POST-AUTHORISATION SAFETY STUDY (PASS)

Final Study Report

Title	Patient and Prescriber Survey: Effectiveness measures to investigate awareness, knowledge, and adherence to the Risk Minimisation Measures (RMMs) of the Pregnancy Prevention Programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin)
Version	1.0
Date of last version of the final study report	15 February 2022
EU PAS/ENCePP register number	EUPAS38096 **http://www.encepp.eu/encepp/viewResource.htm?id=40500**
Active substance	Oral retinoids: • Acitretin: D05BB02 • Alitretinoin: D11AH04 • Isotretinoin: D10BA01
Medicinal product	List is provided in Annex 2.4
Product reference	List is provided in Annex 2.5
Procedure number	DE/H/xxxx/WS/1115
Marketing authorisation holder(s)	The joint initiative involves several companies *via* a consortium (a full list of all Marketing Authorisation Holders [MAHs] is provided below)

	ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS LIMITED, ALMIRALL, AUROBINDO, ARISTO PHARMA, BAILLEUL, BAUSCH HEALTH COMPANIES, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GLAXOSMITHKLINE, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, KARLING PHARMA, MEDINFAR, MORNINGSIDE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, SANOWISS, STADA, SUN PHARMA, TARGET, and TEVA
Joint PASS	Yes
Research question and objectives	This survey aims to assess the effectiveness of the updated RMMs among female oral retinoid patients/caregivers who are of childbearing potential and their prescribers and to assess patients'/caregivers' and prescribers' (healthcare professionals [HCPs]) awareness, knowledge, and adherence to the PPP. **Objectives - HCP and Patient/Caregiver Survey** Primary objective: • To assess the effectiveness of the PPP based on pre-defined success thresholds for PPP awareness, knowledge, and adherence in HCPs and patients/caregivers Secondary objectives: • To assess HCPs' and patients'/caregivers' awareness of the updated PPP • To assess HCPs' and patients'/caregivers' knowledge of the risks and RMMs associated with the use of oral retinoids • To assess whether HCPs and patients/caregivers adhere to the RMMs of the updated PPP

Country(-ies) of study	France, Germany, Greece, Spain, Norway, United Kingdom and Poland
Author	[redacted] [redacted] IQVIA Real World Solutions, France [redacted] IQVIA Real World Solutions, Portugal [redacted] IQVIA Real World Solutions, India [redacted] IQVIA Real World Solutions, India On behalf of the oral retinoids consortium

This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the guideline on good pharmacovigilance practices (GVP) Module VIII – Post-Authorisation Safety Studies, and the guidelines for good pharmacoepidemiology practice (GPP) (ISPE).

MARKETING AUTHORISATION HOLDER(S)

MAHs	ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS LIMITED, ALMIRALL, AUROBINDO, ARISTO PHARMA, BAILLEUL, BAUSCH HEALTH COMPANIES, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GLAXOSMITHKLINE, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, KARLING PHARMA, MEDINFAR, MORNINGSIDE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, SANOWISS, STADA, SUN PHARMA, TARGET, and TEVA
MAHs contact person	On behalf of MAHs for the purpose of the CMDh work-sharing procedure: [redacted] Head of Regulatory Affairs Diamond BioPharm Limited, [redacted]

1 ABSTRACT

Title	Prescriber and Patient/Caregiver Survey: Effectiveness measures to investigate awareness, knowledge, and adherence to the Risk Minimisation Measures (RMMs) of the Pregnancy Prevention Programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin)
Keywords	Healthcare professional survey, Patient/Caregiver survey, Oral retinoids, Pregnancy Prevention Programme, Risk Minimisation Measures
Background and rationale	Retinoic acid analogues comprise of a group of compounds known as the retinoids and are available as topical and oral preparations. Oral (systemic) retinoid therapy is associated with teratogenicity. Therefore, women who are pregnant or are planning a pregnancy must not be prescribed oral retinoids. Strict prescription guidelines and a PPP have been put in place since 2003, but exposure during pregnancy still occurs. In January 2016 the Pharmacovigilance Risk Assessment Committee (PRAC) noted that there were concerns about the effectiveness of the PPP and the need for a further assessment. In July 2016, the United Kingdom (UK) initiated an Article 31 referral requesting the PRAC to review the benefit-risk profile of oral and topical retinoids. The PRAC completed the review on February 2018 and concluded that despite the PPP, cases of pregnancy during treatment with oral retinoids continued to occur and studies assessing effectiveness of the PPP for isotretinoin described poor compliance, particularly with pregnancy testing and the use of contraception. After the review, the PRAC recommended amendments to the product information consistently for acitretin, alitretinoin, and isotretinoin as well as updates to the PPP including the associated educational materials (EMs). In June 2018, the decision to strengthen the recommendations for pregnancy

	prevention for oral retinoids was endorsed by the European Commission (EC). In addition to an update of the RMMs, as an outcome of Article 31 referral, the PRAC requested assessment of effectiveness of the RMMs through the conduct of two Post-Authorisation Safety Studies (PASS) particularly with regards to patient and prescriber awareness, and adherence to the PPP. A survey (Category 3 PASS), described in the current report, was conducted to assess healthcare professionals' (HCPs') and patients'/caregivers' awareness, knowledge, and adherence to the PPP.
Research question and objectives	This survey aimed to assess the effectiveness of the updated RMMs among females of childbearing potential who are treated with oral retinoids, and to assess prescribers' and patients'/caregivers' awareness, knowledge, and adherence to the PPP. **Primary objective:** • To assess the effectiveness of the PPP based on the pre-defined success thresholds for PPP awareness, knowledge, and adherence in HCPs and patients/caregivers. **Secondary objectives:** • To assess HCPs' and patients'/caregivers' awareness of the updated PPP. • To assess HCPs' and patients'/caregivers' knowledge of the risks and RMMs associated with the use of oral retinoids. • To assess whether HCPs and patients'/caregivers adhere to the RMMs of the updated PPP.
Study design	This survey was cross-sectional, multinational, and conducted among HCPs (dermatologists and general practitioners [GPs]) and patients/caregivers in seven European countries (i.e., France, Germany, Greece, Norway, Poland, the UK, and Spain [the latter included in HCP survey only]).

	The HCP survey was initiated first. This was followed by the patient/caregiver survey, where the participants were invited by their HCPs. The questionnaire of the survey was web-based. Access to the web-based questionnaire interface was limited to the invited participants. Each participant received a unique link to the questionnaire and the survey was designed for the respondents to participate only once.
Setting	Based on sales data (IQVIA MIDAS June 2018), implementation, and uptake of the RMMs and geographical distribution in Europe, countries such as France, Germany, Greece, Norway, Poland, the UK, and Spain (the latter in HCP survey only) were included in the survey. In order to have a uniform approach across all target countries, a decision was made to include only dermatologists and GPs, who represented 98% of the oral retinoid prescribers in three of the major European markets. HCPs from both office-based practices and hospitals were considered for the study. In each country, eligible HCPs were identified according to their speciality as specified in IQVIA *OneKey* database and stratified using a pragmatic split of two dermatologists for every one GP. Recruitment of HCPs was carried out in batches, each created by random sampling of HCPs belonging to each stratum from the entire *OneKey* database. When the targeted sample size for a specific stratum was not reached by the end of outreach to all HCPs in one batch, more batches within each stratum were further selected from *OneKey* database in order to reach out to HCPs from those batches. The recruitment in each stratum (HCP speciality/country) was stopped when the target number was reached. If the list of HCPs was exhausted in any particular

	stratum, recruitment in this stratum was prematurely ended, and a strategy was determined to adjust the sample size with associated weighting. Patients (females of childbearing potential [i.e., 13 to 49 years of age]) and caregivers (for patients between 13 and 17 years of age, their parent, guardian, or caregiver participated in the study) were invited by HCPs who had participated in the HCP survey (and had agreed to distribute the patient/caregiver questionnaires). After the HCP target was met, additional HCPs from the same sampling frame were no longer asked to complete the questionnaire but were requested to continue recruiting patients/caregivers. Each HCP could invite up to six patients/caregivers from the same HCP practice.
Subjects and study size	A sample size of 450 completed questionnaires from HCPs who had treated female patients of childbearing potential with oral retinoids according to the local label at least once in the six months prior to participation in the survey was targeted. A sample size of 150 completed patient/caregiver questionnaires was targeted for patients who had been prescribed with oral retinoids according to the local label at least once in the six months prior to participation in the survey. The study sample was complemented with the recruitment of additional individuals who prescribed and/or used alitretinoin (sample boost) to mitigate the fact that alitretinoin had a small market compared with isotretinoin and acitretin.

Variables	***Variables collected through the HCP questionnaire*** The following variables were collected through the HCP questionnaire: • Variables related to HCPs inclusion/exclusion criteria (used to determine survey eligibility; not part of the statistical analysis): o Status of employment by any pharmaceutical company, IQVIA or regulatory bodies (Yes, No) (Screening question [S]1) o Prescription of oral retinoids to female patients in the previous six months (Yes, No) (S2) • Variables related to HCPs retinoid-prescribing practice: o Type of practice setting (Private practice/office-based, University hospital, Public hospital, Private hospital, Other) (Q1) o Type of oral retinoids HCP ever prescribed (Acitretin, Alitretinoin, Isotretinoin) (Q2) o Estimate number of female patients treated with each oral retinoid in the previous six months (Q2a) o Age group(s) of the female patients to whom oral retinoids were prescribed in the previous six months (Female [<13 years], Female of childbearing potential [>13 years and <50 years], Female >50 years, I do not recall) (Q3) o HCP main specialisation (General practice [GP]/family physician, Dermatologist, Other speciality) (Q4) o Duration of practice in main specialisation (<1 year, 1–5 years, 6–10 years, >10 years) (Q4a) o Whether HCP require the patient to consult a dermatologist in order to confirm the need to use oral retinoids (Yes, No) (Q4b) o Documents read/consulted when prescribing oral retinoids (Summary of Product Characteristics [SmPC/Label], Physician guide/checklist

	depending on the country, Direct Healthcare Professional Communication [DHPC], Other EMs, None) (Q5) • Variables related to HCPs' awareness of the PPP for oral retinoids: o Receipt of materials concerning the treatment of women of childbearing potential with oral retinoids (SmPC/Patient information leaflet, Physician guide or checklist/acknowledgement depending on the country, Patient reminder card, Other EMs, None of the above) (Q8) o Reading the materials concerning the treatment of women of childbearing potential with oral retinoids (SmPC/Patient information leaflet, Physician guide or checklist/acknowledgement depending on the country, Patient reminder card, Other EMs, None of the above) (Q10) • Variables related to knowledge of the risks of oral retinoid use and the PPP: o Risks of oral retinoid use (True, False, I do not know) (Q11) o PPP important messages regarding oral retinoid treating practices for female patients (True, False, I do not know) (Q12) o PPP important messages regarding oral retinoids prescribing restrictions (True, False, I do not know) (Q13) • Variables related to HCPs' adherence to the PPP: o Frequency of monitoring measures, namely requirement for medically supervised pregnancy test and timing for female patients who are of childbearing potential (see different answer options in Annex 2.6) (Q6) o Prescription practices regarding oral retinoids, namely how frequently HCP discussed and/or prescribed contraception to female patients of

	childbearing potential before prescribing oral retinoids (Always, Often, Sometimes, Seldom, Never) (Q7, Q7a) o Time period(s) of prescribing or ensuring contraception for female oral retinoid patients who are of childbearing potential or referring them to a gynaecologist for contraception (see different answer options in Annex 2.6)) (Q7b) o Discussion and distribution of PPP EMs to female patients treated with oral retinoids who are of childbearing potential or their respective caregivers (SmPC/Patient information leaflet, Physician guide or checklist/acknowledgement form depending on the country, Patient reminder card, Other EMs, None of the above) (Q8a, Q8b) o Schedule of follow-up visits with their female oral retinoid patients of childbearing potential (Every two weeks, Every month, Every three months, Every six months, Less often than every six months, I do not schedule follow-up visits) (Q9) • Additional variables to characterise adherence to the PPP: o Rationale for not asking female patient on oral retinoids to undergo medically supervised pregnancy testing (Not being of childbearing age [<13 or >49 years old], Abstaining from sexual activity/having no sexual partner, Having amenorrhea, Having undergone hysterectomy or bilateral [salpingo-]oophorectomy, Having a medical condition that led to infertility, Having undergone a non-reversible sterilisation procedure, Other reasons, I always consider medically supervised pregnancy testing for all female oral retinoid patients regardless of the above-mentioned conditions) (Q6a) o Rationale for not prescribing or ensuring contraception to female oral retinoid patient or not referring them to a gynaecologist for

	contraception (Not being of childbearing age [<13 or >49 years old], Abstaining from sexual activity/having no sexual partner, Having amenorrhea, Having undergone hysterectomy or bilateral [salpingo-]oophorectomy, Having a medical condition that led to infertility, Having undergone a non-reversible sterilisation procedure, Other reasons, I always consider medically supervised pregnancy testing for all female oral retinoid patients regardless of the above-mentioned conditions) (Q7c) ***Variables collected through the patient/caregiver questionnaire*** The following variables were collected through the patient/caregiver questionnaire: • Variables related to patient/caregiver inclusion/exclusion criteria (used to determine survey eligibility; not part of the statistical analysis): o Patient age group (<13 years old, 13 to 17 years old, 18 to 49 years old, ≥50 years old) (S1) o Confirming being a parent or a guardian of a patient from 13 to 17 years old where applicable (Yes, No) (S1a)[1] o Patient gender (Female, Male) (S2)[1] o Status of employment by any pharmaceutical company or advertising/ research agency (Yes, No) (S3)[1] o Current or previous oral retinoid product used within the last six months for the longest period (list presented in Annex 2.7.) (S4) o Having a medical condition that prevents patient to become pregnant at the time of the survey (S5) o Condition preventing patient to become pregnant (S5a)[1]

[1] Information used to determine survey eligibility; not part of the statistical analysis

	• Variables related to the patients treated with oral retinoids: o Length of treatment during the previous six months (less than one month, one to two months, two to four months, four to six months) (Q1) o Treatment status (Currently on treatment, Finished most recent treatment course less than one month before, Finished most recent course of oral retinoids more than one month before) (Q1a) o Whether most recent treatment course of oral retinoids was more than six months ago (Yes, No) (Q1b) • Variables related to the prescribing HCPs: o Main specialisation of HCP who initiated oral retinoid (GP/dermatologist/other/I do not recall) (Q2) • Variables related to the patients'/caregivers' awareness of PPP for oral retinoids: o Whether HCP discussed the risks associated with becoming pregnant while taking oral retinoids with the patient (Yes, No) (Q5) o Receipt of EMs containing information on the risks of oral retinoids use from the HCP (Yes, No), namely ▪ Patient reminder cards before starting the treatment with oral retinoids that patient received from HCP/ inside the package (for those recruited from Germany) (Q6) ▪ Read or discussed the patient reminder card with HCP (Q6a) • Additional variables to characterise awareness of the PPP: o Receipt of other materials containing information on the risks of oral retinoids use from the HCP, namely:

	▪ Other EMs apart from the patient reminder card containing information on the risks of oral retinoids use that patient received from the HCP (Yes, No, I do not recall) (Q7) ▪ Whether the patient read or discussed the other EMs with HCP (Yes, No, I do not recall) (Q7a) o Found information on the use of oral retinoids during pregnancy in medicine package (Yes, No, The medication was received directly from the HCP, and it was not in the package, I do not recall) (Q8) o Advice(s) that patient received from the HCP while taking oral retinoids (Receiving contraception for the entire duration of treatment with oral retinoid, Conducting regular pregnancy testing for the entire duration of treatment with oral retinoids, None of the above, I do not recall) (Q9) • Variables related to then patients'/caregivers' knowledge of the risks of oral retinoid use and the PPP: o Knowledge of risks associated with oral retinoid use (True, False, I do not know) (Q11) o Knowledge of RMMs for oral retinoids (True, False, I do not know) (Q12) • Additional variables to characterise knowledge of the PPP: o Confidence in understanding the topics discussed with the HCP or described in EMs (Yes, No, I am not sure) (Q10) • Variables related to the patients'/caregiver's adherence to the PPP: o Pregnancy testing before, during and after treatment with oral retinoids (Yes, No) (Q3a, Q3b, Q3c, Q3d and Q3e) o Use of contraceptives before, during and after treatment with oral retinoids (Yes, No) (Q4a, Q4b, Q4c, and Q4d)

	• Additional variables to characterise adherence to the PPP: o Types of pregnancy test taken while being treated with oral retinoids, before treatment initiation or after treatment discontinuation (Medically supervised pregnancy test, Home pregnancy test) (Q3f) o Reason(s) for not taking pregnancy test during the most recent treatment course with oral retinoids (if applicable) (Did NOT have any sexual activity with a man during treatment with [product], Forgot to take a pregnancy test, Was NOT aware that taking pregnancy tests was needed while taking [product], Was aware that taking pregnancy tests was needed, but decided NOT to take any, Missing or irregular menstrual cycle, Having a medical condition that prevents me from becoming pregnant and having children, None of the above) (Q3g) o Types of contraceptives used before, during and after treatment with oral retinoids (list presented in Annex 2.7.ist) (Q4e) o Reason(s) for not using contraceptives during the most recent treatment course with oral retinoids (if applicable) (Did NOT have any sexual activity with a man during treatment with [product], Forgot to take contraception, Was NOT aware that taking contraception tests was needed while taking [product], Was aware that taking contraception tests was needed, but decided NOT to take any, Missing or irregular menstrual cycle, Having a medical condition that prevents me from becoming pregnant and having children, None of the above) (Q4f)
Results	***Participants*** ***HCPs: Descriptive Data*** Out of 14,996 reachable and eligible HCPs, 3.2% (n=477) submitted the complete questionnaire and thus, were available for analysis. Approximately two thirds of the 477 HCPs were dermatologists (n=313, 65.6%) and the remaining were

	GPs/family physicians (n=164, 34.4%). Overall, 64.8% (n=309) of the HCPs reported working in a private practice/office-based setting, 26.6% (n=127) in university hospital, 21.0% (n=100) in public hospital, 5.0% (n=24) in private hospital, and 2.7% (n=13) working in other practice setting (categories for Q1 are not mutually exclusive). Overall, 98.5% (n=470) of the HCPs had prescribed isotretinoin, 64.6% (n=308) had prescribed acitretin and 47.4% (n=226) had prescribed alitretinoin at least once in the past. When considering the number of HCPs who prescribed each oral retinoid to at least one patient in the previous six months, 59.5% (n=284) prescribed acitretin, 98.3% (n=469) prescribed isotretinoin and 41.5% (n=198) prescribed alitretinoin (categories for Q2 and Q2a are not mutually exclusive). Among 198 alitretinoin prescribers, 172 (86.9%) were recruited from the main sample and 26 (13.1%) from the boost sample. ***Patients/caregivers: Descriptive Data*** There were 116 participating patients/caregivers, with 85.3% (n=99) of them belonging to the 18 to 49 years age group. When queried about the oral retinoid they had been taking the longest in the previous six months, most patients/caregivers (n=97, 83.6%) indicated isotretinoin whereas 11.2% (n=13) and 5.2% (n=6) indicated alitretinoin and acitretin, respectively. Among the 13 patients receiving alitretinoin, one was recruited from the main study sample and 12 from the boost sample. Most of the patients (n=92, 79.3%) were taking the oral retinoids at the time of survey participation, whereas 12.9% (n=15) patients had finished the most recent course of oral retinoids within the previous month and 7.8% (n=9) finished the most recent course more than one month before participation. When asked about the medical speciality which initiated the most recent treatment course of oral retinoids, 87.1% (n=101) recognised them to be dermatologists.

	Analysis of Overall Success in HCPs Success of the PPP for HCPs in all three domains was not met in this survey as only the awareness domain achieved its pre-defined success threshold of 75% (weighted proportion for awareness: 92.6% [95% confidence interval {CI}: 89.4%, 94.9%]). The weighted proportions of HCPs who achieved individual success in the knowledge domain was close to the pre-defined protocol threshold of 80% (weighted proportion for knowledge: 75.3% [95% CI: 70.4%, 79.5%]). In addition, the pre-defined protocol threshold of 80% for the adherence domain was not met (weighted proportion for adherence: 37.4% [95% CI: 32.3%, 42.8%]). ***HCPs: Analysis of Success in Awareness Domain*** The overall weighted mean score estimate for the awareness domain was 93.4% (95% CI: 90.9%, 95.9%), with standard deviation (SD) of 24.01% and a median (Q_1, Q_3) of 100% (100%, 100%). Overall, 93.3% had access to the SmPC/patient information leaflet or the physician guide/checklist (depending on the country) and 91.6% had read any of those materials. ***HCPs: Analysis of Success in Knowledge Domain*** The overall weighted mean score was 83.2% (95% CI: 81.8%, 84.6%), with SD of 13.68% and median (Q_1, Q_3) of 80% (80%, 90%). For questions concerning risk of oral retinoid use, >95% HCPs agreed with all the statements except for "Oral retinoid treatment during pregnancy poses a risk of miscarriage", which was agreed by only 64.8% (95% CI: 59.4%, 69.8%) of HCPs. For the questions related to PPP and important messages for oral retinoid practices among female patients, >95% agreed that women of childbearing potential must use at least one highly effective method of contraception and undergo pregnancy testing before treatment initiation, regularly during treatment, and after discontinuation with oral retinoids; also, that they must be provided with EMs and

advice on contraception in relation to their oral retinoid treatment. The vast majority (87.0% [95% CI: 83.3%, 90.0%]) also correctly identified that the statement "Women of childbearing potential MUST continue using contraception and undergoing pregnancy testing for AT LEAST 5 years after discontinuation of treatment with any oral retinoid" was false. In general, a lower proportion of HCPs agreed with the statements regarding prescribing restrictions: 68.6% (95% CI: 63.4%, 73.3%) agreed that prescriptions of oral retinoids for women of childbearing potential should be limited to 30 days' supply and 76.5% (95% CI: 71.6%, 80.7%) agreed that continuation of treatment with oral retinoids for women of childbearing potential requires a new prescription every month throughout the course of treatment. In addition, nearly half of the HCPs (49.3% [95% CI: 43.9%, 54.6%]) identified that the statement "Prescriptions for oral retinoids for women of childbearing potential are valid for up to 14 days from the date of prescription" was false, while 21.2% (95% CI: 17.3%, 25.7%) did not know.

HCPs: Analysis of Success in Adherence Domain Among HCPs

The overall weighted mean score was 69.4% (95% CI: 67.2%, 71.6%), with SD of 20.47% and median (Q_1, Q_3) of 75% (57%, 86%). For questions concerning the requirement and timing for medically supervised pregnancy testing, 60%-70% correctly indicated requiring their female patients of childbearing age to undergo a medically supervised pregnancy test during oral retinoid and after isotretinoin and alitretinoin treatment. Only 18.7% (95% CI: 15.1%, 23.0%) correctly indicated requiring their female patients of childbearing age to undergo a medically supervised pregnancy test within a maximum of seven days before the first dose, with 52.1% (95% CI: 46.8%, 57.4%) requiring it to be done within a maximum of three days before first dose, followed by 23.3% (95% CI: 19.1%, 28.1%) requiring it to be done in ten days at most before the first dose. Among the prescribers of acitretin in the previous six months, 29.6% (95% CI: 24.1%, 35.8%)

	correctly indicated requiring their female patients of childbearing age to undergo a medically supervised pregnancy test regularly for three years after treatment discontinuation. A similar proportion (29.8% [95% CI: 24.4%, 35.8%]) indicated not requiring tests to be done after treatment discontinuation, and 23.3% (95% CI: 18.2%, 29.2%) and 17.3% (95% CI: 13.3%, 22.3%) required tests to be done regularly for two years and one year after discontinuation, respectively. For questions related to the contraception recommendations/prescription practice, 92.3% (95% CI: 89.1%, 94.6%) of the HCPs reported that they always spoke to their female patients of childbearing potential regarding their contraception practices before prescribing oral retinoids, and the majority always (68.4% [95% CI: 63.3%, 73.1%]) or often (19.8% [95% CI: 16.0%, 24.3%]) prescribed/recommended contraception for their patients or referred them to a gynaecologist for contraception. Among 469 HCPs who prescribed/recommended contraception or refer patients to gynaecologist at least once, 92.4% (95% CI: 89.1%, 94.8%) did so before the first oral retinoid prescription, 88.4% (95% CI: 84.7%, 91.3%) regularly during the oral retinoid treatment course, 80.1% (95% CI: 75.5%, 84.0%) at one month after isotretinoin or alitretinoin discontinuation, and 68.0% (95% CI: 61.9%, 73.6%) regularly for three years after acitretin discontinuation. Among 336 HCPs who received/had access to the physician guide/checklist (depending on the country), 85.9% (95% CI: 81.1%, 89.7%) conveyed that they would go through the materials with their female patients of childbearing potential or caregivers and 71.7% (95% CI: 65.8%, 76.9%) said they would distribute them to their patients or caregivers. Among 246 HCPs who received/had access to the patient reminder cards, 86.4% (95% CI: 81.5%, 90.1%) said they would distribute them to their female patients of childbearing potential or their caregivers. Overall, 70.6% of HCPs had a monthly or every 2 weeks

	follow-up visit with their female oral retinoid patients who are of childbearing potential, which were the options considered for answering the question correctly. ***Analysis of Overall Success in Patients/Caregivers*** Success of the PPP for patients/caregivers in all three domains was not met in this survey as only the awareness domain achieved its pre-defined success threshold of 60% (weighted proportion for awareness 90.5% [95% CI: 83.2%, 94.8%]). The weighted proportions of patients/caregivers who achieved individual success in the knowledge domain was close to the pre-defined protocol threshold of ≥80% (weighted proportion for knowledge: 78.9% [95% CI: 59.4%, 90.5%]). Moreover, the pre-defined protocol threshold of ≥80% for the adherence domain was not met (weighted proportion for adherence: 58.4% [95% CI: 41.4%, 73.6%]). ***Patients/caregivers: Analysis of Success in Awareness Domain*** The overall weighted mean success score estimate for the awareness domain among patients/caregivers was 94.0% (95% CI: 90.6%; 97.4%), with SD of 16.42% and median (Q_1, Q_3) of 100% (100%, 100%). Overall, >90% of the patient/caregivers had discussions with their HCPs on the risks associated with becoming pregnant while taking oral retinoids, received patient reminder cards from HCP before starting the treatment with oral retinoid, and read or discussed patient reminder cards with their HCP before starting the treatment with oral retinoids. ***Patients/caregivers: Analysis of Success in Knowledge Domain*** For patients, the overall weighted mean success score estimate for the knowledge domain was 88.1% (95% CI: 81.9%, 94.3%), with SD of 16.53% and the median (Q_1, Q_3) of 100% (80%, 100%). For question related to knowledge of risks associated with oral retinoid use >98% of the patients/caregivers correctly agreed that treatment with oral retinoid is harmful to an unborn baby and that oral retinoids must not be taken during

	pregnancy. For questions related to the knowledge of RMMs for oral retinoids, >80% of patients/caregivers correctly agreed that women who could become pregnant and are taking oral retinoids must use at least one highly effective method of contraception for one month before treatment initiation and continuously during treatment and must not stop taking contraception immediately after discontinuation of treatment with oral retinoids. A lower proportion (68.0% [95% CI: 48.4%, 82.4%]) agreed that women who could become pregnant and are taking oral retinoids must undergo medically supervised pregnancy testing before during and after treatment. ***Patient/caregivers: Analysis of Success in Adherence Domain*** For patients/caregivers, the overall weighted mean success score for the adherence domain was 77.8% (95% CI: 66.6%, 89.1%), with SD of 30.65% and median (Q_1, Q_3) of 100% (50%, 100%). For questions related to pregnancy testing, 93.6% (95% CI: 86.0%, 97.3%) of patients were tested for pregnancy before starting treatment with oral retinoids, 84.7% (95% CI: 68.3%, 93.4%) of the patients who had been taking oral retinoids for two to six months had undergone regular monthly pregnancy testing while on treatment, 76.1% (95% CI: 51.4%, 90.5%) of the patients who had been taking oral retinoids for one to two months had undergone at least one pregnancy test and 81.9% (95% CI: 49.2%, 95.5%) of the patients who finished the most recent treatment course of alitretinoin or isotretinoin more than a month before, had undergone at least one pregnancy test approximately one month after treatment discontinuation. No information was available for acitretin as no patient finished the most recent treatment course with this oral retinoid more than one month before the survey participation. For questions related to contraception use, 68%-73% of patients used at least one form of contraception for one month before starting treatment and continuously while taking oral retinoids. In addition, 81.9% (95% CI: 49.2%, 95.5%) of the

	alitretinoin or isotretinoin users who finished their last treatment course more than one month before participation and 96.3% (95% CI: 78.2%, 99.5%) of the acitretin users or alitretinoin/isotretinoin users who finished their last treatment course less than one month before participation used at least one form of contraception for one month continuously after treatment with oral retinoids was stopped.
Discussion	This study gave important insights about awareness, knowledge, and adherence to the RMMs of the PPP for oral retinoids among HCPs and patients/caregivers. Success of the PPP for HCPs and patients/caregivers in all three domains was not met in this survey as the success criteria were achieved only for the awareness domain. The pre-defined success threshold was neither met for knowledge (nearly met) nor adherence among both HCPs and patients/caregivers. HCPs and patients/caregivers were well aware about the RMMs of the PPP. Both indicated that oral retinoids should not be taken during pregnancy as they posed a risk of teratogenicity. They also indicated the importance of contraception and pregnancy testing. Success in the knowledge domain for HCPs was conditioned to strict criteria for assessing days' supply/length of prescription while differences in healthcare systems and the patients' individual circumstances influence how frequently patients are followed-up and renew their prescriptions which may differ from the expected monthly monitoring. The European Medicines Agency (EMA) acknowledged that "while it was recognised that there should be regular follow-up, which ideally should be on a monthly basis, there may be situations where this is not absolutely essential". The reason why the knowledge criteria were not met was likely due to the majority of patients responding that they have taken home pregnancy tests and thus did not consider that medically supervised pregnancy tests were needed. The pre-defined threshold for success in the adherence domain was not met by HCPs nor patients/caregivers. The adherence among patients/caregivers who are

	the ultimate users of the product was higher than HCPs in the survey sample but results cannot be directly compared as the questions were different (e.g. pregnancy testing for HCPs referred to "medically supervised pregnancy testing" whereas patients could have complied with the home pregnancy tests). In addition, the criteria for HCPs to correctly answer the questions regarding medically supervised pregnancy tests were restrictive as they warranted specific timing and frequency. In addition, despite the questions referred to women of childbearing age, it cannot be excluded that some HCPs responded after considering their overall pool of patients treated with oral retinoids criteria, which may include female patients for whom contraception or pregnancy testing may not be relevant. Another finding was that the adherence of HCPs to both conduct of medically supervised pregnancy testing and contraception seemed to decrease once the treatment with oral retinoids was stopped.
MAHs	ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS LIMITED, ALMIRALL, AUROBINDO, ARISTO PHARMA, BAILLEUL, BAUSCH HEALTH COMPANIES, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GLAXOSMITHKLINE, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, KARLING PHARMA, MEDINFAR, MORNINGSIDE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, SANOWISS, STADA, SUN PHARMA, TARGET, and TEVA

Name(s) and affiliation(s) of principal investigator(s)	Not applicable