Addendum to the final report

PASS Information

Title	**Drug Utilization Study on the Prescribing Indications for CPA/EE[1] in 5 European Countries**
Version identifier of the addendum to the final study report	ZEG2016_12
Date of last version of the final study report	21th Dec 2016
EU PAS register number	ENCEPP/SDPP/8365
Active substance	Pharmacotherapeutic group: antiandrogens and estrogens ATC code: G03HB01 Active substances: cyproterone acetate and ethinylestradiol
Medicinal product	Diane-35 and its generics: coated tablets 0.035 mg ethinylestradiol, 2.0 mg cyproterone acetate (CPA/EE)
Product reference	n/a
Procedure number	EMEA/H/A-107i/1357
Marketing authorization holder(s)	Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany On behalf of a group of MAHs
Joint PASS	Yes
Research question and objectives	This drug utilization study is designed to compile the reasons and specific indications for the prescription of CPA/EE. The primary objective of the study is to characterize the prescribing behaviors for CPA/EE in 5 European countries including: • prescription indications for CPA/EE • use of CPA/EE in accordance with the updated label • concomitant use of CPA/EE and CHCs • second-line treatment with CPA/EE for the indication acne
Country(-ies) of study	Austria, Czech Republic, France, The Netherlands, and Spain

[1] Cyproterone acetate and ethinylestradiol

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Title

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

Signature

21.12.2016

Date

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1. List of abbreviations

Abbreviation	*Definition*
CCTIRS	Comité consultative sur le traitement de l'information en matière de recherche dans le domaine de la santé
CNIL	Commission nationale de l'information et des libertés
CNOM	Conseil national de l'Ordre des médicins
CPA	Cyproterone Acetate
DUS	Drug Utilization Study
EE	Ethinylestradiol
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP	General Practitioner
MAH	Marketing Authorization Holder
OTC	Over-the-counter
PCOS	Polycystic Ovary Syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
ZEG	Berlin Center for Epidemiology & Health Research (acronym for the German term 'Zentrum für Epidemiologie & Gesundheitsforschung Berlin')

2. Investigator

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4. Milestones

Task	Planned date	Actual date
Study protocol submission	June 2014	June 2014
Registration in the EU PAS register		January 2015
Start of physician recruitment (Austria)	February 2015	March 2015
First patient (Austria)	February 2015	March 2015
Start of physician recruitment (Czech Republic)	February 2015	March 2015
First patient (Czech Republic)	February 2015	April 2015
Start of physician recruitment (The Netherlands)	February 2015	March 2015
First patient (The Netherlands)	February 2015	April 2015
Start of physician recruitment (Spain)	February 2015	May 2015
First patient (Spain)	February 2015	May 2015
Start of physician recruitment (France)	February 2015	December 2015
First patient (France)	February 2015	January 2016
End of data collection (excluding France)	October 2015	April 2016
Final report of study results	May 2016	May 2016
End of data collection (France)	October 2015	October 2016
Addendum to final report	December 2016	December 2016

5. Introduction

Following the completion of the DUS survey CPA/EE study (main study) in April 2016, the study report was submitted to the relevant authorities for assessment within the agreed timetable. However, due to the late start of recruitment in France, it was decided to continue the study in France in order to obtain more documented prescription events, leading to a clearer view of the prescribing behavior of French physicians. This addendum reports the new set of data from France and compares it to results reported in the main study.

6. Results

6.1 Physician Recruitment

Initiation of recruitment in France was delayed due to a prolonged approval process (for details see CSR main study, section 10.1.1).

Recruitment of physicians commenced in France at the end of 2015. The first patient was enrolled in January 2016 and recruitment went on until 31st October 2016.

The distribution of physician specialties in France was planned to be 40% gynecologists, 40% GPs, 20% dermatologists. Per protocol, a total of 50 doctors was envisaged for France.

Due to slow recruitment, more physicians than expected were contacted but the final distribution of specialties of contacted physicians did not deviate from initial estimates. In sum, 336 physicians were contacted in France, 134 gynecologists, 62 dermatologists and 140 GPs. Of these, 39 gynecologists, 13 dermatologists and 16 GPs agreed to participate in the study (a total of 68 - 20.2% of all contacted physicians). 18 gynecologists, five dermatologists and eight of the GPs recruited at least one patient (a total of 31 - 9.2% of all contacted physicians).

The main reasons for non-participation were the low number of prescriptions (n = 58), lack of time/too time-consuming (n = 23), no interest in the study (n = 12) and no prescriptions of CPA/EE-containing drugs at all (n = 8). Furthermore, four physicians stated that the possibility of source data verification in the doctor's office was the reason for non-participation, two declined due to retirement and ten gave no reason. For 151 non-participating physicians, this information is missing. All of those 151 non-participating physicians agreed to take part in the study in a recruitment phone call, but never signed any physician's information.

Gynecologists were more likely to participate in France (29.1% of all contacted gynecologists), than dermatologists (21.0% of all contacted dermatologists) and GPs (11.4% of all contacted GPs).

The above data for France are summarized in 9.1.1, 9.1.1.1, 9.1.1.2 and 9.1.1.3 (see List of tables).

6.1.1 Physician age

The mean age of the participating physicians in France was 56.2 years, which was the highest of all participating countries (Austria 53.2, Czech Republic 52.6, The Netherlands 48.6, Spain 49.1). The mean age of the all physicians in the main report was 52.2 years.

The mean age of the non-participating physicians in France was 55.2.

The above data for France are summarized in 9.1.2 (see List of tables).

6.1.2 Physician gender

In France, 51.5% of the participating physicians were male and 48.5% female. The distribution for the non-participating physicians was 56.7% male and 43.3% female. In the main report from the main study, the overall physician gender distribution was 57.6% male and 42.4% female.

The above data for France are summarized in 9.1.3 (see List of tables).

6.1.3 Physician specialties

Of the 68 participating physicians 39 (57.4% of all participating physicians) were gynecologists, 13 (19.1% of all participating physicians) dermatologists and 16 GPs (23.5% of all participating physicians).

The overall distribution in the main report was 63.1% Gynecologists, 16.9% dermatologists and 20.1% GPs.

The physician specialties in France were contacted according to the planned distribution, i.e. 40% gynecologists, 40% GPs, 20% dermatologists. Within these specialties, gynecologists were the most likely to participate when contacted.

The above data for France are summarized in 9.1.4(see List of tables).

6.1.4 Physician level of experience

Of the participating French physicians 85.3% (n = 58) stated 15 years or more of experience, 7.4% (n = 5) stated 5 – 9 years of experience, 1.5% (n = 1) 10 – 14 years and 1.5% (n = 1) stated 1 – 4 years of

experience. The overall distribution in the main report was 71.0% with 15 or more years of experience, 9.2% had 10 – 14 years, 5.4% had 5 – 9 and 1.3% had 1 – 4 years of experience.

The above data for France are summarized in 9.1.5 (see List of tables).

6.2 Patient recruitment and eligibility

In France, the first patient was recruited on 15th January 2016. By 31st October 2016, 148 patients had been recruited of whom 108 (73.0%) were eligible and 40 (27.0%) were not. 68 of the eligible patients were recruited by gynecologists, 27 by dermatologists and 13 by GPs. Of the high number of ineligible patients 27 patients had been enrolled by one physician, who could not provide sufficient patient information in his database during the source data verification process. The information in his patient files was very scarce and he had no patient files for three patients. Additionally, some patients' names were wrong. Therefore, all patients who had been enrolled by this physician were excluded from the study.

Furthermore, seven Patients had to be excluded from the study because the parents' written consent would have been needed due to their age, but only their own signature was provided. Also, five patients who had been recruited after the planned end of recruitment and were not included.

The above data for France are summarized in the table below and 9.1.6 (see List of tables).

Table 1 - Patient recruitment by country

	AT	CZ	FR	NL	ES	**Total**
Number (%) of recruited patients	292 (100%)	581 (100%)	148 (100%)	45 (100%)	632 (100%)	**1698 (100%)**
Eligible	282 (96.6%)	563 (96.9%)	108 (100%)	32 (71.1%)	612 (96.8%)	**1597 (94.1%)**
Specialty:						
Gynecology	*282 (100%)*	*526 (93.4%)*	*68 (63.0%)*	*0 (0.0%)*	*121 (19.8%)*	***997 (62.4%)***
Dermatology	*0 (0.0%)*	*37 (6.6%)*	*27 (25.0%)*	*8 (25.0%)*	*110 (18.0%)*	***182 (11.4%)***
General Practitioner (GP)	*0 (0.0%)*	*0 (0.0%)*	*13 (12.0%)*	*24 (75.0%)*	*381 (62.3%)*	***418 (26.2%)***
Ineligible	10 (3.4%)	18 (3.1%)	40 (27.0%)	13 (28.9%)	20 (3.2%)	**101 (5.9%)**
Duplicate	0 (0.0%)	5 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**5 (0.3%)**
No complete informed consent available	1 (0.3%)	0 (0.0%)	7 (4.7%)	1 (2.2%)	20 (3.2%)	**29 (1.7%)**
No Baseline questionnaire available	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (4.4%)	0 (0.0%)	**3 (0.2%)**
No basleline prescription	0 (0.0%)	0 (0.0%)	25 (16.9%)	0 (0.0%)	0 (0.0%)	**25 (1.5%)**
Recruited after study recruitment closure	1 (0.3%)	11 (1.9%)	5 (3.4%)	0 (0.0%)	0 (0.0%)	**17 (1.0%)**
No CPA/EE prescription	8 (2.7%)	2 (0.3%)	2 (1.4%)	10 (22.2%)	0 (0.0%)	**22 (1.3%)**

Date of analysis: 10 DEC2016

Note: For specialties (in italics) the percentages relate to the number of eligible patients. All other percentages relate to “Number (%) of recruited patients”.

6.2.1 Age distribution of eligible patients

The mean age of recruited patients in France was 27.1 years with a range of 15 to 47 years. The age range from 18 to 34 years accounted for 76.8% of the users and there were six (5.6%) eligible patients, who were younger than 18 years. The mean age of the overall eligible patient population in the main report was 26.0 years.

The above data for France are summarized in 9.2.1 (see List of tables).

6.3 CPA/EE prescriptions

6.3.1 Prescription status

In France, 28.7% of the eligible patients were first-time users, 59.3% continuous users, and 12.0% were restarters.

The proportion of restarters was similar to the proportion found in the overall data of the main report (14.7%), whereas the first-time users (42.0%) and continuous users (42.6%) were more evenly distributed in the main report.

The above data for France are summarized in 9.2.2 (see List of tables).

6.3.2 Prescribing reasons

In the context of this study, the following androgen-dependent conditions were predefined in the questionnaire: acne, hirsutism, seborrhea, androgenetic alopecia and Polycystic Ovary Syndrome (PCOS). In addition to questions on the relevant condition, the physicians were asked to document whether CPA/EE was prescribed for contraception and whether the patient was using a hormonal contraceptive at the time of prescription. Mentioning more than one reason for the prescription on the questionnaire was possible.

The main reason for CPA/EE prescription in France was acne (88.9%, n = 96). The second most stated reason was contraception (32.4%, n = 35) followed by seborrhea (11.1%) and hirsutism (10.2%). PCOS, androgenetic alopecia and “other reasons” were mentioned less frequently with 5.6%, 3.7% and 2.8%, respectively. In 2.8% (n = 3) contraception was the only listed reason for the prescription. The proportions for “PCOS only” and “androgenetic alopecia” only were 0.9% (n = 1) each.

In the data of the main report acne was stated less frequently as a reason for prescription (65.6%), whereas PCOS (11.4%) and contraception (66.7%) were more frequently stated as a reason for prescription. All other reasons for prescription show a similar trend in the overall data of the main report and the updated data for France.

The above data for France are summarized in the table below and 9.2.3 (see List of tables).

Table 2 – Prescription Reason France and overall data of main report

	CPA/EE France	95%-CI	CPA/EE main report	95%-CI
Number (%) of eligible patients	108 (100%)		1513 (100%)	
Reason				
Acne	96 (88.9%)	[80.6%;94.5%]	993 (65.6%)	[57.2%;73.4%]
Seborrhea	12 (11.1%)	[5.9%;18.6%]	195 (12.9%)	[9.3%;17.3%]
Hirsutism	11 (10.2%)	[4.8%;18.4%]	191 (12.6%)	[9.8%;15.9%]
Androgenetic alopecia	4 (3.7%)	[0.9%;9.6%]	75 (5.0%)	[3.2%;7.2%]
PCOS	6 (5.6%)	[1.3%;14.7%]	173 (11.4%)	[7.9%;15.8%]
Contraception	35 (32.4%)	[17.3%;50.8%]	1009 (66.7%)	[58.8%;74.0%]
Other reasons	3 (2.8%)	[0.5%;8.2%]	56 (3.7%)	[1.9%;6.5%]
Bleeding problems	0 (0.0%)	[0.0%;0.0%]	34 (2.2%)	[0.9%;4.5%]
Other skin problems	2 (1.9%)	[0.2%;6.7%]	14 (0.9%)	[0.3%;2.0%]
Other hair problems	0 (0.0%)	[0.0%;0.0%]	2 (0.1%)	[0.0%;0.5%]
Gynecologic problems	1 (0.9%)	[0.0%;5.4%]	4 (0.3%)	[0.0%;1.1%]
Personal reasons	0 (0.0%)	[0.0%;0.0%]	4 (0.3%)	[0.1%;0.7%]
Missing	0 (0.0%)	[0.0%;0.0%]	0 (0.0%)	[0.0%;0.0%]
Contraception only	3 (2.8%)	[0.6%;7.9%]	246 (16.3%)	[9.1%;25.9%]

Note: Multiple prescribing indications per patient may be possible.
Note: Frequencies of reasons for prescription are displayed relatively to the number of patients .
Note: Exact 95% CI for proportions are given, variance inflation is considered in terms of effective sample size (Clopper & Pearson, 1934, Korn & Graubard, 1998)
Date of analysis: 06DEC2016

6.4 Previous and concomitant treatment of androgen-dependent conditions

6.4.1 Previous treatment of acne

Of the 99 patients who had a diagnosis of acne in France, 50 had mild acne (50.5% of all patients with a diagnosis of acne), 35 moderate (35.4% of all patients with a diagnosis of acne) and 14 severe acne (14.1% of all patients with a diagnosis of acne). 75.8% (n = 75) of the patients who had an acne diagnosis had received previous treatment. There was little difference in the percentage of patients who had previously been treated for acne according to the diagnostic severity of disease; previous treatment was stated in 74.0% of the patients with mild acne, 77.1% with moderate acne and 78.6% of the severely affected patients.

The percentage of mild, moderate, and severe acne in France differed from the overall data in the main report. Mild acne accounted for 36.7% of all acne diagnoses, moderate acne for 54.7% and severe acne for 8.7%. The overall previous treatment percentage of all acne patients in the main report (57.0%) was lower than in France. The overall data in the main study showed an increasing percentage of previous acne treatment with increasing severity (42.7% previous treatment in patients diagnosed with mild acne, 63.2% moderate, 78.7% severe).

89.9% of all patients with acne in France have had their acne diagnosis for more than 12 months and 51.5% (n = 51) of the previous treatments were documented as failed or insufficient. For moderate to severe acne (i.e. without mild acne) previous treatment failure was 61.2%.

In comparison, previous treatment failure in all acne patients combined in the main report was 41.6%. For moderate to severe acne this number was 51.8%.

For patients with mild acne in France, the most frequently mentioned previous treatments were ”various topical therapies/keratolytics” (n = 11, 22.0%), which include OTC medications and washing lotions, followed by antibiotics without known form of application and systemic antibiotics (both n = 7, 14.0%). 12% (n = 6) had previously been treated with systemic isotretinoin, 8.0% (n=4) with oral contraceptives (excluding CPA/EE), anti-androgenic therapy and CPA/EE (all three categories 8.0%). In 42.0% of the cases, the previous treatment was documented as failed or insufficient.

In the overall data of the main report the most frequently mentioned previous treatments in patients with mild acne were also “various topical therapies/keratolytics” (n = 46, 12.2%) which include OTC medications and washing lotions, topical antibiotics without combinations (n = 39, 10.3%) and CPA/EE (n = 32, 8.5%). In 24.1% of the cases, the previous treatment was documented as failed or insufficient.

For patients with moderate acne in France the most common previous treatments were antibiotics without known form of application (n = 6, 17.1%), systemic antibiotics (n = 6, 17.1%) and systemic isotretinoin (n = 4, 11.4%). In patients with moderate acne the proportion of failed or insufficient previous treatments was 60.0%.

In the overall data of the main report, the most common previous treatments for patients with moderate acne were topical antibiotics without combinations (n = 100, 17.8%), antibiotics combined with benzoyl peroxide (n = 77, 13.7%), systemic antibiotics (n = 68, 12.1%), various topical therapies/keratolytics (n = 55, 9.8%) and CPA/EE (n = 44, 7.8%). The percentage of failed or insufficient previous treatment for these patients was stated as 49.6%.

For patients with severe acne the most frequently mentioned previous treatments in the main report were systemic antibiotics (n = 7, 50.0%) and topical retinoids (n = 4, 28.6%). Patients with severe acne had the highest proportion of failed or insufficient treatments (64.3%).

In the overall data of the main report, the most common previous treatments for patients with severe acne were systemic antibiotics (n = 19, 21.3%), topical antibiotics (n = 14, 15.7%), and antibiotics

combined with benzoyl peroxide (n = 10, 11.2%). These patients with severe acne had a proportion of failed or insufficient treatments of 65.2%.

The above data for France are summarized in the table below and 9.2.4 (see List of tables).

Table 3 – Previous treatment of acne France

	Mild	Moderate	Severe	**Total**
Number (%) of eligible patients with acne	50 (100%)	35 (100%)	14 (100%)	**99 (100%)**
Previous treatment				
No	13 (26.0%)	8 (22.9%)	3 (21.4%)	**24 (24.2%)**
Yes	37 (74.0%)	27 (77.1%)	11 (78.6%)	**75 (75.8%)**
Anti-androgenic therapy	4 (8.0%)	3 (8.6%)	0 (0.0%)	**7 (7.1%)**
Antibiotic combined with retinoid (topical)	0 (0.0%)	1 (2.9%)	0 (0.0%)	**1 (1.0%)**
Antibiotics (form of application not specified/unclear)	7 (14.0%)	6 (17.1%)	2 (14.3%)	**15 (15.2%)**
CPA/EE	4 (8.0%)	3 (8.6%)	0 (0.0%)	**7 (7.1%)**
Estradiol systemic	1 (2.0%)	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Isotretinoin (form of application not specified/unclear)	1 (2.0%)	1 (2.9%)	1 (7.1%)	**3 (3.0%)**
Isotretinoin systemic	6 (12.0%)	4 (11.4%)	1 (7.1%)	**11 (11.1%)**
Monoclonal antibody	1 (2.0%)	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Oral Contraceptives (not including CPA/EE)	4 (8.0%)	3 (8.6%)	1 (7.1%)	**8 (8.1%)**
Retinoids combined with benzoyl peroxide (topical)	1 (2.0%)	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Systemic antibiotics	7 (14.0%)	6 (17.1%)	7 (50.0%)	**20 (20.2%)**
Topical antibiotics	0 (0.0%)	2 (5.7%)	1 (7.1%)	**3 (3.0%)**
Topical corticosteroids	0 (0.0%)	1 (2.9%)	0 (0.0%)	**1 (1.0%)**
Topical retinoids	2 (4.0%)	3 (8.6%)	4 (28.6%)	**9 (9.1%)**
Topical treatment with benzoyl peroxide	1 (2.0%)	3 (8.6%)	2 (14.3%)	**6 (6.1%)**
Various topical therapies/ keratolytics	11 (22.0%)	3 (8.6%)	0 (0.0%)	**14 (14.1%)**
Zinc tablets/various oral therapies	1 (2.0%)	3 (8.6%)	2 (14.3%)	**6 (6.1%)**
Missing	2 (4.0%)	0 (0.0%)	1 (7.1%)	**3 (3.0%)**
Treatment failed / insufficient				
Yes	21 (42.0%)	21 (60.0%)	9 (64.3%)	**51 (51.5%)**
No	16 (32.0%)	6 (17.1%)	2 (14.3%)	**24 (24.2%)**
Not applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**

Note: Patient may have more than one entry for previous and concomitant treatment.
Note: For the missing day of disease, the 1st was set; if the month was missing additionally, the 31st of December was used for calculation of the duration.
Date of analysis: 06DEC2016

6.4.2 Concomitant treatment of acne

Overall, 30.3% (n = 30) of the patients with an acne diagnosis in France received treatment in addition to CPA/EE. There was a marked difference in concomitant treatment percentage between the three groups of severity; 18.0% (n = 9) of the patients with mild acne received concomitant treatment, whereas 31.4% (n = 11) with moderate acne, and 71.4% (n = 10) of the patients severely affected by

acne received concomitant treatment. This marked difference was also found in the overall data of the main report (16.4% of the patients with mild acne received concomitant treatment, 37.9% with moderate acne and 51.7% with severe acne).

Of the 18.0% of patients (n = 9) with mild acne receiving concomitant therapy, the most frequently mentioned concomitant treatment was topical treatment with benzoyl peroxide (n = 5, 10.0%).

In the overall data of the main report, the most common treatments for patients with mild acne receiving concomitant therapy, were various topical therapies/keratolytics (n = 24, 6.4%) and topical antibiotics (n = 12, 3.2%).

For patients with moderate acne receiving concomitant treatment (n = 11) the most frequently mentioned concomitant treatments in France were systemic antibiotics (n = 5, 14.3%), topical retinoids and topical treatment with benzoyl peroxide (both n = 4, 11.4%).

In the overall data of the main report, the most common treatments for patients with moderate acne receiving concomitant therapy (n = 187), were topical antibiotics (n = 46, 8.2%), various topical therapies / keratolytics (n = 45, 8.0%), antibiotics combined with benzoyl peroxide (n = 33, 5.9%), and systemic antibiotics (n = 24, 4.3%).

For patients with severe acne who receive concomitant treatment (n = 10), the most frequently mentioned treatments in France were systemic antibiotics, topical retinoids and isotretinoin (form of application not specified (all n = 3, 21.4%)).

In the overall data of the main report, the most common treatments for patients with severe acne receiving concomitant therapy (n = 40), were systemic isotretinoin (n = 9, 10.1%), various topical treatments / keratolytics (n = 8, 9.0%) and topical antibiotics (n = 8, 9.0%).

The above data for France are summarized in the table below and 9.2.4 (see List of tables).

Table 4 – Concomitant treatment of acne France

	Mild	Moderate	Severe	**Total**
Number (%) of eligible patients with acne	50 (100%)	35 (100%)	14 (100%)	**99 (100%)**
Concomitant treatment				
No	35 (70.0%)	21 (60.0%)	3 (21.4%)	**59 (59.6%)**
Yes	9 (18.0%)	11 (31.4%)	10 (71.4%)	**30 (30.3%)**
Anti-androgenic therapy	0 (0.0%)	1 (2.9%)	2 (14.3%)	**3 (3.0%)**
Antibiotics (form of application not specified/unclear)	0 (0.0%)	2 (5.7%)	2 (14.3%)	**4 (4.0%)**
Estradiol systemic	0 (0.0%)	1 (2.9%)	0 (0.0%)	**1 (1.0%)**
Isotretinoin (form of application not specified/unclear)	1 (2.0%)	0 (0.0%)	3 (21.4%)	**4 (4.0%)**
Isotretinoin systemic	0 (0.0%)	0 (0.0%)	1 (7.1%)	**1 (1.0%)**
Retinoids combined with benzoyl peroxide (topical)	0 (0.0%)	2 (5.7%)	0 (0.0%)	**2 (2.0%)**
Systemic antibiotics	1 (2.0%)	5 (14.3%)	3 (21.4%)	**9 (9.1%)**
Topical antibiotics	0 (0.0%)	0 (0.0%)	1 (7.1%)	**1 (1.0%)**
Topical retinoids	2 (4.0%)	4 (11.4%)	3 (21.4%)	**9 (9.1%)**
Topical treatment with benzoyl peroxide	5 (10.0%)	4 (11.4%)	2 (14.3%)	**11 (11.1%)**
Various topical therapies/ keratolytics	2 (4.0%)	1 (2.9%)	0 (0.0%)	**3 (3.0%)**
Zinc tablets/various oral therapies	0 (0.0%)	1 (2.9%)	1 (7.1%)	**2 (2.0%)**
Missing	6 (12.0%)	3 (8.6%)	1 (7.1%)	**10 (10.1%)**

Note: Patient may have more than one entry for previous and concomitant treatment.

Date of analysis: 11MAY2016

6.4.3 Previous and concomitant treatment of seborrhea

Seborrhea was diagnosed in 32 patients in France, of which 28.1% (n = 9) had received previous treatment and only one patient received concomitant treatment. The most frequently stated previous treatment was local/topical keratolysis/therapy (21.9%, n = 7). The information on the medication given to the one patient who received concomitant treatment is missing.

In the overall data of the main report, 267 patients had a diagnosis of seborrhea, of which 39.0% (n = 104) had received previous treatment. The most frequently stated treatment was local/topical keratolysis/therapy (11.2%, n = 30), antimycotics (4.9%, n = 13), CPA/EE (4.1%, n = 11) and topical treatment with benzoyl peroxide (4.1%, n = 11). Furthermore, 52 of the 267 (19.5%) patients with a seborrhea diagnosis received concomitant treatment. Local/topical keratolysis/therapy accounted for the highest percentage of the concomitant treatment (n = 26) followed by topical antibiotics (n = 10).

The above data for France are summarized in 9.2.5 (see List of tables).

6.4.4 Previous and concomitant treatment of hirsutism

Hirsutism affected 14 patients in the French study population. Of these, four (28.6%) stated, that they had received previous treatment, nine (64.3%) had not been previously treated for their disorder. Information was missing for one (7.1%) of patient. The four previous treatments were anti-androgenic therapy, CPA/EE, systemic antibiotics and various topical therapies. Two patients with hirsutism diagnosis received concomitant treatment. Both stated various topical therapies as concomitant treatment.

In the overall data of the main report, 221 patients had a diagnosis of hirsutism. Of these, 42 (19.0%) stated they had received previous treatment, 162 (73.3%) have not been previously treated for their disorder. Information was missing for 17 (7.7%) of patients. The most frequently used previous treatments in this (sub)-cohort was CPA/EE (5.0%, n = 11), anti-androgenic therapy (3.6%, n = 8), oral contraceptives not including CPA/EE (2.3%, n = 5), Eflornithine (2.3%, n = 5) and laser diode hair removal (1.8%, n = 4). 16 (7.2%) of the 221 patients affected by hirsutism received concomitant treatment. Laser diode hair removal (n = 5) and anti-androgenic therapy (n = 3) were reported most frequently as concomitant treatments.

The above data for France are summarized in 9.2.6 (see List of tables).

6.4.5 Previous and concomitant treatment of androgenetic alopecia

Androgenetic alopecia was diagnosed insix patients in France, of which one received previous treatment and two received concomitant treatment. The patient with the previous treatment stated vitamins and nutrients as medication, whereas the two concomitant therapies received Minoxidil.

In the overall data of the main report, 89 patients had a diagnosis of androgenetic alopecia, of which 37 (41.6%) had been previously treated. Of the previous treatments Minoxidil was the leading prescription with 21 (23.6%). 17 (19.1%) of the patients with androgenetic alopecia received concomitant treatment and nine (10.1%) of these were prescribed Minoxidil as concomitant treatment.

The above data for France are summarized in 9.2.7 (see List of tables).

6.4.6 Previous and concomitant treatment of PCOS

Eleven patients were diagnosed with PCOS in France of whom one received previous treatment and none received concomitant treatment. The medication of the patient, who was previously treated was an oral contraceptive (excluding CPA/EE).

In the overall data of the main report, 192 patients with a diagnosis of PCOS were recruited into the study, of which 22.4% (n = 43) had received previous treatment. Oral contraceptives (not including CPA/EE) stood out as being the most frequent previous treatment mentioned (13.0%; n = 25), followed by folic acid plus inositol and anti-androgenic therapy (both 2.6%; n = 5). 13 Patients received concomitant treatment. Metformin (1.6%; n = 3) was the most frequently mentioned concomitant treatment.

The above data for France are summarized in 9.2.8 (see List of tables).

6.4.7 Concomitant use of other hormonal contraceptives and CPA/EE

Of the 108 eligible patients in France, five (4.6%) were prescribed an additional hormonal contraceptive. Four of those were oral contraceptives and one non-oral contraceptive.

In comparison, in the overall data of the main report, 44 (2.9%) patients stated that they used additional hormonal contraception, of whom 42 (2.8% of the total) used oral contraceptives and two (0.1% of the total) non-oral contraceptives.

It is important to consider that these patients were reported as using other hormonal contraceptives at the time of issuance of CPA/EE prescription. It cannot be assumed that all of them would be using other hormonal contraceptives along with CPA/EE. They might stop using other hormonal contraceptive once they start using CPA/EE.

The above data for France are summarized in 9.2.9 (see List of tables).

6.5 Utilization of CPA/EE for the indication of acne and hirsutism

According to the updated label CPA/EE is indicated for the treatment of moderate to severe acne when topical therapy or systemic antibiotic treatments have failed, and for hirsutism in women of reproductive age.

Of the 108 patients eligible in France, the proportion of patients with moderate or severe acne without hirsutism was 40.7% (n=44). Of the eligible patients 4.6% (n = 5) had received “previous topical treatment only” and 7.4% (n = 8) “previous systemic antibiotic treatment only”. Of the 24 patients (22.2%) who had received “previous topical and/or systemic antibiotic treatment”, failed or insufficient treatment was explicitly reported for 21 cases (16.4%).

In France, 11 patients were diagnosed with acne combined with hirsutism and three patients with hirsutism only.

Thus, 38 patients (35.2% of the total study population in France) reflect an approximation of the strict in-label use of CPA/EE in the study population of 108 patients in France: 24 patients with a diagnosis of moderate to severe acne who had “previous topical and/or systemic antibiotic treatment” and those with hirsutism (n = 14).

In comparison, for the overall 1513 patients (100%) of the main report, the proportion of patients with moderate or severe acne without hirsutism was 37.3% (n = 564). Of the total study population 13.2% (n = 199) had received “previous topical treatment only” and 2.2% (n = 34) “previous systemic antibiotic treatment only”. Of the 301 patients (19.9%) who had received “previous topical and/or systemic antibiotic treatment”, failed or insufficient treatment was reported for 249 cases (16.5%).

In the main report a total of 221 (14.6%) patients had a diagnosis of hirsutism, thereof 118 patients (7.8% of all patients) were diagnosed with acne with hirsutism and 103 (6.8%) were diagnosed with hirsutism without acne.

Thus, 522 patients (34.5% of the total study population) reflect an approximation of the strict in-label use of CPA/EE in the study population of 1513 patients in the main report: 301 patients with a diagnosis of moderate to severe acne who had “previous topical and/or systemic antibiotic treatment” and those with hirsutism (n = 221).

It should be considered, that the above analyses do not completely reflect CPA/EE use according to the updated indication wording, since the proportion of cases where previous treatment for acne had failed could not be reliably established. Restricting analysis within this report to cases where previous “failed treatment” is explicitly stated would ignore cases where unsatisfactory treatment results triggered the new treatment with CPA/EE.

The above data for France are summarized in 9.2.10 (see List of tables).

Table 5 – CPA/EE use and treatment for the indication of acne and hirsutism France and overall data of main report

	CPA/EE France	CPA/EE main report
Number (%) of eligible patients with	108 (100%)	1513 (100%)
Moderate or severe acne (without hirsutism)	44 (40.7%)	564 (37.3%)
Previous topical treatment only	5 (4.6%)	199 (13.2%)
Previous systemic antibiotic treatment only	8 (7.4%)	34 (2.2%)
Previous topical and/or systemic antibiotic treatment	24 (22.2%)	301 (19.9%)
No previous topical and systemic antibiotic treatment	20 (18.5%)	263 (17.4%)
Other previous treatment only	10 (9.3%)	60 (4.0%)
Missing	1 (0.9%)	1 (0.1%)
Acne with hirsutism	11 (10.2%)	118 (7.8%)
Previous topical treatment only	0 (0.0%)	43 (2.8%)
Previous systemic antibiotic treatment only	2 (1.9%)	6 (0.4%)
Previous topical and/or systemic antibiotic treatment	5 (4.6%)	64 (4.2%)
No previous topical and systemic antibiotic treatment	6 (5.6%)	54 (3.6%)
Other previous treatment only	3 (2.8%)	13 (0.9%)
Missing	0 (0.0%)	1 (0.1%)
Hirsutism (without acne)	3 (2.8%)	103 (6.8%)
Neither moderate or severe acne nor hirsutism	50 (46.3%)	728 (48.1%)

Note: Exact 95% CI for proportions are given, variance inflation is considered in terms of effective sample size (Clopper & Pearson, 1934, Korn & Graubard, 1998)
Date of analysis: 06DEC2016

"Previous topical treatment only" means that the patients received topical treatment (no systemic antibiotics) and may have received other treatments additionally excluding systemic antibiotics.
"Previous systemic antibiotic treatment only" means that the patients were prescribed a systemic antibiotic (no topical treatment) and may have received other treatments additionally excluding topical treatment.
"Previous topical and/or systemic antibiotic treatment" means that the patients received topical treatment and/or systemic antibiotic treatment and may have received other treatments additionally.
"No previous topical and systemic antibiotic treatment" means that the patients did not receive topical treatment and/or systemic antibiotic treatment but may have been treated with other treatments.
"Other previous treatments only" means that the patients did not receive topical treatment and/or systemic antibiotic treatment but do have been treated with other treatments.

6.6 CPA/EE use and androgen-sensitive diseases

For 97.2% (n=105) of all patients included in France, the prescribing physician either reported an underlying androgenic disease (acne, seborrhea, hirsutism, androgenetic alopecia or PCOS) or named at least one of these disease entities as a reason for today's CPA/EE prescription.

In the overall data of the main study, 83.3% of all patients included in the study were reported either to have at least one underlying androgenic disease (acne, seborrhea, hirsutism, androgenetic alopecia or PCOS) or to have been prescribed CPA/EE today for at least one of these disease entities.

The above data for France are summarized in 9.2.11 (see List of tables).

Table 6 – CPA/EE use and androgen-sensitive diseases, France and overall data of main report

	CPA/EE France	CPA/EE main report
Number (%) of eligible patients with	108 (100%)	1513 (100%)
Acne	99 (91.7%)	1028 (67.9%)
Seborrhea	32 (29.6%)	267 (17.6%)
Hirsutism	14 (13.0%)	221 (14.6%)
Androgenetic alopecia	6 (5.6%)	89 (5.9%)
PCOS	11 (10.2%)	192 (12.7%)
At least one of the 5 androgen-sensitive diseases	105 (97.2%)	1261 (83.3%)

Date of analysis: 06DEC2016

7. Discussion

The reason for conducting this study was the request by the EMA to investigate the implementation of the revised label following the Article 107i referral in 2013.

In the main report, the contribution of French data was too low to allow comparison with the overall European data. The extension of the recruiting period for France has yielded additional data, which allow a better assessment of the prescribing behavior with respect to the utilization of CPA/EE.

The data describing the French physicians participating in the study show a slightly higher mean age when compared to the range found in the main report. The patient characteristics are compatible with the range observed in the main report, thus demonstrating a sufficient degree of homogeneity within the overall study. As already discussed in the main report it is questionable whether the categorization of the severity of acne is a reliable source of information, because of the subjective component on the side of physicians and patients. Strict criteria, e.g. quantifications as used in clinical trials, are rarely applied in practical medicine; such criteria would also not take account of the relative importance of the disease for individual patients. Apart from that, fluctuations of the disease with seasonal changes or other aggravating factors, as well as changes in the patients' perception of the disease, are not fully captured.

It is reasonable to assume that a real life therapeutic strategy is not only based on the current state of acne; the preceding development of the disease severity may guide a decision to include anti-androgenic therapy even if the criteria in the label are not met at the time of prescription.

The original goal for the number of CPA/EE prescriptions, i.e. 1,000 per participating country was, like in the other four countries, not reached in France (108 prescriptions). The low number of documented prescriptions achieved may reflect the fact that CPA/EE is only rarely used or that the patients were not willing to participate. Also, the number of physicians who became active after joining the study, by signingthe physician information, was low (31 of 68). Those physicians, who became active during the

study, only contributed 3.5 eligible patients per physician. This number is substantially lower than in Austria (12.8), Czech Republic (17.6) and Spain (12.0). It has to be noted though, that the recruitment phase was slightly shorter in France (ten months) compared to other countries (Austria 13 months, Czech Republic 13 months, Spain 11 months).

As in the main report including all participating countries, the analysis for France shows that not all prescriptions fully reflect the updated label criteria. However, French physicians follow a stricter observance of the basic principles of the use of anti-androgenic therapy: In the majority of cases (n = 105; 97.2%) the diagnosis and/or the reason for prescription were related to androgen-dependent conditions. This degree of adherence to the pharmacological rationale for the use of CPA/EE exceeds the result found in the main report (83.3%).

Verification of previous failed treatment of acne is generally difficult to achieve as was seen here also. Documentation of this item is not explicit about the term failure, which could have various meanings, e.g. unsatisfactory response, method of application unacceptable for the patient, etc. Applying stricter criteria, but excluding precise documentation of previous treatment failure, there is no significant difference between the data from France and the data in the main report: This approximation of the strict in-label use of CPA/EE in France shows 35.2%, while the main report including data from all participating countries show 34.5%.The 14 French cases suffering from hirsutism are prescribed strictly within the current label, since hirsutism is an indication that requires neither quantification nor previous treatment.

In the 99 French cases of acne, the situation is more complex because of the two additional conditions that required fulfilment: 1. the acne has to be classified as moderate or severe, in order to qualify for treatment with CPA/EE, 2. previous treatment with topical therapy or with systemic antibiotics must have failed. The actual distribution was as follows:

Of the 108 recruited patients 99 (91.7%) had either been diagnosed with acne and/or acne was given as the reason for the prescription. Fortyfour of these patients without hirsutism were classified into the categories moderate and severe. Since the questionnaire did not state which point in time the severity referred to, i.e. at the time of the prescription of CPA/EE or an earlier status of the disease that has been addressed only insufficiently by the previous treatment scheme, some ambiguity remains with the data captured. Furthermore, the categorization of acne in mild, moderate or severe may be subjective depending on individual physicians. Qualified previous treatment (topical treatment or systemic antibiotics) for moderate to severe acne was documented in 24 cases.

Overall, previous treatment failure was documented for 51.5% of the 99 cases of acne treatment. Whether the 48.5% had really been completely successful or whether the patients regarded them as sufficient/satisfactory remains unclear, especially as the questionnaire was completed by the physician and the patient's perspective was not directly targeted. The term treatment failure covers a broad range of constellations and cannot capture the clinical situation comprehensively. Failure could either mean total lack of efficacy or unsatisfactory efficacy or unpleasant side effects (e.g. burning sensation with topical treatments; diarrhea or other gastrointestinal symptoms with systemic antibiotics). However, the fact that a new treatment modality is being initiated gives some indication that the preceding measures might have not been adequate for the given patient.

8. Conclusions

The extension of the recruitment period in France enabled a certain increase of local data on prescription behavior. However, the actual achieved number of documented prescriptions (108) is lower than originally intended. Therefore, general conclusions on the prescription behavior in France are only possible to a limited extent. Overall, the French data are in line with the data gathered and assessed in the main report.

Altogether, on an aggregate level, the study is informative with regard to the clinical scenario when prescribing CPA/EE by gynecologists, dermatologists, and GPs.

9. List of Tables

DUS CPA/EE - Tables (SAP)

9.1 Section A - Administrative data

9.1.1 Table A1 - Physician recruitment by country

	Austria	Czech Republic	France	The Netherlands	Spain	**Total**
Number (%) of contacted physicians	718 (100%)	695 (100%)	336 (100%)	802 (100%)	139 (100%)	**2690 (100%)**
Participating	119 (16.6%)	44 (6.3%)	68 (20.2%)	19 (2.4%)	95 (68.3%)	**345 (12.8%)**
Active	22 (3.1%)	32 (4.6%)	31 (9.2%)	7 (0.9%)	51 (36.7%)	**143 (5.3%)**
Non-participating	599 (83.4%)	651 (93.7%)	268 (79.8%)	783 (97.6%)	44 (31.7%)	**2345 (87.2%)**
Physician has been screened out (no CPA/EE prescriptions)	92 (12.8%)	346 (49.8%)	8 (2.4%)	34 (4.2%)	23 (16.5%)	**503 (18.7%)**
Physician has been screened out (too low number of CPA/EE prescriptions)	243 (33.8%)	179 (25.8%)	58 (17.3%)	8 (1.0%)	14 (10.1%)	**502 (18.7%)**
Physician declined (generally/without giving a reason)	3 (0.4%)	3 (0.4%)	10 (3.0%)	1 (0.1%)	0 (0.0%)	**17 (0.6%)**
Physician declined (due to scope of survey)	0 (0.0%)	4 (0.6%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	**5 (0.2%)**
Physician declined (due to possibility of validation in doctor's office)	0 (0.0%)	2 (0.3%)	4 (1.2%)	3 (0.4%)	0 (0.0%)	**9 (0.3%)**
Physician declined (due to payment)	0 (0.0%)	81 (11.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**81 (3.0%)**
Physician declined (due to no interest in studies)	119 (16.6%)	30 (4.3%)	12 (3.6%)	0 (0.0%)	0 (0.0%)	**161 (6.0%)**
Physician declined (due to lack of time/too time-consuming)	68 (9.5%)	4 (0.6%)	23 (6.8%)	10 (1.2%)	0 (0.0%)	**105 (3.9%)**
Physician declined (due to retirement/close of practice)	16 (2.2%)	2 (0.3%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	**20 (0.7%)**
Other reason	58 (8.1%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	7 (5.0%)	**68 (2.5%)**
Missing	0 (0.0%)	0 (0.0%)	151 (44.9%)	723 (90.1%)	0 (0.0%)	**874 (32.5%)**

Participating physicians are defined as those that agreed to participate (irrespective of returned questionnaires).
Active physicians are defined as those that returned at least one analyzable questionnaire (including a corresponding informed consent from the woman).
Non-participating physicians are defined as those who had not signed the physician information and therefore, declined participation.
Date of analysis: 06DEC2016

9.1.1.1 Table A1.1 Physician recruitment by country - gynecology

	Austria	Czech Republic	France	The Netherlands	Spain	**Total**
Number (%) of contacted physicians	495 (100%)	276 (100%)	134 (100%)	1 (100%)	50 (100%)	**956 (100%)**
Participating	115 (23.2%)	33 (12.0%)	39 (29.1%)	1 (100%)	27 (54.0%)	**215 (22.5%)**
Active	22 (4.4%)	26 (9.4%)	18 (13.4%)	0 (0.0%)	11 (22.0%)	**77 (8.1%)**
Non-participating	380 (76.8%)	243 (88.0%)	95 (70.9%)	0 (0.0%)	23 (46.0%)	**741 (77.5%)**
Physician has been screened out (no CPA/EE prescriptions)	14 (2.8%)	104 (37.7%)	3 (2.2%)	0 (0.0%)	15 (30.0%)	**136 (14.2%)**
Physician has been screened out (too low number of CPA/EE prescriptions)	207 (41.8%)	85 (30.8%)	20 (14.9%)	0 (0.0%)	4 (8.0%)	**316 (33.1%)**
Physician declined (generally/without giving a reason)	3 (0.6%)	2 (0.7%)	4 (3.0%)	0 (0.0%)	0 (0.0%)	**9 (0.9%)**
Physician declined (due to scope of survey)	0 (0.0%)	4 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**4 (0.4%)**
Physician declined (due to possibility of validation in doctor's office)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	**1 (0.1%)**
Physician declined (due to payment)	0 (0.0%)	23 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**23 (2.4%)**
Physician declined (due to no interest in studies)	62 (12.5%)	19 (6.9%)	4 (3.0%)	0 (0.0%)	0 (0.0%)	**85 (8.9%)**
Physician declined (due to lack of time/too time-consuming)	64 (12.9%)	4 (1.4%)	7 (5.2%)	0 (0.0%)	0 (0.0%)	**75 (7.8%)**
Physician declined (due to retirement/close of practice)	13 (2.6%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**15 (1.6%)**
Other reason	17 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (8.0%)	**21 (2.2%)**
Missing	0 (0.0%)	0 (0.0%)	56 (41.8%)	0 (0.0%)	0 (0.0%)	**56 (5.9%)**

Participating physicians are defined as those that agreed to participate (irrespective of returned questionnaires).
Active physicians are defined as those that returned at least one analyzable questionnaire (including a corresponding informed consent from the woman).
Non-participating physicians are defined as those who had not signed the physician information and therefore, declined participation.
Date of analysis: 06DEC2016

9.1.1.2 Table A1.2 Physician recruitment by country - dermatology

	Austria	Czech Republic	France	The Netherlands	Spain	**Total**
Number (%) of contacted physicians	223 (100%)	419 (100%)	62 (100%)	53 (100%)	42 (100%)	**799 (100%)**
Participating	4 (1.8%)	11 (2.6%)	13 (21.0%)	2 (3.8%)	28 (66.7%)	**58 (7.3%)**
Active	0 (0.0%)	6 (1.4%)	5 (8.1%)	1 (1.9%)	8 (19.0%)	**20 (2.5%)**
Non-participating	219 (98.2%)	408 (97.4%)	49 (79.0%)	51 (96.2%)	14 (33.3%)	**741 (92.7%)**
Physician has been screened out (no CPA/EE prescriptions)	78 (35.0%)	242 (57.8%)	2 (3.2%)	14 (26.4%)	5 (11.9%)	**341 (42.7%)**
Physician has been screened out (too low number of CPA/EE prescriptions)	36 (16.1%)	94 (22.4%)	11 (17.7%)	2 (3.8%)	8 (19.0%)	**151 (18.9%)**
Physician declined (generally/without giving a reason)	0 (0.0%)	1 (0.2%)	3 (4.8%)	0 (0.0%)	0 (0.0%)	**4 (0.5%)**
Physician declined (due to scope of survey)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Physician declined (due to possibility of validation in doctor's office)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**2 (0.3%)**
Physician declined (due to payment)	0 (0.0%)	58 (13.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**58 (7.3%)**
Physician declined (due to no interest in studies)	57 (25.6%)	11 (2.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	**69 (8.6%)**
Physician declined (due to lack of time/too time-consuming)	4 (1.8%)	0 (0.0%)	4 (6.5%)	0 (0.0%)	0 (0.0%)	**8 (1.0%)**
Physician declined (due to retirement/close of practice)	3 (1.3%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	**4 (0.5%)**
Other reason	41 (18.4%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (2.4%)	**43 (5.4%)**
Missing	0 (0.0%)	0 (0.0%)	27 (43.5%)	34 (64.2%)	0 (0.0%)	**61 (7.6%)**

Participating physicians are defined as those that agreed to participate (irrespective of returned questionnaires).
Active physicians are defined as those that returned at least one analyzable questionnaire (including a corresponding informed consent from the woman).
Non-participating physicians are defined as those who had not signed the physician information and therefore, declined participation.
Date of analysis: 06DEC2016

9.1.1.3 Table A1.3 Physician recruitment by country - general practitioner (GP)

	Austria	Czech Republic	France	The Netherlands	Spain	**Total**
Number (%) of contacted physicians	0 (0.0%)	0 (0.0%)	140 (100%)	748 (100%)	47 (100%)	**935 (100%)**
Participating	0 (0.0%)	0 (0.0%)	16 (11.4%)	16 (2.1%)	40 (85.1%)	**72 (7.7%)**
Active	0 (0.0%)	0 (0.0%)	8 (5.7%)	6 (0.8%)	32 (68.1%)	**46 (4.9%)**
Non-participating	0 (0.0%)	0 (0.0%)	124 (88.6%)	732 (97.9%)	7 (14.9%)	**863 (92.3%)**
Physician has been screened out (no CPA/EE prescriptions)	0 (0.0%)	0 (0.0%)	3 (2.1%)	20 (2.7%)	3 (6.4%)	**26 (2.8%)**
Physician has been screened out (too low number of CPA/EE prescriptions)	0 (0.0%)	0 (0.0%)	27 (19.3%)	6 (0.8%)	2 (4.3%)	**35 (3.7%)**
Physician declined (generally/without giving a reason)	0 (0.0%)	0 (0.0%)	3 (2.1%)	1 (0.1%)	0 (0.0%)	**4 (0.4%)**
Physician declined (due to scope of survey)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	**1 (0.1%)**
Physician declined (due to possibility of validation in doctor's office)	0 (0.0%)	0 (0.0%)	3 (2.1%)	3 (0.4%)	0 (0.0%)	**6 (0.6%)**
Physician declined (due to payment)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Physician declined (due to no interest in studies)	0 (0.0%)	0 (0.0%)	7 (5.0%)	0 (0.0%)	0 (0.0%)	**7 (0.7%)**
Physician declined (due to lack of time/too time-consuming)	0 (0.0%)	0 (0.0%)	12 (8.6%)	10 (1.3%)	0 (0.0%)	**22 (2.4%)**
Physician declined (due to retirement/close of practice)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	**1 (0.1%)**
Other reason	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	2 (4.3%)	**4 (0.4%)**
Missing	0 (0.0%)	0 (0.0%)	68 (48.6%)	689 (92.1%)	0 (0.0%)	**757 (81.0%)**

Participating physicians are defined as those that agreed to participate (irrespective of returned questionnaires).
Active physicians are defined as those that returned at least one analyzable questionnaire (including a corresponding informed consent from the woman).
Non-participating physicians are defined as those who had not signed the physician information and therefore, declined participation.
Date of analysis: 06DEC2016

9.1.2 Table A2 - Physician age by participation - France

	Participating physicians	Non-participating physicians	**Total**
Number (%) of contacted physicians	68 (100%)	268 (100%)	**336 (100%)**
Age (years)			
n	65 (95.6%)	159 (59.3%)	**224 (66.7%)**
Missing	3 (4.4%)	109 (40.7%)	**112 (33.3%)**
Mean	56.2	55.2	**55.5**
SD	8.57	9.14	**8.97**
Min	33	29	**29**
Q1	53.0	50.0	**50.0**
Median	59.0	58.0	**58.0**
Q3	61.0	61.0	**61.0**
Max	69	68	**69**
Age groups (years)			
<30	0 (0.0%)	1 (0.4%)	**1 (0.3%)**
30 - 39	6 (8.8%)	15 (5.6%)	**21 (6.3%)**
40 - 49	3 (4.4%)	16 (6.0%)	**19 (5.7%)**
50 - 59	26 (38.2%)	60 (22.4%)	**86 (25.6%)**
>= 60	30 (44.1%)	67 (25.0%)	**97 (28.9%)**
Missing	3 (4.4%)	109 (40.7%)	**112 (33.3%)**

Date of analysis: 06DEC2016

9.1.3 Table A3 - Physician gender by participation - France

	Participating physicians	Non-participating physicians	**Total**
Number (%) of contacted physicians	68 (100%)	268 (100%)	**336 (100%)**
Gender			
Male	35 (51.5%)	152 (56.7%)	**187 (55.7%)**
Female	33 (48.5%)	116 (43.3%)	**149 (44.3%)**
Missing	0 (0.0%)	0 (0.0%)	**0 (0.0%)**

Date of analysis: 06DEC2016

9.1.4 Table A4 - Physician specialty by participation – France

	Participating physicians	Non-participating physicians	**Total**
Number (%) of contacted physicians	68 (100%)	268 (100%)	**336 (100%)**
Specialty			
Gynecology	39 (57.4%)	95 (35.4%)	**134 (39.9%)**
Dermatology	13 (19.1%)	49 (18.3%)	**62 (18.5%)**
General Practitioner (GP)	16 (23.5%)	124 (46.3%)	**140 (41.7%)**

Date of analysis: 06DEC2016

9.1.5 Table A5 - Physician level of experience by participation - France

	Participating physicians	Non-participating physicians	**Total**
Number (%) of contacted physicians	68 (100%)	268 (100%)	**336 (100%)**
Level of experience (years in medical professional life)			
< 1	0 (0.0%)	1 (0.4%)	**1 (0.3%)**
1 - 4	1 (1.5%)	6 (2.2%)	**7 (2.1%)**
5 - 9	5 (7.4%)	7 (2.6%)	**12 (3.6%)**
10 - 14	1 (1.5%)	9 (3.4%)	**10 (3.0%)**
>= 15	58 (85.3%)	136 (50.7%)	**194 (57.7%)**
Missing	3 (4.4%)	109 (40.7%)	**112 (33.3%)**

Date of analysis: 06DEC2016

9.1.6 Table A6 - Patient recruitment by country

	Austria	Czech Republic	France	The Netherlands	Spain	**Total**
Number (%) of recruited patients	292 (100%)	581 (100%)	148 (100%)	45 (100%)	632 (100%)	**1698 (100%)**
Eligible	282 (96.6%)	563 (96.9%)	108 (73.0%)	32 (71.1%)	612 (96.8%)	**1597 (94.1%)**
Ineligible	10 (3.4%)	18 (3.1%)	40 (27.0%)	13 (28.9%)	20 (3.2%)	**101 (5.9%)**
Duplicate	0 (0.0%)	5 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**5 (0.3%)**
No complete informed consent available	1 (0.3%)	0 (0.0%)	7 (4.7%)	1 (2.2%)	20 (3.2%)	**29 (1.7%)**
No Baseline questionnaire available	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (4.4%)	0 (0.0%)	**3 (0.2%)**
No baseline prescription	0 (0.0%)	0 (0.0%)	25 (16.9%)	0 (0.0%)	0 (0.0%)	**25 (1.5%)**
Recruited after study recruitment closure	1 (0.3%)	11 (1.9%)	5 (3.4%)	0 (0.0%)	0 (0.0%)	**17 (1.0%)**
No CPA/EE prescription	8 (2.7%)	2 (0.3%)	2 (1.4%)	10 (22.2%)	0 (0.0%)	**22 (1.3%)**

Date of analysis: 06DEC2016

9.1.7 Table A7 - Number of eligible patients by physician specialty and country

	Austria	Czech Republic	France	The Netherlands	Spain	**Total**
Number (%) of eligible patients	282 (100%)	563 (100%)	108 (100%)	32 (100%)	612 (100%)	**1597 (100%)**
Specialty						
Gynecology	282 (100%)	526 (93.4%)	68 (63.0%)	0 (0.0%)	121 (19.8%)	**997 (62.4%)**
Dermatology	0 (0.0%)	37 (6.6%)	27 (25.0%)	8 (25.0%)	110 (18.0%)	**182 (11.4%)**
General Practitioner (GP)	0 (0.0%)	0 (0.0%)	13 (12.0%)	24 (75.0%)	381 (62.3%)	**418 (26.2%)**

Date of analysis: 06DEC2016

9.2 Section B - Demographic and prescription data

9.2.1 Table B1 - Age distribution of eligible patients - France

	CPA/EE
Number (%) of eligible patients	108 (100%)
Age (years)	
n	108 (100%)
Missing	0 (0.0%)
Mean	27.1
SD	8.19
Min	15
Q1	20.8
Median	25.0
Q3	30.6
Max	47
Age groups (years)	
<18	6 (5.6%)
18 - 24	48 (44.4%)
25 - 34	35 (32.4%)
35 - 49	19 (17.6%)
>=50	0 (0.0%)
Missing	0 (0.0%)

Date of analysis: 06DEC2016

9.2.2 Table B2 - Prescription status of CPA/EE users - France

	CPA/EE
Number (%) of eligible patients	108 (100%)
Prescription status	
First-time user (starter)	31 (28.7%)
Continuous user (no break or break of <4 weeks)	64 (59.3%)
Re-starter (break of 4 weeks or more)	13 (12.0%)
Missing	0 (0.0%)

Date of analysis: 06DEC2016

9.2.3 Table B3 - Prescribing reasons for CPA/EE - France

	CPA/EE	95%-CI
Number (%) of eligible patients	108 (100%)	
Reason		
Acne	96 (88.9%)	[80.6%;94.5%]
Seborrhea	12 (11.1%)	[5.9%;18.6%]
Hirsutism	11 (10.2%)	[4.8%;18.4%]
Androgenetic alopecia	4 (3.7%)	[0.9%;9.6%]
PCOS	6 (5.6%)	[1.3%;14.7%]
Contraception	35 (32.4%)	[17.3%;50.8%]
Other reasons	3 (2.8%)	[0.5%;8.2%]
Bleeding problems	0 (0.0%)	[0.0%;0.0%]
Other skin problems	2 (1.9%)	[0.2%;6.7%]
Other hair problems	0 (0.0%)	[0.0%;0.0%]
Gynecologic problems	1 (0.9%)	[0.0%;5.5%]
Personal reasons	0 (0.0%)	[0.0%;0.0%]
Missing	0 (0.0%)	[0.0%;0.0%]
Contraception only	3 (2.8%)	[0.6%;7.9%]

Note: Multiple prescribing indications per patient may be possible.
Note: Frequencies of reasons for prescription are displayed relatively to the number of patients.
Note: Exact 95% CI for proportions are given, variance inflation is considered in terms of effective sample size (Clopper & Pearson, 1934, Korn & Graubard, 1998)
Date of analysis: 15DEC2016

Table B4 - Duration and treatment of androgen-sensitive diseases

9.2.4 Table B4-1 Duration and treatment of acne by severity - France

	Mild	Moderate	Severe	**Total**
Number (%) of eligible patients with acne	50 (100%)	35 (100%)	14 (100%)	**99 (100%)**
Duration (in months)				
<1	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
1 - <6	1 (2.0%)	1 (2.9%)	0 (0.0%)	**2 (2.0%)**
6 - <12	0 (0.0%)	0 (0.0%)	2 (14.3%)	**2 (2.0%)**
>=12	43 (86.0%)	34 (97.1%)	12 (85.7%)	**89 (89.9%)**
Missing	6 (12.0%)	0 (0.0%)	0 (0.0%)	**6 (6.1%)**
Previous treatment				
No	13 (26.0%)	8 (22.9%)	3 (21.4%)	**24 (24.2%)**
Yes	37 (74.0%)	27 (77.1%)	11 (78.6%)	**75 (75.8%)**
Anti-androgenic therapy	4 (8.0%)	3 (8.6%)	0 (0.0%)	**7 (7.1%)**
Antibiotic combined with retinoid (topical)	0 (0.0%)	1 (2.9%)	0 (0.0%)	**1 (1.0%)**
Antibiotics (form of application not specified/unclear)	7 (14.0%)	6 (17.1%)	2 (14.3%)	**15 (15.2%)**
CPA/EE	4 (8.0%)	3 (8.6%)	0 (0.0%)	**7 (7.1%)**
Estradiol systemic	1 (2.0%)	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Isotretinoin (form of application not specified/unclear)	1 (2.0%)	1 (2.9%)	1 (7.1%)	**3 (3.0%)**
Isotretinoin systemic	6 (12.0%)	4 (11.4%)	1 (7.1%)	**11 (11.1%)**
Monoclonal antibody	1 (2.0%)	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Oral Contraceptives (not including CPA/EE)	4 (8.0%)	3 (8.6%)	1 (7.1%)	**8 (8.1%)**
Retinoids combined with benzoyl peroxide (topical)	1 (2.0%)	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Systemic antibiotics	7 (14.0%)	6 (17.1%)	7 (50.0%)	**20 (20.2%)**
Topical antibiotics	0 (0.0%)	2 (5.7%)	1 (7.1%)	**3 (3.0%)**
Topical corticosteroids	0 (0.0%)	1 (2.9%)	0 (0.0%)	**1 (1.0%)**
Topical retinoids	2 (4.0%)	3 (8.6%)	4 (28.6%)	**9 (9.1%)**
Topical treatment with benzoyl peroxide	1 (2.0%)	3 (8.6%)	2 (14.3%)	**6 (6.1%)**
Various topical therapies/ keratolytics	11 (22.0%)	3 (8.6%)	0 (0.0%)	**14 (14.1%)**
Zinc tablets/various oral therapies	1 (2.0%)	3 (8.6%)	2 (14.3%)	**6 (6.1%)**
Missing	2 (4.0%)	0 (0.0%)	1 (7.1%)	**3 (3.0%)**
Treatment failed / insufficient				
Yes	21 (42.0%)	21 (60.0%)	9 (64.3%)	**51 (51.5%)**
No	16 (32.0%)	6 (17.1%)	2 (14.3%)	**24 (24.2%)**
Not applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Concomitant treatment				
No	35 (70.0%)	21 (60.0%)	3 (21.4%)	**59 (59.6%)**
Yes	9 (18.0%)	11 (31.4%)	10 (71.4%)	**30 (30.3%)**
Anti-androgenic therapy	0 (0.0%)	1 (2.9%)	2 (14.3%)	**3 (3.0%)**
Antibiotics (form of application not specified/unclear)	0 (0.0%)	2 (5.7%)	2 (14.3%)	**4 (4.0%)**
Estradiol systemic	0 (0.0%)	1 (2.9%)	0 (0.0%)	**1 (1.0%)**

	Mild	Moderate	Severe	**Total**
Isotretinoin (form of application not specified/unclear)	1 (2.0%)	0 (0.0%)	3 (21.4%)	**4 (4.0%)**
Isotretinoin systemic	0 (0.0%)	0 (0.0%)	1 (7.1%)	**1 (1.0%)**
Retinoids combined with benzoyl peroxide (topical)	0 (0.0%)	2 (5.7%)	0 (0.0%)	**2 (2.0%)**
Systemic antibiotics	1 (2.0%)	5 (14.3%)	3 (21.4%)	**9 (9.1%)**
Topical antibiotics	0 (0.0%)	0 (0.0%)	1 (7.1%)	**1 (1.0%)**
Topical retinoids	2 (4.0%)	4 (11.4%)	3 (21.4%)	**9 (9.1%)**
Topical treatment with benzoyl peroxide	5 (10.0%)	4 (11.4%)	2 (14.3%)	**11 (11.1%)**
Various topical therapies/ keratolytics	2 (4.0%)	1 (2.9%)	0 (0.0%)	**3 (3.0%)**
Zinc tablets/various oral therapies	0 (0.0%)	1 (2.9%)	1 (7.1%)	**2 (2.0%)**
Missing	6 (12.0%)	3 (8.6%)	1 (7.1%)	**10 (10.1%)**

Note: Patient may have more than one entry for previous and concomitant treatment.
Note: For the missing day of disease, the 1st was set; if the month was missing additionally, the 31st of December was used for calculation of the duration.
Date of analysis: 06DEC2016

9.2.5 Table B4-2 Duration and treatment of seborrhea - France

	CPA/EE
Number (%) of eligible patients with seborrhea	32 (100%)
Duration (in months)	
<1	0 (0.0%)
1 - <6	1 (3.1%)
6 - <12	1 (3.1%)
>=12	28 (87.5%)
Missing	2 (6.3%)
Previous treatment	
No	20 (62.5%)
Yes	9 (28.1%)
Isotretinoin (form of application not specified/unclear)	1 (3.1%)
Local therapy/Topical keratolytics	7 (21.9%)
Not applicable	1 (3.1%)
Topical antibiotics	1 (3.1%)
Zinc	1 (3.1%)
Missing	3 (9.4%)
Concomitant treatment	
No	25 (78.1%)
Yes	1 (3.1%)
Missing	1 (3.1%)
Missing	6 (18.8%)

Note: Patient may have more than one entry for previous and concomitant treatment.
Note: For the missing day of disease, the 1st was set; if the month was missing additionally, the 31st of December was used for calculation of the duration.
Date of analysis: 06DEC2016

9.2.6 Table B4-3 Duration and treatment of hirsutism - France

	CPA/EE
Number (%) of eligible patients with hirsutism	14 (100%)
Duration (in months)	
<1	0 (0.0%)
1 - <6	1 (7.1%)
6 - <12	1 (7.1%)
>=12	11 (78.6%)
Missing	1 (7.1%)
Previous treatment	
No	9 (64.3%)
Yes	4 (28.6%)
Anti-androgenic therapy	1 (7.1%)
CPA/EE	1 (7.1%)
Systemic antibiotics	1 (7.1%)
Various topical therapies	1 (7.1%)
Missing	1 (7.1%)
Concomitant treatment	
No	12 (85.7%)
Yes	2 (14.3%)
Various topical therapies	2 (14.3%)
Missing	0 (0.0%)

Note: Patient may have more than one entry for previous and concomitant treatment.
Note: For the missing day of disease, the 1st was set; if the month was missing additionally, the 31st of December was used for calculation of the duration.
Date of analysis: 06DEC2016

9.2.7 Table B4-4 Duration and treatment of androgenetic alopecia - France

	CPA/EE
Number (%) of eligible patients with androgenetic alopecia	6 (100%)
Duration (in months)	
<1	0 (0.0%)
1 - <6	0 (0.0%)
6 - <12	1 (16.7%)
>=12	5 (83.3%)
Missing	0 (0.0%)
Previous treatment	
No	5 (83.3%)
Yes	1 (16.7%)
Vitamins and nutrients	1 (16.7%)
Missing	0 (0.0%)
Concomitant treatment	
No	3 (50.0%)
Yes	2 (33.3%)
Minoxidil	2 (33.3%)
Missing	1 (16.7%)

Note: Patient may have more than one entry for previous and concomitant treatment.
Note: For the missing day of disease, the 1st was set; if the month was missing additionally, the 31st of December was used for calculation of the duration.
Date of analysis: 06DEC2016

9.2.8 Table B4-5 Duration and treatment of PCOS - France

	CPA/EE
Number (%) of eligible patients with PCOS	11 (100%)
Duration (in months)	
<1	0 (0.0%)
1 - <6	2 (18.2%)
6 - <12	0 (0.0%)
>=12	7 (63.6%)
Missing	2 (18.2%)
Previous treatment	
No	7 (63.6%)
Yes	1 (9.1%)
Oral contraceptives (not including CPA/EE)	1 (9.1%)
Missing	3 (27.3%)
Concomitant treatment	
No	6 (54.5%)
Yes	0 (0.0%)
Missing	5 (45.5%)

Note: Patient may have more than one entry for previous and concomitant treatment.
Note: For the day of disease, the 1st was set. If the month was missing, the 31st of December was used for calculation of the duration.
Date of analysis: 06DEC2016

9.2.9 Table B5 - Concomitant use of hormonal contraceptives and CPA/EE - France

	CPA/EE
Number (%) of eligible patients with	108 (100%)
No additional HC	103 (95.4%)
Additional HC	5 (4.6%)
Oral contraceptive	4 (3.7%)
Non-oral contraceptive	1 (0.9%)
Missing	0 (0.0%)
Missing	0 (0.0%)

Date of analysis: 06DEC2016

9.2.10 Table B6 - CPA/EE use and treatment for the indication of acne and hirsutism - France

	CPA/EE	95%-CI
Number (%) of eligible patients with	108 (100%)	
Moderate or severe acne (without hirsutism)	44 (40.7%)	[25.9%;56.9%]
Previous topical treatment only	5 (4.6%)	[1.5%;10.5%]
Previous systemic antibiotic treatment only	8 (7.4%)	[3.3%;14.1%]
Previous topical and/or systemic antibiotic treatment	24 (22.2%)	[10.7%;38.1%]
No previous topical and systemic antibiotic treatment	20 (18.5%)	[10.2%;29.7%]
Other previous treatment only	10 (9.3%)	[4.2%;17.1%]
Missing	1 (0.9%)	[0.0%;5.5%]
Acne with hirsutism	11 (10.2%)	[4.1%;20.2%]
Previous topical treatment only	0 (0.0%)	[0.0%;0.0%]
Previous systemic antibiotic treatment only	2 (1.9%)	[0.2%;6.5%]
Previous topical and/or systemic antibiotic treatment	5 (4.6%)	[1.0%;12.8%]
No previous topical and systemic antibiotic treatment	6 (5.6%)	[1.7%;13.0%]
Other previous treatment only	3 (2.8%)	[0.3%;10.4%]
Missing	0 (0.0%)	[0.0%;0.0%]
Hirsutism (without acne)	3 (2.8%)	[0.5%;8.2%]
Neither moderate or severe acne nor hirsutism	50 (46.3%)	[29.4%;63.8%]

Note: Exact 95% CI for proportions are given, variance inflation is considered in terms of effective sample size (Clopper & Pearson, 1934, Korn & Graubard, 1998)
Date of analysis: 06DEC2016

9.2.11 Table B7 - CPA/EE use and androgen-sensitive diseases – France

	CPA/EE	95%-CI
Number (%) of eligible patients with	108 (100%)	
Acne	99 (91.7%)	[84.2%;96.4%]
Seborrhea	32 (29.6%)	[18.8%;42.5%]
Hirsutism	14 (13.0%)	[6.0%;23.4%]
Androgenetic alopecia	6 (5.6%)	[1.9%;12.3%]
PCOS	11 (10.2%)	[3.7%;21.4%]
At least one of the 5 androgen-sensitive diseases	105 (97.2%)	[91.7%;99.5%]
Androgenetic alopecia only	1 (0.9%)	[0.0%;5.5%]
PCOS only	1 (0.9%)	[0.0%;5.1%]

Date of analysis: 06DEC2016