Post-Authorisation Safety Study (PASS) Information

Acronym/Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 FEB 2021
IMPACT study number	21490
Study type / Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS register number	Study not yet registered
Active substance	INN: Cyproterone; ATC code: G03HA01
Medicinal product	Androcur (cyproterone) and its generics
Product reference	BAY94-8367
Procedure number	EMEA/H/A-31/1488
Study Initiator and Funder	Bayer Pharma AG on behalf of a group of MAHs

Research question and objectives	The primary objective of this study is to measure physician awareness and level of knowledge of the key safety information included in the revised summary of product characteristics (SmPC) and the Direct Healthcare Professional Communication (DHPC) for CPA monotherapy regarding the risk of meningioma.
	Specifically, the following information will be collected:
	• Investigate whether physicians have received and reviewed the revised SmPC and DHPC
	• Assess physicians' knowledge and understanding of key safety information pertaining to the following restrictions for the use of CPA due to the risk of meningioma. Specifically:
	  • The occurrence of meningiomas (single and multiple) in association with CPA monotherapy doses ≥ 25 mg/day
	  • Restriction of use of CPA monotherapy 10 mg/50 mg in women when no results have been achieved at lower dose CPA-containing products or with other treatment options
	  • Restriction of use of high-dose CPA in men with sexual deviations when other interventions are not appropriate
	  • After clinical improvement with CPA monotherapy is achieved, treatment should be maintained with the lowest possible dose
	  • The risk of meningioma increases with increasing cumulative doses of CPA
	  • CPA is contraindicated in patients with a meningioma or a history of meningioma
	  • If a patient treated with CPA monotherapy is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped
	  • Awareness of signs and symptoms of meningiomas

Country(-ies) of study	France, Germany, Poland, Spain, the Netherlands
Author	PPD PPD

ATC = Anatomical Therapeutic Chemical Classification System; CPA = Cyproterone Acetate; DHPC = Direct Healthcare Professional Communication; EMA = European Medicines Agency; EU = European Union; INN = International Nonproprietary Name; MAH = Marketing Authorisation Holder; PAS = Post-Authorisation Study; PASS = Post-Authorisation Safety Study; PPD ; SmPC = Summary of Product Characteristics.

Marketing authorisation holder

Marketing authorisation holder(s)	Bayer AG
MAH contact person	PPD Bayer AG Muellerstrasse 178 13353 Berlin, Germany

MAH = Marketing Authorisation Holder.

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AE	Adverse Event
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use
CNAM	French Health Insurance
CPA	Cyproterone Acetate
DHPC	Direct Healthcare Professional Communication
DMP	Data Management Plan
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICH-GCP	International Council for Harmonisation–Good Clinical Practice
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
MAH	Marketing Authorisation Holder
OQA	Office of Quality Assurance
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PPD	
Safe-CAM	Safety of Cyproterone Acetate Monotherapy
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

3. Responsible parties

Bayer AG is the marketing authorisation holder of Androcur (cyproterone acetate) in the European Union (EU) and the study initiator and partial funder of the study. Other Marketing Authorisation Holders (MAH) of cyproterone acetate (CPA) monotherapy products are also funding the study. Bayer is responsible for fulfilling any obligations for reporting results to regulatory agencies. Bayer is collaborating with PPD an independent non-profit research organisation. PPD is responsible for the design, conduct, analysis, and reporting of the study. PPD a global research operations partner, is responsible for physician recruitment and data collection.

3.1 Study initiator and funder

Role:	OS Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	MAH contact person (Regulatory Affairs)
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician (Internal)
Name:	PPD
Role:	OS Statistician (External)
Name:	PPD
Role:	OS Epidemiologist (Internal)
Name:	PPD
Role:	OS Epidemiologist (External)
Name:	PPD
Role:	Regulatory Affairs responsible (External)
Name:	PPD

MAH = Marketing Authorisation Holder; OS = Observational Study.

Contact details of the responsible parties at Bayer AG are available upon request. Signatures of the responsible parties are collected in Annex 5.

3.2 Collaborators/Committees

Contact details on the coordinating and/or principal investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Annex 1. List of stand-alone documents), which is available upon request.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type / Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
Author	PPD
Rationale and background	As an outcome of an Article 31 referral for CPA monotherapy, Bayer has revised the summary of product characteristics (SmPC) and developed a DHPC to describe the risk of meningioma associated with the use of CPA. Bayer along with the other Marketing Authorisation Holders (MAHs) for CPA are conducting a joint observational cross-sectional survey to assess physicians' awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC regarding risk of meningioma.
Research question and objectives	The primary objective of this study is to measure physician awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC for CPA monotherapy regarding the risk of meningioma. Specifically, the following information will be collected:

	• Investigate whether physicians have received and reviewed the revised SmPC and DHPC
	• Assess physicians' knowledge and understanding of key safety information pertaining to the following restrictions for the use of CPA due to the risk of meningioma. Specifically:
	  • The occurrence of meningiomas (single and multiple) in association with CPA monotherapy doses ≥ 25 mg/day
	  • Restriction of use of CPA monotherapy 10 mg/50 mg in women when no results have been achieved at lower dose CPA-containing products or with other treatment options
	  • Restriction of use of high-dose CPA in men with sexual deviations when other interventions are not appropriate
	  • After clinical improvement with CPA monotherapy is achieved, treatment should be maintained with the lowest possible dose
	  • The risk of meningioma increases with increasing cumulative doses of CPA
	  • CPA is contraindicated in patients with a meningioma or a history of meningioma
	  • If a patient treated with CPA monotherapy is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped
	  • Awareness of signs and symptoms of meningiomas

Study design	The study will be an observational, cross-sectional survey to assess knowledge and understanding among a diverse sample of physicians who have recently prescribed (e.g., within previous 12 months) CPA monotherapy in France, Germany, Poland, Spain, and the Netherlands. Physicians from a physician panel will be invited to complete a brief web-based questionnaire regarding their knowledge of the revised SmPC and DHPC.
Population	Physicians eligible to participate will include dermatologists, endocrinologists, gynaecologists, general practitioners, urologists, oncologists (who treat prostate cancer), and psychiatrists involved in the treatment of hypersexuality/reduction of drive in sexual deviations who have prescribed CPA in the past 12 months and work in an office or hospital-based setting. Countries included are France, Germany, Poland, Spain, and the Netherlands.

Variables	The physician questionnaire will assess physician knowledge of the key safety messages outlined in the revised SmPC and evaluate their receipt and understanding of the DHPC.
Data sources	Data will be obtained through questionnaire responses from physicians enrolled in panels from targeted countries.
Study size	The study will target the recruitment of a minimum of 600 participating physicians across the 5 countries. Specifically, we will target a minimum of 200 physicians in France and a minimum of 100 physicians each in Germany, Poland, the Netherlands, and Spain. In Poland and the Netherlands, the estimated patient exposure is low, and it may not be feasible to recruit 100 physicians in those countries within the study timeline. If this is the case, a minimum of 60 physicians will be targeted in Poland and the Netherlands and more physicians will be recruited among the other countries to ensure a total of at least 600 participating physicians. The study will target recruitment based on the following parameters: • Up to 30% of the total respondents in each country will be general practitioners • Up to 25% of the total respondents in each country will be urologists or oncologists with a minimum of 5 of each type (e.g., 10% urologists and 15% oncologists) The remaining respondents in each country will be dermatologists, psychiatrists, gynaecologists, and endocrinologists, with a minimum of 5 physicians each for dermatologists, psychiatrists, and gynaecologists in each country. Given the high prescribing pattern of CPA monotherapy by gynaecologists in France, up to 40% of total respondents in France will be gynaecologists. Efforts will be made to recruit 5 endocrinologists in each country.
Data analysis	Analyses will be descriptive in nature and no hypothesis testing will be performed. Tables displaying the frequency distribution of responses to each individual question will be created. Physician results will be stratified by country and other logical variables (e.g., practice setting, whether the physician received the DHPC). A detailed analysis plan that describes methods of analysis and presentation, including table shells, will be developed before data collection is initiated. In addition to a description of the analysis of the questionnaire data, the analysis plan will include a comparison of characteristics of participants

	to the overall population of each specialty, based on available data, to gauge how representative the final sample is.
Milestones	• Registration in the EU PAS Register: before the start of data collection • Ethical review (as required): before the start of data collection • Distribution of revised SmPC and DHPC: estimated through May 2020 • Start of data collection: Q3 2021 • Analytical data set completely available: Q1 2022 • Final study report available: Q2 2022

5. Amendments

None

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Annex 1) that is available upon request.

Table 1: Milestones

Milestone	Planned date[1]
Registration in the EU PAS Register	Before the start of data collection
Ethical review (as required)	Before the start of data collection
Start of data collection	Q3 2021
End of data collection	Q4 2021
Final report of study results	Q2 2022

EU PAS Register = European Union electronic Register of Post-Authorisation Studies.
[1] Planned dates are based on timely approval of the study protocol by EMA; delays in approval will impact these timelines.

7. Rationale and background

Cyproterone acetate (CPA) is a synthetic progesterone derivative with antiandrogenic properties and is available as monotherapy in dosages of 10 mg, 50 mg, and 100 mg for oral administration and 300 mg/3 mL in depot formulation for intramuscular administration in multiple European countries. The CPA monotherapy 10 mg and 50 mg strengths authorised indications are for moderate and severe signs of androgenisation in women (e.g., hirsutism, androgenetic alopecia, acne and seborrhoea), while the authorised indications for formulations of 50 mg and above and depot formulations are for reduction of sex drive in hypersexuality and sexual deviations in men and antiandrogen treatment in inoperable carcinoma of the prostate or palliative antiandrogenic treatment of prostate cancer. Approved indications for CPA monotherapy differ among the different strengths and among countries in which CPA monotherapy products are authorised.

A recent French pharmacoepidemiology study was conducted by Weill and colleagues (1) to estimate the number of cases of meningioma that are deemed attributable to prolonged exposure of CPA 50 mg and 100 mg in women between 2007 and 2015. A further overview was conducted by the French National Agency for Medicines and Health Products Safety to evaluate meningioma cases in which the use of CPA was reported. On 07 July 2019, the French National Agency for Medicines and Health Products Safety triggered a referral under Article 31 of Directive 2001/83/EC resulting from both of these resources, and requested that Pharmacovigilance Risk Assessment Committee (PRAC) assess the benefit-risk of CPA-containing products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended, or revoked (2). In addition, the PRAC reviewed data from epidemiological studies, including the French Health Insurance (CNAM) study, postmarketing case reports, and data submitted by MAHs (2). The authors of the review concluded that while the absolute risk of meningioma in association with CPA use remains low, the risk increases with increasing cumulative doses. The PRAC noted that most cases occur after prolonged exposure to high doses of CPA (25 mg/day or higher), but cases of meningioma have also been identified after short-term exposure to high doses (cumulative dose > 12 g) of CPA (2). The PRAC concluded that the benefit-risk balance of CPA-containing products remains favourable.

The PRAC recommended that for all indications except prostate carcinoma, treatment with CPA should be restricted to situations where alternative treatments are unavailable or considered inappropriate, and that the lowest possible effective dose should be used. The PRAC also noted that available data do not indicate an increased risk of meningioma in association with low-dose combination products containing 2 mg or less of CPA. The PRAC further recommended updates to the product information of CPA-containing products to reflect current knowledge on the risk of meningioma. In addition, PRAC recommended the sponsors conduct a joint observational cross-sectional survey to assess physicians' awareness and level of knowledge of this risk.

In response to the PRAC recommendation to reflect current knowledge on the risk of meningioma, Bayer Pharma AG (Bayer) developed a Direct Healthcare Professional Communication (DHPC), in line with the content proposed by PRAC, associated with the risk minimisation plan for CPA monotherapy and has revised the summary of product characteristics (SmPC) to describe the risks associated with the use of CPA monotherapy. The DHPC and amendments to the relevant sections of the SmPC and package leaflet were adopted and distributed on a national level.

The PRAC has agreed that Bayer, along with the other MAHs for CPA monotherapies, conduct a joint observational cross-sectional survey to assess physicians' awareness and level of knowledge of

the key safety information included in the revised SmPC and the DHPC regarding risk of meningioma. The Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use (CMDh) endorsed the DHPC.

This is an observational post-authorisation safety study (PASS) with the purpose of assessing physician knowledge and understanding of the key safety information included in the CPA educational material developed by Bayer. To meet the study objective, a physician questionnaire will be developed and administered to physicians prescribing CPA monotherapy to assess their knowledge and understanding of the key safety information in this material.

8. Research questions and objectives

The primary objective of this study is to measure physician awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC for CPA monotherapy regarding the risk of meningioma. Specifically, the following information will be collected:

- Investigate whether physicians have received and reviewed the revised SmPC and DHPC
- Assess physicians' knowledge and understanding of key safety information pertaining to the following restrictions for the use of CPA due to the risk of meningioma. Specifically:
  - The occurrence of meningiomas (single and multiple) in association with CPA monotherapy doses ≥ 25 mg/day
  - Restriction of use of CPA monotherapy 10 mg/50 mg in women when no results have been achieved at lower dose CPA-containing products or with other treatment options
  - Restriction of use of high-dose CPA in men with sexual deviations when other interventions are not appropriate
  - After clinical improvement with CPA monotherapy is achieved, treatment should be maintained with the lowest possible dose
  - The risk of meningioma increases with increasing cumulative doses of CPA
  - CPA is contraindicated in patients with a meningioma or a history of meningioma
  - If a patient treated with CPA monotherapy is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped
  - Awareness of signs and symptoms of meningiomas

9. Research methods

9.1 Study design

The study will be an observational, cross-sectional survey to assess knowledge and understanding among a diverse sample of physicians who have recently prescribed (e.g., within the previous 12 months) CPA monotherapy.

Recruitment of the participating physicians will be performed by PPD and PPD an internationally based data collection agency focused solely on health care research that maintains proprietary physician panels.

An invitation will be sent via e-mail to the selected sample of physicians, inviting them to participate and providing a link to a web-based questionnaire. To ensure physician eligibility, the web-based questionnaire will include a screening question to confirm the physician has prescribed CPA monotherapy in the past 12 months. Following consent, physicians will be asked to complete the questionnaire evaluating their knowledge and understanding of key safety information, as well as their receipt of the revised SmPC and the DHPC.

A cross-sectional survey approach was selected for this study because the main information on knowledge and understanding of the revised SmPC and the DHPC could be obtained only through direct interaction with physicians. 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 physicians have convenient access to complete a web-based questionnaire, so the use of this technology is not thought to introduce respondent bias.

Participating physicians will be paid nominal incentives to compensate them for their time in completing the study questionnaire.

9.1.1 Primary endpoint(s)

This is a PASS survey study; no clinical endpoints will be assessed.

The questionnaire will collect information related to physician characteristics and experience with CPA monotherapy, as well as assess physicians' knowledge and understanding of risk and occurrence of meningiomas with CPA monotherapy, signs and symptoms of meningiomas, and treatment recommendations for CPA monotherapy. In addition, the questionnaire will include items to investigate physician receipt and use of the SmPC and DHPC for CPA monotherapy.

The primary endpoints to be assessed are the percentage of physicians responding correctly to each individual knowledge question.

9.2 Setting

This cross-sectional study will be conducted in five European countries: France, Germany, Poland, Spain, and the Netherlands. Five countries are included to provide some diversity in practice patterns and to observe physician knowledge in different settings, which will maximise the generalizability of the study. 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 CPA monotherapy to participate in the study. A brief informal feasibility assessment was performed in France, Germany, Poland, and Spain, and the results suggest that recruitment efforts will yield a sufficient number of eligible physicians to meet the targeted sample sizes in each country. The timing and sequence of study initiation in each country will be determined to allow for at least 6 months since the distribution of the SmPC and DHPC for CPA monotherapy.

9.2.1 Eligibility

Physicians eligible to participate will include dermatologists, endocrinologists, gynaecologists, general practitioners, urologists, oncologists (who treat prostate cancer), and psychiatrists involved

in the treatment of hypersexuality/reduction of drive in sexual deviations who have prescribed CPA monotherapy within past year and work in an office or hospital-based setting. The sampling frame will be constructed from a physician panel with the aim to select a sample that is generally representative of the types of physicians prescribing CPA monotherapy in each country.

9.2.1.1 Inclusion criteria

1. Licensed and practising dermatologist, endocrinologist, gynaecologist, general practitioners, urologist, oncologist (who treats prostate cancer), or psychiatrist involved in the treatment of hypersexuality/reduction of drive in sexual deviations
2. Prescribed CPA monotherapy to at least one patient in the past 12 months
3. Work in an office or hospital-based setting
4. Electronic acknowledgement of informed consent

9.2.2 Withdrawal

Each physician may discontinue participation at any time during the survey without giving a reason. If a physician wants to stop participating in the study, no further data will be collected.

9.2.3 Representativeness

The aim of physician recruitment is to obtain a sample generally representative of the physicians in the selected countries who potentially prescribe CPA monotherapy. 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. To the extent possible, available information for nonrespondents or from national prescribing resources will be evaluated to assess if there are any differences (e.g., geography, specialty, sex, years in practice).

9.3 Variables

A questionnaire will be developed to elicit responses measuring physician knowledge and understanding of the key information included in the revised SmPC and DHPC for CPA monotherapy. This questionnaire will contain closed-ended questions (e.g., multiple choice, true/false) with no free-text response fields, eliciting responses measuring physician knowledge and understanding of the key information in the revised SmPC and DHPC for CPA monotherapy. The physician questionnaire will include items in the following content areas:

- Approved indications of CPA monotherapy
- Occurrence of meningiomas in association with CPA monotherapy
- Contraindications relevant to meningioma
- Signs and symptoms of meningioma
- Restriction of the indication to second-line treatment

- Approved dosing (i.e., treatment should be prescribed for the shortest possible time and with the lowest effective dose)
- Risk factors associated with meningioma (i.e., risk increases with increasing cumulative doses)

The questionnaire will also include the following items to investigate physician receipt and use of the DHPC and revised SmPC:

- Receipt and review of the DHPC and SmPC
- Estimated time between the physicians' review of the DHPC and SmPC and completion of the survey

In addition, the physician questionnaire will include queries on the following items to characterise the physicians and their practices:

- Physicians' practice setting
- Average number of CPA monotherapy prescriptions each month
- Years in practice
- Gender
- Age

Because approved indications and dosing vary by country, adaptations may be made to the questionnaire to ensure that it is specific and applicable to the country where it is being administered.

The questionnaire is anticipated to take 10 to 15 minutes to complete and will be administered in the local language for each country. The questionnaire will be administered electronically and programmed so that respondents will not be able to move backward in the survey to change their answers to previous questions.

The draft 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 using a standard questionnaire with closed-ended response choices.

Data will be obtained through questionnaire responses from physicians enrolled in panels from targeted countries. The panels of physicians are convenience samples of physicians derived from multiple sources (e.g., hospital books, medical directories, yellow pages, peer referrals). A stringent sampling procedure for panel member recruitment is in place to target a representative demographic cross section. A rigorous verification process is implemented to confirm potential panellists' practising status. The verification process includes checking physician background data against medical directories. Panel membership will only be finalised once live contact and verification is made with the physician at an office location.

The questionnaire was developed and tested using best practices for instrument development (3). Before study implementation, the questionnaire will be tested through cognitive pretest interviews with physicians in each country.

Cognitive pretest interviewing is a well-established qualitative research methodology used to identify problems with questionnaire items and response options (4). The questionnaire will 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 will ask interview participants to complete the questionnaire while thinking aloud or describing their thought processes as they answer the questionnaire items. Pretest interviewers will use an interview guide that includes probe questions designed to help interviewers understand how each participant interprets and chooses his or her answers for each item in the questionnaire. The pretest interviews are 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 will be used to optimise the language used in the questionnaire prior to fielding the study. Likewise, the cognitive pretest interviews will help identify cultural or translational issues with the questionnaire so that the questionnaire can be modified to meet the individual needs of each country while maintaining comparability across the study.

Cognitive pretesting of the physician questionnaire will be conducted with 25 physicians across the five participating countries who prescribe CPA monotherapy.

9.5 Study size

The study will target the recruitment of a minimum of 600 participating physicians across the 5 countries. Specifically, we will target a minimum of 200 physicians in France and a minimum of 100 physicians each in Germany, Poland, the Netherlands, and Spain. In Poland and the Netherlands, the estimated patient exposure is low, and it may not be feasible to recruit 100 physicians in those countries within the study timeline. If this is the case, a minimum of 60 physicians will be targeted in Poland and the Netherlands and more physicians will be recruited among the other countries to ensure a total of at least 600 participating physicians.

The study will target recruitment based on the following for each country:

- Up to 30% of the total respondents in each country will be general practitioners
- Up to 25% of the total respondents in each country will be urologists or oncologists with a minimum of five of each type (e.g., 10% urologist and 15% oncologist)
- The remaining respondents in each country will be dermatologists, psychiatrists, gynaecologists, and endocrinologists, with a minimum of five physicians each for dermatologists, psychiatrists, and gynaecologists in each country. Given the high prescribing pattern of CPA monotherapy by gynaecologists in France, up to 40% of total respondents in France will be gynaecologists. Efforts will be made to recruit five endocrinologists in each country.

The final sample size for each specialty will ultimately depend upon the actual number of physicians among each specialty who prescribe CPA monotherapy in each country, the availability of eligible physicians on the panels, and the response rates for the survey, which are as yet unknown. Recruitment will be monitored throughout data collection. If recruitment of a particular specialty is slow in one country, then PPD will consult with Bayer to consider modifications to the initial sampling frame and/or target recruitment goals to achieve a diverse sample that is representative of the type of physicians prescribing CPA monotherapy.

Table 2 shows the exact 95% confidence limits assuming various combinations of sample size and correct response percentages (5). 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 600, the two-sided 95% confidence limits will be 82% 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 2: Exact 95% Confidence Limits for Various Combinations of Physician Sample Size and Percentage of Correct Responses (5)

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

9.6 Data management

A web-based electronic data capture (EDC) system will be used in this study. Information on the EDC system will be available upon request. Detailed information on data management, including procedures for data collection, retrieval, and preparation are given in the Data Management Plan (DMP), which will be available upon request.

For information on quality control, refer to Section 9.8.

9.7 Data analysis

All statistical details including calculated variables and proposed format and content of tables will be detailed in the statistical analysis plan (SAP). The SAP will be finalised before study database lock. The SAP will be available upon request.

All analyses will be descriptive in nature, and no hypothesis testing will be performed. Tables displaying the frequency distribution of responses to each individual question will be created. Potentially, summary measures may be developed by combining responses across logical grouping of the survey questions. For example, four true/false questions about similar topics may be combined into a single summary score variable with values that range from 0 to 4 depending on how many of the four questions were answered correctly.

Descriptive tables will be generated for the physicians overall, stratified by specialty and country and other identified variables of interest. Analysis tables will include the frequency and percentage of physicians who select each response to each individual question.

As outlined in Section 9.1.1, the endpoints to be assessed are the percentage of physicians responding correctly to each individual knowledge question. In addition, for knowledge questions with multiple correct responses, derived variables will be created to summarise the number of correct responses selected.

Exact Clopper-Pearson 95% confidence intervals will be reported around the percentage of participants that answer each knowledge question correctly for the overall, by-specialty, and by-country results. The specific tables to be included will be finalised in the analysis plan.

Results from this study will be reviewed qualitatively to identify patterns suggesting that the educational activities have been successful (e.g., consistently high percentages of correct responses across all questions), not successful (e.g., consistently low percentages of correct responses), or partially successful (e.g., high percentages for most responses and low percentages for selected responses). The results for each country will be evaluated and interpreted in the context of the local medical practices and the method and timing of the risk minimisation measures implementation.

Survey results will be stratified on selected variables (e.g., age, gender, practice setting, type of physician) to see whether an imbalance of the characteristics of responders versus nonresponders could cause a bias in the overall study results. An imbalance would lead to a bias in the knowledge results only if there were differences in knowledge between the different levels of the imbalanced characteristic. For example, if the study sample includes a much higher percentage of males than that of the overall population of each specialty, an examination of knowledge by gender will identify whether this imbalance would cause a bias in the overall results. If the stratified results show that knowledge is similar by gender, the imbalance should not bias the overall results.

In addition to the stratification performed to assess responder bias, the overall results tables of the knowledge questions will be stratified by other variables (e.g., number of years treating patients, time between when the physicians reviewed the prescriber guide and took the survey, average number of prescriptions of CPA monotherapy each month) to identify whether any of these variables have an impact on knowledge.

Typically, questionnaire data are mostly complete, and each question will be analysed individually among those participants who respond. The analysis population will consist of respondents who were eligible for the study, provided informed consent, and completed at least one of the knowledge questions. No imputation of missing data will be performed.

All analyses will be performed using SAS version 9.4 (or higher) statistical software. Programmes, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

9.7.1 Statistical considerations

No *a priori* thresholds of correct responses to the questions are established as targets for this study given the variability in prescriber specialty and indication. However, having a minimum of 60% of respondents selecting the correct response for each question would be considered reassuring regarding physician awareness and knowledge of the product's safety information. In a review of survey-based studies evaluating the effectiveness of risk minimisation measures in Europe, most participants responding correctly was considered a successful result in 9 of 11 surveys registered in the EU PAS Register (6).

9.8 Quality control

9.8.1 Data quality

PPD will be responsible for EDC system development, quality control, and verification of the data collection. PPD will be responsible for data analysis and data transfer to Bayer.

Detailed information on checks for completeness, accuracy, plausibility, and validity will be given in the DMP, which will be available upon request.

National and international data protection laws as well as regulations on observational studies will be followed.

9.8.2 Quality review

This project will be conducted in accordance with the guidance described in Section 10.2 (regulatory authority approvals/authorisations) and the internal standard operating procedures of participating institutions. The PPD Office of Quality Assurance (OQA), an independent unit that reports to the vice president of PPD, will oversee quality assurance for this study.

Standard operating procedures will be used to guide 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, questionnaire, and study report, will undergo quality-control review, senior scientific review, and editorial review.

For PPD, 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, 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.

A communication plan will be prepared to identify communication roles and responsibilities of key stakeholders and to describe the procedures for communicating the intent and conduct of the study.

9.8.3 Storage of records and archiving

All data for the physician survey will be electronic. Bayer will ensure that all relevant documents of this study will be stored after the end or discontinuation of the study for at least 15 years. Any data as well as programmes from statistical programming performed to generate results will be stored within the programming system for at least 15 years.

9.9 Limitations of the research methods

As with all cross-sectional surveys that depend on health care professionals agreeing to participate, some limitations are inherent. Many methodologic and operational challenges are well recognised (7). Although the study is designed to select a diverse and generally representative sample of physicians who have recent experience with CPA monotherapy, there is no exhaustive list of all physicians who have prescribed or administered CPA monotherapy from which to draw a sample; hence, it is not possible to select a random sample of all physicians. Therefore, the study participants may not necessarily represent all physicians who have prescribed/administered CPA monotherapy. However, to the extent possible, information for respondents and nonrespondents will be evaluated to assess if there are any differences in available characteristics (e.g., geography, specialty, sex, years in practice).

In general, physician response rates for surveys have been somewhat low historically. In Germany, for post-authorisation safety studies, the German Medicinal Products Act (§ 67 Abs. 6 AMG, § 63f AMG) requires that physician participation in the study, as well as any associated compensation, be reported to the Federal Association of Panel Doctors, the Central Federal Association of the Health Insurance Funds, and the German Association of Private Health Insurance Funds. To meet this reporting requirement, physicians must provide their name and lifelong physician identification number as part of the survey. As a result, it is anticipated that the physician response to the survey may be particularly low in Germany.

Low response rates may result in a higher likelihood that participating physicians are not representative of all prescribing physicians. Thus, the resulting estimates of physician understanding about CPA monotherapy may be biased. If participants discontinue the survey because they do not know how to answer the knowledge questions, 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. This information can be used to help assess this potential bias. However, in our experience, almost all participants complete all items of the questionnaire.

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 SmPC and DHPC). The direction and magnitude of such potential participant bias is not known.

In addition, the sample does not account for individuals who could not participate because of the mode of data collection (i.e., Internet access). However, it is anticipated that the vast majority of physicians will have Internet access.

The study will target 600 physicians. The majority of the analysis will focus on aggregated data across all countries. Although the report will display country-specific findings, there may be limitations with drawing country-specific conclusions.

Bayer anticipates initial distribution of the SmPC and DHPC through May 2020. The survey will be conducted after physicians have received the CPA monotherapy educational material and have had a chance to use the information in their practice, which allows for evaluation of how well they understand the safety information provided in the SmPC and DHPC and apply it to their practices.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study to evaluate physicians' knowledge and understanding of key safety information, as well as their receipt and use of the SmPC and DHPC for CPA monotherapy. There is no patient involvement in the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorisations

The study will be carried out within an approved indication in accordance with guidelines and regulations of the European Medicines Agency (EMA), FDA and applicable local law(s) and regulation(s) (e.g., Regulation (EU) No 520/2012 (8)). Recommendations given by other organisations will be followed as well (e.g., EFPIA (9), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP] (10)). International Council for Harmonisation–Good Clinical Practice (ICH-GCP) guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (Good Pharmacovigilance Practice [GVP] module VI (11) and since the study qualifies as a PASS, GVP module VIII (12, 13)) will be followed.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an independent ethics committee (IEC)/IRB is required, documented approval and/or notification from appropriate IECs/IRBs will be obtained prior to study start. When necessary, an extension, amendment, or renewal of the IEC/IRB approval must be obtained and also forwarded to the study initiator and funder. The IEC/IRB must supply to the study initiator and funder, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organised and operates according to applicable laws and regulations.

10.4 Physician formation and consent

Physicians who are interested in participating in the study will be required to provide electronic acknowledgement of informed consent before completing the web-based questionnaire.

10.5 Patient insurance

Not applicable.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to reidentify natural persons. The investigators are obligated to ensure that no documents contain such data.

Physicians will be given unique login information to complete the survey. The personal identifying information collected from physicians will be limited to that which is necessary for compensation purposes and to meet regulatory requirements for reporting payments made to physicians in each country, as applicable. Only deidentified data will be made available to Bayer. Thus, any reports generated will not contain any participant identifiers. Data will be provided to Bayer in aggregate only and will not be linked to individual physicians.

Study findings stored on a computer will be stored in accordance with local data protection laws.

11. Management and reporting of adverse events/adverse reactions

This study is not designed to collect information on individual adverse events (AEs) or adverse drug reactions, which are better collected using other study designs. Adverse events are not anticipated to be part of the web-based physician survey because there will be no open-ended questions, and survey questions do not identify experience with an individual patient. However, an AE could be reported to the interviewers during the cognitive pretesting interviews. The interviewers will undergo safety training prior to conducting the pretesting interviews.

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 (14) 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 conducted according to the pharmacovigilance agreement between Bayer AG and PPD transposing the collaboration agreement between Bayer AG and the MAHs participating in the consortium.

12. Plans for disseminating and communicating study results

This study will be registered at http://www.clinicaltrials.gov and in in the EU PAS Register at http://www.encepp.eu/encepp_studies/indexRegister.shtml. Results will be disclosed in a publicly available database within the standard timelines.

If a competent authority or EMA requests progress reports, these will be provided in agreed frequency and content.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on good publication practice will be followed (e.g., Good Clinical Practice [GPP]2 Guidelines (15), Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] (16)). No individual investigator may publish on the results of this study without prior approval from the MAH.

13. References

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Annex 1. List of stand-alone documents

Document Name

- 21490_Physician Questionnaire_v2.0_18FEB2021
- 21490_DMP
- 21490_SAP
- Direct Healthcare Professional Communication: Restrictions in use of cyproterone acetate due to risk of meningioma
- Team Contact List

Annex 2. ENCePP checklist for post-authorisation safety study (PASS) protocols

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title:
Safety of Androcur Monotherapy (SAM): Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

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 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2/9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.1

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☐	☐	☒	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1/9.2.2

Comments:

This is a cross-sectional study with a one-time questionnaire with physicians

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

Comments:

This is a study to evaluate physician's knowledge of safety and safe use of CPA monotherapy.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.1/9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This is a study to evaluate physician's knowledge of safety and safe use of CPA monotherapy

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.3/9.7
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.2.3/9.7

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical [ATC] Classification System)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases [ICD], Medical Dictionary for Regulatory Activities [MedDRA])	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: PPD

Date: 18/February/2021

Signature: _____

Annex 3. Additional information

Not applicable

Annex 4. Description of updates and amendments

None

Annex 5. Signature pages

Signature Page - Principal Investigator

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type / Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/18/2021, PPD

Signature Page – OS Conduct Responsible and OS Epidemiologist (Internal)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type/Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	Study not yet registered
Medicinal product/Active substance/Medical device/ Combination product	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/18/2021, _____ PPD _____

Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type/Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	Study not yet registered
Medicinal product/Active substance/Medical device/ Combination product	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/19/2021, _____ PPD _____

Signature Page – MAH contact person (Regulatory Affairs)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
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Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/18/2021, _____ PPD _____

Signature Page – OS Safety Lead

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
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Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/18/2021, _____ PPD _____

Signature Page – OS Medical Expert

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type/Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	Study not yet registered
Medicinal product/Active substance/Medical device/ Combination product	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/22/2021, _____ PPD _____

Signature Page – OS Statistician (Internal)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type/Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	Study not yet registered
Medicinal product/Active substance/Medical device/ Combination product	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/19/2021, _____ PPD _____

Signature Page – OS Statistician (External)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type/Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	Study not yet registered
Medicinal product/Active substance/Medical device/ Combination product	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/18/2021, _____ PPD _____

Signature Page – OS Epidemiologist (External)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
IMPACT study number	21490
Study type/Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	Study not yet registered
Medicinal product/Active substance/Medical device/ Combination product	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/18/2021, _____ PPD _____

Signature Page –Regulatory Affairs responsible (External)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Protocol version and date	v 2.0, 18 Feb 2021
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Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2/21/2021, PPD