The Oral Retinoids MAH Consortium

POST-AUTHORISATION SAFETY STUDY (PASS)
Drug Utilisation Study – Final Report

Title	Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilisation study (DUS) using secondary data
Version	Version 1.0
Date of last version of the final study report	02 December 2022
EU PAS / ENCePP register number	EUPAS32302
Active substance	Oral retinoids: • Acitretin: D05BB02 • Alitretinoin: D11AH04 • Isotretinoin: D10BA01
Medicinal product	See List of Medicinal Products Marketed by the Oral Retinoids Consortium Per Country Included in the Study
Product reference	See Annex 1 of the Protocol submission package to PRAC
Procedure number	EMEA/H/N/PSP/J/0069.2
Marketing authorisation holder(s)	The joint initiative involves several companies via consortium (a full list of all Marketing Authorisation Holders (MAHs) is provided in Appendix 2.1 List of Medicinal Products Marketed by the Oral

	Retinoids Consortium Per Country Included in the Study Appendix 2.1 List of Medicinal Products Marketed by the Oral Retinoids Consortium Per Country Included in the Study 2CARE4GENERICS, ALFASIGMA ESPAÑA, , ALMIRALL, ARISTO PHARMA, AUROBINDO, BAILLEUL, BAUSCH HEALTH, DERMAPHARM, ENNOGEN HEALTHCARE, ESPECIALIDADES FARMACÉUTICAS CENTRUM, EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, ISDIN, MEDINFAR, MORNINGSIDE HEALTHCARE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SANOSWISS, LABORATOIRES SMB S.A., STADA, SUN PHARMA, TARGET, and TEVA
Joint PASS	Yes
Research question and objectives	**Research question**: Is there a difference in physicians' prescribing and monitoring practice in the periods before and after the update of the pregnancy prevention programme (PPP) for the oral retinoids acitretin, alitretinoin, and isotretinoin when treating women of childbearing potential? ***1) Primary objective:*** To evaluate the changes in the prescribing and monitoring practices following the update of the PPP in females of childbearing potential receiving prescriptions of the oral retinoids acitretin, alitretinoin, or isotretinoin by comparing the following key elements of the PPP between the pre- and the post-implementation period: (prescription) contraceptive use before, during, and after treatment with oral retinoids, time interval between prescription dates for oral retinoids during treatment episode and laboratory pregnancy tests – where available – before, during, and after treatment with oral retinoids ***2) Secondary objectives:*** • To describe the patient profile during the pre- and the post- implementation period, with respect to: o Patient age o Indication for oral retinoids

	• To describe the prescriber speciality during the pre- and the post-implementation period
	• To describe the exposure characteristics during the pre- and the post-implementation period, with respect to:
	  ○ Active substance
	  ○ Dose
	  ○ Treatment duration
	• To describe the incidence and, where available, outcomes of pregnancies exposed to oral retinoids during the pre- and the post-implementation period
	• To stratify the key elements of the PPP described in the primary objective by oral retinoid substance
	• To describe trends in the physician's prescribing and monitoring practice of oral retinoids with respect to measures of the PPP (contraceptive use, performance of pregnancy tests) over the entire study duration

Country(-ies) of study	France, Germany, Spain, and Sweden
Author team	[redacted], IQVIA Real-World Solutions [redacted], IQVIA Real-World Solutions [redacted] IQVIA Real-World Solutions [redacted]IQVIA Real World Solutions [redacted] IQVIA Real-World Solutions [redacted]IQVIA Real-World Solutions On behalf of the Oral Retinoids MAH 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) (1).

1 MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Oral retinoids consortium of MAH (see below the list of MAHs)
MAH contact person	On behalf of MAHs: [redacted]

Marketing Authorisation Holders (MAHs) involved in the oral retinoids consortium: 2CARE4GENERICS, ALFASIGMA ESPAÑA, , ALMIRALL, ARISTO PHARMA, AUROBINDO, BAILLEUL, BAUSCH HEALTH, DERMAPHARM, ENNOGEN HEALTHCARE, ESPECIALIDADES FARMACÉUTICAS CENTRUM, EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, ISDIN, MEDINFAR, MORNINGSIDE HEALTHCARE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SANOSWISS, LABORATOIRES SMB S.A., STADA, SUN PHARMA, TARGET, and TEVA. For a full list of companies and contact details see Appendix 2.2 List of Companies - MAHs that constitute the oral retinoids consortium and Appendix 2.3 List of Represented MAHs Contact Details.

2 ABSTRACT

Title	Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilisation study (DUS) using secondary data
Keywords	Oral retinoids, pregnancy prevention programme (PPP), drug utilisation study (DUS), post-authorisation safety study (PASS)
Rationale and background	Oral retinoids are used to treat severe acne and other skin conditions. Retinoid therapy is associated with teratogenicity. Therefore, women who are pregnant or planning a pregnancy must not be prescribed retinoids. Strict prescription guidelines and a pregnancy prevention programme (PPP) have been put in place, but exposure during pregnancy still occurs. The European Medicines Agency (EMA) therefore mandated a DUS to assess the effectiveness of the updated risk minimisation measures (RMMs).
Research question and objectives	**Research Question:** Is there a difference in physicians' prescribing and monitoring practice in the periods before and after the update of the PPP for the oral retinoids acitretin, alitretinoin, and isotretinoin when treating women of childbearing potential? **Primary objective:** To evaluate the changes in the prescribing and monitoring practices following the update of the PPP in females of childbearing potential receiving prescriptions of the oral retinoids acitretin, alitretinoin, or isotretinoin by comparing the following key elements of the PPP between the pre- and the post-implementation period: • Contraceptives1 before, during, and after treatment with oral retinoids • Time interval between oral retinoid prescription dates • Laboratory pregnancy tests - before, during, and after oral retinoid treatment **Secondary objectives:** • To describe the patient profile during the pre- and the post-implementation period, with respect to: o Patient age o Indication for oral retinoids

[1] contraceptive methods that require prescription/reimbursement and which are, therefore, captured in the administrative databases

	• To describe the prescriber speciality during the pre- and the post-implementation period
	• To describe the exposure characteristics during the pre- and the post-implementation period, with respect to:
	  ○ Active substance
	  ○ Dose
	  ○ Treatment duration
	• To describe, where available, the incidence and, outcomes of pregnancies exposed to oral retinoids during the pre- and the post-implementation period
	• To stratify the key elements of the PPP described in the primary objective by oral retinoid substance
	• To describe trends in the physician's prescribing and monitoring practice of oral retinoids with respect to measures of the PPP (contraceptive use and pregnancy testing) over the entire study duration

Study design	The study employed a multicountry, multisource, observational cohort design using secondary data with a pre-post comparison and presents the results of the analysis for 3 time periods: 1) pre-referral: July 2014 to June 2016, 2) post-referral (of the updated RMMs): July 2016 to the month of implementing the RMMs in each country, and 3) post-implementation: month of implementing the RMMs in each country to December 2020. The study was mainly descriptive.
Setting	France, Germany, Spain, and Sweden.
Subjects and study size	*Subjects:* Female patients of childbearing potential receiving oral retinoids. *Inclusion criteria:* Female, childbearing potential (aged 13-49 years), having had at least 1 prescription of oral retinoids in the pre- or post-implementation periods. *Exclusion criteria:* Information of not being of childbearing potential before oral retinoid initiation. *Study size:* A minimum of 385 patients were required to achieve a sufficient accuracy, i.e., within a margin of accuracy +/- 5%, of the estimation by a two-sided 95% confidence interval (CI) for a percentage of 50% for the variables that addressed the primary objective.

Variables and data sources	Variables:
	• Exposure variables:
	  ○ Active substance (acitretin, alitretinoin, isotretinoin)
	  ○ Date of prescription issuance (or when unavailable date of filling)

	○ Prescribed drug amount or days' supply ○ Prescribed daily dose (if available) • Primary outcome variables: ○ Contraceptives ○ Periodicity of oral retinoid prescriptions ○ Laboratory pregnancy tests • Secondary outcome variables: ○ Patient age ○ Indication for oral retinoids ○ Prescriber speciality ○ Treatment characteristics ▪ Prescription count and prescription length ▪ Duration of treatment ▪ Average daily dose ○ Pregnancy ▪ Pregnancies exposed to oral retinoids ▪ Incidence rate of pregnancies exposed to oral retinoids ▪ Outcomes of exposed pregnancies, where available ○ Aggregated primary outcome measures for the 4 countries together ○ Trends in the prescribing practice of oral retinoids with respect to measures of the PPP **Databases:** ***Claims:*** France: Système National des Données de Santé (SNDS) and Germany: Collective of insurants from company health insurance funds, ***Primary care:*** Spain: Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP), ***National health registers***: Sweden: national drug-, patient-, and birth registers.
Results	This report presents the results of the analysis for the pre- and post-referral periods (i.e., pre-implementation period) and the post-implementation period of the updated RMMs in France, Germany, Spain and Sweden. The study sample in the pre-/post-referral and pre-implementation periods comprised 87,818/111,897 and 92,582 patients on oral retinoid treatment in France, 1,953/3,100 and 1,598 patients in Germany, 3,004/4,211 and 4,100 patients in Spain, and 9,182/14,594 and 16,709 patients in Sweden. In the pre-referral period, the proportion of patients with isotretinoin prescriptions were 95.5% in France, 94.0% in Germany, 92.9% in Spain and 97.8% in Sweden.

	The respective proportions with acitretin prescriptions were 3.1%, 4.0%, 7.0%, and 2.2%. The respective proportions with alitretinoin prescriptions were 1.5%, 2.5% and 0.4% in France, Germany and Spain. Alitretinoin did not have marketing authorisation in Sweden. In the post-referral period, the proportion of patients with isotretinoin prescriptions were 96.5% in France, 95.1% in Germany, 94.0% in Spain and 98.6% in Sweden. The respective proportions with acitretin prescriptions were 2.4%, 2.7%, 5.8%, and 1.5%. The proportions with alitretinoin prescriptions were 1.2%, 2.4% and 0.4% in France, Germany and Spain. In the post-implementation period, the proportion of patients with isotretinoin prescriptions were 97.7% in France, 95.4% in Germany, 94.7% in Spain and 98.8% in Sweden. The respective proportions with acitretin prescriptions were 1.6%, 2.5%, 5.1%, and 1.1%. The proportions with alitretinoin prescriptions were 0.7%, 2.2%, 0.2% and 0.1% in France, Germany, Spain and Sweden. **Primary objective:** • Contraceptives use (proportions for prior, during and after treatment episodes are presented respectively per each country, for each period) *France:* In the pre-referral period, a 30-day contraceptive prescription prior to oral retinoid treatment start was observed in 38.9% of treatment episodes. Continuous concomitant contraceptive prescriptions were observed in 35.2% of episodes and a 30-day contraceptive prescription after treatment stop in 43.8% of episodes. The corresponding numbers in the post-referral period were 42.3%, 38.0% and 46.6%, respectively. The corresponding numbers in the post-implementation period were 42.3%, 38.1% and 46.7%, respectively. *Germany:* Pre-referral 8.6%, 7.0% and 8.8%, post-referral 8.5%, 6.9%, 8.6%, post-implementation 11.0%, 9.4%, 11.0%. *Spain:* Pre-referral 14.5%, 13.5% and 16.1%, post-referral 14.9%, 12.7% and 16.9%, post-implementation 14.1%, 13.0%, 17.0%. *Sweden:* Pre-referral 33.1%, 32.3% and 38.9%, post-referral 36.7%, 36.3% and 42.0%, post-implementation 39.2%, 40.3%, 44.6%. • Periodicity of oral retinoid prescriptions *France:* In the pre-referral period, the mean time interval between oral retinoid prescriptions was 32.3 days. Oral retinoids were prescribed at monthly intervals in 38.9% of treatment episodes. The corresponding numbers in the post-referral and

	post-implementation periods were 32.4 days and 40.5% and 31.9 days and 48.6%, respectively. *Germany:* Pre-referral 39.2 days and 28.2%, post-referral 37.8 days and 27.2%, post-implementation 36.0 days and 38.2%. *Spain:* Pre-referral 96.5 days and 2.8%, post-referral 95.8 days and 3.7%, post-implementation 103.5 days and 3.0%. *Sweden:* Pre-referral 41.8 days and 8.5%, post-referral 42.9 days and 8.6%, post-implementation 44.5 days and 9.6%. • Laboratory pregnancy tests (proportions for prior, during and after treatment episodes are presented respectively per each country, for each period) *France:* In the pre-referral period, a laboratory pregnancy test was performed in 72.9% of the treatment episodes within 7 days prior to oral retinoid treatment. The average percentage of treatment episodes time fully covered by laboratory pregnancy tests was 50.8%. After treatment 13.0% of episodes showed laboratory pregnancy testing. The corresponding numbers in the post-referral and post-implementation periods were 75.5%, 52.5% and 12.8%, and 76.4%, 50.4% and 12.6%, respectively. *Germany:* Pre-referral 19.3%, 19.3%, and 2.9%, post-referral 21.6%, 21.4% and 3.4%, post-implementation: 25.6%, 24.4% and 3.1%. *Spain:* Pre-referral 2.6%, 38.4%, and 1.2%, post-referral 3.5%%, 33.9% and 1.3%, post-implementation 4.1%, 25.9% and 1.1%. *Sweden:* Data on laboratory pregnancy testing was not available in the national registers. **Secondary objective:** **Patient age.** The average age of women included in the 4 study countries during the pre- and post-referral periods ranged from 23.9-26.9 years (median range: 20-24 years). The age range in the post-implementation period was 23.5-25.5 (median range: 20-23 years). **Indication for oral retinoids.** In the pre-referral period, acne was the indication for the majority oral retinoid prescriptions accounting for 89.4% in Germany, 83.1% in Spain, and 67.7% in Sweden. Dermatitis and eczema were second most common with 15.3% in Germany, 10.4% in Spain, and 4.3% in Sweden. Psoriasis was the indication for 3.3% of prescriptions in Germany, 6.8% in Spain, and 1.3%

	in Sweden. Other indications were rare (⩽0.8%). For the different countries the missing indications ranged from 3.0% (Germany) to 30.2% (Sweden). In the post-referral period, acne was the indication for the majority of the oral retinoid prescriptions accounting for 92.2% in Germany, 83.0% in Spain, and 65.4% in Sweden. Dermatitis and eczema were second most common with 14.1% in Germany, 13.8% in Spain, and 4.4% in Sweden. Psoriasis was the indication for 2.6% of prescriptions in Germany, 6.1% in Spain, and 1.2% in Sweden. Other indications were rare (⩽0.7%). For the different countries the missing indications ranged from 2.2% (Germany) to 32.9% (Sweden). Also, in the post-implementation period acne was the indication for the majority of the oral retinoid prescriptions accounting for 92.5% in Germany, 85.0% in Spain, and 63.4% in Sweden. Dermatitis and eczema were second most common with 13.8% in Germany, 19.1% in Spain, and 3.8% in Sweden. Psoriasis was the indication for 3.2% of prescriptions in Germany, 5.0% in Spain, and 0.9% in Sweden. Other indications were rare (⩽0.7%). For the different countries the missing indications ranged from 2.4% (Germany) to 35.0% (Sweden). Data on the indication for oral retinoid treatment was unavailable for France. **Prescriber speciality.** In the pre-referral period, most oral retinoid prescriptions in France, Germany and Sweden were given by dermatologists with 83.4%, 90.1%, and 88.0%, respectively. General practitioners (GP) gave 14.8%, 6.0% and 1.1% of prescriptions, in France, Germany and Sweden, respectively. In Spain the proportions were 27.6% for dermatologists and 21.2% for GPs. However, data on prescriber speciality was missing for 44.1% of prescriptions. In the post-referral period, most oral retinoid prescriptions in France, Germany and Sweden were given by dermatologists with 83.9%, 89.9%, and 88.4%, respectively. GPs gave 14.2%, 6.0% and 1.6% of prescriptions, in France, Germany and Sweden, respectively. In Spain the proportions were 22.8% for dermatologists and 21.5% for GPs. Data on prescriber speciality was missing for 47.4% of prescriptions. In the post-implementation period, most oral retinoid prescriptions in France, Germany and Sweden were given by dermatologists with 81.1%, 89.7%, and 87.4% respectively. GPs gave 16.7%, 6.3% and 2.0% of prescriptions, in France, Germany and Sweden, respectively. In Spain the proportions were 16.8% for dermatologists and 21.4% for GPs. Data on prescriber speciality was missing for 50.5% of prescriptions. The missing data on prescriber speciality ranged for 0.6-10.7% of prescriptions in France, Germany and Sweden.

	Treatment characteristics. (1) In the pre-referral period the ***mean number of oral retinoid prescriptions per patient*** ranged from 1.6 to 5.3 across the 4 countries, in the post-referral period the range was 1.6 to 5.5 , in the post-implementation period the range was 1.7 to 4.8 **(2)** in the pre-referral period the ***average prescription length*** was 28.1 days in France, 43.2 days in Germany, 94.1 days in Spain and 55.2 days in Sweden; in the post-referral period the respective durations were: 28.9 in France, 42.5 in Germany, 117.0 in Spain and 55.4 in Sweden; in the post-implementation period the respective durations were: 27.4 in France, 38.2 in Germany, 125.9 in Spain and 54.9 in Sweden **(3)** in the pre-referral period the ***mean duration of treatment*** was 135.3 (acitretin: 55.7, alitretinoin: 125.3, isotretinoin: 140.1) days in France, 114.6 (acitretin: 139.6, alitretinoin: 91.8, isotretinoin: 114.5) days in Germany, 133.7 (acitretin: 146.6, alitretinoin: 118.5, isotretinoin: 133.1) days in Spain, and 173.9 (acitretin: 64.2, isotretinoin: 179.9) days in Sweden; in the post-referral period the respective durations were 150.7 (acitretin: 58.1, alitretinoin: 126.7, isotretinoin: 155.1) days in France, 129.8 (acitretin: 127.4, alitretinoin: 106.4, isotretinoin: 130.4) days in Germany, 166.2 (acitretin: 173.6, alitretinoin: 104.9, isotretinoin:165.9) days in Spain, and 181.8 (acitretin: 60.7, isotretinoin: 186.3) days in Sweden; in the post-implementation period the respective durations were 133.8 (acitretin: 57.2, alitretinoin: 106.1, isotretinoin: 136.7) days in France, 102.2 (acitretin: 99.8, alitretinoin: 97.6, isotretinoin: 102.3) days in Germany, 169.9 (acitretin: 171.1, alitretinoin: 75.0, isotretinoin: 170.0) days in Spain, and 162.9 (acitretin: 62.6, alitretinoin: 39.0, isotretinoin: 165.9) days in Sweden; **(4)** in the pre-referral period the ***average daily dose*** was 27.3 (acitretin: 30.2, alitretinoin: 19.3, isotretinoin: 27.3) mg in France, 17.6 (acitretin: 30.6, alitretinoin: 24.9, isotretinoin: 17.1) mg in Germany, 26.8 (acitretin: 21.3, alitretinoin: 30.0, isotretinoin: 27.1) mg in Spain, and 31.4 (acitretin: 32.6, isotretinoin: 31.3) mg in Sweden. In the post-referral period the results were 27.3 (acitretin: 30.3, alitretinoin: 19.3, isotretinoin: 27.2) mg in France, 17.2 (acitretin: 31.5, alitretinoin: 23.8, isotretinoin: 16.7) mg in Germany, 28.8 (acitretin: 21.4, alitretinoin: 24.3, isotretinoin: 29.1) mg in Spain, and 31.3 (acitretin: 32.4, isotretinoin: 31.3) mg in Sweden. In the post-implementation period the results were 27.0 (acitretin: 30.2, alitretinoin: 19.1, isotretinoin: 26.9) mg in France, 17.1 (acitretin: 27.6, alitretinoin: 25.5, isotretinoin: 16.7) mg in Germany, 27.4 (acitretin: 20.8, alitretinoin: 30.0, isotretinoin: 27.7) mg in Spain, and 30.5 (acitretin: 32.3, alitretinoin: 20.0, isotretinoin: 30.4) mg in Sweden.

	Pregnancy. (1) ***exposure to oral retinoids*** in the pre-referral period occurred in 13.4% of pregnancies in France, 12.1% in Germany, 20.2% in Spain, and 5.9% in Sweden. The proportions in the post-referral period were 10.4% in France, 6.1% in Germany, 14.6% in Spain, and 7.8% in Sweden and in the post-implementation period were 16.6% in France, 36.7% in Germany, 19.0% in Spain, and 15.1% in Sweden; **(2)** the ***incidence rate*** of exposed pregnancies per 1000 patient years during the pre-referral period was 18.6 in France, 5.4 in Germany, 11.3 in Spain, and 1.1 in Sweden. Post-referral incidence rates were 17.7 in France, 4.1 in Germany, 9.5 in Spain, and 1.9 in Sweden. Post-implementation incidence rates were 14.1 in France, 7.9 in Germany, in 10.2 Spain, and in 2.7 Sweden; **(3)** terminations were generally the most common among ***pregnancies exposed with available information on outcome*** during the pre-referral period, ranging from 50.0% to 77.8% in France, Germany and Spain. Live births occurred in 11.1% to 39.6% of exposed pregnancies across countries and miscarriages in <1.7% to 11.1% except for Sweden where miscarriages were the most common outcome of the 4 exposed pregnancies with available data by 75.0%. Stillbirths were not observed in France, Germany, Spain and Sweden. Birth defects were reported to have occurred in up to 1.7% exposed pregnancies. France reported up to 2% non-live births which may have included terminations, still births or miscarriages. In the post-referral period, the observed outcomes were 56.2% to 82.6% for termination across the 4 countries. Live births occurred in 0.0% to 38.7% of exposed pregnancies and miscarriages in 0.0% to 25.0%. There were 0.0% still-births, and up to 1.3% birth defects reported in the exposed pregnancies. In the post-implementation period, the observed outcomes were 0.0% to 71.4% for termination. Live births occurred in 0.0% to 83.3% of exposed pregnancies and miscarriages in <2.7% to 34.3%. There were no reported stillbirths or birth defects. **Meta-analysis.** All meta-analyses were characterised by substantial heterogeneity. The key results for change from the pre-referral to the post-implementation period showed that the proportions of oral retinoid treatment episodes with contraceptive use before, during and after treatment increased by 2.9%, 3.0% and 3.1%, respectively. From pre-referral to post-implementation period there was an overall increase in oral retinoid prescription interval length from 51.7 to 53.6 days and treatment episodes with monthly prescription intervals increased from 13.9% to 17.3%. For treatment episodes with laboratory pregnancy testing before treatment start, an overall change of around 5% to 6% was observed from pre-referral to post-implementation period (up to 7 days: 20.6% vs. 26.6%, up to 30 days: 35.4% vs.

	40.8%, respectively). Proportions of treatment episode time covered by compliant monthly laboratory pregnancy testing (2.8% vs. 2.0%), as well as laboratory pregnancy testing after treatment stop (3.7% vs. 3.6%) were almost similar during the pre-referral and post-implementation period. **Trends in the Prescribing Practice of Oral Retinoids with Respect to Measures of the PPP - Interrupted time series.** ***Contraceptive use before oral retinoid treatment.*** During the pre-referral period there were significantly increasing slopes (i.e. trends) in the proportion of treatment episodes with contraceptive use before oral retinoid treatment in France and Sweden, but not in Germany or Spain. During the post-referral period significantly increasing trends were observed for France and Sweden. For France, this was less pronounced compared to during pre-referral. For Sweden the trend remained unchanged. An increasing trend was now also observed for Germany. Spain showed a significantly decreasing trend. France, Germany and Sweden showed small negative significant level changes, i.e. a decrease in proportions of treatment episodes with contraceptive use before oral retinoid treatment, from the pre-referral to the post-implementation period. The opposite pattern was observed for Spain. During the post-implementation period significantly increasing trends in proportions were observed for Germany and Sweden. For Germany this increase was faster when compared to the post-referral period. For Sweden the previously observed trend remained unchanged. A slight negative trend was observed for France and no significant trend was observed for Spain. France and Germany showed small negative significant level changes from post-referral to post-implementation period. No such level changes were observed for Spain and Sweden. ***Contraceptive use during oral retinoid treatment:*** France and Sweden showed significant increasing trends in the proportions of oral retinoid treatment episodes with concomitant contraceptive use in all 3 study periods. For France the trend was more pronounced during the pre- compared to the post-referral or post-implementation periods. For Germany a significant positive trend was observed during the post-implementation period. For Spain no significant trend was observed during the pre-referral period. However, slight negative trends were observed during the post-referral and post-implementation period. France and Sweden showed small negative level changes between all study periods, i.e. pre-referral, post-referral and post-implementation periods. For Germany significant negative

	level changes were observed between pre-referral and post-implementation period. A significant opposite pattern was observed for Spain between pre-referral and post-referral and post-implementation period, respectively. Some effects of the ITS appear to be caused by the high proportions observed at the end of the study periods. The high proportions are likely due to the fact that treatment episodes that start in the last months of a study period have less episode-time to be analysed in the study period and there is therefore less opportunity to discontinue contraceptive use. ***Laboratory pregnancy testing before oral retinoid treatment:*** For France there were no significant trends in the proportion of oral retinoid treatment episodes with prior laboratory pregnancy testing in the two pre-implementation periods. There were no significant level and trend changes during any of the study periods, with the exception of a positive change from post-referral to post-implementation, where a significant increasing trend over time was observed. All 3 study periods were characterized by a seasonal pattern whereby the proportion of treatment episodes with prior laboratory pregnancy testing was the highest in episodes that spanned September to November. For Germany no significant trends, changes in trends, or levels were observed. For Spain a significant decreasing trend was observed during the pre-referral period. There was a significant level change from pre- to post-referral period and a significant change in trend from negative to flat. This trend changed again significantly towards the post-implementation period, where it became positive. Insufficient data points were available for Sweden to conduct ITS. ***Laboratory pregnancy testing during oral retinoid treatment:*** There were no significant trends in the proportion of oral retinoid treatment episodes with monthly laboratory pregnancy testing during the pre- or post-referral periods in France. There were (marginally) significant level changes from pre- to post-referral and from post-referral to post-implementation period, which appeared to be due to seasonal patterns in the proportions of treatment episodes with monthly pregnancy tests. There was a statistically significant trend change from flat during the post-referral period towards a significantly increasing trend during the post-implementation period, which appeared largely driven by the data of the last quarter of the post-implementation period. For Germany, there was a significantly increasing trend during the pre-referral period that remained during the post-referral period. There was a negative level change from the pre- to the post-referral period, which was caused by the high proportions of treatment episodes covered

	with pregnancy tests observed in last quarter of the pre-referral period. A statistically significant change in the trend occurred from the post-referral to post-implementation period, which was characterised by a faster increase in the proportion of oral retinoid treatment episodes that were covered with pregnancy tests. No significant trends or changes in trends or levels were observed for Spain. Insufficient data points were available for Sweden to conduct ITS. Overall, the ITS analysis results suggest that the implementation of the updated PPP was associated with small and statistically significant improvements with respect to monthly pregnancy testing during oral retinoid treatment in 2 of the 3 countries with available data. A limitation is, that this interpretation is complicated by the fact that the higher testing rates observed at the end of the study periods are likely at least partially due to the shorter time analysed per episode rather than an effect of the implementation.
Discussion	This report provides insights into key aspects of clinical practice with respect to oral retinoid treatment in the pre- and post-implementation periods of the updated RMMs in 4 European countries. During the pre-implementation period, less than half of the women who received oral retinoid treatment in France and Sweden and even fewer in Spain and Germany were prescribed contraceptives as per PPP recommendations. A slight increase (~2.0%-8.0%) in the proportions of treatment episodes with PPP compliant contraceptive prescriptions during the post-referral or post-implementation period was observed in France, Germany and Sweden, but not Spain. Overall, small, positive trends with respect to PPP compliant contraceptive use before and during oral retinoid treatment were observed in France and Sweden and to a lesser degree also Germany, however this was not the case for Spain. The findings need to be interpreted after considering that only reimbursed contraceptives were captured in the majority of data bases that were included in this study. The PPP further recommends 30-day intervals for oral retinoid prescriptions and that prescriptions must be dispensed within 7 days of issuance. This recommendation was generally met in France, Germany, and Sweden. However, in Spain the interval was substantially longer in both of the pre-implementation periods and the post-implementation period, which may be due to local prescribing practice. Finally, according to the PPP, pregnancy must be excluded before oral retinoid treatment, test results must be documented within 3 days before issuing prescriptions and females should undergo pregnancy testing at monthly follow-ups. A positive

	change in laboratory pregnancy testing prior to oral retinoid treatment was seen from the pre-referral to post-referral period in France (72.9% vs. 75.5%), Germany (19.3% vs. 21.6%) and Spain (2.6% vs. 3.5%). France, Germany and Spain showed a further positive trend during post-implementation (76.4%, 25.6% and 4.1%). Across study periods about 50% of oral retinoid treatment episode time was fully covered by compliant laboratory pregnancy testing in France. In Germany, the proportions increased from 19.3% to 24.4% across study periods. Spain showed an opposite trend with 38.4% to 25.9% of treatment episode time that was covered by compliant laboratory pregnancy testing. Interrupted time series analysis showed that some, but not all, trends were significant. The proportions of oral retinoid treatment episodes covered by laboratory pregnancy testing after oral retinoid treatment ranged from only 0.0% to 13.1% and where relatively stable within the respective countries over study periods. The proportions may reflect an underestimation of PPP compliant pregnancy testing, given that they are only based on laboratory pregnancy tests. During a large part of the post-implementation period the world was affected by a pandemic of the SARS-CoV-2 virus (COVID-19). The emergency response of the governments in France, Germany and Spain, but not Sweden, included strict stay-at-home requirements and national household lockdowns, particularly during the spring, autumn and winter months of 2020. Also in Sweden notable changes occurred with respect to the healthcare utilization. It is likely that these changes influenced the implementation of the updated PPP in clinical practice negatively. This RWE study used secondary data that was not collected primarily for research purposes and therefore information on certain parameters, such as PPP compliant laboratory pregnancy tests, contraceptive use, or pregnancy outcomes may reflect an underestimation of actual PPP compliance. The findings of this study should therefore be interpreted cautiously and under consideration of the specific limitations. Moreover, findings may not generalise to all individuals in the respective study countries or other countries. *Conclusion.* Some of the current findings support concerns in line with those raised by the 2016 PRAC review and suggest the need for a better adherence to the updated PPP. However, prescribing patterns were mostly in line with the recommendations in France, Germany and Sweden and positive trends were observed in the 3 countries with respect to PPP adherence from the pre- to the post-implementation periods of the updated PPP with respect to contraceptive use and

	pregnancy testing. It needs to be noted that these changes were generally of small magnitude and likely impacted by safety measures and behaviours associated with the COVID-19 pandemic.
Marketing authorisation holder (MAH)	Marketing authorisation holders (MAHs) involved in the oral retinoids consortium: 2CARE4GENERICS, ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS, ALMIRALL, ARISTO PHARMA, AUROBINDO, BAILLEUL, BAUSCH HEALTH, DERMAPHARM, ENNOGEN HEALTHCARE, ESPECIALIDADES FARMACÉUTICAS CENTRUM, EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, ISDIN, MEDINFAR, MORNINGSIDE HEALTHCARE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SANOSWISS, LABORATOIRES SMB S.A., STADA, SUN PHARMA, TARGET, and TEVA
Name(s) and affiliation(s) of principal investigator(s)	Massoud Toussi, MD, PhD, MBA Senior Principal, Global Lead PASS/PAES/REMS & Phase IV, Real-World Solutions, IQVIA