASS) with the purpose of assessing physician knowledge and understanding of the key safety information outlined by the PRAC and included in the Diane-35 educational material developed by Bayer. The Dutch Medicines Evaluation Board (MEB) will be the regulatory lead and will communicate with the PRAC as needed regarding this study. The MEB and Bayer have agreed that Bayer will be responsible for liaising with the generic companies, and the study will share this common core protocol. To meet the study objective, a physician questionnaire will be developed and administered to physicians prescribing brand Diane-35 or its generics to assess their knowledge and understanding of the key safety information in this material. The educational material, Diane-35 Patient Card and Prescriber Checklist is included in Annex 3.

8 Research Question and Objectives

The primary objective of this study is to measure physician knowledge and understanding of the key information outlined by the PRAC and included in the educational material for Diane-35 developed by Bayer. Specifically, the following objectives will be addressed:

- Investigate whether physicians have received any educational material related to Diane-35 or its generics
- Assess physicians' knowledge and understanding of key safety information pertaining to the patient information card
- Assess physicians' knowledge and understanding of key safety information pertaining to the following areas:
  - Contraindications relevant to thromboembolism
  - Risk factors for thromboembolism
  - Signs and symptoms of thromboembolism

9 Research Methods

9.1 Study Design

The study will be an observational (non-interventional), cross-sectional study of knowledge and understanding among a generally representative sample of physicians who have recently prescribed (e.g., within previous 6 months prior to recruitment) Diane-35 or its generics. A cross-sectional survey approach was selected for this study because the main information on knowledge and understanding of the educational material could be obtained only through direct interaction with health care professionals.

Recruitment of the participating physicians will be performed by RTI Health Solutions (RTI-HS) and a European operations partner, an internationally based data collection

agency focused solely on health care research that maintains proprietary physician panels. The panels of physicians are convenience samples of physicians derived from multiple sources (e.g., hospital books, medical directories, yellow pages, peer referrals). Each panel member is recruited by telephone and opts into the panel twice.

Physicians will be given the option to complete the survey via the Internet or a telephone interview. The Web-based format for completion of the consent form and questionnaire was chosen because of the efficiency of the method and the utility of the available electronic questionnaire tools (e.g., question branching logic and ability to display correct educational information at the conclusion of the questionnaire without allowing the participant to correct prior answers). Most health care professionals have convenient access to complete a Web-based questionnaire, so the use of this technology is not considered to introduce a respondent bias; however, an option for a telephone interview will be offered to physicians who prefer this mode of survey administration.

9.2 Setting

This cross-sectional study will be conducted in five European countries: Austria, the Czech Republic, the Netherlands, Spain, and France. Five countries are included to provide some diversity in practice patterns and to observe physician knowledge in different settings. In addition, it is anticipated that the drug utilisation in these countries will be such that there will be a sufficient number of eligible physicians who have experience with Diane-35 or its generic versions to participate in the study. The timing and sequence of study initiation in each country will be determined by the distribution of the Diane-35 educational material.

9.2.1 Physician Selection and Recruitment

The aim of physician recruitment is to obtain a sample generally representative of the physicians in the selected countries who potentially prescribe Diane-35 or its generics. Geographic location, specialty, and potentially other factors will be considered when selecting the sample in each country. The sample may include a simple random sample from the physician panels in each country. However, to achieve the appropriate distribution of prescribers in each specialty, we may adopt a sampling approach stratified by prescriber specialty in France and Spain. In smaller countries, the entire population of eligible physicians in the panel may be invited rather than a sample.

As a consequence of the revised Diane-35 indication, the study will target recruitment of up to 25% dermatologists in each country. Physician specialty will be considered when selecting the sample in each country based on the Diane-35 prescribing patterns in each country:

- Austria and the Czech Republic: gynaecologists and dermatologists
- The Netherlands: general practitioners and dermatologists
- France: general practitioners, gynaecologists, and dermatologists
- Spain: general practitioners, gynaecologists, and dermatologists

In each country, physicians will be recruited from panels that are maintained by a proprietary organisation. To be eligible for the study, physicians must meet all of the following eligibility criteria:

- Licensed and practicing dermatologist, gynaecologist, or general practitioner
- Prescribed Diane-35 or a generic version to at least one patient in the past 6 months

An invitation will be sent by e-mail or issued by phone to the selected physicians inviting them to participate via the Internet and providing a link to a Web-based questionnaire or via telephone. To ensure physician eligibility, the Web-based and telephone-based questionnaires will include a screening question regarding recent prescribing of Diane-35 or its generics. Following consent, physicians will be asked to complete the questionnaire evaluating their knowledge and understanding of key safety information, as well as their receipt and use of educational material related to Diane-35 or its generics.

9.3 Variables

A questionnaire will be developed to elicit responses measuring physician knowledge and understanding of the key information included in the Diane-35 educational material. This questionnaire will contain closed-ended multiple choice questions, with no free-text response fields, eliciting responses measuring physician knowledge and understanding of the key information in the Diane-35 educational material. The physician questionnaire will include items in the following content areas:

- The approved indication of Diane-35 and its generics
- Contraindications relevant to thromboembolism (i.e., current VTE, ATE, or cerebrovascular accident; history of VTE, ATE, or cerebrovascular accident; and selected comorbid conditions)
- Risk factors associated with thromboembolism (e.g., obesity, prolonged immobilisation, surgery, positive family history, age, smoking, selected comorbid conditions)
- Signs and symptoms of a thrombus (e.g., unusual unilateral leg pain; sudden severe pain in the chest; sudden breathlessness, visual disturbances; weakness or numbness in face, arm, or leg)

The questionnaire will include additional items to characterise the physicians and their practices (e.g., physician specialty, years in practice, patient volume) and investigate physician receipt and use of any educational materials related to Diane-35 or its generics.

Data from the questionnaire responses will be analysed to ascertain the level of physician knowledge and understanding stratified by country and other relevant characteristics (e.g., physician specialty).

The final version of the questionnaire is included in Annex 3.

9.4 Data Sources

The source of information for the study will be self-reported data collected from physicians using a standard questionnaire with closed-ended response choices. The physician questionnaire was developed and tested using best practices for instrument development (DiBenedetti et al., 2013). The questionnaire was tested through cognitive pretest interviews with physicians in each country.

9.4.1 Cognitive Pretest

Cognitive pretest interviewing is a well-established qualitative research methodology used to identify problems with questionnaire items and response options (Groves et al., 2009). The questionnaire were be tested in local languages to ensure that the introductory material, consent forms, and questionnaire items (question stems and response choices) are culturally appropriate and easily and correctly understood by physicians similar to those who will participate in the study.

Specifically, trained interviewers asked interview participants to complete the questionnaire while thinking aloud or describing their thought processes as they answered the questionnaire items. Pretest interviewers used an interview guide that included probe questions designed to help interviewers understand how each participant interpreted and chose his or her answers for each item in the draft questionnaire. The pretest interviews were designed to help identify problems with questionnaire items, including the question stems and response choices, and to ensure that participants understand the instructions. The pretest interview data was used to optimise the language used in the questionnaire prior to fielding the study. Likewise, the cognitive pretest interviews helped identify cultural or translational issues with the draft questionnaire so that the questionnaire could be modified to meet the individual needs of each country while maintaining comparability across the study.

Cognitive pretesting of the physician questionnaire was conducted with 25 physicians across the participating countries who prescribe Diane-35 or its generic versions.

9.5 Study Size

The study will target recruitment of 60 to 120 physicians each in Austria, Czech Republic, and the Netherlands and 100 to 200 physicians each in France and Spain, for a total of at least 500 participating physicians. The final sample size will ultimately depend upon the actual number of physicians who prescribe Diane-35 or its generics in each country, the availability of eligible physicians on the panels, and the response rates for the survey, which are as yet unknown. The proposed sample size will allow reasonable precision around estimates of knowledge and understanding of the key safety information for the total sample and within each country to the extent possible.

Table 1 shows the exact 95% confidence limits assuming various combinations of sample size and correct response percentages. For example, if we assume that the *total* sample of participants can be treated as a simple random sample and that the percentage of correct responses to a yes/no question is 85%, then for a total sample size of 500, the two-sided 95% confidence limits will be 81.6% to 88%. For the smaller countries, if we assume that the sample of participants in each country can be treated as a simple random sample and that the percentage of correct responses to a yes/no question is 85%, then for a sample size of 60, the two-sided 95% confidence limits will be 73.4% to 92.9%. For the larger countries, if we assume that the percentage of correct responses to a yes/no question is 85%, then for a sample size of 200, the two-sided 95% confidence limits will be 79.3% to 89.6%.

Table 1. Exact 95% Confidence Limits for Various Combinations of Physician Sample Size and Percentage of Correct Responses

Sample Size	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
60	80	67.7	89.2
60	85	73.4	92.9
100	80	70.8	87.3
100	85	76.5	91.4
200	80	73.8	85.3
200	85	79.3	89.6
300	80	75.0	84.4
300	85	80.4	88.8
400	80	75.7	83.8
400	85	81.1	88.4
500	80	76.2	83.4
500	85	81.6	88.0
600	80	76.6	83.1
600	85	81.9	87.8
700	80	76.8	82.9
700	85	82.1	87.6

9.6 Data Collection and Management

9.6.1 Data Collection

A Web-based electronic data capture (EDC) system will be used in this study for physicians who complete the survey via the Internet or a telephone interview. An invitation will be sent via e-mail or made by phone to the selected sample of physicians, inviting them to participate and providing a link to the Web-based questionnaire. An option for a telephone interview will be offered to physicians who prefer this mode of survey administration.

For physicians who elect to complete the questionnaire via the Internet, each invited physician will be asked to log in to the study Web site by entering a unique identification number and password assigned to each participant and provided in the invitation to participate. The questionnaire will begin with an electronic informed consent. After participants consent, they will be prompted to complete the questionnaire.

For physicians who elect to complete the questionnaire via a telephone interview, the interviewer will enter a unique identification number assigned to each participant into the EDC system. Prior to administering the questionnaire, the interviewer will obtain a verbal informed consent. After participants consent, the interviewer will administer the questionnaire.

The questionnaire (closed-ended questions with predefined answers) can be completed at the participants' convenience. Although participants will be encouraged to complete

the questionnaire in a timely manner, once they start the questionnaire via the Internet, they will be able to stop at any point and, at a later time, pick up where they left off, should that be necessary. Participants will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the respondent searching for answers via the Web or other sources or being influenced by answers to subsequent questions. Participants who elect to complete the questionnaire via a telephone interview will also be encouraged to complete the questionnaire during one telephone interview.

Participants will also not be allowed to regain access to the questionnaire once it has been completed. Based on potential country-specific requirements, the recruitment process and physician questionnaire may be different between countries. Country-specific differences will be described and appended to the final study protocol.

9.6.2 Data Management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements. Physician data will be entered directly into a Web-based EDC system. Edit and logic checks will be specified in a data cleaning specifications document and will be programmed into the Web-based EDC system to ensure high-quality data. However, due to the self-reported nature of the data, changes to data that appear to be incorrect or inconsistent during data cleaning may not be possible.

RTI-HS data managers will conduct user acceptance testing of the physician data entry system and will sign the user acceptance testing report before the EDC system is used in the field. Additionally, data managers will approve the data management plan, the annotated physician questionnaire, the data cleaning specifications document, and the testing summary reports before authorising the data systems to go “live.” Data managers will ensure that the EDC data system remains tested and valid and will require that testing documentation, database documentation, and change control documentation will be created and maintained.

Once the Web-based EDC system is in the field, data management activities will include review of interim analysis files for consistency, programming edit checks in preparation for statistical analysis, and merging data sets if required.

9.6.3 Record Retention

All data for the physician assessment will be electronic. Only de-identified data based on case identification numbers will be transferred to the United States (US) for the purpose of analysis and generation of the final report. De-identified electronic data sets will be stored in the US for 15 years from the time of final results submission. If requested by Bayer, the de-identified electronic data sets can be provided to Bayer at the end of the study, in which case Bayer will be responsible for long-term storage of the data. If RTI-HS stores the de-identified data, RTI-HS will obtain authorization from Bayer to destroy the data after 15 years of storage.

9.7 Data Analysis

Data analyses will be descriptive and focus on summarising questionnaire responses to individual questions among logical groupings of response items (e.g., Physician and Practice Characteristics, Physician Prescribing Practices). Results across all countries will be presented as well as stratified by country and possibly other variables, such as physician specialty and experience with Diane-35 or its generics. A detailed analysis plan describing the planned analysis of the physician questionnaire and data presentation, including table shells, will be developed prior to starting data collection. In addition to a description of the questionnaire data analysis, the analysis plan will describe comparisons of participants and non-participants, based on the data available on non-participants. Demographic (e.g., sex and age) and practice characteristics will be collected and compared amongst the eligible physicians (both for those who provided consent and for those who did not) as well as physicians who were not eligible to participate in the survey based on the screening question. In addition, the demographic and practice characteristics will be compared to characteristics available for prescribing physicians from other sources outside the survey data collection efforts.

Descriptive tables summarising demographics, questionnaire response results, and other available characteristics will be generated for the physicians, stratified by country and other variables of interest (e.g., physician specialty). For continuous-type data, the mean, standard deviation, median, and range will be presented. For categorical data, frequencies and percentages will be reported. The specific tables to be produced will be included in the analysis plan. An exploratory analysis will be conducted to evaluate predictors of physician knowledge level.

Typically, questionnaire data are mostly complete, and each question will be analysed individually among those participants who respond. However, as part of the analysis plan, we may establish a threshold of data required for a participant's questionnaire to be included in the analysis (e.g., completion of at least 11 of 14 knowledge questions).

The analysis plan will also describe the following:

- Analysis of subgroups
- Methods for handling missing data
- Level of statistical precision

All analyses will be performed using SAS 9.3 (or higher) statistical software (SAS, Cary, North Carolina). Programs, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

9.8 Quality Control

This project will be conducted in accordance with the guidances described in Section 10.4 (Ethical, Regulatory, and Scientific Principles) and the internal standard operating procedures of participating institutions. The RTI-HS Office of Quality Assurance (OQA), an independent unit that reports to the Vice President of RTI-HS, will oversee quality assurance for this study.

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage,

methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, data collection forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

For RTI-HS, the OQA will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the OQA according to established criteria in standard operating procedures and other applicable procedures.

9.9 Limitations of the Research Methods

As with all cross-sectional surveys that depend on healthcare professionals agreeing to participate, some limitations are inherent. Although the study is designed to select a diverse and generally representative sample of prescribers, there exists no exhaustive list of all prescribers of Diane-35 or its generics from which to draw a sample; hence, it is not possible to select a random sample of all prescribers. Therefore, the study participants may not necessarily represent all prescribers of Diane-35 and its generics.

In general, physician response rates for surveys have been somewhat low historically. Low response rates may result in higher likelihood that participating physicians are not representative of all prescribing physicians. Thus, the resulting estimates of physician understanding about Diane-35 and its generics may be biased. If participants discontinue the survey because they do not know how to answer the knowledge questions, then the frequency of substantial physician knowledge will be overestimated. Data will be collected to assess the number of physicians who begin but do not complete the questionnaire via the Internet or a telephone interview. This information can be used to help assess this potential bias. However, in our experience, almost all participants complete all items of the questionnaire.

In addition, as is true with most surveys, it is possible that participants who complete the questionnaire will differ from non-participants in characteristics measured in the questionnaire (e.g., knowledge of or reading the educational materials). The direction and magnitude of such potential participant bias is not known.

The study will target a total of at least 500 physicians (approximately 60 to 200 physicians per country). The majority of the analysis will focus on aggregated data across all countries. Although the report may display country-specific findings, there may be limitations with drawing country-specific conclusions.

The physician assessment will be conducted after physicians have received the Diane-35 educational material and have had a chance to utilise that information in their practice, allowing for evaluation of how well they understand the safety information provided in the educational materials and apply it to their practices.

10 Protection of Human Subjects and Other Good Research Practice

This study will be conducted in accordance with all applicable ethical and regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki. The IRB at RTI International (of which RTI-HS is a division) will review the study protocol, questionnaires, and informed consent documents. RTI-HS researched the requirements for ethics committee review in each country and concluded that ethics committee reviews are not required for the study. Recruitment of the participating physicians will be performed by RTI-HS and a European operations partner.

10.1 Informed Consent

Participant informed consent will be obtained for each physician who agrees to complete a questionnaire. Physicians will be asked to provide electronic acknowledgement of consent prior to completing the Web-based questionnaire or verbal consent prior to completing the telephone interview. The questionnaire will not collect any identifying information about the physician, and each respondent will be tracked using a unique study identifying number.

10.2 Participant Confidentiality

The research team will not have access to any participant-identifying information. Only de-identified data will be made available to the research staff and Bayer. Thus, any reports that are generated will *not* contain any participant identifiers. Data will be provided to Bayer in aggregate only and will not be linked to individual physicians.

10.3 Compensation

Physicians will be paid nominal incentives to compensate them for their time in completing the study questionnaire. The amount and payment methods will be reviewed and approved by Bayer to ensure that payments are commensurate with the time needed to complete the forms, are not coercive, and are made according to local regulations in each country.

10.4 Ethical, Regulatory, and Scientific Principles

This study is being conducted as a regulatory commitment. As an observational (non-interventional) study, the risks for physicians linked to their participation in the study are limited to a breach of confidentiality with regard to personal identifiers. Before a physician can participate in the study, he or she must give informed consent. Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accord with applicable national and local regulations. Independent EC approval will be obtained according to the guidance of the each country's research ethics requirements.

The study will be conducted under the International Society for Pharmacoepidemiology (2007) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* and will be designed

in line with the *EMA's Guideline on Good Pharmacovigilance Practices (GVP): Module VIII—Post-Authorisation Safety Studies* (EMA, 2013f), and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2013a). The completed ENCePP *Checklist for Study Protocols* (ENCePP, 2013b) is included in Annex 2.

The study will be registered in the EU PAS Register (ENCePP, 2013c) prior to the start of data collection.

The study will comply with the definition of a non-interventional (observational) study provided i*n the EMA's Guideline on Good Pharmacovigilance Practices (GVP): Module VIII—Post-Authorisation Safety Studies* (EMA, 2013f) and the nature of non-interventional (observational) studies referred to in the ICH harmonised tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004).

11 Management and Reporting of Adverse Events/Adverse Reactions

This study is not designed to collect data on individual adverse drug events, which are better collected using other study designs.

AEs are not anticipated as part of the web-based physician survey assessment because there are no open-ended questions in the survey. However, the survey may be completed by physicians via a telephone interview; therefore, an AE could be reported to the telephone interviewer. For the physician assessment, the telephone interviewer and project manager will undergo safety training and will complete an AE report form if an AE is spontaneously reported.

If an AE is spontaneously reported for any Bayer drugs or a nonspecified version of a generic Diane-35 drug (i.e., the physician did not know the trade name of the generic version of Diane-35), an AE report form will be collected and provided to Bayer within 1 business day. If an AE is spontaneously reported for a non-Bayer product, an AE report form will be collected and provided by RTI-HS to the pharmacovigilance department of the MAH of the non-Bayer product within 1 business day (by 17:00 Central European Time) of the initial report.

During the qualitative cognitive pretesting interviews, the safety training was provided to the interviewers. However, no AEs were reported.

Any unsolicited AE information received will be handled following the *Guideline on Good Pharmacovigilance Practices (GVP) Module VI—Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2013g) and in accordance with Directive 2001/83/EC, Regulation (EC) No. 726/2004 and Commission Implementing Regulation (EU) 520/2012. The process for safety reporting will be further described in the safety reporting plan.

12 Plans for Disseminating and Communicating Study Results

Study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, and other regulatory milestones and requirements.

The final study report will be registered in the EU PAS Register (ENCePP, 2013c).

Study results will be published in the scientific literature following guidelines of the International Committee of Medical Journal Editors (ICMJE, 2013), and communication in appropriate scientific venues, e.g., International Society for Pharmacoepidemiology, will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE, 2007) will be followed.

13 References

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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

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

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

Study title:

Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study

Study reference number:

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[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

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)	☒	☐	☐	13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	see comment

Comments:

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)	☒	☐	☐	14-15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16,16
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)	☒	☐	☐	20

Comments:

[1] 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.

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

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☐	☒	☐	15
4.2.3 Country of origin?	☒	☐	☐	15
4.2.4 Disease/indication?	☒	☐	☐	15
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)	☒	☐	☐	15

Comments:

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:

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?	☒	☐	☐	16
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)	☐	☐	☒	16

Comments:

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)	☐	☒	☐	

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

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	
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.)	☒	☐	☐	16
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.)	☒	☐	☐	16
8.1.3 Covariates?	☒	☐	☐	16
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)	☒	☐	☐	16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	16
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	16
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 Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	17

Comments:

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?	☒	☐	☐	20
10.3 Are descriptive analyses included?	☒	☐	☐	20
10.4 Are stratified analyses included?	☒	☐	☐	20
10.5 Does the plan describe methods for adjusting for				

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

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?	☒	☐	☐	20
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☒	☐	☐	20
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	19
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	21
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)	☒	☐	☐	21
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	21
12.3 Does the protocol address other limitations?	☒	☐	☐	21

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	22

Comments:

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

Comments:

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)?	☒	☐	☐	24
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	24

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3.
Additional Information

Patient information card:

Indication for which Diane-35 is prescribed:

Treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

For the treatment of acne, Diane-35 should only be used after topical therapy or systemic antibiotic treatments have failed.

Since Diane-35 is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives.

IMPORTANT INFORMATION ABOUT [PRODUCT NAME] AND RISK OF BLOOD CLOTS

All estrogen-progestagen combination products like [product name] increase the rare but important risk of having a blood clot. The overall risk of a blood clot is small but clots can be serious and may in very rare cases even be fatal.

It is very important that you recognise when you might be at greater risk of a blood clot, what signs and symptoms you need to look out for and what action you need to take.

In which situations is the risk of a blood clot highest?

- in the first year of using [product name] (including if you are re-starting use after a break of 1 month or more)
- if you are very overweight (body mass index over 30 kg/m2)
- if you are older than 35 years
- if you have a close family member who has had a blood clot at a relatively young age (e.g. below 50)
- if you have given birth in the previous few weeks

If you smoke and are over 35 years old you are strongly advised to stop smoking or use a non-hormonal treatment for your acne and/or hirsutism.

Seek medical attention immediately if you experience any of the following symptoms:

- Severe pain or swelling in either of your legs that may be accompanied by tenderness, warmth or changes in the skin colour such as turning pale, red or blue. You may be experiencing a **deep vein thrombosis**.
- Sudden unexplained breathlessness or rapid breathing; severe pain in the chest which may increase with deep breathing; sudden cough without an obvious cause (which may bring up blood); You may be experiencing a serious complication of deep vein thrombosis called a **pulmonary embolism**. This occurs if the blood clot travels from the leg to the lung.
- Chest pain, often acute, but sometimes just discomfort, pressure, heaviness, upper body discomfort radiating to the back, jaw, throat, arm together with a feeling of fullness associated with indigestion or choking, sweating, nausea, vomiting or dizziness. You may be experiencing a **heart attack**
- Face, arm or leg weakness or numbness, especially on one side of the body; trouble speaking or understanding; sudden confusion; sudden loss of vision or blurred vision; severe headache/migraine that is worse than normal. You may be experiencing a **stroke**.

Watch out for symptoms of a blood clot, especially if you have:

- Just had an operation
- been off your feet for a long time (e.g. because of an injury or illness, or if your leg is in a cast)
- a long journey (e.g. a long-haul flight)

Remember to tell your doctor, nurse or surgeon that you are taking [product name] if you:

- Are due to or have had surgery
- Are asked by a healthcare professional if you are taking any medication

For further information please read the accompanying Patient Information Leaflet or go to [NCA web address].

If you suspect you have an undesirable effect associated with the use of your medication, you can report it to a Healthcare professional.

Prescribers' Checklist:

CHECKLIST FOR PRESCRIBERS – cyproterone/ethinylestradiol [Product name]

Please use this checklist in conjunction with the Summary of Product Characteristics and at regular intervals.

Indication for which Diane-35 is prescribed:

Treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

For the treatment of acne, Diane-35 should only be used after topical therapy or systemic antibiotic treatments have failed.

Since Diane-35 is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives.

- Thromboembolism (e.g. deep vein thrombosis, pulmonary embolism, heart attack and stroke) is a rare but important risk with use of cyproterone/ethinylestradiol [Product name].
- A woman's risk will also depend on her baseline risk of thromboembolism. The decision to use cyproterone/ethinylestradiol [Product name] should therefore take into consideration the contraindications and a woman's risk factors, particularly those for thromboembolism – see boxes below and the Summary of Product Characteristics.
- The risk of a thromboembolism with cyproterone/ethinylestradiol [Product name] is higher:
  - during the first year of use
  - when re-starting use after an intake break of 1 month or more.
- The decision to use cyproterone/ethinylestradiol [Product name] should be taken only after a discussion with the woman to ensure she understands
  - the effect of any intrinsic risk factors on her risk of thrombosis
  - the risk of thromboembolism with [Product name]
  - that she must be alert for signs and symptoms of a thrombosis

Please be reminded to consider the possibility of a thromboembolic event in healthy girls/women also in case of non-distinct, unexplained complaints like pain in the leg, cough/dyspnoea, or headache.

Do not prescribe cyproterone/ethinylestradiol [Product name] **if you tick any of the boxes in this section. Does the woman have:**	
☐	Concomitant use with another hormonal contraceptive?
☐	Current or personal history of a thromboembolic event e.g. deep vein thrombosis, pulmonary embolism, heart attack, stroke, transient ischaemic attack, angina pectoris?
☐	Knowledge of predisposition for a blood clotting disorder personally?
☐	History of migraine with aura?
☐	Diabetes mellitus with vascular complications?
☐	Very high blood pressure eg systolic ≥160 or diastolic ≥100mm Hg?

☐	Very high blood lipids?
☐	Major surgery or a period of prolonged immobilisation coming up? If so, advise the patient to stop using Diane-35 and to use a non-hormonal treatment for their skin condition and if necessary a non-hormonal method of contraception for at least 4 weeks beforehand and two weeks after full ambulation*.

Discuss the suitability of cyproterone/ethinylestradiol [Product name] **with the woman if you tick any of the boxes in this section:**

☐	Is her BMI over 30 kg/m²?
☐	Is she aged over 35 years?
☐	Is she a smoker? If yes and also over the age of 35 she should be strongly advised to stop smoking or use a non-hormonal treatment for her acne and/or hirsutism.
☐	Does she have high blood pressure eg systolic 140-159 or diastolic 90-99mm Hg?
☐	Does she have a close relative (e.g. parent or sibling) who has had a thromboembolic event (see above list) at a young age (e.g before 50)?
☐	Does she or someone in her immediate family have high blood lipids?
☐	Does she get migraines?
☐	Does she have a cardiovascular condition such as atrial fibrillation, arrhythmia, coronary heart disease, cardiac valve disease?
☐	Does she have diabetes mellitus?
☐	Has she given birth in the last few weeks?
☐	Does she have any other medical conditions that might increase the risk of thrombosis (eg. cancer, systemic lupus erythematosus, sickle cell disease, Crohn's disease, ulcerative colitis, haemolytic uraemic syndrome)?
☐	Is she taking any other medicines that can increase the risk of thrombosis (e.g. corticosteroids, neuroleptics, antipsychotics, antidepressants, chemotherapy etc)?

More than one risk factor may mean cyproterone/ethinylestradiol [Product name] **should not be used.**

Don't forget, a woman's risk factors may change over time and might need to be revisited at regular intervals.

Please make sure your patient understands that she should tell a healthcare professional she is taking cyproterone/ethinylestradiol [Product name] **if she:**

- Needs an operation
- Needs to have a period of prolonged immobilisation (eg because of an injury or illness, or if her leg is in a cast)

➢ In these situations it would be best to discuss to discontinue cyproterone/ethinylestradiol [Product name] until the risk returns to normal.

Please also tell your patient that the risk of a blood clot is increased if she:

- Travels for extended periods (e.g. on long-haul flights)
- Develops one or more of the above risk factors for cyproterone/ethinylestradiol [Product name].
- Has given birth within the last few weeks

- In these situations your patients should be particularly alert for any signs and symptoms of a thromboembolism.

Please **advise your patient to tell you** if any of the above situations change or get much worse.

Please strongly encourage women to read the Patient Information Leaflet that accompanies each pack of [product name]. This includes the symptoms of blood clots that she must watch out for.

Please report any adverse events suspected to be caused by cyproterone/ethinylestradiol [Product name] to the [company] or the [NCA]

Diane-35 (cyproterone acetate 2 mg/ethinylestradiol 35 µg) Risk Minimisation Plan Evaluation

Physician Questionnaire

Study Objective

RTI International, an independent, not-for-profit research firm engaging in numerous health and medicine research studies, is conducting a research study on behalf of Bayer HealthCare and would like to invite you to participate. This study is being conducted as part of the ongoing safety and risk management process for the drug, Diane-35, and its generic versions (cyproterone acetate 2 mg/ethinylestradiol 35 µg). This questionnaire is not part of a marketing study, but a scientific study conducted at the request of the European Medicines Agency, the drug regulatory body in the European Union (EU). The purpose of the study is to assess prescribers' understanding of and compliance with the safe use of Diane-35 and its generic versions.

You have been identified as a potential participant for this evaluation because you are a physician who treats women of reproductive age and may prescribe Diane-35 or its generic versions. This questionnaire, which takes approximately 15-20 minutes to complete, is being administered to approximately 500 physicians across several countries within the EU.

Demographic Questions

First, please tell us a little about yourself and your clinical practice.

Q1. What is your specialty?

- ☐ General medicine or family practice
- ☐ Dermatology
- ☐ Obstetrics and gynaecology
- ☐ Internal medicine
- ☐ Other

Q2. Overall, how many years have you been practicing medicine?

- ☐ 5 years or less
- ☐ 6 to 10 years
- ☐ 11 to 15 years
- ☐ 16 to 20 years
- ☐ 21 to 25 years
- ☐ More than 25 years

Q3. Are you male or female?

- ☐ Male
- ☐ Female

Q4. How old are you?

- ☐ 18 - 29 years
- ☐ 30 - 39 years
- ☐ 40 - 49 years
- ☐ 50 - 59 years
- ☐ 60 - 69 years
- ☐ 70 years or older

Q5. How would you characterise your practice? Tick <u>all</u> that apply.

- ☐ General practice
- ☐ Hospital-based clinic
- ☐ Other

Screening Question

To confirm your eligibility to participate in this brief survey, please answer the following question.

Q6. In the past 6 months, have you prescribed Diane-35® or its generic versions (cyproterone acetate 2 mg/ethinylestradiol 35 µg) to any patient of reproductive age?

- ☐ Yes
- ☐ No

Confidentiality

Any information you provide to us is confidential, and every precaution will be taken to protect your privacy. Your responses will be used only for statistical purposes and will not be disclosed or used in any personally identifiable form for any other purpose, unless required by law. Your responses will not be linked to your name in any report or publication. The risk of participation in this study relates to data security and is minimal, given the strict confidentiality and security procedures in place. Your de-identified data will be stored on a secure server in the United States.

You will be compensated for your participation in this study. Per the code of conduct set by the European Federation of Pharmaceutical Industries and Associations (EFPIA), Bayer HealthCare will post a summary of the total aggregated payments provided to physicians who participated in this study to a public website. **No information that identifies individual physicians will be reported.**

We respect any requirements your employer might have for your participation in research studies and ask that you please ensure that any relevant approvals have been given prior to completing the survey.

Informed Consent

Q7. Please indicate below if you agree to participate in the current study.

- ☐ Yes, I have read the study information provided and agree to participate in this study.
- ☐ No, I do not agree to participate in this study. [TERMINATE]

Physician Questionnaire

This questionnaire is designed to gain a better understanding of prescribers' knowledge and understanding of key safety information for Diane-35 and its generics. This questionnaire will be used to determine if the educational materials for Diane-35 and its generics are understood accurately and whether these materials could be improved.

Q8. Diane-35 and its generics are indicated for the following purposes. Tick Yes, No, or I don't know for each purpose listed.

Purpose	Yes	No	I don't know
For the treatment of mild acne related to androgen sensitivity (with or without seborrhoea) in women of reproductive age	☐	☐	☐
For the treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) in women of reproductive age	☐*	☐	☐
For contraception only	☐	☐	☐
For the treatment of androgenic alopecia in women of reproductive age	☐	☐	☐
For the treatment of hirsutism in women of reproductive age	☐*	☐	☐

Q9. For the treatment of acne, Diane-35 and its generics should be used only after topical therapy or systemic antibiotic treatments have failed.

- ☐ True*
- ☐ False
- ☐ I don't know

Q10. Patients should be informed that when taking Diane-35 or its generics that the risk of thrombosis is highest during which time periods? Tick Yes, No, or I don't know for each circumstance listed.

Circumstance	Yes	No	I don't know
During the first year of use	☐*	☐	☐
After using the medication for more than 1 year	☐	☐	☐
When re-starting use after a break of 1 month or more	☐*	☐	☐

Q11. When taking Diane-35 or its generics, the risk of a thrombosis is highest with which of the following risk factors? Tick Yes, No, or I don't know for each risk factor listed.

Risk Factors	Yes	No	I don't know
If the patient is very overweight (body mass index greater than 30 kg/m^2)	☐*	☐	☐
If the patient is 35 years of age or younger	☐	☐	☐
If the patient is older than 35 years of age	☐*	☐	☐
If the patient has a close family member who has had a thrombosis at a relatively young age (e.g., younger than 50 years of age)	☐*	☐	☐
If the patient smokes and is older than 35 years of age	☐*	☐	☐
If the patient has a family history of hypertension and/or dyslipidemia	☐	☐	☐

Q12. Patients taking Diane-35 or its generics should watch out for symptoms of a thrombosis in which of the following situations? Tick Yes, No, or I don't know for each situation listed.

Situation	Yes	No	I don't know
Just after having an operation	☐*	☐	☐
When participating in exercise activities such as short-distance running or jogging	☐	☐	☐
When the patient has been off her feet for a long time (e.g., because of an injury or illness or if her leg is in a cast)	☐*	☐	☐
During or after a long journey (e.g., a long flight)	☐*	☐	☐
When initiating treatment with Diane-35 or its generics within a few weeks after having a baby	☐*	☐	☐

Q13. What instructions should patients taking Diane-35 or its generics receive regarding the potential need for a <u>major</u> surgery, or occurrence of an

injury or condition that may also require a period of prolonged immobilisation?
Tick Yes, No, or I don't know for each instruction listed.

Instruction	Yes	No	I don't know
Tell their doctor, nurse, or surgeon that they are taking Diane-35 or its generics	☐*	☐	☐
Stop using Diane-35 or its generics for at least 2 weeks in advance of a major surgery or a required period of prolonged immobilisation	☐	☐	☐
Stop using Diane-35 or its generics for at least 4 weeks in advance of a major surgery or a required period of prolonged immobilisation	☐*	☐	☐
Use a non-hormonal treatment for their skin condition and, if necessary, a non-hormonal method of contraception during this time	☐*	☐	☐
Resume treatment with Diane-35 or its generics at 1 week after complete remobilisation	☐	☐	☐
Resume treatment with Diane-35 or its generics at 2 weeks or later after complete remobilisation	☐*	☐	☐

Q14. Diane-35 and its generics are <u>contraindicated</u> in which of the following patient populations?
Tick Yes, No, or I don't know for each patient population listed.

Population	Yes	No	I don't know
Patients who are currently using another hormonal contraceptive	☐*	☐	☐
Patients who have a current or history of a thromboembolic event (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident , transient ischaemic attack, angina pectoris)	☐*	☐	☐
Patients with a history of childhood asthma	☐	☐	☐
Patients who have knowledge of a predisposition for a blood clotting disorder	☐*	☐	☐
Patients with a history of migraine with aura	☐*	☐	☐
Patients with moderate anaemia	☐	☐	☐
Patients with diabetes mellitus and concurrent vascular complications	☐*	☐	☐
Patients with hypertension (e.g., systolic ≥ 160 or diastolic ≥ 100 mm Hg)	☐*	☐	☐
Patients with dyslipidemia	☐*	☐	☐
Patients who have had a recent major surgery	☐*	☐	☐
Patients who are experiencing or expected to experience a period of prolonged immobilisation	☐*	☐	☐

Q15. Which of the following <u>risk factors</u> for the development of <u>thrombosis</u> should be considered prior to prescribing Diane-35 and its generics? Tick Yes, No, or I don't know for each risk factor listed.

Risk Factor	Yes	No	I don't know
Body mass index over 30 kg/m^2	☐*	☐	☐
Age greater than 35 years	☐*	☐	☐
Smoker	☐*	☐	☐
Hypertension (i.e., systolic 140-159 or diastolic 90-99 mm Hg)	☐*	☐	☐
The patient has a close relative (e.g., parent or sibling) who has had a thromboembolic event at a young age (e.g., before 50)	☐*	☐	☐
History of renal calculus (kidney stone)	☐	☐	☐
Patient or someone in her immediate family has dyslipidemia	☐*	☐	☐
History of migraines	☐*	☐	☐
A cardiovascular condition such as atrial fibrillation, arrhythmia, coronary heart disease, cardiac valve disease	☐*	☐	☐
Diabetes mellitus	☐*	☐	☐
Chronic lassitude	☐	☐	☐
Practicing sports under no medical supervision	☐	☐	☐
Given birth in the last few weeks	☐*	☐	☐
Medical conditions that might increase the risk of thrombosis (e.g., cancer, systemic lupus erythematosus, sickle cell disease, Crohn's disease, ulcerative colitis, haemolytic uraemic syndrome)	☐*	☐	☐
Use of other medicines that can increase the risk of thrombosis (e.g., corticosteroids, neuroleptics, antipsychotics, antidepressants, chemotherapy)	☐*	☐	☐

Q16. What is the <u>prescribing guidance</u> on the use of Diane-35 or its generics for women who smoke?

Tick Yes, No, or I don't know for each prescribing guidance.

Prescribing Guidance	Yes	No	I don't know
Women who are greater than 35 years of age should strongly be advised to stop smoking or use a non-hormonal treatment for her acne and/or hirsutism	☐*	☐	☐
Women who are greater than 35 years of age and	☐	☐	☐

smoke can be prescribed Diane-35 and should be warned about potential risks of thrombosis			
Women of any age don't need to be advised to stop smoking if they smoke less than 5 cigarettes a day	☐	☐	☐

Q17. Which medical conditions can increase the risk of <u>thrombosis</u>? Tick Yes, No, or I don't know for each medical condition listed.

Medical Condition	Yes	No	I don't know
Cancer	☐*	☐	☐
Diabetes mellitus	☐*	☐	☐
Systemic lupus erythematosus	☐*	☐	☐
Haemolytic uraemic syndrome	☐*	☐	☐
Urinary tract infection	☐	☐	☐
Chronic inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)	☐*	☐	☐
Asthma	☐	☐	☐
Sickle cell disease	☐*	☐	☐

Q18. A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible <u>deep vein thrombosis</u>? Tick Yes, No, or I don't know for each symptom listed.

Symptoms	Yes	No	I don't know
Severe pain in a leg	☐*	☐	☐
Swelling in a leg	☐*	☐	☐
Skin rash on leg	☐	☐	☐
Changes in skin colour (e.g., pale, red, or blue) in a leg	☐*	☐	☐
Feeling of tenderness or warmth in a leg	☐*	☐	☐
A headache that has been lasting for more than a week	☐	☐	☐
Insomnia	☐	☐	☐

Q19. A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible <u>pulmonary embolism</u>? Tick Yes, No, or I don't know for each symptom listed.

Symptoms	Yes	No	I don't know
Sudden unexplained breathlessness or rapid breathing	☐*	☐	☐
Chronic fatigue	☐	☐	☐
Severe pain in the chest which may increase with deep breathing	☐*	☐	☐
Sudden cough without an obvious cause (which may bring up blood)	☐*	☐	☐
A tingling or burning sensation limited to the left hand fingers	☐	☐	☐

Q20. A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible <u>myocardial infarction</u>? Tick Yes, No, or I don't know for each symptom listed.

Symptoms	Yes	No	I don't know
Chest pain (often acute)	☐*	☐	☐
Chest discomfort, pressure, or heaviness	☐*	☐	☐
Upper body discomfort radiating to the back, jaw, throat, and arm together with a feeling of fullness associated with indigestion or choking	☐*	☐	☐
Sweating	☐*	☐	☐
Insomnia that started in the previous month	☐	☐	☐
Nausea or vomiting	☐*	☐	☐
Dizziness	☐*	☐	☐

Q21. A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible <u>cerebrovascular accident</u>? Tick Yes, No, or I don't know for each symptom listed.

Symptoms	Yes	No	I don't know
Weakness or numbness of the face, arm, or leg, especially on one side of the body	☐*	☐	☐
Trouble speaking or understanding	☐*	☐	☐
A gradually increasing memory loss over the past year	☐	☐	☐
Sudden confusion	☐*	☐	☐

Sudden loss of vision or blurred vision	☐*	☐	☐
Hearing loss that has been increasing over the past year	☐	☐	☐
Severe headache/migraine that is worse than normal	☐*	☐	☐

The following questions ask about information you have received about Diane-35 or its generics.

Q22. Which of the following material(s) have you received? Tick <u>all</u> that apply.

- ☐ Dear Healthcare Provider Letter for Diane-35 and/or its generics
- ☐ Diane-35 Patient Card
- ☐ Diane-35 Prescriber Checklist
- ☐ Other [PROGRAMMING NOTE: SKIP TO Q24]
- ☐ None of the above [PROGRAMMING NOTE: SKIP TO Q24]

[PROGRAMMING NOTE: ONLY DISPLAY RESPONSES THAT WERE TICKED IN Q22]

Q23. How helpful were these materials to you in treating and educating your patients?

Materials	Not at all helpful 1	2	3	Extremely helpful 4
Dear Healthcare Provider Letter for Diane-35 and/or its generics	☐	☐	☐	☐
Diane-35 Patient Card	☐	☐	☐	☐
Diane-35 Prescriber Checklist	☐	☐	☐	☐

Q24. In the past 3 months, for how many <u>total patients</u> have you prescribed Diane-35 for the treatment of acne or hirsutism?

- ☐ None
- ☐ 1 to 3 patients
- ☐ 4 to 6 patients
- ☐ 7 to 10 patients
- ☐ 11 to 15 patients
- ☐ More than 15 patients
- ☐ I'm not sure

Thank you for completing the questionnaire!