

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 Appendix 2.1 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	EMA/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 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: ○ Patient age ○ 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	Anne-Kathrin Fett, IQVIA Real-World Solutions Sonia Guleria, IQVIA Real-World Solutions Raymond Griner, IQVIA Real-World Solutions Niina Leinonen, IQVIA Real World Solutions Bernadette Dwan, IQVIA Real-World Solutions Massoud Toussi, 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: Manuela Kohler Regulatory Team Leader Established Products F. Hoffmann-La Roche Ltd, Bld. 686 Centralbahnstrasse 4 4051 Basel Switzerland +41 61 688 43 23 manuela.kohler.mk1@roche.com

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.

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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: ○ Patient age ○ 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	<i>Subjects:</i> Female patients of childbearing potential receiving oral retinoids. <i>Inclusion criteria:</i> Female, childbearing potential (aged 13-49 years), having had at least 1 prescription of oral retinoids in the pre- or post-implementation periods. <i>Exclusion criteria:</i> Information of not being of childbearing potential before oral retinoid initiation. <i>Study size:</i> 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. <i>Germany:</i> Pre-referral 39.2 days and 28.2%, post-referral 37.8 days and 27.2%, post-implementation 36.0 days and 38.2%. <i>Spain:</i> Pre-referral 96.5 days and 2.8%, post-referral 95.8 days and 3.7%, post-implementation 103.5 days and 3.0%. <i>Sweden:</i> 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) <i>France:</i> 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. <i>Germany:</i> 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%. <i>Spain:</i> 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%. <i>Sweden:</i> 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 ($\leq 0.8\%$). 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 ($\leq 0.7\%$). 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 ($\leq 0.7\%$). 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 were 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
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3 LIST OF ABBREVIATIONS

ASSIR	Atenció a la salut sexual i reproductiva
ATC	Anatomical Therapeutic Chemical Classification System
CCAM	Classification Commune des Actes Médicaux
CES	Complete episodes set
CI	Confidence interval
CIP	Club Inter Pharmaceutique
CHMP	Committee for Medicinal Products for Human Use
COC	Combined oral contraceptives
DDD	Defined daily dose
DRG	Diagnosis-related groups
DUS	Drug utilisation study
EBM	Einheitlicher Bewertungsmaßstab
EC	European Commission
eCAP	L'estació clínica d'atenció primària
EES	Ending episodes set
EFG	Equivalente farmacéutico genérico
EM	Educational materials
EMA	European Medicines Agency
EMR	Electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full analysis set
GP	General practitioner
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice

HCG	Human chorionic gonadotropin
ICD	International Classification of Diseases
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ITS	Interrupted time series
IUD	Intrauterine device
MAH	Marketing authorisation holder
NBHW	National Board of Health and Welfare
PDD	Prescribed daily dose
PMSI	Programme de Médicalisation des Systèmes d'Information
PPP	Pregnancy prevention programme
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk minimisation measure
RWS	Real-World Solutions
SAP	Statistical analysis plan
SD	Standard deviation
SES _{Contraception}	Starting episodes set – contraception
SES _{Testing}	Starting episodes set – pregnancy testing
SIDIAP	Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària
SLM	Sections locales mutualists
SmPC	Summary of product characteristics
SNDS	Système National des Données de Santé
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie
SOP	Standard operating procedures
SPDR	Swedish Prescribed Drug Register
UID	Unique individual number

4 INVESTIGATORS

Responsible Party	Name and Affiliation
Consortium	Oral retinoids consortium of MAHs (Appendix 2.3 List of Represented MAHs Contact Details)
Sponsors	All MAHs involved in the oral retinoids consortium
MAH responsible for submissions to health authorities	Roche
Contracting vendor	IQVIA Real-World Solutions (RWS) Kirschgartenstrasse 14 4051 Basel Switzerland Phone: +41 61 204 5000 Contact: Bernadette Dwan
Principal Investigator	Massoud Toussi, MD, PhD, MBA Senior Principal, Global Lead PASS/PAES/REMS & Phase IV, Real-World Solutions, IQVIA

5 OTHER RESPONSIBLE PARTIES

This study was performed by IQVIA, a contract research organisation (CRO), with guidance, input, review, and approval from the oral retinoids consortium of MAHs.

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6 MILESTONES

Table 1 Study Milestones

Milestone	Planned date	Actual date	Comments
Date of first IEC/IRB approval	NA	NA	NA
Date of last IEC/IRB approval	NA	NA	NA
Start of data collection for the interim report	01 January 2020	01 January 2020	NA
End of data collection for the interim report	31 December 2020	18 January 2021	NA
Registration in the EU PAS register	After approval of protocol	13 November 2019	After approval of protocol
Interim report	12 May 2021	14 May 2021	
Final report of study results	31 December 2022	02 December 2022	

7 RATIONALE AND BACKGROUND

This is the final report for the post-authorisation safety study (PASS) ‘*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*’, as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (European Union (EU)) No 520/2012.

7.1 Background

Retinoic acid analogues comprise a group of active substances known as the retinoids and are available as topical and oral preparations. Their therapeutic indications include the treatment of severe acne (such as nodular or conglobate acne, isotretinoin) resistant to adequate courses of standard therapy, hand eczema resistant to empirical treatment measures (alitretinoin), and severe forms of psoriasis (acitretin) and other skin conditions (2) Due to their anticarcinogenic activity, retinoids are also used to treat certain types of cancers. Therapy with systemic retinoids is

associated with both acute and chronic toxicities, as well as teratogenicity. Therefore, women who are pregnant or are planning a pregnancy must not be prescribed oral retinoids. A pregnancy prevention programme (PPP) comprising educational materials (EM) for patients, physicians, and pharmacists as well as strict prescription guidelines had been put in place, but exposure during pregnancy continued to occur.

In January 2016, a Pharmacovigilance Risk Assessment Committee (PRAC) review noted that there are concerns about how well the requirements of the PPP are followed in clinical practice. In July 2016, the PRAC initiated an article 31 referral to assess the effectiveness of risk minimisation in relation to the PPP. As stated in the article 31 referral, ‘Pregnancy is an absolute contraindication in the summary of product characteristics (SmPC) for all oral retinoids in the EU’. A referral in 2003 for isotretinoin only, led to introduction of the isotretinoin PPP in the EU. Since the introduction of the PPP for isotretinoin, similar programmes have been introduced for the other retinoids used to treat dermatological conditions. The effectiveness of these PPPs has been kept under close review and although a reduction in the number of pregnancies exposed to these retinoids has been observed, cases of pregnancies exposed to retinoids, as mentioned earlier, continued to occur. The PRAC decision was endorsed by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in March 2018 and by the European Commission (EC) in June 2018 (published in the EMA’s press release EMA/261767/2018 on 21 June 2018) (2–4). Based on this decision, the PPP was updated to include:

- Pregnancy tests before, during, and after stopping treatment;
- The need to use at least 1 effective method of contraception during and after treatment;
- An ‘acknowledgement form’ to confirm that appropriate advice has been given to patients;
- A ‘patient reminder card’ stating that the medicine must not be used during pregnancy and including information about pregnancy testing and the need to use effective contraception.

The PPP addresses the issues of effective contraceptive use, pregnancy testing, and rigorous monitoring of treating physicians (i.e., dermatologists or general practitioners [GPs]). The differences between the PPP before and after updating the risk minimisation measures (RMMs) are relatively small (Table 2). The updated RMMs include updated EMs, in some countries a

patient reminder card and a pictogram on the outer package, and in addition, the redistribution of direct healthcare professional communication (DHPC). The measures of the PPP are similar in the countries of interest for this study. However, differences in the set of implemented tools may exist between countries due to the requirements of the national authorities.

Table 2 Requirements of the pregnancy prevention programme before and after the newly implemented, updated risk minimisation measures

Active substance	PPP	Contraception		Pregnancy test			Days' supply/Length of prescription	
		Before treatment start	During treatment	After treatment stop	Before treatment start	During treatment	After treatment stop	
Acitretin	Old ^a	Yes	Yes	For 3yrs	Yes	Monthly	For 3yrs	Limited to 30d
	New ^b	For 1mo	Yes	For 3yrs	Yes	Ideally monthly	For 3yrs	Ideally limited to 30d
Alitretinoin	Old ^a	For 1mo	Yes	Yes	Yes	Monthly	For 5wks	Limited to 30d
	New ^b	For 1mo	Yes	For 1mo	Yes	Ideally monthly	For 1mo	Ideally limited to 30d
Isotretinoin	Old ^a	For 1mo	Yes	For 1mo	Yes	Monthly	For 5wks	Limited to 30d
	New ^b	For 1mo	Yes	For 1mo	Yes	Ideally monthly	For 1mo	Ideally limited to 30d

d, day(s); wks, weeks; mo(s), month(s); yr(s), year(s); PPP, pregnancy prevention programme.

^aSource: Summary of product characteristics for acitretin, alitretinoin, and isotretinoin in countries of interest (i.e., France, Germany, Spain, and Sweden); for the time period 2012-2017.

^bSource: EMA Appendix to the amendments to relevant sections of the product information from 22 March 2018

7.2 Rationale

In January 2016, the PRAC reviewed the effectiveness of the PPP for oral isotretinoin. This review noted post-marketing data and published studies raising concerns about how well the requirements of the PPP are followed in clinical practice. These data suggested that there were a number of areas that may impact the effectiveness of the PPP, including inconsistencies in information provided with regard to contraceptive measures and a lack of up-to-date information about the most effective contraceptive methods; inadequate documentation of the required patient

monitoring, and potential differences in the PPPs implemented across the various active substances. Consequently, the PRAC identified a need for a detailed assessment of compliance with the requirements of the PPP and initiated the Art 31 referral for all retinoids (Procedure number: EMEA/H/A-31/1446). As an outcome of the Art 31 referral on retinoids the PRAC (endorsed by the CHMP and EC) has requested evidence on the effectiveness of the PPP. Therefore, the MAHs suggested a DUS (category 1 study) and a complementary survey (category 3 study) to assess the effectiveness of the updated RMMs. This study aimed to evaluate and quantify the effectiveness of the updated RMMs, based on pre- and post-implementation analysis and assessment. This report describes the final results of the DUS. The results of the survey study are presented in a separate report.

8 RESEARCH QUESTIONS AND OBJECTIVES

This DUS addressed the following 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?

8.1 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:

- Contraceptives² before, during, and after treatment with oral retinoids
- Time interval between prescription dates for oral retinoids during the treatment episode
- Laboratory pregnancy tests – where available - before, during, and after treatment with oral retinoids

²Contraceptive methods that require prescription/reimbursement and which are, therefore, captured in the administrative databases

8.2 Secondary Objectives

The secondary objectives were, where available:

- To describe the patient profile during the pre- and the post-implementation period, with respect to:
 - Patient age
 - 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 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 performance of pregnancy tests) over the entire duration of the study

9 AMENDMENTS AND UPDATES

The below changes were made in the statistical analysis plan (SAP) from the protocol. Changes to the SAP v1.0 were agreed upon with the MAHs on 15-Nov-2019 (Table 3 Additional changes for the SAP v2.0 were agreed upon with the MAHs on 16-Jul-2021. The SAP v2.0 (p. 3) details further modifications from SAP v1. Changes made to the analysis plan after SAP v2.0 are noted in Section 10.9.4.5

Table 3). Additional changes for the SAP v2.0 were agreed upon with the MAHs on 16-Jul-2021. The SAP v2.0 (p. 3) details further modifications from SAP v1. Changes made to the analysis plan after SAP v2.0 are noted in Section 10.9.4.5

Table 3 Summary of key updates to the statistical methods from the protocol

No.	SAP	SAP section	Update	Reason for update
1	1	All relevant sections	“Main analysis” in the protocol has been renamed to “primary analysis”.	To match “primary objectives”
2	1	All relevant sections	It was planned in the protocol to include patients with records of at least 3 months prior to oral retinoids treatment start to cover contraceptives prescriptions before treatment initiation. This was changed to 1 month for contraception and 7 days for pregnancy testing.	To align with the updated RMMs and avoid losing information on patients who were prescribed a contraceptive or tested for pregnancy in line with the RMMs, i.e., just 1 month and 7 days, respectively, before treatment initiation, and have records in the databases just for such instances. This data availability requirement only applied to pregnancy testing and contraception analysis before treatment start.
3	1	All relevant sections	It was planned in the protocol to include patients with follow-up records of at least 2 months after treatment stop. This was changed to 1 month.	To align with the updated RMMs and avoid losing information on patients who were prescribed a contraceptive or tested for pregnancy in line with the RMMs, i.e., just 1 month after treatment stop, and have records in the databases just for such instances. This data availability requirement only applied to pregnancy testing and contraception analysis after treatment stop.
4	1	Primary analysis	The statistical unit was changed from “patient” to “treatment episode”.	To provide more details and align with the nature of the dermatologic conditions for which oral retinoids are prescribed
5	1	Primary analysis	The analysis “Frequency of laboratory pregnancy tests during treatment, by month of treatment” in protocol was changed to “Percentage of treatment episode time covered with compliant laboratory pregnancy tests”.	To provide more information about how often effective pregnancy testing is performed within an episode

No.	SAP	SAP section	Update	Reason for update
6	1	Primary analysis	The analysis: “For all retinoids: Percentage of patients with laboratory pregnancy test performed within 2 months after treatment stop” in the protocol was changed to “For all retinoids: percentage of episodes with laboratory pregnancy test performed at one month (30 (-/+ 7) days) after treatment stop”.	To be consistent with the updated measures of the PPP
7	1	Primary analysis	The analysis “For acitretin: Performance of laboratory pregnancy tests beyond 1 month up to 3 years after treatment stop (depending on the length of individual follow-up of patients)” in the protocol was changed to “For acitretin: Percentage of episodes with laboratory pregnancy tests performed regularly in intervals shorter than 3 months (90 days), for up to 3 years after treatment stop (depending on the length of individual follow-up of patients)”.	To be consistent with the updated measures of the PPP
8	1	Primary analysis	The analyses “Percentage of patients with prescription of hormonal contraceptives before treatment start (up to 3 months before the exposure start date or longer depending on the type of contraceptive)” and “Percentage of episodes with use of intrauterine devices (IUDs) before treatment start (up to 5 years before exposure start date)” in the protocol were merged to “Percentage of episodes with use of contraceptives for one month (30 days) immediately before treatment start”.	To provide more informative and concise results

No.	SAP	SAP section	Update	Reason for update
9	1	Primary analysis	The analysis “Percentage of patients with use of contraceptives (hormonal contraceptives and / or IUD) within two months after treatment stop” in the protocol was changed to “For all retinoids: Percentage of episodes with use of contraceptives for 30 days after treatment stop”.	To be consistent with the updated measures of the PPP
10	1	Primary analysis	The analysis “For acitretin: Percentage of patients with use of contraceptives (hormonal contraceptives and / or IUD) beyond 1 month up to 3 years after treatment stop (depending on the length of individual follow-up of patients)” in the protocol was changed to “For acitretin: percentage of episodes with concomitant use of contraceptives up to 3 years after treatment stop (depending on the length of individual follow-up of patients)”.	To be consistent with the updated measures of the PPP
11	1	Secondary analysis	In <i>Trends in the prescribing and monitoring practice of oral retinoids with respect to measures of the PPP</i> (10.9.4.2.7) the statistical unit was changed from “users” to “episode”.	To provide more details and align with the nature of the dermatologic conditions for which oral retinoids are prescribed
12	2	Secondary analysis	Change confidence interval for proportion to Wilson method.	This method gives coverage probabilities close to nominal levels, even for small sample sizes
13	2	Secondary analysis	Update interrupted time series to include pre- and post-referral periods instead of pooling together as one pre-implementation period.	To provide granularity of the results in line with the other sections of the report
14	2	Secondary analysis	Split 18-33 years age category into 18-25 years and older 26-33 years to align with age categories in related survey.	To align the 2 work streams and allow for comparison.

No.	SAP	SAP section	Update	Reason for update
15	2	Secondary analysis	Additional covariates have been added to the interrupted time series analysis to use 3 periods (pre-referral, post-referral, post-implementation) rather than two periods (pre-intervention vs post-intervention).	To update the model parameterization to align with Change 13 listed above.

IUD(s), intrauterine device(s); PPP, pregnancy prevention programme; RMM, risk minimisation measures, SAP, statistical analysis plan.

10 RESEARCH METHODS

10.1 Study Design

This retrospective, multicountry, multisource, observational cohort study in females of childbearing potential receiving oral retinoids (i.e., acitretin, alitretinoin and isotretinoin) used established secondary data sources, including claims databases, national registries and primary care databases from 4 European countries (i.e., France, Germany, Spain, and Sweden). The study employed a pre-post design to fulfil the primary (i.e., evaluating the effectiveness of the implementation of the updated RMMs with respect to the PPP) and secondary objectives (i.e., describing patient, prescriber and exposure characteristics, section 10.4). The study was mainly descriptive; comparisons were made descriptively between the pre-referral and the post-implementation periods (without performing a statistical test).

- **Pre-implementation period:** The period before the implementation of the updated RMMs. The pre-implementation period captured 2 periods:
 - *Pre-referral:* The 2-year period before referral start in July 2016. This period was used for the before and after comparison with the post-implementation period.
 - *Post-referral:* The period between the referral start date in July 2016 and the distribution of the RMM tools in the target countries
 -

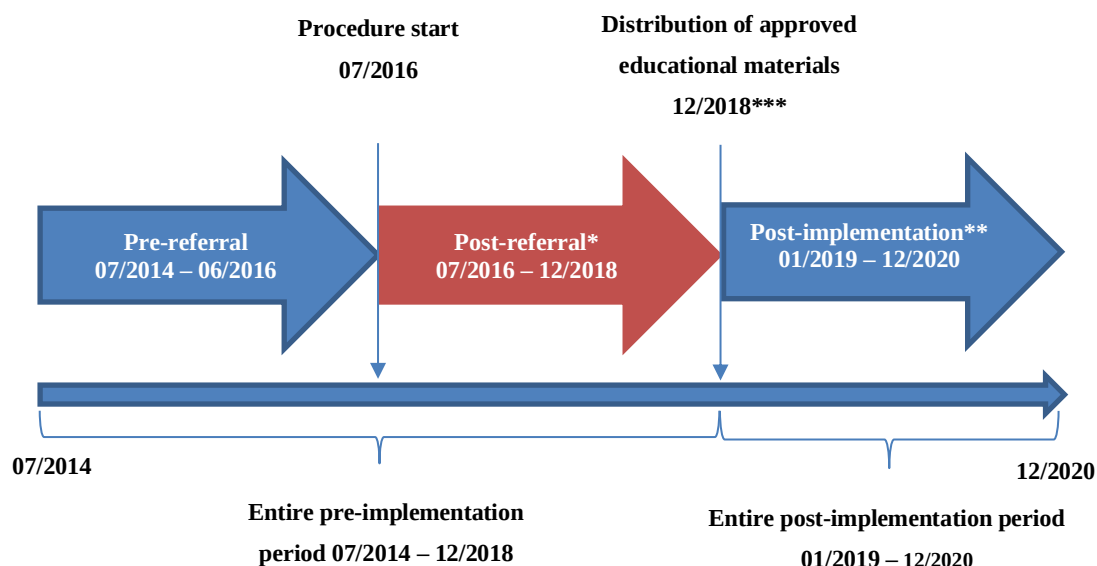
- Table 4).
- The duration of this period varied depending on the duration of the approval and the distribution of the EM in each country that took place by December 2018 in Spain and Sweden, by February 2019 in France, and by September 2019 in Germany. Accordingly, the duration of the post-referral period was 30 months (July 2016 – December 2018) in Spain and Sweden, 32 months (July 2016 – February 2019) in France and 39 months (July 2016 – September 2019) in Germany.
- **Post-implementation period:** This period captured the time starting after the distribution of the EM until December 2020. The start date of the period in each country was the date on which the EM was approved by the respective national competent authorities.

Table 4 Study time periods by country

	France	Germany	Spain	Sweden
PRAC referral announcement	07/2016	07/2016	07/2016	07/2016
Distribution of updated RMMs	02/2019	09/2019	12/2018	12/2018
Pre-implementation period				
Pre-referral period	07/2014-06/2016	07/2014-06/2016	07/2014-06/2016	07/2014-06/2016
Post-referral period	07/2016-02/2019	07/2016-09/2019	07/2016-12/2018	07/2016-12/2018
Post-implementation period	03/2019-12/2020	10/2019-12/2020	01/2019-12/2020	01/2019-12/2020

PRAC, Pharmacovigilance Risk Assessment Committee; RMM, risk minimisation measures.

Figure 1 Overview of study design and study periods



* Post-referral period in France: 07/2016 – 02/2019; in Germany: 07/2016 – 09/2019

** Post-implementation period in France: 03/2019 – 12/2020; in Germany: 10/2019 – 12/2020

*** Distribution of updated RMMs in France 02/2019; in Germany 09/2019

10.2 Setting

No primary data collection was performed for this study. The investigation utilised secondary data from France, Germany, Spain, and Sweden, which were selected based on the following criteria: having a high number of exposed patients based on market share, coverage of different regions in Europe, availability and accessibility of patient level databases, availability of the information required to meet the study objectives, and sales data (section 10.5.1). No single database was available for all countries. Therefore, multiple data sources were included, and country-specific

estimates were pooled (section 10.9.4.2.6) to generate overall estimates. The included longitudinal data sources (claims databases, national registries and primary care databases) are described in section 10.5.

10.3 Subjects

This final report includes all eligible patients in the secondary data sources from France, Germany, Spain, and Sweden during all study periods. The following inclusion and exclusion criteria were applied:

10.3.1 Inclusion Criteria

1. Female gender
2. Childbearing potential (13 to 49 years of age, inclusive) – on at least one of a patient's oral retinoid prescriptions' start dates in the corresponding study period
3. Having received or been prescribed at least 1 prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in either the pre-implementation or post-implementation period

10.3.2 Exclusion Criterion

1. Having available information indicating not being of childbearing potential before initiation of oral retinoids (e.g., records of hysterectomy or sterilisation) were excluded (Supplement 1.3).

To check for fulfilment of the exclusion criterion, the patient history was retrieved and checked back to the earliest available records in the database of each study country.

10.4 Variables

10.4.1 Exposure Definition and Measures

Exposure was defined as one or more prescriptions of oral retinoids during one of the study periods. Prescriptions were identified using the Anatomical Therapeutic Chemical Classification System (ATC) or the International non-proprietary name system (INN) for the active substances. It was assumed that all prescriptions and their associated dates recorded in the databases reflected

actual behaviours of the patients included in the study (prescription issuance, prescription fill or drug-taking) of the patients included in the study. Definitions of the variables related to exposure are provided in Table 5. To describe medication exposure, the following variables were extracted from the data sources:

- Active substance
 - Acitretin
 - Alitretinoin
 - Isotretinoin
- Date of prescription issuance (or filling)
- Prescribed drug amount or days' supply
- Prescribed daily dose (PDD) (if available)

Table 5 Definitions related to exposure

Content	Definition
Patient exposure start date	Issuance (preferably) or filling date of the first oral retinoid prescription of the first treatment episode for the patient during the corresponding study periods (pre-referral, post-referral, or post-implementation)
Prescription start date	Date on which a prescription was filled or, preferably, issued
Prescription length / Expected days of supply	Expected number of days of supply from this prescription, calculated via: days' supply reported with a prescription (either as a stand-alone variable or derivable as [prescription end date – prescription start date + 1] for Spain) or, when not available, calculated via dividing the prescribed drug amount by the prescribed daily dose (PDD), preferably, or the defined daily dose (DDD)
Prescribed daily dose (PDD)	If not captured directly in the database, the PDD was calculated as the average of all doses prescribed from the same oral retinoid within a single treatment episode
Defined daily dose (DDD)	The DDD was the assumed average maintenance dose per day for a drug used for its main indication. Each oral retinoid has a DDD specified as shown in http://www.whocc.no/atc_ddd_index/
Prescription end date	The end date of each prescription is the start date plus the expected number of days of supply
Gap	Number of days with no supply of a particular drug
Treatment episode	Consecutive prescriptions of oral retinoids were considered as one treatment episode if gaps between consecutive prescriptions of the same retinoid did not exceed 30 days. For contraceptives, a gap of any size was considered the end of continuous contraceptive use. A gap between 2 consecutive prescriptions of the same oral retinoid (end date of a last prescription and start date of a new prescription) longer than the allowed gap (30 days) indicated an episode end; the latter prescription was considered as the first prescription of another treatment episode

Content	Definition
Episode exposure start date	Start date of the first prescription of an episode Patients who had multiple treatment episodes of oral retinoid use had multiple episode exposure start dates.
Episode end date	The end date of a treatment episode was determined with the last day with supply of an oral retinoid followed by a gap of more than the allowed gap with no supply from the same oral retinoid, taking into consideration stockpiling of all prescriptions in the episode, if any. Up to 6 months of stockpiling was allowed.
Length/duration of a treatment episode	Number of days between episode exposure start date and episode end date For the overall class of oral retinoids, an episode was defined as any episode of any oral retinoid.
Follow-up end date/Censoring date	Date of patient death, loss to follow-up (transfer out of the database), progress to being not at risk (50 years old or performing an irreversible sterilization procedure as coded Supplement 1.3 or end of a study period, whichever came first) <i>Country-specific Definitions</i> • France: Dates of deaths were collected by the local health insurance fund and transmitted to SNDS. This usually happens within 3 months in ~95% of cases but can take up to 27 months for death information. In few cases, the lack of linkage between several PseudoIDs may have occurred (e.g., in case of change between insurance schemes). In such cases, data were censored at the day of the last record • Germany: Patients were followed up for as long as they were insured for without a break until the end of the study period or loss to follow-up due to change of insurance or due to death, whichever occurred first. • Spain: When a patient moved to another healthcare system or transferred out of the database or the exact date of death. • Sweden: Entry into the Swedish registers happens upon birth or immigration to Sweden and exit happens upon emigration or death.

Content	Definition
Stockpiling	The event of receiving a second prescription or refilling a prescription from the same drug within the same treatment episode earlier than the supply from the previous prescription would last. In this case, the start date of the new prescription or refill is counted as the last day of supply from the previous prescription so that the treatment duration equals the sum of the prescription lengths (days of supply) from the individual overlapping prescriptions.
Use	Prescribing, dispensing, or consuming a medication, or prescribing or applying an intrauterine device (IUD)
Month	30 days, except when associated with the use of combined oral contraceptive pills: 28 days

ATC, Anatomical Therapeutic Chemical Classification System; DDD, defined daily dose; ICD, International Classification of Diseases; IUD, intrauterine device; PDD, prescribed daily dose; SNDS, Système National des Données de Santé.

10.4.2 Outcome Definition and Measures

10.4.2.1 Variables Related to the Primary Objective

The primary outcome variables were measures related to PPP that were extracted from the databases and included:

- Contraceptives
 - Prescription of contraceptives (date of prescription issuance/filling, type, dispensed amount, or days' supply)
 - Prescription of implant/ intrauterine device (IUD) (date of prescription/dispensing or procedure)
- Periodicity of oral retinoid prescriptions (date of prescription issuance/filling, type, dispensed amount, or days' supply)
- Laboratory pregnancy tests
 - Laboratory pregnancy tests (blood or urine, type, if available, and date of test)

- Records (e.g., International Classification of Diseases 10 [ICD-10] code related to an exam) which documented the performance of a laboratory pregnancy test (date of record)

Emergency contraceptives (ATC codes:G03AD01 and G03AD02) were not considered as one of the highly effective methods of contraception as per the EMA guidelines, which state that: “*They should only be used as an occasional 'rescue' method as they do not work as well as regular contraceptive methods*” (5). Emergency contraception pills do not protect against pregnancy if patients have sex again after taking them and patients should continue using their normal contraception after using emergency pills (6). Hence, such instances of emergency contraception intake that were recorded in the databases for the patients who entered the study cohorts were not counted in the calculation of adherence to contraception. The ICD-10 codes and ATC codes for contraception and pregnancy testing are listed under the Supplement 1. Target time windows for the PPP measures with respect to contraception and pregnancy tests are shown in

Table 6.

Table 6 Target time windows for measures of the pregnancy prevention programme

Active substance	Contraception			Pregnancy test			Days' supply/Length of prescription
	Before treatment episode	During treatment episode	After treatment episode	Before treatment episode	During treatment episode	After treatment episode	
Acitretin	1 month (30 days)*	Yes	Continuous, up to 3 years	Up to 7 days	Monthly	In intervals shorter than 3 months (90 days), up to 3 years	1 month (30 days)
Alitretinoin	1 month (30 days)*	Yes	1 month (30 days)*	Up to 7 days	Monthly	1 month (30 (-/+ 7) days)**	1 month (30 days)
Isotretinoin	1 month (30 days)*	Yes	1 month (30 days)*	Up to 7 days	Monthly	1 month (30 (-/+ 7) days)**	1 month (30 days)

* Or 28 days in case of hormonal contraceptives that simulate the menstrual cycle (e.g., combined oral contraceptives)

** To account for real-life situations, pregnancy testing done within 23 – 37 days after end of a treatment episode would be considered acceptable.

Note. Alitretinoin did not have marketing authorisation in Sweden in the pre-implementation period.

10.4.2.2 Variables Related to the Secondary Objectives

The following variables and derivatives applied to the secondary outcomes (Supplement 2.2).

- Patient age
- Indication for oral retinoids
 - Indication for oral retinoids were identified by ICD-10 diagnosis codes
- Prescriber speciality (not available for France)
- Treatment characteristics
 - Prescription count and prescription length including:
 - Number of oral retinoid prescriptions per patient
 - Average length of oral retinoid prescriptions (in days) per treatment episode
 - Duration of treatment
 - Duration of oral retinoid treatment episodes (in days)
 - Number of oral retinoid prescriptions per treatment episode
 - Number of oral retinoids treatment episodes per patient
 - Average daily dose
 - Analysed over a treatment episode based on directly captured daily dose (if available) or prescribed drug amount and period between 2 prescriptions, as per data availability.
- Pregnancy
 - All available records related to pregnancies and pregnancy outcomes including diagnoses (based on ICD-10 coding, listed in Supplement 1.2), tests and exams usually performed during pregnancy were searched in the databases to extract:
 - Number and percentage of pregnancies exposed to oral retinoids
 - Incidence rate of pregnancies exposed to oral retinoids
 - Outcome in exposed pregnancies
- Meta-analysis of aggregated primary outcome measures for the 4 countries together
- Trends in the prescribing practice of oral retinoids with respect to measures of the PPP

- To identify ongoing trends in the countries of interest - especially after the implementation of the updated PPP, interrupted time series (ITS) analysis using segmented regression method was performed for the following key parameters:
 - Proportion of episodes with use of contraception for 1 month before treatment start
 - Proportion of episodes with continuous concomitant use of contraception during the entire period of the treatment episodes
 - Proportion of episodes with laboratory pregnancy tests at treatment start (up to 7 days before oral retinoid prescriptions start dates)
 - Proportion of episodes with monthly laboratory pregnancy tests during treatment

10.5 Data Sources and Measurement

All information on exposure and outcomes were derived from established secondary longitudinal data sources. A single database for all target countries was not available. Therefore, a study approach was chosen which includes using multiple established data sources to gather drug utilisation data for oral retinoids in the countries of interest.

10.5.1 Selection of the Target Countries and Data Sources

The included countries for the DUS were selected based on the following criteria:

- Countries in which the number of exposed patients is high based on market share
- Coverage of different regions in Europe
- Availability and accessibility of patient-level databases
- Availability of the information required to meet the study objectives

First, the top 5 countries in term of sales, France, the UK, Poland, Spain, and Germany, were checked with respect to geographical distribution and the availability of longitudinal patient-level data sources. Initially considered countries included Central (France, Germany), Western (UK), Southern (Spain) and Eastern Europe (Poland), but not Northern Europe. Sweden was suggested as an additional target country because the Swedish national registry data provides national coverage and is a well-established data source with high-quality data for pharmacoepidemiologic

studies. This led to a further selection of target countries to be France, Germany, Sweden, and the UK. Spain was not considered initially, because the database with patient-level data covers only the region of Catalonia (SIDIAP). However, given the relatively low number of oral retinoid prescriptions in the UK data source (THIN), Spain was included. For Poland, a patient-level prescription database (IMS LRx) was available. However, this database did not include information on diagnosis, pregnancies and pregnancy outcomes or lab tests, and was therefore not included. Another claims database with national coverage in Poland held by the National Health Fund (NHF), was available but has not been widely used in pharmacoepidemiologic research and was therefore not included. The included 4 data sources are outlined in

Table 7.

1. Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) of the Système National des Données de Santé (SNDS) in France (Claims database)
2. Collective of insurants from company health insurance funds in Germany (Claims database)
3. Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) in Spain (Primary care database)
4. National Health registers in Sweden

10.5.2 Claims Data – France and Germany

10.5.2.1 France – Système National des Données de Santé

The Système National des Données de Santé (SNDS) is a claims database, following the National Health Insurance expenses. The primary purpose of the SNDS is to determine the costs for all National Health Insurance System schemes in office-based care (SNIIRAM databases) and hospitalisation (Programme de Médicalisation des Systèmes d'Information (PMSI) databases). The SNDS database is very comprehensive. It is a claims database covering all the Health Insurance schemes based on individuals' employment status in office-based care and hospitalisation for each beneficiary. With this very large coverage (>99% of the French population), the SNDS provides comprehensive and detailed health information, which is relevant and very useful for epidemiological and health economic studies (7).

The vast majority of pregnancies and pregnancy outcomes are covered in the SNDS. In 2018, an algorithm was published to identify pregnancy episodes in the French healthcare database (8). The SNDS database was used to evaluate the compliance with PPP recommendations in women of childbearing potential exposed to retinoids. The study included about 9000 women initiated on acitretin in France (9). The data of medical services list all the closing transactions related to the payment of services to the beneficiaries. These files include information related to the care recipient, the type of caregiver, the type of care and the monetary flows induced. However, in these files of medical services, some healthcare utilisation cannot be seen, such as utilisation not claimed for reimbursement, non-reimbursable health services or self-medication. The SNIIRAM is linked to the PMSI. The PMSI is a comprehensive national database, which classifies all hospital stays in all public and private healthcare institutions in France. Access to PMSI is managed by the Hospitalisation Information Technical Agency (ATIH). The PMSI data covers 3 different types of care centres:

- Acute care (short duration stays) at hospital: the PMSI MCO (medicine, chirurgie, obstétrique)
- Home hospitalisations stays: the PMSI HAD (Hospitalisation à domicile)
- Follow-up and rehabilitation care stays: the PMSI Hospitalisation à domicile SSR (Soins de suite ou de réadaptation)

In PMSI, a unique identifier for each patient makes it possible to track the hospital course of patients over years. The data are updated once a year with the data from the full previous year. Available data are:

- Demographic: Age, gender, place of residence, and date of death at hospital
- Medical: Diagnoses (main, related and associated), medical procedures performed (including surgeries), duration of stay, and month of hospital discharge
- Economic: Fee schedule associated with each hospital stay, with additional costs for medicinal products and medical devices from the “liste en sus”, since 2009

Diagnoses are coded in the database according to the ICD-10 and expensive drugs and devices with major benefits for patients are charged apart from the global stay’s cost and are recorded in a specific list of drugs, the “liste en sus”. IUDs and the first and second generation of hormonal

contraceptives are covered, the third and fourth generation, however, are not (10). All reimbursed contraceptives are captured in this database. Based on the results from a survey in 2016 (11) and the reimbursement policies in France, it is expected that records for contraceptives are present for over 50% of women of childbearing potential age in SNIIRAM (12, 13).

10.5.2.1.1 Identification of individuals in SNDS

In France, around 99% of the population is covered by the French universal health insurance. The French National Insurance Health Fund uses 13 health insurance schemes.

The 4 main schemes (covering around 96% of the population) are the following:

- Salaried workers scheme (RG - Régime Général): covering about 77% of the affiliated population
- Government and national education employees and students scheme (sections locales mutualists, (SLM): covering about 10% of the affiliated population
- Agricultural workers scheme (MSA): covering about 5% of the affiliated population
- Self-employed workers scheme (RSI): covering about 5% of the affiliated population

The other 9 schemes (about 3%) are smaller schemes (including notaries and associates, harbour workers, railway workers, etc.).

SNDS databases were first designed and built for reimbursement of healthcare services. Hence, only encrypted IDs (PseudoID) of the beneficiaries are used. In this system, a person can be affiliated on their own or via a main beneficiary who passes the rights to healthcare services to the sub-beneficiary. Therefore, in some cases, an individual may have several PseudoIDs in the databases. This is usually the case for children (sub-beneficiaries of parents) or unemployed people affiliated via a third party (e.g., spouse). In such cases, the PseudoID is constructed by the unique individual number (UID) of the main beneficiary and the date of birth and the sex code (1 for male, 2 for female) of the sub-beneficiary. The UID is given to each French individual by the National Institute for Statistics and Economic Studies (INSEE).

For instance, a child could be covered via her father (she gets PseudoID 1 = PseudoID of her father + the child's date of birth + the child's sex code), but also via her mother (she gets PseudoID 2 = PseudoID of her mother + the child's date of birth + the child's sex code). Consequently, this child

gets 2 PseudoIDs in the databases. When the child grows older and becomes a high-school student (or finds a job), she gets a new PseudoID (PseudoID 3) derived from her own UID + her date of birth + her code sex. Consequently, linking all PseudoIDs is necessary in order to be able to track individuals over time. Therefore, the National Health Insurance Fund, in 2010, has added to SNDS the “Beneficiary Repository” correspondence database that allows the linkage all PseudoIDs to UIDs. However, 2 important concerns must be addressed because a few health insurance schemes do not transmit the UIDs to the beneficiary repository database:

- When children get affiliated to the student health insurance fund, i.e. the SLM scheme, the linkage between their previous child PseudoID(s) and their new SLM PseudoID (mainly at 16, 17 or 18 years old) is weak (because SLM transmits only about 25-30% of UIDs to the databases system);
- Each individual who gets affiliated to SLM during his/her lifetime could not be followed after joining the SLM, due to the lack of the linkage between his/her new SLM PseudoID and his/her UID.

This issue can be overcome using a third specific ID recorded in the databases, which links changes in PseudoIDs to UIDs. However, this is only feasible when an individual or his/her sub-beneficiaries become affiliated to the salaried workers scheme (RG). Children, whose parents (at least one of the parents) are covered by the RG scheme, can be followed. The consequence is that only individuals affiliated to the RG scheme can be included (77% of French population) in a longitudinal cohort study. Notwithstanding, linkage between a patient’s data during childhood and the same patient’s data during adulthood would be possible for about 90% of the individuals (about 10% are lost due to lack of linkage). Considering adults newly affiliated to SLM (about 5-6% per year), no follow-up was possible after joining SLM, and their data was censored at the last date of reimbursement by the RG scheme.

10.5.2.2 Germany – Collective of Insurants from Company Health Insurance Funds

For Germany, different data sources were considered. Due to reasons of availability that conflicted with the milestones of this study, the database with the largest coverage (17%, GePaRD) could not be included. Instead, a large database consisting of claims data of people covered by statutory

health insurance in Germany (SHI) was used. The analysis was conducted by Team Gesundheit, Gesellschaft für Gesundheitsmanagement GmbH, based in Germany (certified according to ISO 9001:2015). For the pre- and post-referral period covering 2014 to 2019, data was available for 5 million insured patients representative of the entire insured German population with a coverage of about 6%. However, for the year 2020, i.e. the post-implementation period, only about 70% of the data (~3.5m) was available due to the impact of global COVID-19 pandemic, which has resulted in an elevated numbers of sick-leaves and political changes within the German health care sector, which has caused additional work burden for the sickness funds and their data service providers. To ensure that pre- and post-implementation periods are similar only the ~70%* data from the sickness funds that have data available from 2014-2020 were included. The privacy of patients in the database is protected at all times and the available information cannot be used for re-identification of patients. The database allows for the analysis of patient-level demographic and clinical characteristics, healthcare resource utilisation (e.g., number and/or duration of inpatient and outpatient visits) and dated prescriptions. The coverage of pregnancies in women receiving healthcare services is high because all reimbursable services are comprehensively recorded in the claims data. The completeness of reported outcomes varies depending on the type of outcome, e.g., an underreporting of induced abortions is possible (14). The database also allows comparisons between patient and control groups with respect to specific utilisation of healthcare services. Longitudinal pre-index and follow-up periods were defined according to the study requirements. Diagnoses and procedures were coded using ICD-10 (German modification) and include treatments that are reimbursed in accordance with the German law. The following data sets were available via the database:

- **Registration data**
 - Demography: Age, gender, insurance status
 - Time since joining the sickness fund
 - Regional distribution (places of residence) of the insured persons within Germany
- **Outpatient care and its cost**
 - ICD-10 diagnoses
 - Code identifying the speciality of the physician in charge

- Billed fee order numbers (*Gebührenordnungsnummern*) according to Einheitlicher Bewertungsmaßstab (*EBM*, German system of medical remuneration for outpatient services) and related costs
- **Inpatient care and its cost**
 - ICD-10 diagnoses (up to 3 principal and 30 secondary diagnoses per case)
 - Billed diagnosis-related groups (DRGs) (German classification) and related costs
 - Up to 30 OPS-Codes per case
 - Duration of hospitalisations
 - Medical department of the hospital involved
- **Drug prescriptions and their cost**
 - ATC Code of prescribed medications and related costs
 - PZN (*Pharmazentralnummer*) of prescribed medications
 - Date of prescription (on a daily basis)
 - Receipt number
- **Sick leaves & sick benefits**
 - ICD-10 diagnoses
 - Duration of sick leaves
 - Sum of sick benefits by sick leaves
- **Prescriptions of medical aids and their cost**
 - Identification code of medical aids and related costs
 - Date of prescription (on a daily basis)
 - Receipt number
- **Other services (e.g., remedies, cures, individual prevention courses)**
 - Type of service and related costs
 - Start and end dates of services (on a daily basis)

The German claims database covers all reimbursed contraceptives. In 2016, 1.1 million females in the age group between 13 to 49 years were captured in the company health insurance database. Thereof, 7% had records of contraceptives for topical use (ATC G02B) or for systemic use (G03A). Preliminary data showed that 16% of the women receiving oral retinoids used

contraceptives concomitantly. Although contraceptives can be reimbursed if contraception is medically indicated, only 2% of the women above the age of 20 years had a record of contraceptives. Before the 29th of March 2019, prescribed contraceptives in Germany were only reimbursed for women under the age of 20. Since then, the age limit has been increased to 22 years. To the best of our knowledge, there is no other type of data source which provides such comprehensive information across the healthcare setting in Germany suitable to be used as data source to address the study objective of this DUS. An electronic medical record (EMR) database available for Germany, the Disease Analyzer, was not a suitable option in this case because patients could not be tracked across different physician specialties. This makes it impossible to track patients from a dermatologist who prescribes oral retinoids to the gynaecologist who prescribes contraceptives and monitors women during pregnancies.

10.5.3 Primary Care Database – Spain

10.5.3.1 Spain – Information System for Research in Primary Care

The Information System for Research in Primary Care (SIDIAP) contains data of anonymised healthcare records for nearly 5.8 million people who receive primary care in one of the primary care centres of Catalonia, representing approximately 80% of the Catalan population. SIDIAP covers 274 centres and approximately 3,400 GPs. The SIDIAP database is highly representative of the population of Catalonia in terms of geographical, age, and sex distributions (15). Data collected by health professionals during routine visits in primary care includes:

- EMR captured using the L'Estació clínica d'atenció primària (ECAP) platform (the electronic health records software used in primary care in Catalonia) at the centre-level: demographics, primary care appointments, diseases (ICD-10), clinical variables, prescriptions, immunizations, and derivations
- Laboratory results: since 2006 all laboratory results are included
- Prescribed medication: since 2009 all prescribed medicinal products with the national healthcare system are included in the database

Laboratory pregnancy testing, contraception, and pregnancy outcomes are covered in the SIDIAP database for women of childbearing potential aged 13-49 years. The way of calculating the beginning of a pregnancy is standardised in daily clinical practice, which includes laboratory pregnancy tests, last menstrual period and other confirmation criteria (16). Approximately, 66% of all term pregnancies in Catalonia were recorded in SIDIAP during the period in which the study by Aliaga and colleagues was conducted (16). A study published in 2011 reported a prevalence of contraceptive use (including hormonal contraceptives, condoms, and IUDs) of approximately 86% in sexually active adolescent to young adult women (ages 16-29) (17). The most commonly used method of contraception was the condom followed by hormonal contraceptives. Only some of the hormonal contraceptives are reimbursed and therefore recorded in SIDIAP. Non-reimbursed contraceptives are recorded in the database but not systematically. To guarantee the quality of the data, a scoring system was applied (18). SIDIAP has been used extensively in medical research, including DUS, since 2010 and across Europe, and has been found to be a valid source for research (19). A study on the association between affective disorders presenting before and during pregnancy considering the use of medication has recently been published (16).

10.5.4 National Registry Data – Sweden

10.5.4.1 Sweden – National Registries

IQVIA was provided with a linked research database for Sweden with full national coverage through combining data from the National patient register, covering all specialist and hospital care in Sweden, with the National drug register, covering all drugs dispensed at pharmacies in Sweden, and the Medical Birth register covering all pregnancies resulting in delivery. With the linkage (done via a unique identifier) between these registries, a comprehensive longitudinal view of healthcare provided in Swedish secondary care and above and drugs dispensed can be provided. This longitudinal data enables the study of historical clinical information on the subjects treated with oral retinoids. The data sources did not include information on clinical anamnesis and lab results for the patients, nor information on the care provided for the patients in the primary care setting. Individual patient data were collected from both in- and outpatient hospital-based specialist care across Sweden. The National Patient Register dates to 1964. From 1987 there is information on all completed inpatient admissions. The collection of out-patient care data began

in 2000. The register is updated annually and available from September/October the following year. The available data in the National Patient Register included:

- Demographics (age, gender)
- Medical information: diagnoses (ICD-10 code and associated position), DRG code, care setting (inpatient or outpatient), admission date and discharge date (for inpatient care), surgeries and procedure performed)
- Hospital information (region, clinic, etc.).

Information on patient anthropometrics (height, weight, etc.), lifestyle (smoking, etc.), laboratory and clinical measurements, such as blood pressure and blood lipid levels were not available. In addition, information on drugs administered at the hospital was not available. All medicines are prescribed electronically in Sweden. The National Prescription Register tracks the full details of all dispensed medications at individual patient-level in Sweden since 01-Jul-2005. Patients are followed longitudinally through their personal identification number, regardless of which pharmacy they visit. The National Drug Register is updated monthly and covers all sales from Swedish pharmacies. The available data in the National Drug Register included:

- Demographics (age, gender, and residency)
- Prescription information (date of prescription, prescriber's speciality, World Health Organization (WHO) ATC code, and brand name)
- Dispatch information (dispatch date, product number, total dose dispatched, number of packages dispatched, and drug cost)
- Product information (package size, formulation, etc.)
- Information on prescribed dose was only documented in free text format where available, and days' supply was not recorded. However, an average daily dosage was used following section 16.2.3.6 of the SAP.

In Sweden, the online database on prescription held by the National Board of Health and Welfare (NBHW) provides the following information on the annual prevalence of Swedish women aged 15-49 years who filled at least 1 prescription for hormonal contraceptives in 2012-2017: ATC G02B contraceptives for topical use: 4.3-5.4%; ATC G03A hormonal contraceptives for systemic

use: 22.4-26.1% (reference: prescription registry). Of note, to gain access to the linked register, an approval from the local ethical review board is necessary, whereby the research project and ethical aspects should be explained in a formal application. The ethics approval is dependent on the data being made publicly available in some form. The Medical Birth Register contains information on 97% to 99.4% of all pregnancies resulting in delivery in Sweden and is frequently used for quality work and for research (NBHW (20, 21)). The register contains detailed information about mothers and new-borns. However, pregnancies are only captured after 22 weeks. Records on pregnancies are documented in the National Patient Register regardless of the duration of pregnancy, but missing information regarding early termination needs to be taken into account.

Table 7 shows the availability of data by country.

Table 7 Summary of the included databases and availability of data by country

	France	Germany	Spain	Sweden
Name and Type	<i>SNIIRAM of the SNDS</i> Claims database	<i>Company Health Insurance funds</i> Claims database	<i>SIDIAP</i> Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Information System for Research in Primary Care	<i>National Health registers</i> National Drug-, Patient- and Birth registers
Overall representativeness	>99% of French population	~6% of German population	>80% of Catalanian population, ~16% of Spanish population	National coverage for Sweden

	France	Germany	Spain	Sweden
Size	57 million, all health insurance schemes in office-based care and hospitalisations	5 million insurants	About 5 million active people and about 7 million active, transferred and dead people	10 million, specialist and hospital out- and inpatient care and all drugs dispensed for the Swedish population
Historical information	Data for beneficiaries covered by general insurance scheme was available since 2006, but not complete for the years 2006 and 2007. For this reason, data was retrieved only from January 2008 to June 2014.	Data was available from 2008.	Electronic health records were available since ~2005-2006 (the year depended on the area), although health professionals could already manually register data (e.g., diagnoses) prior to 2006. Data on reimbursed drugs dispensed were available since 2005- 2006. The electronic prescription records were available since 2009.	Availability of historical medical information in the National Patient Registry was from 1997 (surgical and medical history), the Swedish Prescribed Drug Register was from July 2005 (pre- existing contraception), and the Medical Birth Registry was from 1973 (records of procedures for female sterilisation).
Analysis done by	IQVIA	Research Partner	Research Partner	IQVIA
Data lag time	9 months	12 months	1 year	1 - 9 months (depending on the type of registry)
Patient age	Available	Available	Available	Available

	France	Germany	Spain	Sweden
Diagnosis	Available in the hospital setting only ¹ ; ICD-10 codes	Available; ICD-10 codes	Available; ICD-10 codes	Available; ICD-10 codes
Information on physician visits	Available	Available	Available	Available
Pregnancy	Available	Available	Available	Available

ICD, International classification of diseases; SIDIAP, Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària; SNDS, Système National des Données de Santé; SNIIRAM, Système National d'Information Inter-Régimes de l'Assurance Maladie.¹Diagnosis is only recorded in case of inpatient hospitalisations related to the indication of interest, therefore data on indications is missing in the majority of cases.

The availability of information relevant to the primary outcomes is summarised in Table 8.

Table 8 Availability of parameters used to evaluate the primary outcomes

	France	Germany	Spain	Sweden
Data Source	<i>SNIIRAM of the SNDS</i>	<i>Company Health Insurance funds</i>	<i>SIDIAP</i>	<i>National Health registers</i>
Records of contraceptives use before, during and after oral retinoid treatment	Only reimbursed contraceptives	Only reimbursed contraceptives	Prescribed and reimbursed	Prescribed contraceptives
Records of laboratory pregnancy tests before, during and after oral retinoid treatment	Available (Human chorionic gonadotropin (HCG) blood tests performed)	Available	Available (mainly urine pregnancy tests)	ICD-10 codes are available

	France	Germany	Spain	Sweden
Prescription date	Only reimbursement date available	Available	Available; initial and final date of prescription	Prescription date and filling (purchase) date available. Multiple fillings can be made on the same prescription and prescription dates can be quite far apart. Therefore, filling dates are considered a better representation of the episode start.
Periodicity of oral retinoid prescriptions	Available; duration approximated algorithmically	Available; duration approximated algorithmically	Available	Available; duration approximated algorithmically

SIDIAP, Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària; SNDS, Système National des Données de Santé; SNIIRAM, Système National d'Information Inter-Régimes de l'Assurance Maladie.

10.6 Bias

Selection bias

In this study 13-49 year old women were considered to be of childbearing potential. It is possible that some of the women who were not in the age range and excluded from the study were of childbearing potential as well. However, they would comprise only a small group, which would be similar to the women included in the study in terms of oral retinoid use and therefore due to their exclusion the results presented in this report may have only been slightly underestimated (22). Further, although the French and Swedish databases had a good coverage of the populations in the respective countries, the German and Spanish databases had lower coverage of their overall populations. While the databases are considered representative (section 10.5), it is possible that biases may arise if the women included were different from the women not included in the German and Spanish databases.

Information bias

Importantly, *information* bias can result from differences in collected data (e.g., accuracy or completeness) that misclassify patients in terms of exposures or outcomes. In this study, information bias could occur if data were collected differently during the pre- and post-referral periods. Well-established databases that collect information for administrative purposes were used in this report and no major changes in data collection occurred during the study period, therefore, information bias is less likely to have occurred.

Data limitations

Due to inherent differences (e.g., start of database, recording of test results, etc.) in the databases some information was not available and/or limited.

- *Contraceptives use.* Only reimbursed contraceptives were captured in the majority of the databases (France, Germany and Spain). Thus, data availability might have led to an underestimation of contraceptives use. National differences in reimbursement and coverage might partly account for observed differences in contraceptive use between countries.
- *Pregnancy testing.* The availability of data differed between the 4 countries (Table 8 and Supplement 1.2). Point-of-care quick urine tests were not recorded in Spain. In Sweden, data on laboratory pregnancy tests were extracted using ICD-10 code Z32 “Pregnancy examination and test” and therefore may have underestimated the actual number of pregnancy tests performed in routine care.
- *Pregnancy outcomes.* The Swedish birth registry only captured pregnancies after 22 weeks, as such some early negative outcomes may have been missed. Across data sources, incomplete information regarding the pregnancy duration may have led to misclassification of timing of exposure during pregnancy. Moreover, pregnancies that are aborted are shorter than pregnancies that result in live births. As a result, pregnancies with live births, which started in the middle of 2020, were classified as pregnancies without information on outcome since their outcomes would be documented in 2021. In France, the baby’s information was recorded under the mother’s ID in the first two weeks of life. It is possible that records with such codes include birth defects of the mother recorded in this period (e.g., a malformation of the vagina that makes delivery difficult). Therefore, the codes ICD Q00-Q99 were not

used for pregnancy outcome documentation. Finally, administrative claims data may underrepresent pregnancy losses due to lack of care sought early in pregnancy.

- In case the data were unavailable (e.g., for the average daily dose/duration of use, see section 10.9.3), approximation approaches were used which could have led to over- or underestimation of the actual values.
- Estimates related to duration of treatment might have appeared longer when they were based on dispensing date rather than prescription date (e.g., as in France), thus possibly reflecting behaviour of patients, rather than clinicians.

Most of the above-mentioned biases are expected to persist across all study periods with minor variations only. The impact on the descriptive comparison of the pre- and post-implementation periods is therefore considered to be of limited extent.

10.7 Study Size

The final study size was determined by the available patient numbers in the included data sources. Data from all patients available in the databases who are eligible for inclusion in the study were included in the analysis. The estimated sample size was calculated before the study commenced to ensure that the study would obtain meaningful data for descriptive purposes. The sample size calculation was determined by the desired accuracy/precision of the estimation by confidence interval (CI) of the observed percentages for the variables that addressed the primary objective (which considers the 3 oral retinoids pooled rather than individual substances). As the observed percentage (p) was not known in advance, it was considered to be 50% (maximum uncertainty). Table 9 shows that to achieve a sufficient accuracy, i.e., within a margin of accuracy +/- 5%, of the estimation by a two-sided 95% CI for a percentage (p) 50%, a sample size of 385 patients would have been required. The precision for an observed percentage with 95% CI was determined by the formula below (normal approximation):

$$e = \sqrt{\frac{p(1-p)}{n}} \times \varepsilon_{\alpha}$$

With n sample size, p observed percentage, ε_{α} 1.96 for 95% CI, e Precision.

Table 9 Required number of patients by acceptable precision (95%CI) or proportions (normal approximation)

Precision	Observed percentage (accuracy): p(1-p)				
	10% (90%)	20% (80%)	30% (70%)	40% (60%)	50% (50%)
± 2.0%	865	1537	2017	2305	2401
± 3.0%	385	683	897	1025	1068
± 4.0%	217	385	505	577	601
± 5.0%	138	246	323	369	385
± 6.0%	97	171	225	257	267
± 7.0%	71	125	165	189	196
± 10.0%	35	62	81	93	97

CI, confidence interval

10.8 Data Transformation

Not Applicable

10.9 Statistical Methods

The analysis of German and Spanish data was performed by the local research partners (i.e., the external vendors Team Gesundheit and IDIAP, respectively) according to the planned statistical analysis and following their corresponding routine procedures. IQVIA received filled-in results tables but no analytical datasets from the external vendors. For Sweden, IQVIA received study-specific datasets from the NBHW generated according to routine processes at the data holder and a study-specific data application form for data extraction. French data were directly extracted and stored by the CNAM (Caisse nationale de l'Assurance Maladie, national health insurance). IQVIA had access to the study dataset via a secured portal. At IQVIA, all final planned analyses were performed by data source experts and trained statisticians from IQVIA Real-World Solutions (RWS) Biostatistics following Standard Operating Procedures (SOPs). The statistical analysis software used was SAS in Germany and R in Spain, France and Sweden (version 3.5.0 or later).

10.9.1 Analysis Sets

Based on the availability of data, 5 different analysis sets were created:

1. **Full Analysis Set [FAS]** contained all patients who met all inclusion criteria and none of the exclusion criteria. Prescriptions from the FAS were considered for each of the primary

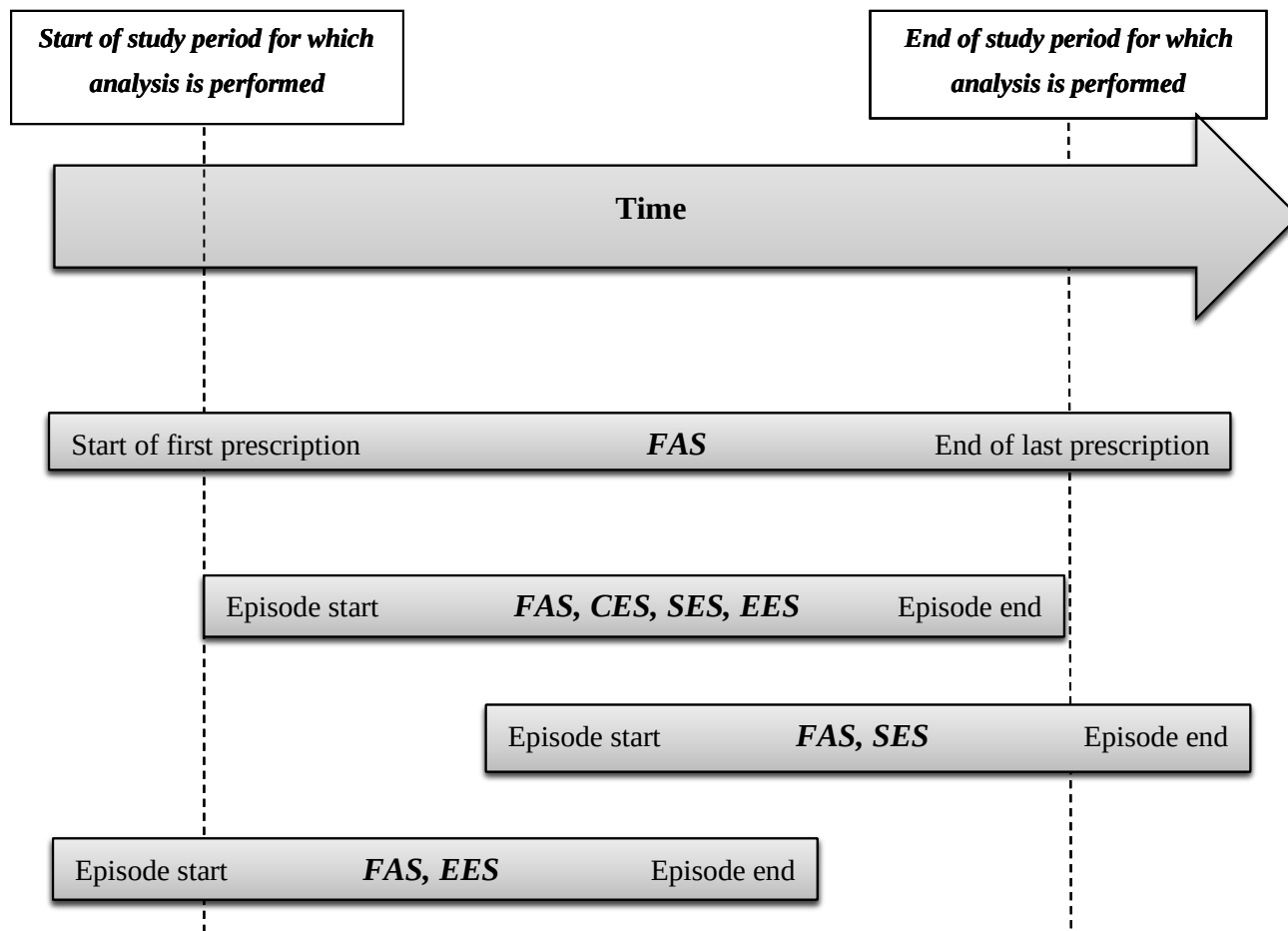
analyses only if patients were 13 – 49 years old on start dates of prescriptions that were used for the corresponding analysis (e.g., first prescription of an episode for analysis of contraception and laboratory pregnancy testing before treatment start). If a FAS episode spanned multiple periods, then the episode was considered as belonging to all periods. The exposure time in each period begins at the first prescription of this period.

2. **Complete Episodes Set [CES]** contained episodes (

3. Table 5 “treatment episode” definition) of patients in the FAS that started (episode exposure start date) and had an issuance/filling date of the last prescription in the episode (after accounting for stockpiling) within the study period of interest.
4. **Starting Episodes Set - Contraception [SESContraception]** contained episodes of patients in the FAS that started within the study period of interest (i.e., having the episode exposure start date within the study period of interest) and had available data for at least 1 month (30 days) before episode start date. Additionally, patient age at episode exposure start date was between 13 – 49 years old.
5. **Starting Episodes Set – Pregnancy testing [SESTesting]** contained episodes of patients in the FAS that started within the study period of interest (i.e., having the episode exposure start date within the study period of interest) and had available data for at least 7 days before episode start date. Additionally, patient age at episode exposure start date was between 13 – 49 years old.
6. **Ending Episodes Set [EES]** contained episodes of patients in the FAS that have at least 1 prescription issued/filled within the study period of interest, end within the same study period (i.e., having the episode end date within the study period of interest) and had data for at least 1 month after treatment stop. Additionally, patient age at episode end date was between 13 – 49 years old.

Figure 2 illustrates the different possibilities of start and end of analysis sets in relation to start and end of study period for which analysis is performed and Table 10 presents a summary of the analysis sets used for each analysis.

Figure 2 Illustration of the different possibilities of start and end of analysis sets in relation to start and end of study period for which analysis is performed



CES, complete episodes set; EES, ending episodes set; FAS, full analysis set; SES_{Contraception}, starting episodes set – contraception; SES_{Testing}, starting episodes set – pregnancy testing

Table 10 Summary of the analysis sets used in the primary and secondary analysis

Analysis	Analysis Set
Primary analysis	
Laboratory pregnancy tests <u>before treatment start</u>	SESTesting
Laboratory pregnancy tests <u>during treatment</u>	FAS
Laboratory pregnancy tests <u>after treatment stop</u>	EES
Contraceptives use <u>before treatment start</u>	SESContraception
Contraceptives use <u>during treatment</u>	FAS
Contraceptives use <u>after treatment stop</u>	EES
Periodicity of oral retinoid prescription	FAS
Secondary analysis	
Patient age	FAS for analysis on the patient level SESTesting for analysis on the episode level
Indication for oral retinoids	FAS for analysis on the prescription level SESTesting for analysis on the episode level
Prescriber speciality	FAS for analysis on the prescription level SESTesting for analysis on the episode level
Prescription count	FAS
Prescription length	CES
Duration of treatment	CES
Average daily dose	CES
Incidence of pregnancies exposed to oral retinoids	FAS
Trends analysis	SESTesting, SESContraception, FAS or EES, as appropriate for the analysis conducted

CES, complete episodes set; EES, ending episodes set; FAS, full analysis set; GP, general practitioner; SAS, statistical analysis system; SESContraception, starting episodes set – contraception; SESTesting, starting episodes set – pregnancy testing

10.9.2 Data Analysis

The statistical unit (level of analysis) was either an oral retinoid treatment episode, a patient, or an oral retinoid prescription, as appropriate. Patients who had multiple treatment episodes of oral retinoids entered the cohort for analysis more than once. In the analysis, patients were followed from the medication (oral retinoids) exposure start date (described in section 10.4.1) to censoring date, i.e., transfer out of the database including death, becoming not at risk (50 years old or performing an irreversible sterilization procedure (Supplement 1.3) or end of a study period, whichever occurred first). Given the study objectives, the analyses were mainly descriptive.

Analyses for the primary and secondary objectives are summarised in Figure 3 and a detailed explanation is provided in section 10.9.4. The analyses were conducted for each study period of the pre-implementation and post-implementation periods, for each country, each oral retinoid and the overall class of oral retinoids. Additionally, country-specific estimates of the primary outcomes were pooled together using a meta-analytic approach (section 10.9.4.2.6, (23, 24)). Categorical variables are presented as frequencies (n), percentages (%) with CI where relevant for parameters used to address the primary objective and for the comparison of the incidence of exposed pregnancies. The 95% CI for proportions were calculated using the Wilson method because this method gives coverage probabilities close to nominal levels, even for small sample sizes (23, 24). Continuous variables are presented as means with standard deviation (SD) and as medians with interquartile range (IQR), where appropriate.

Figure 3 Data analysis

Outcome Variables	Primary analysis		Secondary analysis
	Main analysis	Sensitivity analysis (10.9.4.4)	Main analysis
	- Laboratory pregnancy tests: before, during, and after treatment with oral retinoids - Contraceptives use: before, during, and after treatment with oral retinoids - Periodicity of oral retinoid prescription - Analysis by country and oral retinoid		- Patient profile (age, indication for oral retinoids) - Prescriber speciality - Oral retinoids exposure characteristics (prescription count, prescription length, duration of treatment episodes, daily doses) - Pregnancies and pregnancy outcomes - Aggregate study level estimates of the primary outcomes - Trends in physicians' prescribing and monitoring practice of oral retinoids with respect to measures of the PPP over the entire duration the study (trend analysis) - Analysis by country and oral retinoid
Period	Pre-implementation (pre-/post-referral) - and post-implementation periods		
Type of analysis	Descriptive Comparison		Descriptive Interrupted time series (ITS) analysis

10.9.3 Main Summary Measures

The analysis was mainly descriptive and is therefore described below in the main statistical measures.

10.9.4 Main Statistical Measures

10.9.4.1 Primary Analysis

The primary objective of this study was to describe physicians' prescribing and monitoring practices in females of childbearing potential receiving prescriptions of the oral retinoids acitretin, alitretinoin, or isotretinoin during the pre- or the post-implementation period. The statistical unit for the main analysis was the oral retinoid treatment episode. Exposure was described by prescription length, duration of treatment episode and (average) daily dose and provided for each active substance. Further definitions related to exposure are provided in

Table 5. The main analysis was performed for both the pre- and the post-implementation periods as follows:

10.9.4.1.1 Contraceptives Use

Prior to treatment

- Percentage of episodes with use of contraception 1 month (30 days) prior to treatment start

- For each active substance (acitretin, alitretinoin and isotretinoin):

$$n_{ctr\_bf} = \frac{\text{sum of episodes in the analysis dataset with a 30 – day contraception period prior to episode exposure start date}}{\text{sum of episodes in the analysis dataset}}$$

$$N_{ctr\_bf} = \text{sum of episodes in the analysis dataset}$$

$$\text{Percentage} = \frac{n_{ctr\_bf}}{N_{ctr\_bf}}$$

- For the overall class of oral retinoids:

$$\text{Percentage} = \frac{n_{ctr\_bf} \text{ of Acitretin} + n_{ctr\_bf} \text{ of Alitretinoin} + n_{ctr\_bf} \text{ of Isotretinoin}}{N_{ctr\_bf} \text{ of Acitretin} + N_{ctr\_bf} \text{ of Alitretinoin} + N_{ctr\_bf} \text{ of Isotretinoin}}$$

During treatment

- Percentage of episodes with continuous concomitant use of contraception during treatment
 - An episode with continuous contraception was defined as episode which was fully covered by contraception from the episode exposure start date to the episode end date

- For each active substance (acitretin, alitretinoin and isotretinoin):

$$n_{ctr\_in} = \frac{\text{sum of episodes in the analysis dataset with continuous contraception}}{\text{sum of episodes in the analysis dataset}}$$

$$N_{ctr\_in} = \text{sum of episodes in the analysis dataset}$$

$$\text{Percentage} = \frac{n_{ctr\_in}}{N_{ctr\_in}}$$

- For the overall class of oral retinoids:

$$\text{Percentage} = \frac{n_{ctr\_in} \text{ of Acitretin} + n_{ctr\_in} \text{ of Alitretinoin} + n_{ctr\_in} \text{ of Isotretinoin}}{N_{ctr\_in} \text{ of Acitretin} + N_{ctr\_in} \text{ of Alitretinoin} + N_{ctr\_in} \text{ of Isotretinoin}}$$

After treatment

- For all retinoids: percentage of episodes with use of contraception for at least 1 month (30 days) after treatment stop
 - For each active substance (acitretin, alitretinoin and isotretinoin):

n_{ctr_af} = *sum of episodes in the analysis dataset with a 30 – day contraception period after episode end date*

N_{ctr_af} = *sum of episodes in the analysis dataset*

$$Percentage = \frac{n_{ctr\_af}}{N_{ctr\_af}}$$

- For overall class of oral retinoids:

Percentage

$$= \frac{n_{ctr\_af} \text{ of Acitretin} + n_{ctr\_af} \text{ of Alitretinoin} + n_{ctr\_af} \text{ of Isotretinoin}}{N_{ctr\_af} \text{ of Acitretin} + N_{ctr\_af} \text{ of Alitretinoin} + N_{ctr\_af} \text{ of Isotretinoin}}$$

- For acitretin: percentage of episodes with concomitant use of contraceptives for up to 3 years after treatment stop (depending on the length of individual follow-up of patients)

- For acitretin only:

n_{ctr_3yr}

= *sum of episodes in the analysis dataset with continuous contraception from treatment stop till follow – up end (up to 3 years)*

N_{ctr_3mth} = *sum of episodes in the analysis dataset*

$$Percentage = \frac{n_{ctr\_3yr}}{N_{ctr\_3yr}}$$

The default durations outlined in

Table 11 were considered in case duration information associated with the use of the contraceptive method was missing, unless better real-world estimates were derived from the database. For example, for Spain a duration of 3 years for IUDs [the mean duration observed in the prescription database] unless initial and end dates are present. While end dates are typically present in the prescription database, records from centres for reproductive health care [as recorded in the ASSIR database module, see SAP v2 Appendix 2.2.3.1 for details]. Any treatment gap for contraceptives (after accounting for up to 6 months of stockpiling) was defined as an end of continuous use of contraception. For implants and IUDs, appearance of a new prescription or procedure related to a different contraceptive method before the end of the default duration listed below in the table for the current contraceptive method marked the actual end of contraception by implants/IUDs. Emergency contraceptives were not considered as one of the highly effective methods of contraception.

Table 11 Default duration of contraception of each contraceptive method

Type of contraceptive method*	Default duration of contraception
Hormonal injection	90 days
Hormonal pills	28 days for the combined, 30 days for the progesterone-only pill (84 or 90 days in France, Germany and Sweden as contraceptives in all 3 countries are usually dispensed in a 3-month supply)
Hormonal patches/vaginal rings	28 days
Hormonal implant	3 years
IUD (copper)	5 years (range: 3-12 years)
IUD (hormonal)	5 years (range: 3-7 years)

IUD, intrauterine device.

10.9.4.1.2 Periodicity of Oral Retinoid Prescriptions

- To evaluate the periodicity of prescribing oral retinoids, the following analysis was performed:
 - Time interval (in days) between prescription start dates for oral retinoid prescriptions during treatment episodes

- For each episode:

$$\text{Time interval} = \frac{\text{sum of time intervals between prescriptions within an episode}}{\text{number of prescriptions within the episode} - 1}$$

- Percentage of oral retinoid episodes with monthly prescription intervals during treatment
 - An episode with monthly prescription intervals is defined as: an episode in which all intervals between prescriptions are 30 (-/+ 7) days.

- For each active substance (acitretin, alitretinoin and isotretinoin):

n_{prsc_mth} = sum of episodes in the analysis dataset with monthly prescription intervals

N_{prsc_mth} = sum of episodes in the analysis dataset

$$\text{Percentage} = \frac{n_{prsc\_mth}}{N_{prsc\_mth}}$$

- For overall class of oral retinoids,

$$\text{Percentage} = \frac{n_{prsc\_mth} \text{ of Acitretin} + n_{prsc\_mth} \text{ of Alitretinoin} + n_{prsc\_mth} \text{ of Isotretinoin}}{N_{prsc\_mth} \text{ of Acitretin} + N_{prsc\_mth} \text{ of Alitretinoin} + N_{prsc\_mth} \text{ of Isotretinoin}}$$

10.9.4.1.3 Laboratory Pregnancy Tests

Prior to treatment

- Percentage of episodes with laboratory pregnancy tests performed at treatment start (up to 7 days before episode exposure start date)

- For each active substance (acitretin, alitretinoin and isotretinoin):

$$n_{test\_bf} = \frac{\text{sum of episodes in the analysis dataset with at least one laboratory pregnancy test performed at 0 to 7 days before episode exposure start date}}{\text{sum of episodes in the analysis dataset}}$$

$$N_{test\_bf} = \text{sum of episodes in the analysis dataset}$$

$$\text{Percentage} = \frac{n_{test\_bf}}{N_{test\_bf}}$$

- For the overall class of oral retinoids:

$$\text{Percentage} = \frac{n_{test\_bf} \text{ of Acitretin} + n_{test\_bf} \text{ of Alitretinoin} + n_{test\_bf} \text{ of Isotretinoin}}{N_{test\_bf} \text{ of Acitretin} + N_{test\_bf} \text{ of Alitretinoin} + N_{test\_bf} \text{ of Isotretinoin}}$$

During treatment

- Percentage of episodes with at least 1 laboratory pregnancy test performed during treatment

- For each active substance (acitretin, alitretinoin and isotretinoin):

$$n_{test\_in} = \frac{\text{sum of episodes in the analysis dataset with at least 1 laboratory pregnancy test performed during the episodes}}{\text{sum of episodes in the analysis dataset}}$$

$$N_{test\_in} = \text{sum of episodes in the analysis dataset}$$

$$\text{Percentage} = \frac{n_{test\_in}}{N_{test\_in}}$$

- For the overall class of oral retinoids:

$$\text{Percentage} = \frac{n_{test\_in} \text{ of Acitretin} + n_{test\_in} \text{ of Alitretinoin} + n_{test\_in} \text{ of Isotretinoin}}{N_{test\_in} \text{ of Acitretin} + N_{test\_in} \text{ of Alitretinoin} + N_{test\_in} \text{ of Isotretinoin}}$$

- Percentage of episodes with laboratory pregnancy tests performed monthly according to the SmPC during the entire length of the treatment episodes

- Episodes with performed pregnancy test every 30 days or less during the entire length of the episode, starting from the episode exposure start date to the episode end date are considered as episodes with monthly laboratory pregnancy tests during the entire treatment episodes.

- For each active substance (acitretin, alitretinoin and isotretinoin):

n_{test_mth} = *sum of episodes in the analysis dataset with monthly laboratory pregnancy tests during the entire episode*

N_{test_mth} = *sum of episodes in the analysis dataset*

$$Percentage = \frac{n_{test\_mth}}{N_{test\_mth}}$$

- For the overall class of oral retinoids:

$$Percentage = \frac{n_{test\_mth} \text{ of Acitretin} + n_{test\_mth} \text{ of Alitretinoin} + n_{test\_mth} \text{ of Isotretinoin}}{N_{test\_mth} \text{ of Acitretin} + N_{test\_mth} \text{ of Alitretinoin} + N_{test\_mth} \text{ of Isotretinoin}}$$

- Percentage of treatment episode time covered with compliant laboratory pregnancy tests
 - A laboratory pregnancy test was defined as a compliant laboratory pregnancy test if it was performed no more than 30 days after the previous test (or episode exposure start date if it was the first test within the episode). Non-compliance days were defined as all days between the 30th day after a pregnancy test and the date of the next test in the same treatment episode.

- For each episode:

$$Percentage = 1 - \frac{\text{Number of non – compliance days in a treatment episode}}{(\text{Episode end date} - \text{Episode exposure start date} + 1)}$$

After treatment

- For all retinoids: percentage of episodes with laboratory pregnancy tests performed at 1 month (30 (-/+7) days) after treatment stop (end date of treatment episode)
 - For each active substance (acitretin, alitretinoin and isotretinoin):

n_{test_af} = *sum of episodes in the analysis dataset with at least one laboratory pregnancy test performed at one month (30 (-/+7) days) after episode end date*

N_{test_af} = *sum of episodes in the analysis dataset*

$$Percentage = \frac{n_{test\_af}}{N_{test\_af}}$$

- For the overall class of oral retinoids:

Percentage

$$= \frac{n_{test\_af} \text{ of Acitretin} + n_{test\_af} \text{ of Alitretinoin} + n_{test\_af} \text{ of Isotretinoin}}{N_{test\_af} \text{ of Acitretin} + N_{test\_af} \text{ of Alitretinoin} + N_{test\_af} \text{ of Isotretinoin}}$$

- For acitretin: percentage of episodes with laboratory pregnancy tests performed regularly in intervals shorter than 3 months (90 days), for up to 3 years after treatment stop (depending on the length of individual follow-up of patients)
 - Episodes which met the criterion below were considered episodes with laboratory pregnancy tests performed regularly in intervals shorter than 3 months:
 - The time intervals between each pregnancy test were no more than 90 days
 - For acitretin only:

$$n_{test\_3mth} = \frac{\text{sum of episodes in the analysis dataset with laboratory pregnancy test performed regularly in intervals shorter than 3 months, for up to 3 years after treatment stop}}{\text{sum of episodes in the analysis dataset}}$$

$$N_{test\_3mth} = \text{sum of episodes in the analysis dataset}$$

$$\text{Percentage} = \frac{n_{test\_3mth}}{N_{test\_3mth}}$$

10.9.4.2 Secondary Analysis

10.9.4.2.1 Patient Age

Age was analysed on the patient level and episode level:

- as a continuous variable
- as a categorical variable with 4 categories:
 - 13 – 17 years
 - 18 – 25 years
 - 26 – 33 years
 - 34 – 49 years

Age was analysed as follows:

- On the patient level:
 - For each active substance (acitretin, alitretinoin and isotretinoin): Subtracting the patient's year of birth from the year of the patient exposure start date in the corresponding study period.

- For the overall class of oral retinoids (in case of receiving different oral retinoids within a certain study period): Patient age at the earliest episode exposure start date in the corresponding study period.
- On the episode level:
 - For each active substance (acitretin, alitretinoin and isotretinoin): Subtracting the patient's year of birth from the year of the episode exposure start date in the corresponding study period.
 - For the overall class of oral retinoids (in case of receiving different oral retinoids within a certain study period): Patient age at each episode exposure start date in the corresponding study period.

10.9.4.2.2 Indication for Oral Retinoids

The analysis of indication was performed on the prescription and episode levels as follows:

- **Step 1:** The diagnosis associated with the (prescription or episode) exposure start date was evaluated. If an associated diagnosis was identified as relevant, it was considered as the indication for the prescribed oral retinoid.
- **Step 2:** In case multiple relevant diagnoses were associated with the exposure start date, all the diagnoses were evaluated as the indication.
- **Step 3:** If no diagnosis associated with the exposure start date was identified, all diagnoses were assessed on the exposure start date and in the 12 months prior to and the 30 days after it. The relevant diagnosis closest to the prescription issuance/fill date was considered as the indication. If there were multiple relevant indications on the closest date, all diagnoses were considered. If no relevant diagnosis was found, the indication was considered as missing.

For the **analysis on the prescription level**, the exposure start date referred to the prescription start date. For the **analysis on the episode level**, the exposure start date referred to the episode exposure start date. Results are presented as frequencies and percentages for the different indications.

10.9.4.2.2.1 Country-specific Information

- **France:** The indications for oral retinoid prescriptions were unavailable for the majority of prescriptions (~99%). The indication for oral retinoid prescription was therefore not reported.
- **Germany:** In the database, diagnoses were not directly linked to prescriptions. Hence, all diagnoses that were registered in the database in the specific time period and could be attributed to the oral retinoid substance prescribed were considered for analysis.
- **Spain:** In SIDIAP, diagnoses were not directly linked to prescriptions. Hence, all diagnoses that were registered in the database in the specific time and could be attributed to the oral retinoid substance prescribed were considered for analysis. This included all 'active' diagnoses. A diagnosis is 'active' from the start date of activation to the end date which the physician specifies the diagnosis has finished (some diagnoses are designated as “chronic” and remain active continuously).
- **Sweden:** Indication for oral retinoids was inferred based on records of the relevant diagnoses, as detailed in Supplement 1.1.

10.9.4.2.3 Prescriber Specialty

Prescriber speciality was analysed as a categorical variable and at prescription and episode levels. For prescription level analysis, the prescriber speciality for each prescription, whenever available, was considered. For episode level analysis, the prescriber specialty associated with the first prescription of each episode was considered. For prescriptions without speciality information, the speciality was considered as missing. Generally, retinoids are mainly prescribed by dermatologists, who issue the first prescription, and GPs, who usually continue those prescriptions initiated by dermatologists. In the case of contraceptives, gynaecologists and GPs are the main prescribers. Specialty categories with frequency <5% are summarised as “other specialties” where possible.

10.9.4.2.3.1 Country-specific Information

- **France:** Prescriber specialty was available in SNDS only for physicians working in independent practice. In case of a prescription from a salaried physician or outpatient consultations at a hospital, only the hospital ID (i.e., FINESS) was available.
- **Germany:** The database provided information on the specialty of the prescriber.

- **Spain:** SIDIAP provided information regarding the specialty of the prescriber. In case of absence of direct linkage between a prescription and its issuing physician, the specialty considered was that of the physician whose visit was the closest to the prescription start date with a maximum of 15 days before the start date.
- **Sweden:** Information on prescriber specialty was available from the Swedish prescribed drug registry.

10.9.4.2.4 Treatment Characteristics

10.9.4.2.4.1 Prescription Count and Prescription Length

The overall number of oral retinoid prescriptions per patient was described (continuous variable):

- For each active substance (acitretin, alitretinoin and isotretinoin):

$Npc_{pat} = \text{sum of the number of prescriptions per patient}$

- For the overall class of oral retinoids:

$Npc_{pat} = Npc_{pat} \text{ for Acitretin} + Npc_{pat} \text{ for Alitretinoin} + Npc_{pat} \text{ for Isotretinoin}$

The average length of oral retinoid prescriptions per treatment episode in days (continuous variable) was calculated as follows:

- **Step 1:** Calculate prescription length of each prescription. If stockpiling was detected, it was accounted for as explained in

- Table 5.
- **Step 2:** Sum the length of prescriptions per episode.
- **Step 3:** Sum the number of prescriptions per episode.
- **Step 4:** Calculate the average length of oral retinoid prescriptions per episode (for acitretin, alitretinoin and isotretinoin separately and for the overall class of oral retinoids) as follows:

$$\text{Average length} = \frac{\text{sum of the length of prescriptions in the episode}}{\text{sum of the number of prescriptions in the episode}}$$

10.9.4.2.4.1.1 Country-specific Information

In general, the expected days of supply were defined as days' supply reported with a prescription or, when not available, calculated from prescribed drug amount and PDD, preferably, or drugs' defined daily doses (DDD) (Table 5).

- **France:** Prescriptions are dispensed at pharmacies, but only reimbursed drugs are recorded in the database. The pharmacist reviews, adapts and records the following prescription information when dispensing: physician (prescriber) identification, speciality of prescriber if working in an independent practice (speciality of hospital salaried physicians is not recorded), dispensing date, national drug codes (Club Inter Pharmaceutique [CIP], i.e., French pharmacy association codes): i.e., package information: number of units per pack, strength of product, active ingredient, and number of packages dispensed. Prescription length was calculated as described above. For France prescription length was approximated with dispensation length. For a given dispensation during a given treatment episode, dispensation length was estimated as follows: the amount of dose of the drug product dispensed, identified through its CIP code, was calculated by multiplying the dose of the drug in 1 unit with the number of units in the package and with the number of packages dispensed. Dispensation length was then estimated by dividing the amount of dose by the average daily dose estimated in this treatment episode.
- **Germany:** The dosing regimen prescribed for each patient was not recorded in the database. Prescription length was calculated as the number of days between the prescription start date (the day on which the prescription was issued by the treating physician) and the prescription end date, which was calculated by the total supply of drugs divided by average daily dose as described above.

- **Spain:** Prescription length was calculated as number of days between the prescription start date (the day on which the prescription was issued by the treating physician) and the prescription end date (the date which the treating physician marks as the last day of treatment associated with the prescription). The SIDIAP database registers prescription start dates, prescription end dates, dose and frequency of drug use as prescribed (dosage).
- **Sweden:** The PDD was not available in the Swedish Prescribed Drug Register (SPDR). PDD was estimated using the steps described in

- Table 5.

10.9.4.2.4.2 Duration of Treatment

- Duration of treatment episodes was analysed as a continuous variable on episode level and calculated as follows:

- For each active substance (acitretin, alitretinoin and isotretinoin) and the overall class of oral retinoids:

$$Duration = Episode\ end\ date - Episode\ exposure\ start\ date + 1$$

Episode end date and episode exposure start date are defined in Table 5.

- Number of prescriptions per treatment episode was analysed as a continuous variable on the episode level.

- For each active substance (acitretin, alitretinoin and isotretinoin) and the overall class of oral retinoids:

$$Npc_{ep} = \text{sum of the number of prescriptions per episode}$$

- Number of treatment episodes per patient was analysed as a continuous variable on the patient level.

- For each active substance (acitretin, alitretinoin and isotretinoin):

$$Nep = \text{sum of the number of episodes per patient}$$

- For the overall class of oral retinoids,

$$Nep = Nep\ for\ Acitretin + Nep\ for\ Alitretinoin + Nep\ for\ Isotretinoin$$

10.9.4.2.4.3 Average Daily Dose

The average daily dose was analysed as a continuous variable on the episode level based on directly captured daily dose information (if available) or prescribed drug amount and periods between prescriptions. If a treatment episode consisted of only 1 oral retinoid prescription, the duration of the prescription was considered as 1 month by default, unless better real-world estimates were derived from the database. The following steps were followed:

- **Step 1:** Get the dosage of every prescription in the episode.
 - For prescriptions without dosage information:

$$\text{Dosage} = \text{Units dispensed} \times \text{Drug strength per unit (capsule or tablet)}$$

- **Step 2:** Sum the dosage of all the prescriptions in the episode, except for the last one.
- **Step 3:** If treatment duration information was not captured directly in the database, calculate the number of days between the first and last prescription in the episode.
- **Step 4:** Get the average daily dose using the following formula:

$$\text{Average daily dose} = \frac{\text{sum of the dosage of all the prescriptions in the episode, except for the last one}}{\text{number of days between the first and last prescription in the episode}}$$

To prevent erroneous values, the calculated average daily dose was rounded to the closest logical value, based on the available strength per unit – capsule or tablet – of each drug. Additionally, the minimum and maximum valid values for each active substance (as per the labels of the drugs in each country) were considered if the calculated daily doses deviated from those valid values.

Table 12 shows the recommended daily dosages by country.

Table 12 Recommended daily dose by oral retinoid substance and country

	France	Germany	Spain	Sweden
<u>Maximum daily dose</u>				
Acitretin	75 mg	75 mg	50 mg	75 mg
Alitretinoin	30 mg	30 mg	30 mg	NA
Isotretinoin⁺	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
<u>Minimum daily dose</u>				
Acitretin	10 mg	10 mg	10 mg	10 mg
Alitretinoin	10 mg	10 mg	10 mg	NA
Isotretinoin[*]	0.5 mg/kg	0.5 mg/kg	0.5 mg/kg	0.5 mg/kg
<u>Logical increments in dose</u>				
Acitretin	10 mg, 25 mg	10 mg, 25 mg	10 mg, 25 mg	10 mg, 25 mg
Alitretinoin	10 mg	10 mg	10 mg	NA
Isotretinoin	5 mg	10 mg	5 mg	10 mg

⁺If patient weight was not captured in the database, the maximum daily dose limit for isotretinoin was not considered. ^{*}If patient weight was not captured in the database, the minimum daily dose limit for isotretinoin was not considered. NA - Alitretinoin does not hold marketing authorisation in Sweden.

10.9.4.2.4.3.1 Country-specific Information

The average daily dose was analysed over a treatment episode based on the directly captured daily dose (e.g., for Spain) or calculated from prescribed drug amount and period between 2 prescriptions, as per data availability. This varied by country as outlined below:

- **France:** The average daily dose was not directly recorded in the database and had to be calculated. Key variables used to calculate the total amount of dose dispensed in the treatment episode were: dispensing date, national drug codes (CIP codes): *i.e.*, package information: number of units per pack, strength of product, active ingredient, number of packages dispensed.

Within a treatment episode, the average daily dose of drugs' dispensed was calculated as follows:

- For 1 dispensation, the amount of dose of the drug product dispensed, identified through its CIP code, was calculated by multiplying the dose of the drug in 1 unit with the number of units in the package and with the number of packages dispensed.
 - The total amount of dose dispensed in the treatment episode was calculated by summing the amount dose for each dispensation.
 - The average daily dose was then obtained by dividing the total amount of dose dispensed in the treatment episode by the duration of the treatment episode.
- **Germany:** Average daily dose was not recorded directly in the database but was calculated through the total dosage dispensed from all prescriptions belonging to a single episode (except for the last one) divided by the number of total days between the start dates of the first and the last prescriptions in the same episode.
 - **Spain:** No changes from approach as described in the SAP.
 - **Sweden:** The expected days of supply and the gap and stockpiling definitions were used to define a treatment episode. The information about the prescribed dose was not available in the Swedish prescription registry. The average daily dose, over a treatment episode, was calculated as described above. Sometimes, extreme dose values were obtained when calculating the average daily dose since patients may have purchased multiple times within 1 episode leading to short interval between 2 purchases. In addition, when an episode consisted of just one purchase the average daily dose could not be calculated. In both those scenarios the average daily dose was set to the median observed value for the respective ATC code (D10BA01,

D05BB02) and strength of the package. In order to calculate the maximum daily dose for isotretinoin women's weights were needed but were not available in the data. Therefore, maximum daily dose of 40 mg and 80 mg, respectively was based on strength information (10 mg and 20 mg) and the assumption that the pills are taken twice a day at maximum were applied.

10.9.4.2.5 Pregnancy

If the information on pregnancy dates was available, the pregnancy was considered exposed if at least 1 oral retinoid prescription was recorded in the period between the assumed dates of pregnancy start and end. In case information on pregnancy dates was not available, a pregnancy was considered as exposed to oral retinoids if at least 1 oral retinoid prescription was issued within 90 days before or 180 days after the first record of a given pregnancy or depending on the nature of the pregnancy record (e.g., records related to postpartum necessitated shortening the 180 day period). The statistical unit for this analysis was the pregnancy (counts and incidence rates). The following analyses were performed for the pre- and the post-implementation periods of study:

- Number of pregnancies exposed to oral retinoids
 - For each active substance (acitretin, alitretinoin and isotretinoin):
 $n_{preg} = \text{sum of the number of pregnancies exposed to the substance}$
 - For the overall class of oral retinoids:
 $n_{preg} = n_{preg} \text{ for Acitretin} + n_{preg} \text{ for Alitretinoin} + n_{preg} \text{ for Isotretinoin}$

The incidence rate of pregnancies exposed to oral retinoids was estimated as the rate of pregnancies exposed to oral retinoids calculated as a number of pregnancies exposed to oral retinoids per 1000 patients' years at risk during the defined study period. All patients aged 13 to 49 years at the first episode exposure date of the defined study period were included. Analyses were performed for pregnancies exposed to oral retinoids during the defined study periods. Pregnancies were considered as exposed, if patient's age at pregnancy start date was 13 to 49 years, and if it started after the first episode exposure start date.

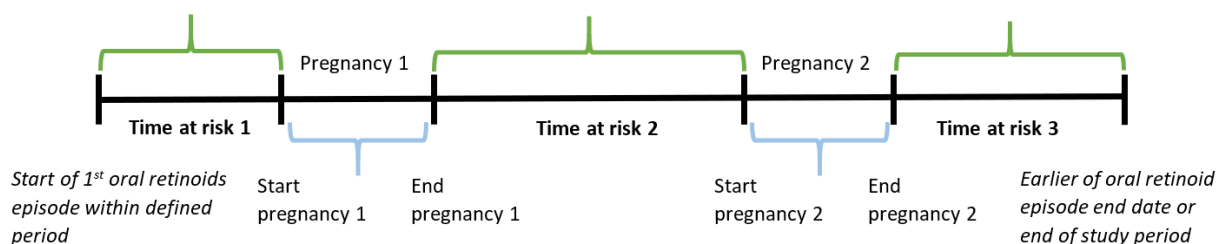
Time at risk was defined as the time between the exposure start date of the first treatment episode and pregnancy start date or time between the exposure start date of the first treatment episode and

the earlier of the oral retinoid episode end date or end of study period (in case of no pregnancy). In case of >1 pregnancy within the same period, all pregnancies were considered and time at risk was calculated as the sum of durations before the first pregnancy, between consecutive pregnancies and between the end of last pregnancy and end of study period (

Figure 4). Time between pregnancies was defined as the difference between end date of previous and start date of the next pregnancy.

$$\text{Incidence rate} = \frac{\text{sum of the number of pregnancies exposed to oral retinoids}}{\text{sum of patients' time at risk (year)}} * 1000$$

Figure 4 Time at risk for analysis of incidence rate of pregnancy (example)



Information on the outcomes of pregnancies exposed to oral retinoids (i.e., live births, termination, stillbirth, miscarriage, or recorded birth defect) is reported as a proportion of pregnancies with each outcome, if available in the databases. Pregnancies that are multiple gestation (e.g., twins) had only one outcome assigned using the following hierarchy (ordered in decreasing precedence): termination, stillbirth, miscarriage, birth defect, live birth. For example, a pregnancy with twins that results in a stillbirth and live birth have only the stillbirth outcome assigned. Pregnancies with birth defects are reported in both the birth defect category and one of the other outcomes: termination, stillbirth, miscarriage, live birth.

10.9.4.2.5.1 Country-specific Information

Country-specific information and codes are included in Supplement 1.

- **France:** The identification variable for the French data extract may not distinguish between the mother and infant in the first 22 weeks after birth. For example, a malformation of the (mother's) vagina that complicates birth might be reported as a birth defect.
- **Germany:** EBM codes are more reliable than ICD codes for determining pregnancy start dates in the German claims database since EBM codes are documented with the specific dates of physicians' visits while ICD codes are documented quarterly. Hence, EBM codes (Supplement 1.2.2.2) were used to identify pregnancies. Records of EBM codes for the same patient with gaps shorter than 200 days were considered belonging to the same pregnancy. Additionally, in order to prevent documentation errors, a pregnancy ICD code was required to be documented within the time period which starts 90 days before the first EBM code and ends 200 days after the last EBM code. A pregnancy was considered to be starting 90 days before and ending 180 days after the first EBM code. A hospital stay with a childbirth or a documented abortion shortened the 180 day period after the first EBM record. The outcomes were checked within the time period from 90 days before the first EBM record to 90 days after the end of pregnancy (270 days after the first EBM code) since diagnoses (ICD codes) are recorded on a quarterly basis.
- **Spain:** No changes from approach as described in the SAP.
- **Sweden:** A similar approach as the one described for German data was also used for the Swedish data using Swedish Klassifikation av vårdåtgärder as listed in Supplement 1.3.

10.9.4.2.6 Meta-Analysis of Primary Outcome Measures for the 4 Countries Together

A meta-analysis of the primary outcome measures for each country was conducted to compute summary outcome measures (i.e., summary proportions or summary means). For binary outcomes, a generalised linear mixed model approach was used to account for possible heterogeneity between estimates. Such an approach yields smaller biases and mean square errors and higher coverage probabilities than more traditional two-step meta-analytic methods (25). A random intercept logistic regression model was used, which assumes that:

- $\text{Event}_i \sim \text{Binomial}(n_i, p_i)$,
- $g(p_i) = \mu + \theta_i$, and
- $\theta_i \sim \text{Normal}(0, \tau^2)$,

where g is the logit function and p_i is the true (unknown) proportion for country i . The effect of interest is μ , which is the median proportion from the latent distribution of proportions that each data source's proportion is assumed to be drawn from. Model parameters were estimated using maximum likelihood. Continuous outcomes were modelled using a random effects model using the Knapp-Hartung with variance correction method, which is preferred over the Knapp-Hartung method when the number of studies is small (26–28).

Heterogeneity was assessed using:

- The Chi-squared test with a significance level of 0.1. The null hypothesis of this test is that all analyses are homogeneous, or that each analysis is measuring an identical effect, and gives us a p-value to test this hypothesis. If the p-value of the test is low, we can reject the null hypothesis and heterogeneity is present. Because the test is often not sensitive enough and the wrong exclusion of heterogeneity happens quickly, a p-value of ≤ 0.1 is typically used as the cut-off.
- I^2 statistic, defined as:

$$I^2 = \frac{Q - df}{Q} * 100\%$$

where Q is the chi-squared statistic and df is its degrees of freedom.

I^2 describes the percentage of total variation across analyses that is due to heterogeneity rather than chance (29). The main advantage of I^2 is that it can be calculated and compared across meta-analyses of different sizes, of different types of study, and using different types of outcome data.

In addition, the sensitivity of the overall pooled estimates to the inclusion or exclusion of certain country-specific estimates were assessed by conducting each meta-analysis with each country omitted (using fixed effect models if appropriate). In some instances, it was not appropriate to pool the data, and in such cases country-specific estimates were excluded from the pooled estimate and presented separately.

10.9.4.2.7 Trends in the Prescribing Practice of Oral Retinoids with Respect to Measures of the PPP – Interrupted Time Series Analysis

To identify ongoing trends in the countries of interest, ITS analysis using segmented regression was performed in case the conditions for this analysis were met (such as the number of time points in the pre-and post-implementation periods and the number of observations). Within the entire pre- and post-implementation periods, a 6-month interval or 3-month interval, in case the number of observations was sufficient (more than 100 observations at each time point for the drug molecule being analysed), were considered as multiple time points. France was an exception, as periods were not all divisible by 3, so 2-month periods were decided upon after confirming that these shorter periods would not change which molecules had a sufficient number of observations. Using ITS analysis, data were evaluated at multiple time points before and after the implementation of the updated RMM to detect whether they had a significantly greater effect than any underlying trend.

The ITS analysis assessed the following key parameters:

- Proportion of episodes with prescriptions of contraceptives or records of implant/IUD use 1 month before treatment start
- Proportion of episodes with continuous concomitant use of contraceptives or implant/IUD during the entire period of the treatment episodes
- Proportion of episodes with laboratory pregnancy tests at treatment start (up to 7 days before start date of oral retinoid prescription)
- Proportion of episodes with monthly laboratory pregnancy tests during treatment

A final decision on key parameters and time points for ITS analysis was made based on results of analyses for primary outcomes (Section 11.3). ITS analysis was only conducted for the outcomes if sufficient data were available for reliable results.

The analyses of outcome measures (key parameters) during the pre- and the post-implementation periods were performed as follows (on example of concomitant use of contraceptives):

The definition and formula for calculation of outcome measure:

$$Concom_{Prop_t} = \frac{NEpisodes\_concom\_t}{NEpisodes\_t} \frac{NEpisodes\_concom\_t}{NEpisodes\_t} \frac{NEpisodes\_concom\_t}{NEpisodes\_t}$$

Where:

$N_{\text{Episodes\_concom\_t}}$: number of episodes with continuous contraception during time (t -1, t)

$N_{\text{Episodes\_t}}$: total number of treatment episodes during time (t -1, t)

The following linear model was defined and applied within a Poisson regression analysis. Effectiveness was measured with the significance level of 0.05.

The following parameterisation was used:

$$\text{Concom}_{\text{Prop}_t} = \beta_0 + \beta_1 \cdot T + \beta_2 \cdot P_t + \beta_3 \cdot (T - T_p) \cdot P_t + \beta_4 \cdot I_t + \beta_5 \cdot (T - T_l) \cdot I_t$$

In this model:

$\text{Concom}_{\text{Prop}_t}$	concomitant use of oral retinoids and contraception at time t
T	time elapsed since study start at the midpoint of the period, defined as (start month of period – end month of period)/2, where months are coded as months since study start (July 2014). For example, for the period July 2014 to September 2014, the calculation is $T=(3-0)/2=1.5$.
P_t	indicator variable coding pre- and post-referral period of the RMM (pre = 0, post =1)
I_t	indicator variable coding pre- and post-implementation period of the RMM (pre = 0, post = 1)
T_p	time of RMM referral intervention in months [=24 for all countries]
T_l	time of implementation in months from study start [values by country are {France: 56; Germany: 63; Spain: 54; Sweden: 54}]
β_0	baseline level at T=0
β_1	outcome change per unit time increase (= pre-referral trend)
β_2	level change following the RMM referral intervention
β_3	difference of outcome change per unit time increase between pre-referral and post-referral period
β_4	level change following the implementation of the RMM
β_5	difference of outcome change per unit time increase between post-referral and post- implementation period

The parameterisation used for analysis was corrected from that specified in the SAP v2.0 Section 16.2.3.9 to match the interpretation of parameters provided in the same section. In particular, $\beta_3 \cdot T \cdot P_t$ was changed to $\beta_3 \cdot (T - T_p) \cdot P_t$, and $\beta_5 \cdot T \cdot I_t$ was changed to $\beta_5 \cdot (T - T_I) \cdot I_t$. For a discussion see (30). Without the change, β_3 has the interpretation of the difference in intercept at $T=0$ (rather than $T = T_p$) for the best-fit lines in the pre-referral period and post-referral period, and β_5 has the interpretation of the difference in intercept at $T=0$ (rather than at T_I) for the lines in the post-referral period and post-implementation period. In addition, when conducting the analysis, it was clarified that T should be set to the midpoint of each period as expressed in months since study start (July 2014). This clarification was to align the interpretation of parameters across countries that might use periods of different lengths (i.e., so that β_0 is the estimate of the level in July 2014, and not the estimate in the first period, the length of which may vary by country).

From this model, slope and level change in each period were estimated. For example, $\beta_1 + \beta_3$ indicate the post-referral trend, and $\beta_0 + \beta_2$ show the level for post-referral interval. As for the post-implementation period, $\beta_1 + \beta_3 + \beta_5$ represent the post-implementation trend and $\beta_0 + \beta_2 + \beta_4$ denote the level during this period. Also, comparisons between each 2 periods are possible from parameter estimators directly or from linear combination of these estimators. The switch effect of referral of intervention can be interpreted as β_3 units of changes in outcome per unit increase in time, beside β_2 units of constant changes in outcome. Similarly, implementation of the RMM not only results in β_4 units of immediate changes in outcome measurement, but also leads to β_5 unit changes per unit increase of time. The referral impact exists in both the pre-referral and post-implementation period, while the implementation effect only exists in the post-implementation period. Therefore, level changes are measured by linear combination of β_2 and β_4 , and slope changes are measured by linear combination of β_3 and β_5 , comparing post-implementation period to pre-referral period.

For the Poisson regression, count data (i.e. $N_{\text{Episodes\_concom\_t}}$) were used directly. To account for the rates and to adjust for changes over time of total episodes of oral retinoids prescriptions with relevant prior medication, the natural log ($\ln$) of the variable $N_{\text{Episodes\_t}}$ was included in the model as an offset parameter. The ratio of deviance to degree of freedom was examined to test for

overdispersion. In case of overdispersion, quasi-Poisson was used. The Ljung-Box test was applied to assess the presence of autocorrelation and Newey-West standard errors was used at the identified order if autocorrelation was detected (31–33). Newey-West standard errors were conducted with Poisson distribution directly for correcting both autocorrelation and heteroscedasticity. The results of the analysis are presented graphically. Parameter estimates, standard errors and p-values are presented in summary tables by country (section 11.4.8).

10.9.4.3 Missing Values

Due to the nature of real-world data, some data points were missing from the databases for a number of reasons. Possible types of missing data include data not recorded in the databases, data recorded as ‘Unknown’, and data recorded as ‘Not Applicable’. The first 2 types (not observed) are reported in the results as ‘Missing’ and the third type (observed but not applicable) as ‘Not Applicable’, where possible. The number and percentage of observations with each type of missing data are reported in separate categories, where possible. Statistical calculations (i.e., the denominator) were adjusted accordingly for the analysis. When calculating proportions for non-missing data, observations with any of the 3 types of missing data were excluded from the denominator. Missing data were not imputed.

10.9.4.4 Sensitivity Analyses

10.9.4.4.1 Sensitivity Analysis 1

A sensitivity analysis was conducted in order to take into account that pregnancy tests might have been recorded earlier than 7 days before oral retinoid treatment start. Accordingly, the time period before the exposure start date was extended to 30 days for analysis of percentage of episodes with laboratory pregnancy tests performed before the episode exposure start date.

10.9.4.4.2 Sensitivity Analysis 2

In order to take into account that the old and the updated RMMs may co-exist during the post-implementation period, a sensitivity analysis for all primary outcome measures was conducted excluding the first 6 months after implementation of the updated RMMs in the target countries.

10.9.4.5 Amendments to the Statistical Analysis Plan

Amendments to the protocol in the SAP are reported in section 9.

The following analyses varied from that described in the SAP. This list includes revisions anticipated in the analysis plan (e.g., the analysis plan noted that code lists “may be subject to amendment or revision during study conduct”).

- The SAP contemplated that prescription dates would not be available for all registries but states that prescription dates would be used wherever possible. However, sometimes the data in the Swedish Prescription registry had large gaps between filling dates such that sometimes the prescription would be filled in different episodes. Therefore, the filling date was considered to be more accurate and used instead of the prescription date for the Swedish registry (Table 8)
- The SAP stated that the time at risk for pregnancies exposed to oral retinoids ends at the end of the study period (in the case of no pregnancies). This was amended to the earlier of the end of the study period or the episode end date (section 10.9.4.2.5).
- The identification variable for the French data extract may not distinguish between the mother and infant in the first 2 weeks after birth. For example, a malformation of the (mother’s) vagina that complicates birth might be reported as a birth defect (section 10.9.4.2.5).
- The parameterisation of the interrupted time series terms for β_3 and β_5 were corrected to ensure parameter estimates have the interpretation intended in the SAP.
- The ITS analysis for France used 2-month periods to maintain periods of equal length and prevent the occurrence of an ITS period that contains two study periods since the post-referral period in France was not divisible by 3.
- The parameterisation of the ITS was clarified so that the midpoint of the period was used for T to more closely align the interpretation of parameter estimates across countries that might use different period lengths for the ITS.
- For the ITS, the trend within the post-referral period and the trend within the post-implementation period were added to facilitate description of the ITS results.
- The proportion of prescriptions with missing dosage instructions was not reported.
- Codelists in the SAP were adapted where necessary for each registry (Supplement 1).

Adaptations of note include:

- The analysis plan indicated that analysis decisions for ICD-10 codes N97.* (female infertility) would be made on an individual basis based on patients' history. For all countries, patients with diagnosis of N97.9 were not treated as infertile when there was subsequent indication of pregnancy or contraception. In all other cases, N97.... +* was treated as infertility (Supplement 1.3).

10.10 Quality Control

The study used existing databases, which are used widely for research, and was executed in line with all applicable regulations and guidelines, such as best-practice guidelines applicable to non-interventional DUS, including but not limited to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (34), the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices (GPPs) of the International Society of Pharmacoepidemiology (35), as well as the specific IQVIA SOPs. All study programs, log files, and output files are stored on secure servers. Where elements of the study were being conducted by a third party, the datasets and analytic programs were stored according to the vendor's procedures. Quality control checklists were developed and used for the study's critical steps, including programming, data management, data analysis, study results generation, and study report writing, as applicable.

10.10.1 Approaches for Validating the Results

The quality control for validation of the results was conducted at 4 levels:

- **At the study planning level:** The statistical methods were developed centrally and aligned with input from experts in the 4 databases to ensure their feasibility and applicability in light of the peculiarities of each database.
- **At the statistical analysis level:** All data management and statistical analysis programs developed and used in the analysis were documented. All versions generated were dated, kept with accompanying documentation and archived. Derived databases were created in order to include recoding and computing of new variables, especially stratification of continuous

variables, combination of modalities for categorical variables, calculation of composite indicators, etc.

- **At the results level:** Data reviews were performed to ensure data integrity. Statistical analysis reports including all results were provided for review and discussion. The final statistical reports took into account the reviewers' comments. Central coordinators with specialist statistical background who participated in developing the statistical methods ensured alignment between the 4 databases in terms of data analysis and results generation in order to minimise heterogeneity of the results.
- **At the study level:** All aspects of the study were conducted according to the SOPs of IQVIA Real World & Analytics Solutions, as well as the SOPs of the participating research partners. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the DUS results and report was conducted by a person who was not in charge of their preparation.

10.10.2 Record Retention

The MAHs maintain adequate and accurate records of the study, including but not limited to the protocol, protocol amendments, documentation of Institutional review board (IRB)/EC and governmental approval/notification (if required) and study reports. Records and documents pertaining to the conduct of this study will be retained for at least 15 years after completion of the study. The length of storage can be extended based on MAH-specific SOPs or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

11 RESULTS

11.1 Participants

11.1.1 France

The French FAS comprised 87,818 patients in the pre- and 111,897 patients in the post-referral period and 92,582 patients in the post-implementation period (Table 13). In both the pre-and post-referral period, most patients were prescribed isotretinoin, with 95.5% and 96.5%, respectively. In the post-implementation period 97.7% had an isotretinoin prescription. Acitretin was prescribed

to 3.1%, 2.4% and 1.6% of patients in the pre-, post-referral (pre-implementation period) and post-implementation periods, respectively. Alitretinoin was prescribed to 1.5%, 1.2% and 0.7% of patients in the pre- and post-referral (pre-implementation period) and post-implementation periods, respectively (Table 14).

Table 13 Attrition by reason and the final patient sample (full analysis set) in France

Country: France						
	Pre-implementation period				Post-implementation period	
	Pre-referral		Post-referral			
	Study Participant		Study Participant		Study Participant	
	Excluded	Remaining	Excluded	Remaining	Excluded	Remaining
Reasons for Inclusion: n (%)						
1. Female		34,143,963 (100)		34,458,516 (100)		34,681,450 (100)
2. Of #1, Received or prescribed at least one prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in any of the study periods	34,054,114 (99.74)	89,849 (0.26)	34,343,593 (99.67)	114,923 (0.33)	34,587,331 (99.73)	94,119 (0.27)
3. Of #2, Childbearing potential (13-49 years of age, inclusive– on at least one of a patient's oral retinoid prescriptions start dates in the corresponding study period)	84 (0.09)	89,765 (99.91)	400 (0.35)	114,523 (99.65)	12 (0.01)	94,107 (99.99)
Reasons for Exclusion: n (%)						
4. Of #3, Exclude all females in the age group 13 to 49 years with available information that they are not of childbearing potential before initiation of oral retinoids (such as records of hysterectomy or sterilisation)	1,947 (2.17)	87,818 (97.83)	2,626 (2.29)	111,897 (97.71)	1,525 (1.62)	92,582 (98.38)
Final study cohort (Full Analysis Set (FAS) in the study): n		87,818		111,897		92,582
n: number of patients, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020						

Table 14 Study cohort in France

Country: France				
		Pre-implementation period		Post-implementation period
		Pre-referral	Post-referral	
Number of oral retinoids patients¹: n (%)		87,818	111,897	92,582
Acitretin		2,688 (3.1)	2,650 (2.4)	1,490 (1.6)
Alitretinoin		1,300 (1.5)	1,290 (1.2)	615 (0.7)
Isotretinoin		83,932 (95.5)	108,075 (96.5)	90,532 (97.7)
Number of prescriptions of oral retinoids: n (%)		467,125	615,844	446,009
Acitretin		15,045 (3.2)	14,508 (2.4)	7,745 (1.7)
Alitretinoin		5,138 (1.1)	5,664 (0.9)	2,361 (0.5)
Isotretinoin		446,942 (95.7)	595,672 (96.7)	435,903 (97.7)
Number of episodes of oral retinoids²: n				
Acitretin	FAS	5,443	5,353	2,822
	CES	4,343	4,573	2,334
	SES _{contraception}	4,827	4,867	2,507
	SES _{testing}	4,829	4,867	2,508
	EES	4,716	4,814	2,256
Alitretinoin	FAS	1,498	1,562	731
	CES	1,056	1,157	489
	SES _{contraception}	1,323	1,375	571
	SES _{testing}	1,323	1,375	571
	EES	1,170	1,294	581
Isotretinoin	FAS	107,185	140,757	112,788
	CES	74,067	101,152	65,853
	SES _{contraception}	94,227	127,015	90,079
	SES _{testing}	94,312	127,124	90,141
	EES	84,712	111,829	75,184
Overall oral retinoids class	FAS	114,126	147,672	116,341
	CES	79,466	106,882	68,676
	SES _{contraception}	100,377	133,257	93,157
	SES _{testing}	100,464	133,366	93,220
	EES	90,598	117,937	78,021

CES, complete episodes set; EES, ending episodes set; FAS, full analysis set; n, number; SES_{contraception}, starting episodes set – contraception; SES_{testing}, starting episodes set – pregnancy testing; pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Patient exposed to 1 or more molecule during the period

² Periods can share an episode (episode ongoing at period switching)

11.1.2 Germany

The German FAS comprised 1,953 patients in the pre- and 3,100 patients in the post-referral period and 1,598 patients in the post-implementation period (Table 15). In both the pre-and post-referral period, most patients were prescribed isotretinoin, with 94.0% and 95.1%, respectively. In the post-implementation period 95.4% had an isotretinoin prescription. Acitretin was prescribed to 4.0%, 2.7% and 2.5% of patients in the pre-, post-referral (pre-implementation period) and post-implementation periods, respectively. Alitretinoin was prescribed to 2.5%, 2.4% and 2.2% of patients in the pre- and post-referral (pre-implementation period) and post-implementation periods, respectively (Table 16).

Table 15 Attrition by reason and the final patient sample (full analysis set) in Germany

Country: Germany

	Pre-implementation period						
	Pre-referral		Post-referral		Post-implementation period		
	Study Participant		Study Participant		Study Participant		
	Excluded	Remaining	Excluded	Remaining	Excluded	Remaining	
Reasons for Inclusion:							
n (%)							
1. Female		1,669,373 (100%)		1,823,180 (100%)		1,732,455 (100%)	
2. Of #1, Received or prescribed at least one prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in any of the study periods	1,663,018 (99.6%)	6,355 (0.4%)	1,816,409 (99.6%)	6,771 (0.4%)	1,726,045 (99.6%)	6,410 (0.4%)	
3. Of #2, Childbearing potential (13-49 years of age, inclusive– on at least one of a patient’s oral retinoid prescriptions start dates in the corresponding study period)	4,292 (67.5%)	2,063 (32.5%)	3,499 (51.7%)	3,272 (48.3%)	4,716 (73.6%)	1,694 (26.4%)	
Reasons for Exclusion: n (%)							

Country: Germany

	Pre-implementation period				Post-implementation period	
	Pre-referral		Post-referral			
	Study Participant		Study Participant		Study Participant	
	Excluded	Remaining	Excluded	Remaining	Excluded	Remaining
4. Of #3, Exclude all females in the age group 13 to 49 years with available information that they are not of childbearing potential before initiation of oral retinoids (such as records of hysterectomy or sterilisation)	110 (5.3%)	1,953 (94.7%)	172 (5.3%)	3,100 (94.7%)	96 (5.7%)	1,598 (94.3%)
Final study cohort (Full Analysis Set (FAS) in the study): n		1,953		3,100		1,598

n: number of patients, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

Table 16 The study cohort in Germany

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of oral retinoids patients¹: n (%)	1,953	3,100	1,598
Acitretin	78 (4.0)	83 (2.7)	40 (2.5)
Alitretinoin	49 (2.5)	75 (2.4)	35 (2.2)
Isotretinoin	1,835 (94.0)	2,949 (95.1)	1,525 (95.4)
Number of prescriptions of oral retinoids: n (%)	8,331	15,697	6,241
Acitretin	307 (3.7)	382 (2.4)	148 (2.4)
Alitretinoin	204 (2.4)	380 (2.4)	116 (1.9)
Isotretinoin	7,820 (93.9)	14,935 (95.1)	5,977 (95.8)
Number of episodes of oral retinoids²: n			
Acitretin			
FAS	94	109	51
CES	56	73	34
SES _{contraception}	75	91	41
SES _{testing}	76	91	41
EES	53	80	28
Alitretinoin			
FAS	64	103	41
CES	50	85	30
SES _{contraception}	61	94	34
SES _{testing}	61	96	34
EES	52	92	24
Isotretinoin			
FAS	2,537	4,447	1,915
CES	1,929	3,755	1,479
SES _{contraception}	2,270	4,144	1,625
SES _{testing}	2,282	4,173	1,630
EES	2,019	3,853	1,204
Overall oral retinoids class			
FAS	2,695	4,659	2,007
CES	2,035	3,913	1,543
SES _{contraception}	2,406	4,329	1,700
SES _{testing}	2,419	4,360	1,705
EES	2,124	4,025	1,256

CES, complete episodes set; EES, ending episodes set; FAS, full analysis set; n, number; SES_{contraception}, starting episodes set – contraception; SES_{testing}, starting episodes set – pregnancy testing; pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020.

¹ Patient exposed to 1 or more molecule during the period

² Periods can share an episode (episode ongoing at period switching)

11.1.3 Spain

The Spanish FAS comprised 3,004 patients in the pre- and 4,211 patients in the post-referral periods and 4,100 patients in the post-implementation period (Table 17). In both the pre-and post-referral periods, most patients were prescribed isotretinoin, with 92.9% and 94.0%, respectively. In the post-implementation period 94.7% had an isotretinoin prescription. Acitretin was prescribed to 7.0%, 5.8% and 5.1% of patients in the pre- and post-referral (pre-implementation period) and post-implementation period, respectively. Alitretinoin was prescribed to 0.4%, 0.4% and 0.2% of patients in the pre- and post-referral (pre-implementation period) and post-implementation period, respectively (Table 18).

Table 17 Attrition by reason and the final patient sample (full analysis set) in Spain

Country: Spain						
	Pre-implementation period				Post-implementation period	
	Pre-referral		Post-referral			
	Study Participant		Study Participant		Study Participant	
	Excluded	Remaining	Excluded	Remaining	Excluded	Remaining
Reasons for Inclusion: n (%)						
1. Female		3,061,072 (100.0)		3,061,072 (100.0)		4,029,112 (100.0)
2. Of #1, Received or prescribed at least one prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in any of the study periods	3,057,044 (99.9)	4,028 (0.1)	3,055,425 (99.8)	5,647 (0.2)	4,024,939 (99.9)	4,173 (0.1)
3. Of #2, Childbearing potential (13-49 years of age, inclusive– on at least one of a patient’s oral retinoid prescriptions start dates in the corresponding study period)	991 (24.6)	3,037 (75.4)	1,388 (24.6)	4,259 (75.4)	39 (0.9)	4,134 (99.1)
Reasons for Exclusion: n (%)						

Country: Spain

	Pre-implementation period				Post-implementation period	
	Pre-referral		Post-referral			
	Study Participant		Study Participant		Study Participant	
	Excluded	Remaining	Excluded	Remaining	Excluded	Remaining
4. Of #3, Exclude all females in the age group 13 to 49 years with available information that they are not of childbearing potential before initiation of oral retinoids (such as records of hysterectomy or sterilisation)	33 (1.1)	3,004 (98.9)	48 (1.1)	4,211 (98.9)	34 (0.8)	4,100 (99.2)
Final study cohort (Full Analysis Set (FAS) in the study): n		3,004		4,211		4,100

n: number of patients, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

Table 18 The study cohort in Spain

Country: Spain		Pre-implementation period		Post-implementation period
		Pre-referral	Post-referral	
Number of oral retinoids patients¹: n (%)		3,004	4,211	4,100
Acitretin		210 (7.0)	245 (5.8)	209 (5.1)
Alitretinoin		12 (0.4)	17 (0.4)	9 (0.2)
Isotretinoin		2,792 (92.9)	3,959 (94.0)	3,887 (94.7)
Number of prescriptions of oral retinoids: n (%)		5,455	7,694	6,984
Acitretin		437 (8.0)	521 (6.8)	362 (5.2)
Alitretinoin		21 (0.4)	21 (0.3)	14 (0.2)
Isotretinoin		4,997 (91.6)	7,152 (93.0)	6,608 (94.6)
Number of episodes of oral retinoids²: n				
Acitretin				
FAS		271	318	243
CES		142	166	110
SES _{contraception}		222	242	174
SES _{testing}		222	242	174
EES		185	232	168
Alitretinoin				
FAS		15	17	10
CES		10	7	3

Country: Spain		Pre-implementation period		Post-implementation period
		Pre-referral	Post-referral	
Isotretinoin	SES _{contraception}	15	12	5
	SES _{testing}	15	12	5
	EES	10	12	7
	FAS	3,376	4,681	4,437
	CES	2,620	3,129	2,329
	SES _{contraception}	3,251	4,051	3,412
	SES _{testing}	3,251	4,051	3,412
	EES	2,740	3,750	3,336
	Overall oral retinoids class			
	FAS	3,662	5,016	4,690
	CES	2,772	3,302	2,442
	SES _{contraception}	3,488	4,305	3,591
	SES _{testing}	3,488	4,305	3,591
	EES	2,935	3,994	3,511

CES, complete episodes set; EES, ending episodes set; FAS, full analysis set; n, number; SES_{contraception}, starting episodes set contraception; SES_{testing}, starting episodes set pregnancy testing; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Patient exposed to 1 or more molecule during the period.

² Periods can share an episode (episode ongoing at period switching).

11.1.4 Sweden

The Swedish FAS consisted of 9,182 patients in the pre-referral and 14,594 patients in the post-referral period and 16,709 patients in the post-implementation period (Table 19). In both the pre- and post-referral period most patients were prescribed isotretinoin, with 97.8% and 98.6%, respectively. In the post-implementation period 98.8% had an isotretinoin prescription. Acitretin was prescribed to 2.2%, 1.5% and 1.1% of patients in the pre- post-referral and post-implementation periods, respectively. Oral alitretinoin was granted a marketing authorisation in April 2020. During the post-implementation period 0.1% women had a prescription of alitretinoin (Table 20).

Table 19 Attrition by reason and the final patient sample (full analysis set) in Sweden

Country: Sweden						
	Pre-implementation period				Post-implementation period	
	Pre-referral		Post-referral			
	Study Participant		Study Participant		Study Participant	
	Excluded	Remaining	Excluded	Remaining	Excluded	Remaining
Reasons for Inclusion:						
n (%)						
1. Female		5,110,096 (100)		5,320,695 (100)		5,597,917 (100)
2. Of #1, Received or prescribed at least one prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in any of the study periods	5,098,794 (99.8)	11,302 (0.2)	5,303,362 (99.7)	17,333 (0.3)	5,578,416 (99.7)	19,501 (0.3)
3. Of #2, Childbearing potential (13-49 years of age, inclusive– on at least one of a patient's oral retinoid prescriptions start dates in the corresponding study period)	1,802 (15.9)	9,500 (84.1)	2,280 (13.2)	15,053 (86.8)	2,314 (11.9)	17,187 (88.1)
Reasons for Exclusion:						
n (%)						
4. Of #3, Exclude all females in the age group 13 to 49 years with available information that they are not of childbearing potential before initiation of oral retinoids (such as records of hysterectomy or sterilisation)	318 (3.3)	9,182 (96.7)	459 (3.0)	14,594 (97.0)	478 (2.8)	16,709 (97.2)
Final study cohort (Full Analysis Set (FAS) in the study): n		9,182		14,594		16,709

n: number of patients, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020

Table 20 The study cohort in Sweden

Country: Sweden				
		Pre-implementation period		Post-implementation period
		Pre-referral	Post-referral	
Number of oral retinoids patients¹: n (%)				
		9,182	14,594	16,709
Acitretin		203 (2.2)	216 (1.5)	182 (1.1)
Alitretinoin*		NA	NA	24 (0.1)
Isotretinoin		8,981 (97.8)	14,384 (98.6)	16,509 (98.8)
Number of prescriptions of oral retinoids: n (%)				
		37,708	61,759	64,526
Acitretin		679 (1.8)	912 (1.5)	738 (1.1)
Alitretinoin*		NA	NA	46 (0.1)
Isotretinoin		37,029 (98.2)	60,847 (98.5)	63,742 (98.8)
Number of episodes of oral retinoids²: n				
Acitretin	FAS	440	526	421
	CES	360	454	359
	SES _{contraception}	418	511	404
	SES _{testing}	418	511	404
	EES	380	467	373
Alitretinoin ²	FAS	NA	NA	24
	CES	NA	NA	5
	SES _{contraception}	NA	NA	24
	SES _{testing}	NA	NA	24
	EES	NA	NA	5
Isotretinoin	FAS	10,407	17,419	20,078
	CES	6,609	12,112	12,138
	SES _{contraception}	9,372	16,076	17,251
	SES _{testing}	9,372	16,076	17,251
	EES	7,635	13,439	14,955
Overall oral retinoids class	FAS	10,846	17,940	20,522
	CES	6,969	12,561	12,502
	SES _{contraception}	9,789	16,582	17,678
	SES _{testing}	9,789	16,582	17,678
	EES	8,015	13,901	15,333

NA, not applicable; CES, complete episodes set; EES, ending episodes set; FAS, full analysis set; n, number; SES_{contraception}, starting episodes set – contraception; SES_{testing}, starting episodes set – pregnancy testing; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Patient exposed to 1 or more molecule during the period.

² Periods can share an episode (episode ongoing at period switching).

*In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.2 Descriptive Data

In the following sections the main results of the primary objectives are presented for all oral retinoids by country (i.e., France, Germany, Spain and Sweden) for the pre-implementation study period (i.e., pre-referral and post-referral periods) and post-implementation study period.

11.3 Results of the Primary Objectives

The stratified results for each oral retinoid molecule are included in the Supplement 2.1.

11.3.1 France

11.3.1.1 Contraceptives Use

During the pre-referral period the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment start was 38.9%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 35.2%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment stop was 43.8%. In the post-referral period, the respective proportions were 42.3%, 38.0% and 46.6%. In the post-implementation period, the respective proportions were 42.3%, 38.1% and 46.7% (Table 21).

Table 21 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 100,377	N¹ = 133,257	N¹ = 93,157
30 days of contraception before treatment start	39,009 (38.9) [38.6-39.2]	56,339 (42.3) [42.0-42.5]	39,386 (42.3) [42.0-42.6]
During treatment²	N² = 114,126	N² = 147,672	N² = 116,341
Continuous concomitant contraception during treatment	40,185 (35.2) [34.9-35.5]	56,069 (38.0) [37.7-38.2]	44,371 (38.1) [37.9-38.4]
After treatment³	N³ = 90,598	N³ = 117,937	N³ = 78,021
30 days of contraception after treatment stop	39,704 (43.8) [43.5-44.1]	54,991 (46.6) [46.3-46.9]	36,448 (46.7) [46.4-47.1]

CI, confidence interval; N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.3.1.2 Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 32.3 days. The proportion of episodes with monthly prescription intervals was 38.9%. During the post-referral period the mean time interval between prescription dates was 32.4 days and 40.5% of episodes had monthly prescription intervals. During the post-implementation period the mean time interval between prescription dates was 31.9 days and 48.6% of episodes had monthly prescription intervals (Table 22).

Table 22 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 87,437	N ¹ = 115,069	N ¹ = 89,021
Time interval between prescription dates during episodes (days):			
Mean (SD)	32.3 (6.4)	32.4 (6.2)	31.9 (6.0)
Median (Q1 – Q3)	31.0 (29.4-34.0)	31.0 (29.4-33.8)	30.7 (29.1-33.2)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]			
	33,995 (38.9) [38.6-39.2]	46,650 (40.5) [40.3-40.8]	43,282 (48.6) [48.3-48.9]

CI, confidence interval; N or n, number of episodes; Q1, first quartile; Q3, third quartile, SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Confidence intervals were calculated using the Wilson method.

11.3.1.3 Laboratory Pregnancy Tests

In the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 72.9% of episodes. The mean percentage of treatment time covered by compliant laboratory pregnancy tests was 50.8%. Laboratory pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 13.0% of episodes. The corresponding proportions were 75.5%, 52.5%, and 12.8% for the post-referral and 76.4%, 50.4%, and 12.6% for the post-implementation periods (Table 23).

Table 23 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in France; analysis based on the episode level

Country: France			
Laboratory pregnancy tests performed: n (%) [95% CI of %]	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Prior to treatment¹	N¹ = 100,464	N¹ = 133,366	N¹ = 93,220
At treatment start (up to 7 days before episode exposure start date)	73,198 (72.9) [72.6-73.1]	100,646 (75.5) [75.2-75.7]	71,245 (76.4) [76.2-76.7]
During treatment²	N² = 114,126	N² = 147,672	N² = 116,341
At least one test during treatment episodes	86,586 (75.9) [75.6-76.1]	114,933 (77.8) [77.6-78.0]	89,326 (76.8) [76.5-77.0]
Monthly during treatment episodes	8,104 (7.1) [7.0-7.3]	10,385 (7.0) [6.9-7.2]	10,406 (8.9) [8.8-9.1]
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	50.8%(32.8%) [50.6%-50.9%]	52.5%(32.3%) [52.4%-52.7%]	50.4%(32.1%) [50.2%-50.6%]
After treatment³	N³ = 90,598	N³ = 117,937	N³ = 78,021
30 (-/+7) days after treatment stop	11,738 (13.0) [12.7-13.2]	15,152 (12.8) [12.7-13.0]	9,855 (12.6) [12.4-12.9]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.3.2 Germany

11.3.2.1 Contraceptives Use

During the pre-referral period the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 8.6%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 7.0%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 8.8%. In the post-referral period, the respective proportions were 8.5%, 6.9%, and 8.6% . In the post-implementation period, the respective proportions were 11.0%, 9.4% and 11.0% (

Table 24).

Table 24 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment	N¹ = 2,406	N¹ = 4,329	N¹ = 1,700
30 days of contraception before treatment start	206 (8.6) [7.5 - 9.7]	369 (8.5) [7.7 - 9.4]	187 (11.0) [9.6 - 12.6]
During treatment	N² = 2,695	N² = 4,659	N² = 2,007
Continuous concomitant contraception during treatment	189 (7.0) [6.1 - 8.0]	322 (6.9) [6.2 - 7.7]	189 (9.4) [8.2 - 10.8]
After treatment	N³ = 2,124	N³ = 4,025	N³ = 1,256
30 days of contraception after treatment stop	186 (8.8) [7.6 - 10.0]	347 (8.6) [7.8 - 9.5]	138 (11.0) [9.4 - 12.8]

CI, confidence interval; N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020.

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.3.2.1 Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 39.2 days. The proportion of episodes with monthly prescription intervals was 28.2%. During the post-referral period the mean time interval between prescription dates was 37.8 days and 27.2% of episodes had monthly prescription intervals. During the post-implementation period the mean time interval between prescription dates was 36.0 days and 38.2% of episodes had monthly prescription intervals (Table 25).

Table 25 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 1,532	N ¹ = 2,688	N ¹ = 1,228
Time interval between prescription dates during episodes (days):			
Mean (SD)	39.2 (16.4)	37.8 (13.4)	36.0 (12.8)
Median (Q1 – Q3)	33.8 (29.7 - 44.0)	33.4 (29.6 - 42.0)	32.0 (29.0 - 39.9)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]	432 (28.2) [26.0 - 30.5]	731 (27.2) [25.5 - 28.9]	469 (38.2) [35.5 - 40.9]

CI, confidence interval; SD, standard deviation; Q1, first quartile; Q3, third quartile; N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020.

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription
Confidence intervals were calculated using the Wilson method.

11.3.2.2 Laboratory Pregnancy Tests

In the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 19.3% of episodes. The proportion of treatment episode time covered by compliant laboratory pregnancy testing was 19.3%. After oral retinoid treatment laboratory pregnancy testing within 30 (-/+7) days was performed in 2.9% of episodes. The corresponding proportions were 21.6%, 21.4% and 3.4% for the post-referral and 25.6%, 24.4% and 3.1% for the post-implementation period (Table 26).

Table 26 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed: n (%) [95% CI of %]			
Prior to treatment	N ¹ = 2,419	N ¹ = 4,360	N ¹ = 1,705
At treatment start (up to 7 days before episode exposure start date)	468 (19.3) [17.8 - 21.0]	941 (21.6) [20.4 - 22.8]	437 (25.6) [23.6 - 27.8]
During treatment	N ² = 2,695	N ² = 4,659	N ² = 2,007
At least one test during treatment episodes	754 (28.0) [26.3 - 29.7]	1,375 (29.5) [28.2 - 30.8]	643 (32.0) [30.0 - 34.1]
Monthly during treatment episodes	190 (7.1) [6.1 - 8.1]	345 (7.4) [6.7 - 8.2]	182 (9.1) [7.9 - 10.4]
	19.3% (34.6%)	21.4% (36.2%)	24.4% (38.5%)

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	[18.0% - 20.6%]	[20.4% - 22.4%]	[22.7% - 26.1%]
After treatment	N³ = 2,124	N³ = 4,025	N³ = 1,256
30 (-/+7) days after treatment stop	61 (2.9) [2.2 - 3.7]	135 (3.4) [2.8 - 4.0]	39 (3.1) [2.3 - 4.2]

CI, confidence interval; N or n: number of episodes, SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.3.3 Spain

11.3.3.1 Contraceptives Use

During the pre-referral period the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 14.5%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 13.5%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 16.1%. In the post-referral period, the respective proportions were 14.9%, 12.7% and 16.9%. In the post-implementation period, the respective proportions were 14.1%, 13.0% and 17.0% (Table 27).

Table 27 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in Spain; analysis based on the episode level

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 3,488	N¹ = 4,305	N¹ = 3,591
30 days of contraception before treatment start	507 (14.5) [13.4 - 15.7]	642 (14.9) [13.9 - 16.0]	506 (14.1) [13.0 - 15.3]
During treatment²	N² = 3,662	N² = 5,016	N² = 4,690
Continuous concomitant contraception during treatment	495 (13.5) [12.4 - 14.7]	638 (12.7) [11.8 - 13.7]	609 (13.0) [12.1 - 14.0]
After treatment³	N³ = 2,935	N³ = 3,994	N³ = 3,511
30 days of contraception after treatment stop	472 (16.1) [14.8 - 17.5]	675 (16.9) [15.8 - 18.1]	597 (17.0) [15.8 - 18.3]

Country: Spain

	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020			
¹ Based on the starting episodes set – contraception (SES _{contraception})			
² Based on the full analysis set (FAS)			
³ Based on the ending episodes set (EES)			
Confidence intervals were calculated using the Wilson method.			

11.3.3.2 Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 96.5 days. The proportion of episodes with monthly prescription intervals was 2.8%. During the post-referral period the mean time interval between prescription dates was 95.8 days and 3.7% of episodes had monthly prescription intervals. During the post-implementation period the mean time interval between prescription dates was 103.5 days and 3.0% of episodes had monthly prescription intervals (Table 28).

Table 28 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in Spain; analysis based on the episode level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 1,426	N ¹ = 1,958	
Time interval between prescription dates during episodes (days):			
Mean (SD)	96.5 (76.4)	95.8 (71.4)	103.5 (76.3)
Median (Q1 – Q3)	74.0 (55.0 - 108.0)	77.0 (56.0 - 112.0)	83.0 (57.8 - 122.5)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]			
	40 (2.8%) [2.1 - 3.8]	73 (3.7%) [3.0 - 4.7]	60 (3.0%) [2.3 - 3.8]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Confidence intervals were calculated using the Wilson method.

11.3.3.3 Laboratory Pregnancy Tests

In the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 2.6% of episodes. The proportion of treatment episode time covered by compliant laboratory pregnancy testing was 38.4%. After oral retinoid treatment laboratory

pregnancy testing within 30 (-/+7) days was performed in 1.2% of episodes. The corresponding proportions were 3.5%, 33.9% and 1.3% for the post-referral and 4.1%, 25.9% and 1.1% for the post-implementation period (Table 29).

Table 29 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in Spain; analysis based on the episode level

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 3,488	N¹ = 4,305	N¹ = 3,591
At treatment start (up to 7 days before episode exposure start date)	92 (2.6) [2.2 - 3.2]	151 (3.5) [3.0 - 4.1]	146 (4.1) [3.5 - 4.8]
During treatment²	N² = 3,662	N² = 5,016	N² = 4,690
At least one test during treatment episodes	532 (14.5) [13.4 - 15.7]	903 (18.0) [17.0 - 19.1]	1072 (22.9) [21.7 - 24.1]
Monthly during treatment episodes	15 (0.4) [0.2 - 0.7]	3 (0.1) [0.0 - 0.2]	4 (0.1) [0.0 - 0.2]
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	38.4% (21.0%) [37.2% - 39.6%]	33.9% (16.5%) [33.0% - 34.9%]	25.9% (20.6%) [24.9% - 27.0%]
After treatment³	N³ = 2,935	N³ = 3,994	N³ = 3,511
30 (-/+7) days after treatment stop	36 (1.2) [0.9 - 1.7]	53 (1.3) [1.0 - 1.7]	38 (1.1) [0.8 - 1.5]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.3.4 Sweden

11.3.4.1 Contraceptives Use

During the pre-referral period, the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 33.1%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 32.3%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 38.9%. In the post-referral period, the respective proportions were 36.7%, 36.3% and 42.0%. In the post-implementation period, the respective proportions were 39.2%, 40.3% and 44.6% (Table 30).

Table 30 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in Sweden; analysis based on the episode level

Country: Sweden

	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 9,789	N¹ = 16,582	N¹ = 17,678
30 days of contraception before treatment start	3,241 (33.1) [32.2 - 34.0]	6,087 (36.7) [36.0 - 37.4]	6,924 (39.2) [38.5 - 39.9]
During treatment²	N² = 10,846	N² = 17,940	N² = 20,522
Continuous concomitant contraception during treatment	3,502 (32.3) [31.4 - 33.2]	6,517 (36.3) [35.6 - 37.0]	8,264 (40.3) [39.6 - 40.9]
After treatment³	N³ = 8,015	N³ = 13,901	N³ = 15,333
30 days of contraception after treatment stop	3,120 (38.9) [37.9 - 40.0]	5,841 (42.0) [41.2 - 42.8]	6,842 (44.6) [43.8 - 45.4]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – contraception (SEScontraception)

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

11.3.4.2 Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 41.8 days. The proportion of episodes with monthly prescription intervals was 8.5%. During the post-referral period the mean time interval between prescription dates was 42.9 days and 8.6% of episodes had monthly prescription intervals. During the post-implementation period the mean time interval between prescription dates was 44.5 days and 9.6% of episodes had monthly prescription intervals (Table 30).

Table 31 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 7,877	Post-referral N ¹ = 12,684	N ¹ = 13,602
Time interval between prescription dates during episodes (days):			
Mean (SD)	41.8 (17.6)	42.9 (17.3)	44.5 (17.7)
Median (Q1 – Q3)	38.6 (30.0-50.8)	40.0 (31.0-51.7)	41.7 (32.0-53.5)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]			
	672 (8.5) [7.9-9.2]	1,092 (8.6) [8.1-9.1]	1,303 (9.6) [9.1-10.1]

CI, confidence interval; SD, standard deviation; Q1, first quartile; Q3, third quartile; N or n, number of episodes; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

11.3.4.3 Laboratory Pregnancy Tests

No laboratory pregnancy tests were recorded in the registry data. Data were only available when documented by ICD-10 codes. The number of laboratory pregnancy observed prior, during and after treatment was therefore close to or 0.0% in the pre-implementation and in the post-implementation period (Table 32).

Table 32 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 9,789	N¹ = 16,582	N¹ = 17,678
At treatment start (up to 7 days before episode exposure start date)	0 (0.0) [0.0-0.0]	0 (0.0) [0.0-0.0]	0 (0.0) [0.0-0.0]
During treatment²	N² = 10,846	N² = 17,940	N² = 20,522
At least one test during treatment episodes	9 (0.1) [0.0-0.2]	7 (0.0) [0.0-0.1]	12 (0.1) [0.0-0.1]

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Monthly during treatment episodes	0 (0.0) [0.0-0.0]	1 (0.0) [0.0-0.3]	2 (0.0) [0.0-0.0]
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	0.0% (0.0%) [0.0% - 0.0%]	0.0% (0.0%) [0.0% - 0.0%]	0.0% (0.0%) [0.0% - 0.0%]
After treatment³	N³ = 8,015	N³ = 13,901	N³ = 15,333
30 (-/+7) days after treatment stop	1 (0.0) [0.0-0.1]	2 (0.0) [0.0-0.1]	2 (0.0) [0.0-0.1]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES testing)

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

11.4 Results of the Secondary Objectives

In the following sections the results of the secondary objectives are presented by country (i.e., France, Germany, Spain and Sweden) for the pre-implementation study period (i.e. pre-referral and post-referral periods) and post-implementation study period. The results for treatment characteristics by oral retinoid are included in APPENDIX 3 RESULTS FOR TREATMENT CHARACTERISTICS BY ORAL RETINOID MOLECULE AND BY COUNTRY. All stratified results for the secondary objectives are included in Supplement 2.2.

11.4.1 Patient Age

11.4.1.1 France

When analysed on patient level, the mean ages were 25.4 and 24.7 years in the pre- and post-referral periods and 24.4 years in the post-implementation period (Table 33). The largest age group in the pre- and post-referral, as well as post-implementation periods was 18-25 year olds (39.5%, 40.8% and 45.0%, respectively). Similar results were obtained when the data was analysed for the oral retinoid treatment episodes. In both pre-

implementation periods and the post-implementation period 18-25 year olds constituted the largest group (Table 34).

Table 33 Demographic characteristics for patients on oral retinoids in France; analysis based on the patient level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 87,818	Post-referral N ¹ = 111,897	N ¹ = 92,582
Age			
Mean (SD)	25.4 (8.8)	24.7 (8.6)	24.4 (8.3)
Median (Q1 – Q3)	23.0 (18.0 - 30.0)	22.0 (18.0 - 29.0)	22.0 (18.0 - 29.0)
Age group: n (%)			
13-17 years	17,858 (20.3)	24,923 (22.3)	19,048 (20.6)
18-25 years	34,686 (39.5)	45,612 (40.8)	41,634 (45.0)
26-33 years	18,845 (21.5)	22,736 (20.3)	18,069 (19.5)
34-49 years	16,429 (18.7)	18,626 (16.6)	13,831 (14.9)

N or n, number of patients; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS)

Table 34 Demographic characteristics for patients on oral retinoids in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 100,464	Post-referral N ¹ = 133,366	N ¹ = 93,220
Age			
Mean (SD)	25.9 (9.4)	25.3 (9.1)	24.9 (8.9)
Median (Q1 – Q3)	24.0 (18.0 - 32.0)	23.0 (18.0 - 30.0)	22.0 (18.0-30.0)
Age group: n (%)			
13-17 years	20412 (20.3)	28718 (21.5)	19696 (21.1)
18-25 years	37899 (37.7)	52945 (39.7)	39736 (42.6)
26-33 years	20558 (20.5)	26093 (19.6)	17416 (18.7)
34-49 years	21595 (21.5)	25610 (19.2)	16372 (17.6)

N or n, number of episodes; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

11.4.1.2 Germany

When analysed on patient level, the mean ages were 26.9, 25.7 in the pre- and post-referral period, respectively and 25.5 in the post-implementation period (Table 35). The largest age group in all study periods were 18-25 year olds (37.0%, 39.9% and 45.4% respectively). Similar results were obtained when the data was analysed for the oral retinoid treatment episodes (Table 36).

Table 35 Demographic characteristics for patients on oral retinoids in Germany; analysis based on the patient level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 1,953	N ¹ = 3,100	N ¹ = 1,598
Age			
Mean (SD)	26.9 (9.8)	25.7 (9.2)	25.5 (8.8)
Median (Q1 – Q3)	24.0 (19.0 – 34.0)	23.0 (19.0 – 31.0)	23.0 (19.0 – 30.0)
Age group: n (%)			
13-17 years	345 (17.7)	605 (19.5)	261 (16.3)
18-25 years	723 (37.0)	1,237 (39.9)	726 (45.4)
26-33 years	386 (19.8)	608 (19.6)	320 (20.0)
34-49 years	499 (25.6)	650 (21.0)	291 (18.2)

N or n, number of patients; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS)

Table 36 Demographic characteristics for patients on oral retinoids in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 2,419	N ¹ = 4,360	N ¹ = 1,705
Age			
Mean (SD)	27.8 (10.3)	26.4 (9.6)	26.4 (9.4)
Median (Q1 – Q3)	25.0 (19.0 – 36.0)	24.0 (19.0 – 32.0)	24.0 (19.0 – 32.0)
Age group: n (%)			
13-17 years	404 (16.7)	778 (17.8)	253 (14.8)
18-25 years	848 (35.1)	1,682 (38.6)	726 (42.6)
26-33 years	452 (18.7)	883 (20.3)	352 (20.6)
34-49 years	715 (29.6)	1,017 (23.3)	374 (21.9)

N or n, number of episodes; Q1, first quartile; Q3, third quartile; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

11.4.1.3 Spain

When analysed on patient level, the mean ages were 24.8 and 24.2 years in the pre- and post-referral periods and 24.1 years in the post-implementation period (Table 37). The 2 largest age groups in the pre- and post-referral periods were 13-17 year olds (32.3% and 35.0%, respectively) and 18-25 year olds (31.7% and 31.2%, respectively). The 2 largest age groups in the post-implementation period were also 13-17 year olds (32.5%) and 18-25 year olds (35.9%). Similar results were obtained when the data was analysed for the oral retinoid treatment episodes (Table 38).

Table 37 Demographic characteristics for patients on oral retinoids in Spain; analysis based on the patient level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 3,004	N ¹ = 4,211	N ¹ = 4,100
Age			
Mean (SD)	24.8 (9.8)	24.2 (9.8)	24.1 (9.5)
Median (Q1 – Q3)	21.9 (16.8 - 30.9)	20.8 (16.5 - 29.8)	20.8 (16.9 - 28.9)
Age group: n (%)			
13-17 years	970 (32.3)	1,474 (35.0)	1,334 (32.5)
18-25 years	951 (31.7)	1,314 (31.2)	1,471 (35.9)
26-33 years	478 (15.9)	619 (14.7)	600 (14.6)
34-49 years	605 (20.1)	804 (19.1)	695 (16.9)

N or n, number of patients; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

Table 38 Demographic characteristics for patients on oral retinoids in Spain; analysis based on the episode level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 3,488	N ¹ = 4,305	N ¹ = 3,591
Age			
Mean (SD)	24.7 (9.8)	24.0 (9.9)	23.7 (9.5)
Median (Q1 – Q3)	21.6 (16.7 - 30.8)	20.3 (16.2 - 29.5)	20.2 (16.6 - 28.5)

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 3,488	N ¹ = 4,305	
	N ¹ = 3,591		
Age group: n (%)			
13-20 years	1,154 (33.1)	1,605 (37.3)	1,267 (35.3)
18-25 years	1,085 (31.1)	1,288 (29.9)	1,235 (34.4)
26-33 years	555 (15.9)	581 (13.5)	498 (13.9)
34-49 years	694 (19.9)	831 (19.3)	591 (16.5)

N or n, number of episodes; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

11.4.1.4 Sweden

When analysed on patient level, the mean ages were 24.5 and 23.9 in the pre- and post-referral periods and 23.5 in the post-implementation period (Table 39). The largest age group in the pre- and post-referral, as well as post-implementation periods was 18-25 year olds (45.1%, 42.8% and 42.2%, respectively). Similar results were obtained when the data was analysed for the oral retinoid treatment episodes. In both pre-implementation periods and the post-implementation period 18-25 year olds constituted the largest group (

Table 40).

Table 39 Demographic characteristics for patients on oral retinoids in Sweden; analysis based on the patient level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 9,182	Post-referral N ¹ = 14,594	N ¹ = 16,709
Age			
Mean (SD)	24.5 (8.2)	23.9 (8.1)	23.5 (8.0)
Median (Q1 – Q3)	23.0 (18.0 - 28.0)	22.0 (18.0 - 28.0)	22.0 (17.0 - 27.0)
Age group: n (%)			
13-17 years	1,883 (20.5)	3,507 (24.0)	4,418 (26.4)
18-25 years	4,140 (45.1)	6,245 (42.8)	7,054 (42.2)
26-33 years	1,800 (19.6)	2,938 (20.1)	3,233 (19.3)
34-49 years	1,359 (14.8)	1,904 (13.0)	2,004 (12.0)

N or n, number of patients; Q1, first quartile; Q3, third quartile; SD, standard deviation; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Table 40 Demographic characteristics for patients on oral retinoids in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 9,789	N ¹ = 16,582	N ¹ = 17,678
Age			
Mean (SD)	25.4 (9.0)	24.8 (8.8)	24.5 (8.9)
Median (Q1 – Q3)	23.0 (18.0 - 30.0)	23.0 (18.0 - 29.0)	22.0 (18.0 - 29.0)
Age group: n (%)			
13-17 years	1,938 (19.8)	3,745 (22.6)	4,357 (24.6)
18-25 years	4,143 (42.3)	6,717 (40.5)	7,072 (40.0)
25-33 years	1,877 (19.2)	3,314 (20.0)	3,407 (19.3)
34-49 years	1,831 (18.7)	2,806 (16.9)	2,842 (16.1)

N or n, number of patients; Q1, first quartile; Q3, third quartile; SD, standard deviation; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.4.2 Indication for Oral Retinoids

11.4.2.1 France

In France, diagnoses are only recorded for inpatient hospitalisations, therefore, the data on indications for treatment with oral retinoids could not be reported.

11.4.2.2 Germany

In the pre-referral period, acne was the most common indication in 89.4% of prescriptions. Dermatitis and eczema were the second most common indication with 15.3%. The respective proportions were 92.2% and 14.1% in the post-referral period and 92.5% and 13.8% in the post-implementation period (

Table 41). Other indications were rare (<3.3%). Similar results were seen in the analysis based on episode level (Table 42).

Table 41 Indication for treatment with oral retinoids in Germany; analysis based on the prescription level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 8,331	N ¹ = 15,697	N ¹ = 6,241
Indication²: n (%)			
Psoriasis	276 (3.3)	407 (2.6)	202 (3.2)
Lichen planus	61 (0.7)	53 (0.3)	18 (0.3)
Ichthyosis	64 (0.8)	110 (0.7)	46 (0.7)
Dermatitis and eczema	1,278 (15.3)	2,206 (14.1)	862 (13.8)
Acne	7,448 (89.4)	14,469 (92.2)	5,775 (92.5)
Other	NA	NA	NA
Missing	248 (3.0)	345 (2.2)	151 (2.4)

N or n, number of prescriptions, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

Other: confirmed non-approved indications as per the medications' labels linked to oral retinoids prescriptions

¹ Based on the full analysis set (FAS)

² Multiple indications possible

Table 42 Indication for treatment with oral retinoids in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 2,419	N ¹ = 4,360	N ¹ = 1,705
Indication²: n (%)			
Psoriasis	75 (3.1)	112 (2.6)	61 (3.6)
Lichen planus	23 (1.0)	26 (0.6)	6 (0.4)
Ichthyosis	14 (0.6)	21 (0.5)	12 (0.7)
Dermatitis and eczema	367 (15.2)	623 (14.3)	248 (14.5)
Acne	2,136 (88.3)	3,940 (90.4)	1,528 (89.6)
Missing	101 (4.2)	165 (3.8)	68 (4.0)

N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

Other: confirmed non-approved indications as per the medications' labels linked to oral retinoids prescriptions

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Multiple indications possible

11.4.2.3 Spain

In the pre-referral, post-referral and post-implementation periods, acne was the most common indication in 83.1%, 83.0%, and 85.0% of prescriptions, respectively. Dermatitis and eczema were the second most common indication with 10.4% of prescriptions, followed by psoriasis with 6.8%

of prescriptions, in the pre-referral period. The respective proportions were 13.8% and 6.1% in the post-referral period and 19.1% and 5.0% in the post-implementation period (Table 43). Similar results were seen in the analysis based on episode level (Table 44).

Table 43 Indication for treatment with oral retinoids in Spain; analysis based on the prescription level

Country: Spain			
Indication ² : n (%)	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 5,455	N ¹ = 7,694	N ¹ = 6,984
Psoriasis	372 (6.8)	466 (6.1)	353 (5.0)
Lichen planus	15 (0.3)	46 (0.6)	43 (0.6)
Ichthyosis	38 (0.7)	38 (0.5)	20 (0.3)
Dermatitis and eczema	570 (10.4)	1,065 (13.8)	1,337 (19.1)
Acne	4,532 (83.1)	6,382 (83.0)	5,936 (85.0)
Other	224 (4.1)	301 (3.9)	234 (3.4)
Missing	222 (4.1)	367 (4.8)	276 (4.0)

N or n, number of prescriptions, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

Other: confirmed non-approved indications as per the medications' labels linked to oral retinoids prescriptions

¹ Based on the full analysis set (FAS)

² Multiple indications possible

Table 44 Indication for treatment with oral retinoids in Spain; analysis based on the episode level

Country: Spain			
Indication ² : n (%)	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 3,488	N ¹ = 4,305	N ¹ = 3,591
Psoriasis	191 (5.5)	219 (5.1)	156 (4.3)
Lichen planus	11 (0.3)	26 (0.6)	24 (0.7)
Ichthyosis	16 (0.5)	10 (0.2)	6 (0.2)
Dermatitis and eczema	383 (11.0)	608 (14.1)	751 (20.9)
Acne	2,907 (83.3)	3,567 (82.9)	3,039 (84.6)
Other	160 (4.6)	183 (4.2)	133 (3.7)
Missing	160 (4.6)	226 (5.2)	152 (4.2)

N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

Other: confirmed non-approved indications as per the medications' labels linked to oral retinoids prescriptions

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Multiple indications possible

11.4.2.4 Sweden

In the pre-referral period, acne was the most common indication in 67.7% of prescriptions. Dermatitis and eczema was the second most common indication with 4.3%. The respective proportions were 65.4% and 4.4% in the post-referral period and 63.4% and 3.8% in the post-implementation period (Table 45). Other indications were rare and data on the indication were missing for 30.2% and 32.9% of prescriptions in the pre- and post-referral periods, respectively, and 35.0% in the post-implementation period. Similar results were seen in the analysis based on episode level (Table 46).

Table 45 Indication for treatment with oral retinoids in Sweden; analysis based on the prescription level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 37,708	N ¹ = 61,759	N ¹ = 64,526
Indication²: n (%)			
Psoriasis	505 (1.3)	726 (1.2)	589 (0.9)
Lichen planus	36 (0.1)	40 (0.1)	20 (0.0)
Ichthyosis	217 (0.6)	256 (0.4)	216 (0.3)
Dermatitis and eczema	1,636 (4.3)	2,689 (4.4)	2,449 (3.8)
Acne	25,532 (67.7)	40,414 (65.4)	40,912 (63.4)
Other	NA	NA	NA
Missing*	11,411 (30.2)	20,266 (32.9)	22,563 (35.0)

N or n, number of prescriptions; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

Other: confirmed non-approved indications as per the medications' labels linked to oral retinoids prescriptions

¹ Based on the full analysis set (FAS)

² Multiple indications possible

*Missing includes records that did not contain the ICD-10 codes for indication included in this study or records with missing data

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Table 46 Indication for treatment with oral retinoids in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 9,789	N ¹ = 16,582	N ¹ = 17,678
Indication²: n (%)			

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 9,789	N ¹ = 16,582	N ¹ = 17,678
Psoriasis	203 (2.1)	268 (1.6)	216 (1.2)
Lichen planus	19 (0.2)	16 (0.1)	13 (0.1)
Ichthyosis	110 (1.1)	129 (0.8)	104 (0.6)
Dermatitis and eczema	388 (4.0)	703 (4.2)	714 (4.0)
Acne	5,982 (61.1)	9,790 (59.0)	9,640 (54.5)
Other	NA	NA	NA
Missing*	3,410 (34.8)	6,245 (37.7)	7511 (42.5)

N or n, number of episodes; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

Other: confirmed non-approved indications as per the medications' labels linked to oral retinoids prescriptions

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Multiple indications possible

* Missing includes records that did not contain the ICD-10 codes for indication included in this study or records with missing data

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.4.3 Speciality of Oral Retinoid-Prescribing Physicians

11.4.3.1 France

In the pre-referral period, dermatologists were the most frequent oral retinoid prescribing physicians, accounting for 83.4% of prescriptions. GPs made 14.8% of prescriptions. The prescriber speciality was missing for 0.6% of prescriptions. The respective proportions were 83.9% and 14.2% in the post-referral period and 81.1% and 16.7% in the post-implementation period. The prescriber speciality was missing for 0.7% and 0.6% of prescriptions, respectively (Table 47). Similar results were seen in the analysis based on episode level (Table 48).

Table 47 Speciality of oral retinoid-prescribing physicians in France; analysis based on the prescription level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 467,125	N ¹ = 615,844	N ¹ = 446,009
Speciality: n (%)			
Dermatologist	389,718 (83.4)	516,589 (83.9)	361,697 (81.1)
General practitioner	68,942 (14.8)	87,146 (14.2)	74,529 (16.7)
Other ²	5,845 (1.3)	7,924 (1.3)	7,227 (1.6)
Missing	2,620 (0.6)	4,185 (0.7)	2,556 (0.6)

N or n, number of prescriptions, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS)

² Other specialties: specialties issuing <5% of prescriptions each

Table 48 Speciality of oral retinoid-prescribing physicians in France; analysis based on the episode level (first prescription in each analysable episode)

Country: France

	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 100,464	Post-referral N ¹ = 133,366	
Speciality: n (%)			N ¹ = 93,220
Dermatologist	81,637 (81.3)	112,373 (84.3)	78,033 (83.7)
General practitioner	16,530 (16.5)	17,893 (13.4)	12,792 (13.7)
Other ²	1,579 (1.6)	2,031 (1.5)	1,723 (1.8)
Missing	718 (0.7)	1,069 (0.8)	672 (0.7)

N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Other specialties: specialties issuing <5% of episodes each

11.4.3.2 Germany

In the pre-referral period, dermatologists were the most frequent oral retinoid prescribing physicians, accounting for 90.1% of prescriptions. General practitioners made 6.0% of prescriptions. The respective proportions were 89.9% and 6.0% in the post-referral period and 89.7% and 6.3% in the post-implementation period (Table 49). Similar results were seen in the analysis based on episode level (

Table 50).

Table 49 Speciality of oral retinoid-prescribing physicians in Germany; analysis based on the prescription level

Country: Germany	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 8,331	Post-referral N ¹ = 15,967	
Speciality: n (%)			
Dermatologist	7,504 (90.1)	14,105 (89.9)	5,601 (89.7)
General practitioner	497 (6.0)	946 (6.0)	394 (6.3)
Other ²	187 (2.2)	488 (3.1)	191 (3.1)
Missing	143 (1.7)	158 (1.0)	55 (0.9)

N or n, number of prescriptions, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS)

² Other specialties: specialties issuing <5% of prescriptions each

Table 50 Speciality of oral retinoid-prescribing physicians in Germany; analysis based on the episode level (first prescription in each analysable episode)

Country: Germany	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 2,419	N ¹ = 4,360	N ¹ = 1,705
Speciality: n (%)			
Dermatologist	2,046 (84.6)	3,705 (85.0)	1,441 (84.5)
General practitioner	220 (9.1)	413 (9.5)	159 (9.3)
Other ²	93 (3.8)	184 (4.2)	88 (5.2)
Missing	60 (2.5)	58 (1.3)	17 (1.0)

N or n: number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Other specialties: specialties issuing <5% of episodes each

11.4.3.3 Spain

In the pre-referral period, dermatologists were the most frequent oral retinoid prescribing physicians, accounting for 27.6% of prescriptions. GPs made 21.2% of prescriptions. The prescriber speciality was missing for 44.1% of prescriptions. The respective proportions were 22.8%, 21.5% and 47.4% in the post-referral period. In the post-implementation period, GPs made 21.4% of prescriptions and dermatologists made 16.8% of prescriptions. The prescriber speciality was missing for 50.5% of prescriptions (Table 51). Similar results were seen at the episode level and post-implementation periods (Table 52).

Table 51 Speciality of oral retinoid-prescribing physicians in Spain; analysis based on the prescription level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 5,455	N ¹ = 7,694	N ¹ = 6,984
Speciality: n (%)			
Dermatologist	1,505 (27.6)	1,751 (22.8)	1,175 (16.8)
General practitioner	1,158 (21.2)	1,654 (21.5)	1,496 (21.4)
Other ²	386 (7.1)	643 (8.4)	787 (11.3)
Missing	2,406 (44.1)	3,646 (47.4)	3,526 (50.5)

N or n, number of prescriptions, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Other specialties: specialties issuing <5% of prescriptions each

Table 52 Speciality of oral retinoid-prescribing physicians in Spain; analysis based on the episode level (first prescription in each analysable episode)

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 3,488	N ¹ = 4,305	N ¹ = 3,591
Speciality: n (%)			
Dermatologist	923 (26.5)	920 (21.4)	572 (15.9)
General practitioner	865 (24.8)	1,037 (24.1)	828 (23.1)
Other ²	299 (8.6)	375 (8.7)	456 (12.7)
Missing	1,401 (40.2)	1,973 (45.8)	1,735 (48.3)

N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Other specialties: specialties issuing <5% of episodes each

11.4.3.4 Sweden

In the pre-referral period, dermatologists were the most frequent oral retinoid prescribing physicians, accounting for 88.0% of prescriptions. GPs made 1.1% of prescriptions. The prescriber speciality was missing for 10.7% of prescriptions. The respective proportions were 88.4%, 1.6% and 9.4% in the post-referral period and 87.4%, 2.0% and 9.9% in the post-implementation period (Table 53). Similar results were seen in the analysis based on episode level (

Table 54).

Table 53 Speciality of oral retinoid-prescribing physicians in Sweden; analysis based on the prescription level

Country: Sweden	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N ¹ = 37,708	N ¹ = 61,759	N ¹ = 64,526
Speciality: n (%)			
Dermatologist	33,170 (88.0)	54,608 (88.4)	56,389 (87.4)
General practitioner	414 (1.1)	1,001 (1.6)	1,317 (2.0)
Other ²	97 (0.3)	316 (0.5)	441 (0.7)
Missing	4,027 (10.7)	5,834 (9.4)	6,379 (9.9)

N or n, number of prescriptions; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Other specialties: specialties issuing <5% of prescriptions each

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Table 54 Speciality of oral retinoid-prescribing physicians in Sweden; analysis based on the episode level (first prescription in each analysable episode)

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 9,789	Post-referral N ¹ = 16,582	N ¹ = 17,678
Speciality: n (%)			
Dermatologist	8,737 (89.3)	14,729 (88.8)	15,623 (88.4)
General practitioner	133 (1.4)	320 (1.9)	396 (2.2)
Other ²	35 (0.4)	108 (0.7)	101 (0.6)
Missing	884 (9.0)	1,425 (8.6)	1,558 (8.8)

N or n, number of episodes; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Other specialties: specialties issuing <5% of episodes each

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.4.4 Treatment Characteristics: Prescription Count, Prescription Length, Duration of Treatment and Average Daily Dose

11.4.4.1 France

In the pre-referral period, the mean number of prescriptions per patient was 5.3 and prescriptions had an average length of 28.1 days per treatment episode. The mean treatment duration was 135.3 days, the mean number of prescriptions per treatment episode was 4.0 and the mean number of treatment episodes per patient was 1.5. The average daily dose was 27.3 mg.

In the post-referral period, the mean number of prescriptions per patient was 5.5 and prescriptions had an average length of 28.9 days per treatment episode. The mean treatment duration was 150.7 days, the mean number of prescriptions per treatment episode was 4.4 and the mean number of treatment episodes per patient was 1.6. The average daily dose was 27.3 mg.

In the post-implementation period, the mean number of prescriptions per patient was 4.8 and prescriptions had an average length of 27.4 days per treatment episode. The mean treatment duration was 133.8 days, the mean number of prescriptions per treatment episode was 4.0 and the mean number of treatment episodes per patient was 1.8. The average daily dose was 27.0 mg (Table 55).

Table 55 Treatment characteristics of patients on oral retinoids in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	114,126	147,672	116,341
Number of episodes (CES): n	79,466	106,882	68,676
Number of prescriptions (FAS): n	467,125	615,844	446,009
Number of prescriptions (CES): n	317,652	465,330	272,548
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	5.3 (3.1)	5.5 (3.3)	4.8 (3.1)
Median (Q1 – Q3)	5.0 (3.0-7.0)	6.0 (3.0-7.0)	4.0 (2.0-7.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	28.1 (11.8)	28.9 (12.0)	27.4 (12.0)
Median (Q1 – Q3)	28.6 (20.0-35.0)	30.0 (20.0-36.4)	27.5 (20.0-35.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	135.3 (109.5)	150.7 (116.9)	133.8 (113.1)
Median (Q1 – Q3)	110.0 (30.0-230.0)	135.0 (35.0-249.0)	96.0 (30.0-233.0)
Number of prescriptions per treatment episode			
Mean (SD)	4.0 (2.9)	4.4 (3.1)	4.0 (3.0)
Median (Q1 – Q3)	3.0 (1.0-6.0)	4.0 (1.0-7.0)	3.0 (1.0-6.0)
Number of treatment episodes per patient			
Mean (SD)	1.5 (1.1)	1.6 (1.5)	1.8 (1.9)
Median (Q1 – Q3)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	27.3 (4.8)	27.3 (4.8)	27.0 (5.0)
Median (Q1 – Q3)	30.0 (25.0-30.0)	30.0 (25.0-30.0)	30.0 (25.0-30.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

11.4.4.2 Germany

In the pre-referral period, the mean number of prescriptions per patient was 4.3 and prescriptions had an average length of 43.2 days per treatment episode. The mean treatment duration was 114.6 days, the mean number of prescriptions per treatment episode was 2.7 and the mean number of treatment episodes per patient 1.0. The average daily dose was 17.6 mg.

In the post-referral period, the mean number of prescriptions per patient was 5.1 and prescriptions had an average length of 42.5 days per treatment episode. The mean treatment duration was 129.8 days, the mean number of prescriptions per treatment episode was 3.2 and the mean number of treatment episodes per patient 1.3. The average daily dose was 17.2 mg.

In the post- implementation period, the mean number of prescriptions per patient was 3.9 and prescriptions had an average length of 38.2 days per treatment episode. The mean treatment duration was 102.2 days, the mean number of prescriptions per treatment episode was 2.8 and the mean number of treatment episodes per patient 1.0. The average daily dose was 17.1 mg (Table 56).

Table 56 Treatment characteristics of patients on oral retinoids in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	2,695	4,659	2,007
Number of episodes (CES): n	2,035	3,913	1,543
Number of prescriptions (FAS): n	8,331	15,697	6,241
Number of prescriptions (CES): n	5,567	12,444	4,250
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	4.3 (3.1)	5.1 (3.9)	3.9 (2.8)
Median (Q1 – Q3)	4.0 (2.0 - 6.0)	4.0 (2.0 - 7.0)	3.0 (2.0 - 5.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	43.2 (20.3)	42.5 (18.7)	38.2 (17.1)
Median (Q1 – Q3)	33.8 (30.0 - 52.0)	33.0 (30.0 - 50.0)	30.3 (30.0 - 43.5)
Duration of oral retinoid treatment²			

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Duration of treatment episodes (days)			
Mean (SD)	114.6 (104.4)	129.8 (118.2)	102.2 (87.7)
Median (Q1 – Q3)	72.0 (30.0 - 164.0)	90.0 (30.0 - 191.0)	66.0 (30.0 - 149.0)
Number of prescriptions per treatment episode			
Mean (SD)	2.7 (2.5)	3.2 (3.0)	2.8 (2.3)
Median (Q1 – Q3)	2.0 (1.0 - 4.0)	2.0 (1.0 - 5.0)	2.0 (1.0 - 4.0)
Number of treatment episodes per patient			
Mean (SD)	1.0 (1.1)	1.3 (1.2)	1.0 (0.8)
Median (Q1 – Q3)	1.0 (0.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)
Average oral retinoid daily dose (mg) ²			
Mean (SD)	17.6 (10.6)	17.2 (9.9)	17.1 (9.1)
Median (Q1 – Q3)	17.0 (10.0 - 20.0)	16.0 (10.0 - 20.0)	17.0 (10.0 - 20.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

11.4.4.3 Spain

In the pre-referral period, the mean number of prescriptions per patient was 1.6 and prescriptions had an average length of 94.1 days per treatment episode. The mean treatment duration was 133.7 days, the mean number of prescriptions per treatment episode was 1.5 and the mean number of treatment episodes per patient was 1.5. The average daily dose was 26.8 mg.

In the post-referral period, the mean number of prescriptions per patient was 1.6 and prescriptions had an average length of 117.0 days per treatment episode. The mean treatment duration was 166.2 days, the mean number of prescriptions per treatment episode was 1.6 and the mean number of treatment episodes per patient was 1.4. The average daily dose was 28.8 mg.

In the post-implementation period, the mean number of prescriptions per patient was 1.7 and prescriptions had an average length of 125.9 days per treatment episode. The mean treatment duration was 169.9 days, the mean number of prescriptions per treatment episode was 1.5 and the

mean number of treatment episodes per patient was 1.4. The average daily dose was 27.4 mg (Table 57).

Table 57 Treatment characteristics of patients on oral retinoids in Spain; analysis based on the episode level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	3,662	5,016	4,690
Number of episodes (CES): n	2,772	3,302	2,442
Number of prescriptions (FAS): n	5,455	7,694	6,984
Number of prescriptions (CES): n	4,531	5,889	4,644
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	1.6 (1.0)	1.6 (1.0)	1.7 (1.1)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	94.1 (73.8)	117.0 (87.5)	125.9 (89.8)
Median (Q1 – Q3)	72.0 (50.0 - 120.0)	90.0 (59.5 - 157.1)	97.0 (60.0 - 178.4)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	133.7 (95.7)	166.2 (112.0)	169.9 (109.6)
Median (Q1 – Q3)	109.0 (57.0 - 184.0)	152.0 (77.0 - 222.0)	156.0 (89.0 - 233.8)
Number of prescriptions per treatment episode			
Mean (SD)	1.5 (0.8)	1.6 (0.9)	1.5 (0.9)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Number of treatment episodes per patient			
Mean (SD)	1.5 (0.8)	1.4 (0.7)	1.4 (0.6)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	26.8 (17.4)	28.8 (19.4)	27.4 (15.9)
Median (Q1 – Q3)	20.0 (20.0 - 30.0)	20.0 (20.0 - 30.0)	20.0 (20.0 - 30.0)

Country: Spain

Pre-implementation period		Post-implementation period
Pre-referral	Post-referral	

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

11.4.4.4 Sweden

In the pre-referral period, the mean number of prescriptions per patient was 4.1 and prescriptions had an average length of 55.2 days per treatment episode. The mean treatment duration was 173.9 days, the mean number of prescriptions per treatment episode was 3.5 and the mean number of treatment episodes per patient was 1.2. The average daily dose was 31.4 mg.

In the post-referral period, the mean number of prescriptions per patient was 4.2 and prescriptions had an average length of 55.4 days per treatment episode. The mean treatment duration was 181.8 days, the mean number of prescriptions per treatment episode was 3.6 and the mean number of treatment episodes per patient was 1.2. The average daily dose was 31.3 mg.

In the post-implementation period, the mean number of prescriptions per patient was 3.9 and prescriptions had an average length of 54.9 days per treatment episode. The mean treatment duration was 162.9 days, the mean number of prescriptions per treatment episode was 3.2 and the mean number of treatment episodes per patient was 1.3. The average daily dose was 30.5 mg (Table 58).

Table 58 Treatment characteristics of patients on retinoids in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	10,846	17,940	20,522
Number of episodes (CES): n	6,969	12,561	12,502
Number of prescriptions (FAS): n	37,708	61,759	64,526
Number of prescriptions (CES): n	24,471	45,693	39,930

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	4.1 (2.4)	4.2 (2.7)	3.9 (2.5)
Median (Q1 – Q3)	4.0 (2.0-5.0)	4.0 (2.0-6.0)	3.0 (2.0-5.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	55.2 (24.4)	55.4 (22.3)	54.9 (20.8)
Median (Q1 – Q3)	50.5 (34.0-67.0)	56.0 (34.0-67.0)	58.0 (34.0-67.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	173.9 (104.3)	181.8 (110.1)	162.9 (110.0)
Median (Q1 – Q3)	195.0 (67.0-258.0)	201.0 (67.0-268.0)	147.0 (67.0-259.0)
Number of prescriptions per treatment episode			
Mean (SD)	3.5 (2.4)	3.6 (2.6)	3.2 (2.5)
Median	3.0 (1.0-5.0)	3.0 (1.0-5.0)	2.0 (1.0-5.0)
Number of treatment episodes per patient			
Mean (SD)	1.2 (0.6)	1.2 (0.7)	1.3 (0.7)
Median (Q1 – Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	31.4 (6.8)	31.3 (6.3)	30.5 (5.6)
Median (Q1 – Q3)	29.9 (29.4-32.7)	29.9 (29.4-32.6)	29.9 (29.4-30.0)

NA, not applicable; CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.4.5 Pregnancy Exposed to Oral Retinoids

11.4.5.1 France

In the pre-referral period, the proportion of exposed pregnancies was 13.4%. Termination was the most common among pregnancies exposed with available information on outcome, occurring in 56.7% of exposed pregnancies. Live births occurred in 39.6% of exposed pregnancies. Miscarriages occurred in less than 1.7% of exposed pregnancies. In France multiple ‘Not live’ births codes were reported (termination and/or stillbirth and/or miscarriage) but it is not possible to determine the exact outcome. These occurred in approximately 2%. Birth defects were recorded in less than 1.7% of exposed pregnancies. No stillbirths were recorded separately.

In the post-referral period 10.4% of pregnancies were exposed to oral retinoids. Terminations occurred in 57.8%, live births in 38.7%, and miscarriage in less than 1.3% of exposed pregnancies. Other ‘not-live’ births occurred in at least 1.9% and birth defects were recorded in less than 1.3% of exposed pregnancies. No stillbirths were recorded separately.

In the post-implementation period, 16.6% of pregnancies were exposed to oral retinoids. Terminations occurred in 68.0%, live births in 26.9%, miscarriage in less than 2.7%, and other ‘not-live’ births in at least 2.7% of exposed pregnancies. No stillbirths and birth defects were recorded (Table 59).

Table 59 Exposure to oral retinoids during pregnancy in France; analysis based on the pregnancy level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral N = 87,818	Post-referral N = 111,897	
Total number of pregnancies: n	7,130	11,240	4,408
Number of pregnancies exposed: n (%)¹	958 (13.4)	1,164 (10.4)	730 (16.6)
Exposed pregnancies with available information on outcomes ²	591 (61.7)	778 (66.8)	372 (51.0)
Pregnancy outcomes in exposed pregnancies: n (%)³			
Live birth	234 (39.6)	301 (38.7)	100 (26.9)
Termination	335 (56.7)	450 (57.8)	253 (68.0)
Stillbirth	0 (0.0)	0 (0.0)	0 (0.0)

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N = 87,818	N = 111,897	N = 92,582
Miscarriage	<10 (<1.7)	<10 (<1.3)	<10 (<2.7)
Not live birth*	≥12 (≥2.0)	≥15 (≥1.9)	≥10 (≥2.7)
Recorded birth defect ⁴	<10 (<1.7)	<10 (<1.3)	0 (0.0)

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Percentage based on total number of pregnancies observed in the patients included the FAS

² Percentage based on total number of pregnancies exposed

³ Percentage based on total number of pregnancies exposed with available information on outcomes

⁴ Percentages may not add up to 100% as recorded birth defect may be included in any of the above categories

* Multiple 'Not live birth' codes were reported (Termination and/or Stillbirth and/or Miscarriage) but it is not possible to decide the exact outcome

11.4.5.2 Germany

In the pre-referral period, the proportion of exposed pregnancies was 12.1%. Termination was the most common among pregnancies exposed with available information on outcome, occurring in 77.8% of exposed pregnancies. Live births occurred in 11.1% of exposed pregnancies. Miscarriages occurred in 11.1% of exposed pregnancies. There were no recorded stillbirths or birth defects.

In the post-referral period 6.1% of pregnancies were exposed to oral retinoids. Terminations occurred in 66.7% of exposed pregnancies and live births in 33.3%. There were no miscarriage, stillbirths or recorded birth defects.

In the post-implementation period 36.7% of pregnancies were exposed to oral retinoids. Terminations occurred in 71.4% of exposed pregnancies, live births in 14.3% and miscarriages in 14.3%. There were no recorded stillbirths or birth defects (Table 60).

Table 60 Exposure to oral retinoids during pregnancy in Germany; analysis based on the pregnancy level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N = 1,953	N = 3,100	N = 1,598
Total number of pregnancies: n	107	230	30
Number of pregnancies exposed: n (%)¹	13 (12.1)	14 (6.1)	11 (36.7)
Exposed pregnancies with available information on outcomes ²	9 (69.2)	9 (64.3)	7 (63.6)

Country: Germany			
Pregnancy outcomes in exposed pregnancies: n (%) ³	Pre-implementation period		Post-implementation period
	Pre-referral N = 1,953	Post-referral N = 3,100	N = 1,598
Live birth	1 (11.1)	3 (33.3)	1 (14.3)
Termination	7 (77.8)	6 (66.7)	5 (71.4)
Stillbirth	0 (0.0)	0 (0.0)	0 (0.0)
Miscarriage	1 (11.1)	0 (0.0)	1 (14.3)
Recorded birth defect ⁴	0 (0.0)	0 (0.0)	0 (0.0)

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10-2019-12/2020

¹ Percentage based on total number of pregnancies observed in the patients included the FAS

² Percentage based on total number of pregnancies exposed

³ Percentage based on total number of pregnancies exposed with available information on outcomes

⁴ Percentages may not add up to 100% as recorded birth defect may be included in any of the above categories

11.4.5.3 Spain

In the pre-referral period, the proportion of exposed pregnancies was 20.2%. Termination was the most common among pregnancies exposed with available information on outcome, occurring in 50.0% of exposed pregnancies. Live births occurred in 38.9% and miscarriages in 11.1% of exposed pregnancies. No stillbirths and birth defects were recorded.

In the post-referral period, 14.6% of pregnancies were exposed to oral retinoids. Terminations occurred in 56.2%, live births in 18.8% and miscarriages in 25.0% of exposed pregnancies. No stillbirths and birth defects were recorded.

In the post-implementation period, 19.0% of pregnancies were exposed to oral retinoids. Live births occurred in 83.3% and miscarriages in 16.7% of exposed pregnancies (Table 61). No termination, still births and birth defects were recorded.

Table 61 Exposure to oral retinoids during pregnancy in Spain; analysis based on the pregnancy level

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral N = 3,004	Post-referral N = 4,211	N = 4,100
Total number of pregnancies: n	104	185	163
Number of pregnancies exposed: n (%) ¹	21 (20.2)	27 (14.6)	31 (19.0)
Exposed pregnancies with available information on outcomes ²	18 (85.7)	16 (59.3)	6 (19.4)
Pregnancy outcomes in exposed pregnancies: n (%) ³			

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N = 3,004	N = 4,211	N = 4,100
Live birth	7 (38.9)	3 (18.8)	5 (83.3)
Termination	9 (50.0)	9 (56.2)	0 (0.0)
Stillbirth	0 (0.0)	0 (0.0)	0 (0.0)
Miscarriage	2 (11.1)	4 (25.0)	1 (16.7)
Recorded birth defect ⁴	0 (0.0)	0 (0.0)	0 (0.0)

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Percentage based on total number of pregnancies observed in the patients included the FAS

² Percentage based on total number of pregnancies exposed

³ Percentage based on total number of pregnancies exposed with available information on outcomes

⁴ Percentages may not add up to 100% as recorded birth defect may be included in any of the above categories

11.4.5.4 Sweden

In the pre-referral period, the proportion of exposed pregnancies was 5.9%. Live births and miscarriages occurred in 25.0% and 75.0% of exposed pregnancies, respectively. Terminations, stillbirths and recorded birth defects did not occur.

In the post-referral period, 7.8% of pregnancies were exposed to oral retinoids. Termination and miscarriage occurred in 82.6% and 17.4% of exposed pregnancies, respectively. Live births, stillbirths and birth defects did not occur.

In the post-implementation period, 15.1% of pregnancies were exposed to oral retinoids. Terminations and miscarriages occurred in 65.7% and 34.3% of exposed pregnancies, respectively. Live births, stillbirths and birth defects did not occur (Table 62).

Table 62 Exposure to oral retinoids during pregnancy in Sweden; analysis based on the pregnancy level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N = 9,182	N = 14,594	N = 16,709
Total number of pregnancies: n	118	398	252
Number of pregnancies exposed: n (%)¹	7 (5.9)	31 (7.8)	38 (15.1)
Exposed pregnancies with available information on outcomes ²	4 (57.1)	23 (74.2)	35 (92.1)
Pregnancy outcomes in exposed pregnancies: n (%)³			
Live birth	1 (25.0)	0 (0.0)	0 (0.0)
Termination	0 (0.0)	19 (82.6)	23 (65.7)
Stillbirth	0 (0.0)	0 (0.0)	0 (0.0)
Miscarriage	3 (75.0)	4 (17.4)	12 (34.3)
Recorded birth defect ⁴	0 (0.0)	0 (0.0)	0 (0.0)

NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Percentage based on total number of pregnancies observed in the patients included the FAS

² Percentage based on total number of pregnancies exposed

³ Percentage based on total number of pregnancies exposed with available information on outcomes

⁴ Percentages may not add up to 100% as recorded birth defect may be included in any of the above categories

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.4.6 Incidence Rate of Pregnancies Exposed to Oral Retinoids

In the pre-referral period the incidence rate for exposed pregnancies per 1000 patient years at risk was 18.6 in France (Table 63), 5.4 in Germany (Table 64), 11.3 in Spain (Table 65) and 1.1 in Sweden (Table 66). The respective rates were 17.7 in France, 4.1 in Germany, 9.5 in Spain and 1.9 in Sweden in the post-referral period and 14.1 in France, 7.9 in Germany, 10.2 in Spain and 2.7 in Sweden in post-implementation period.

11.4.6.1 France

Table 63 Incidence rate of pregnancies exposed to oral retinoids in France

Country: France	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of pregnancies exposed to oral retinoids ¹	958	1,164	730
Patients' time at risk (year) ¹	51,381.9	65,844.2	51,705.3
Incidence rate of pregnancies (per 1000 patients years at risk):	18.6	17.7	14.1

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS)

11.4.6.2 Germany

Table 64 Incidence rate of pregnancies exposed to oral retinoids in Germany

Country: Germany	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of pregnancies exposed to oral retinoids ¹	5	7	5
Patients' time at risk (year) ¹	925.0	1,723.3	631.2
Incidence rate of pregnancies (per 1000 patients years at risk)¹	5.4	4.1	7.9

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS)

11.4.6.3 Spain

Table 65 Incidence rate of pregnancies exposed to oral retinoids in Spain

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of pregnancies exposed to oral retinoids ¹	21	27	31
Patients' time at risk (year) ¹	1,851.3	2,845.0	3,043.1
Incidence rate of pregnancies (per 1000 patient years at risk)¹	11.3	9.5	10.2

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

11.4.6.4 Sweden

Table 66 Incidence rate of pregnancies exposed to oral retinoids in Sweden

Country: Sweden	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of pregnancies exposed to oral retinoids ¹	6	18	26
Patients' time at risk (year) ¹	5,373.7	9,291.9	9,725.8
Incidence rate of pregnancies (per 1000 patients years at risk)¹	1.1	1.9	2.7

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

11.4.7 Multi-Country Meta-Analysis

11.4.7.1 Contraceptives Use

Meta-analysis of aggregated measures for the 4 countries showed that during the pre-referral period, the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 21.0%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 19.1%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 23.7%. In the post-referral period, the respective proportions were 22.4%, 19.9% and 24.9%. In the post-implementation period, the respective proportions were 23.9%, 22.1% and 26.8%. High levels of heterogeneity ($I^2 > 99\%$) were observed for both pre- and the post-implementation periods (Table 67, Figure 5, Figure 6 and Figure 7). Excluding countries one by one from the meta-analysis (France: Table 68, Figure 8, Figure 9 and Figure 10

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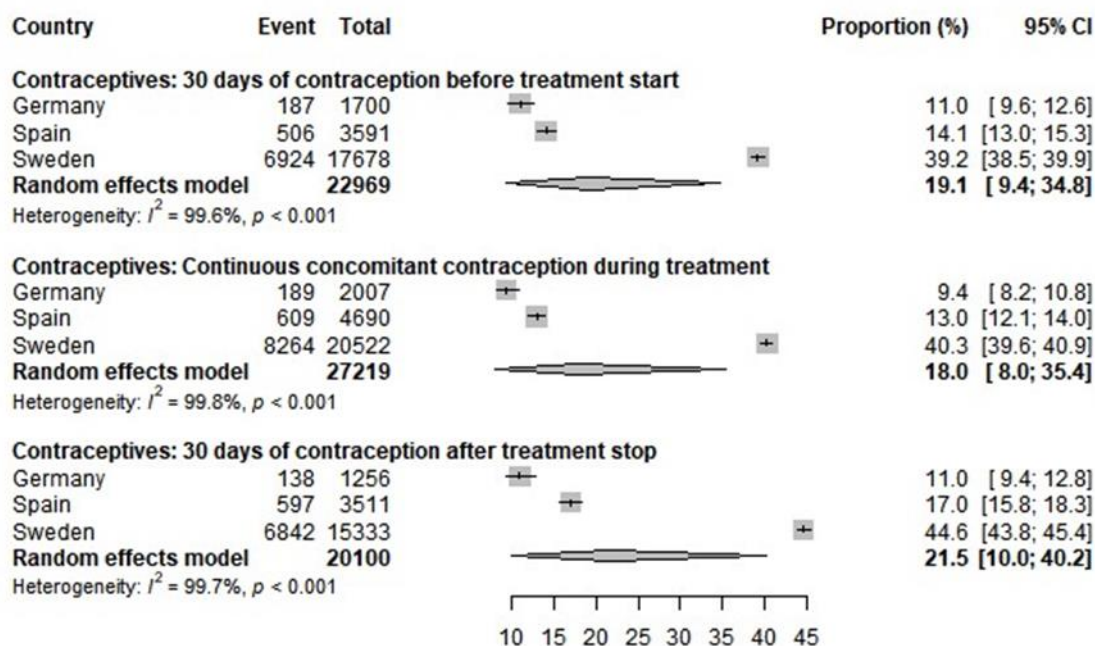


Figure 10, Germany: Table 69, Figure 11, Figure 12 Figure 13, Spain: Table 70, Figure 14, Figure 15, and Figure 16,

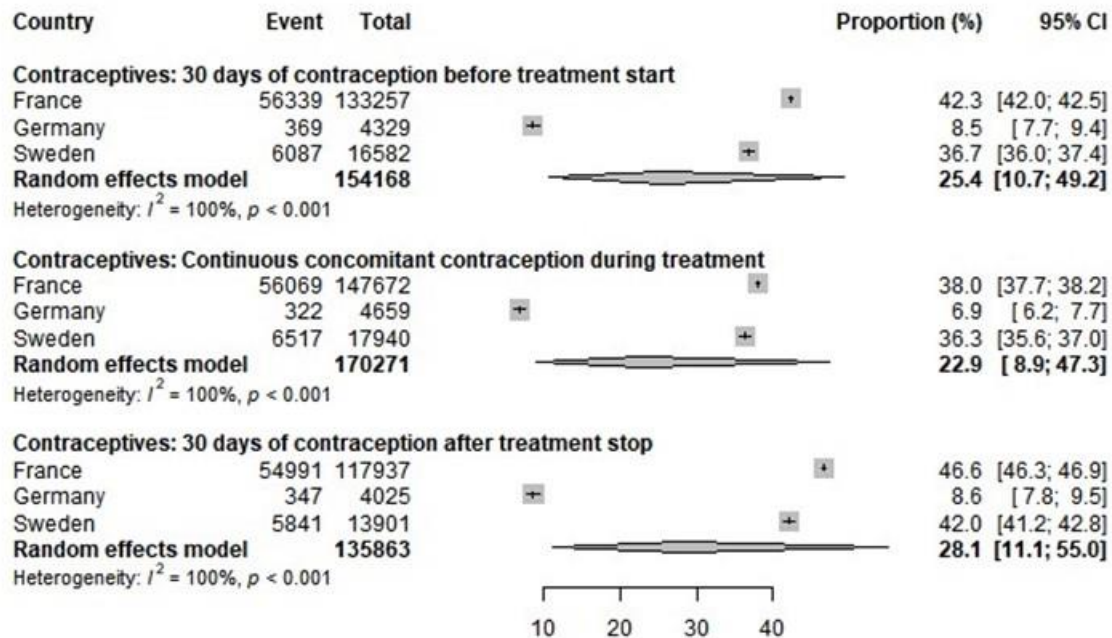


Figure 15 and Sweden: Table 71, Figure 17, Figure 18 and Figure 19) did not have an effect on the heterogeneity levels ($I^2 > 99\%$).

Table 67 Meta-analysis; Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids; analysis based on the episode level

	Pre-implementation period						Post-implementation period			
	Pre-referral			Post-referral						
Contraceptives: n (%) [95% CI of %]										
Prior to treatment	N ¹ = 116,060	χ ² , p	I ²	N ¹ = 158,473	χ ² , p	I ²	N ¹ = 116,126	χ ² , p	I ²	
30 days of contraception before treatment start	24,424 (21.0)	1,498.2	99.9	35,519 (22.4)	2,610.5	100	27,702 (23.9)	1,489.9		
	[11.0 - 36.4]	<0.001			[11.2 - 39.9]		<0.001		[12.6 - 40.6]	<0.001
During treatment	N ² = 131,329			N ² = 175,287			N ² = 143,560			
Continuous concomitant contraception during treatment	25,035 (19.1)	1,342.0	99.9	34,851 (19.9)	2,426.6	100	31,740 (22.1)	1,636.9		100
	[9.6 - 34.4]	<0.001			[9.3 - 37.5]		<0.001		[11.2 - 39.1]	
After treatment	N ³ = 103,672			N ³ = 139,857			N ³ = 98,121			
30 days of contraception after treatment stop	24,520 (23.7)	1,535.7	99.9	34,881 (24.9)	2,742.5	100	26,315 (26.8)	1,477.5		99.9
	[11.7 - 41.9]	<0.001			[11.9 - 45]		<0.001		[13.7 - 45.8]	

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

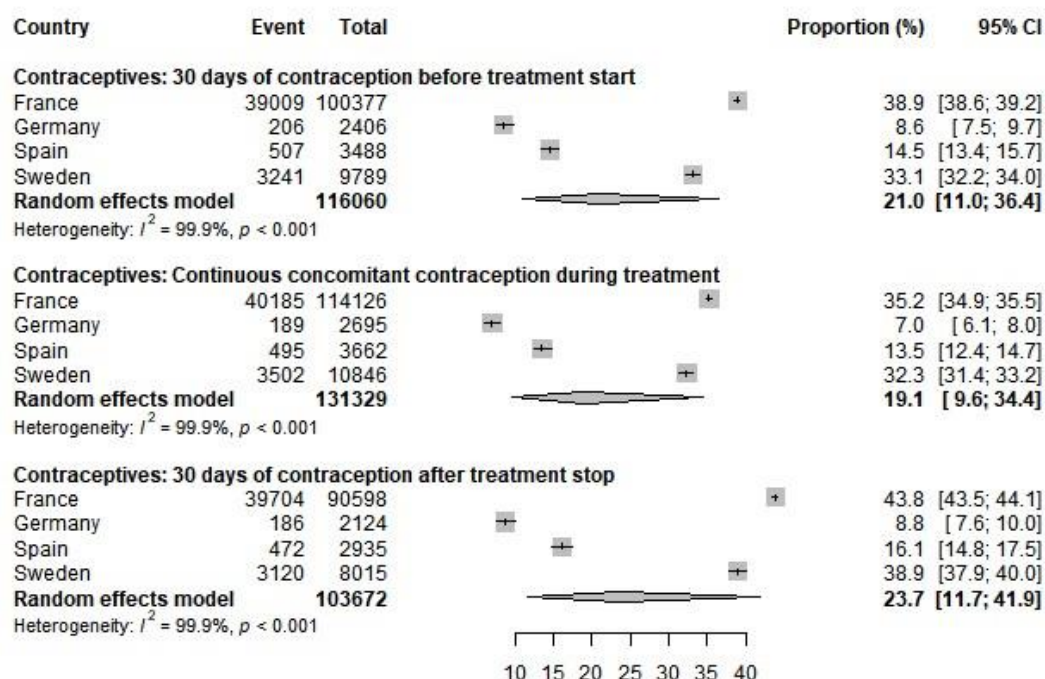


Figure 5 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the pre-referral period; analysis based on the episode level

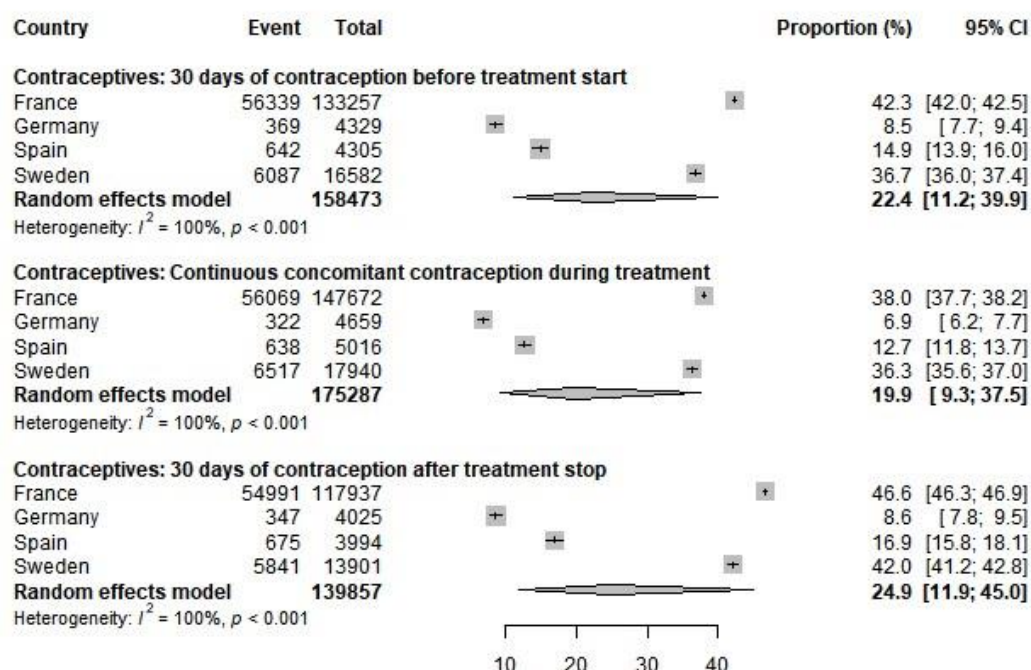


Figure 6 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-referral period; analysis based on the episode level

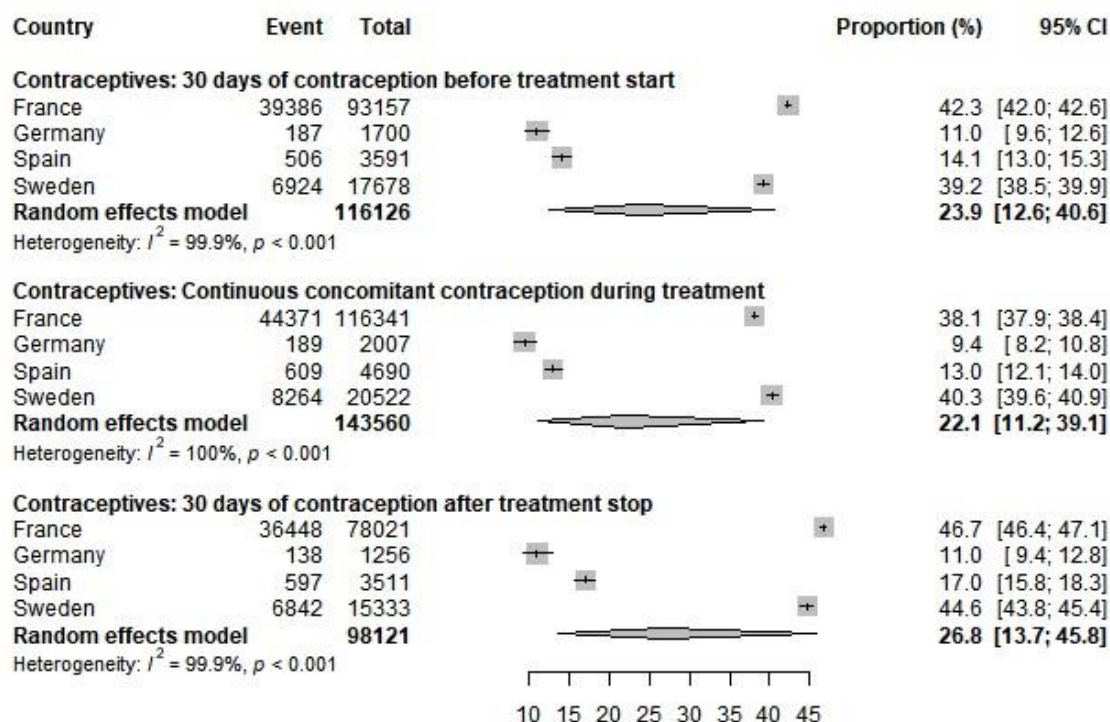


Figure 7 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-implementation period; analysis based on the episode level

Table 68 Meta-analysis; Prescribing patterns for contraceptives before, during and after treatment episodes excluding France; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Contraceptives: n (%)									
[95% CI of %]									
Prior to treatment	N¹ = 15,683	χ^2, p	I²	N¹ = 25,216	χ^2, p	I²	N¹ = 22,969	χ^2, p	I²
30 days of	2,607 (16.6)	800.5		4,407 (17.5)	1,569.8		4,384 (19.1)	1,109.3	
contraception before									
treatment start	[8.4 - 30.3]	<0.001	99.6	[8.2 - 33.3]	<0.001	99.8	[9.4 - 34.8]	<0.001	99.6
During treatment	N² = 17,203			N² = 27,615			N² = 27,219		
Continuous	2,601 (15.1)	914.3		4,283 (15.5)	1,908.1		4,890 (18.0)	1,581.2	
concomitant contraception									
during treatment	[7.0 - 29.6]	<0.001	99.7	[6.6 - 32.4]	<0.001	99.8	[8.0 - 35.4]	<0.001	99.8
After treatment	N³ = 13,074			N³ = 21,920			N³ = 20,100		
30 days of	2,423 (18.5)	923.2		4,252 (19.4)	1,790.5		4,320 (21.5)	1,174.1	
contraception after treatment									
stop	[8.6 - 35.6]	<0.001	99.6	[8.5 - 38.4]	<0.001	99.8	[10.0 - 40.2]	<0.001	99.7

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

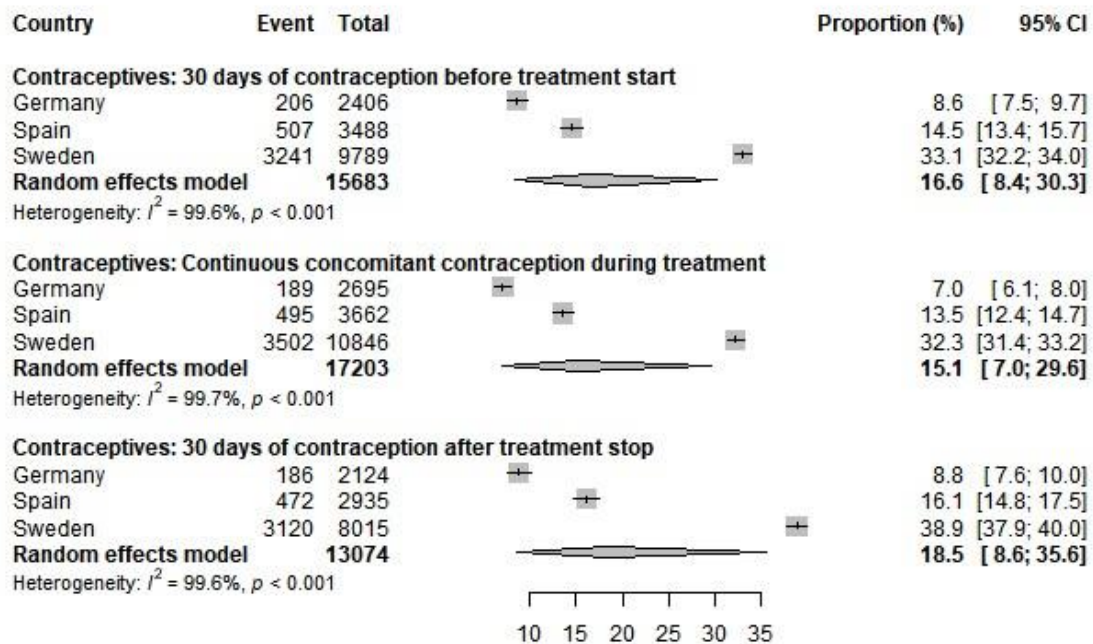


Figure 8 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the pre-referral period excluding France; analysis based on the episode level

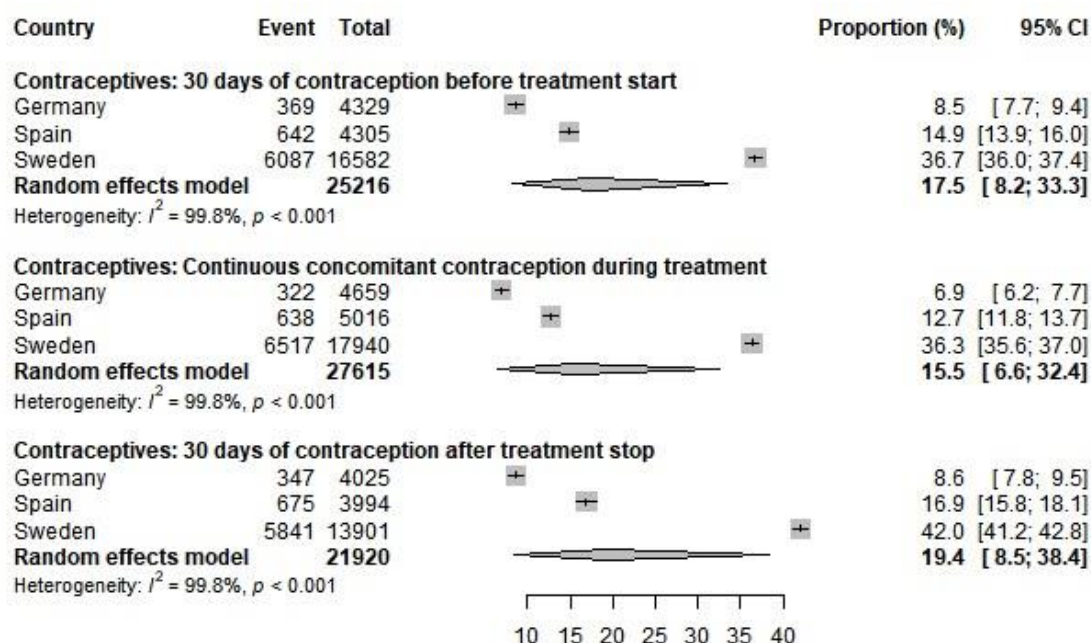


Figure 9 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-referral period excluding France; analysis based on the episode level

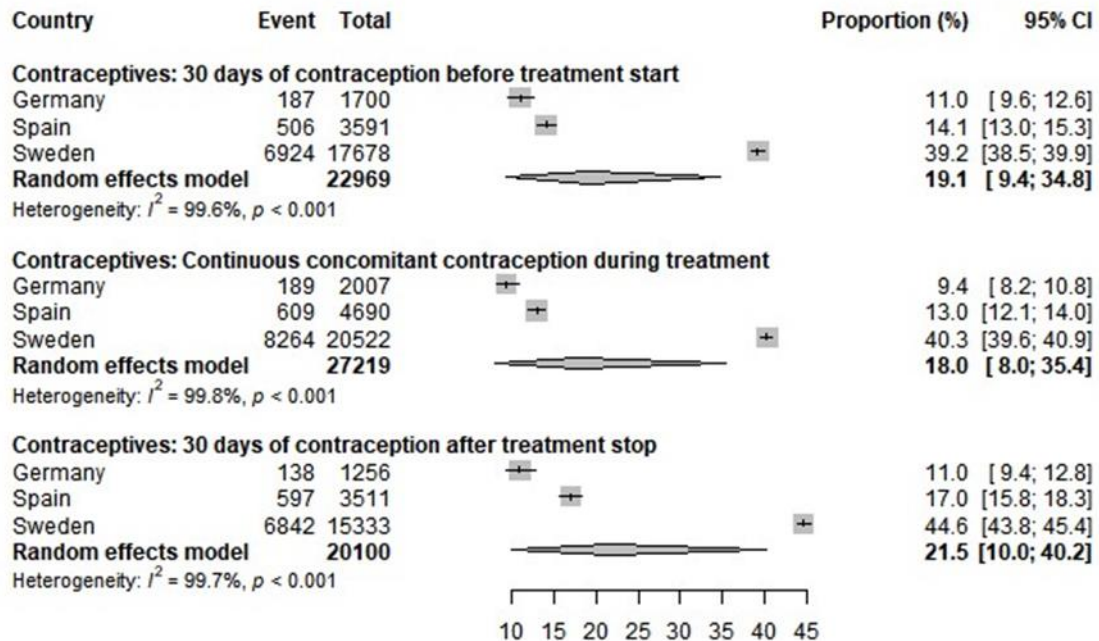


Figure 10 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-implementation period excluding France; analysis based on the episode level

Table 69 Meta-analysis; Prescribing patterns for contraceptives before, during and after treatment episodes excluding Germany; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Contraceptives: n (%) [95% CI of %]									
Prior to treatment	N¹ = 113,654	χ^2, p	I²	N¹ = 154,144	χ^2, p	I²	N¹ = 114,426	χ^2, p	I²
30 days of contraception before treatment start	31,139 (27.4)	842.0	99.9	45,679 (29.6)	1,250.6	99.9	34,217 (29.9)	991.5	99.9
	[16.5 - 41.9]	<0.001		[17.2 - 46.1]	<0.001		[16.6 - 47.8]	<0.001	
During treatment	N² = 12,8634			N² = 170,628			N² = 141,553		
Continuous concomitant contraception during treatment	32,920 (25.6)	680.7	99.9	46,167 (27.1)	1,137.3	99.9	40,171 (28.4)	1103	100
	[15.5 - 39.3]	<0.001		[14.9 - 43.9]	<0.001		[15.4 - 46.4]	<0.001	
After treatment	N³ = 101,548			N³ = 135,832			N³ = 96,865		
30 days of contraception after treatment stop	31,871 (31.4)	822.5	99.9	45,606 (33.6)	1,246.8	99.9	33,372 (34.5)	1,028.6	99.9
	[18.5 - 48]	<0.001		[19.6 - 51.2]	<0.001		[19.8 - 52.8]	<0.001	

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

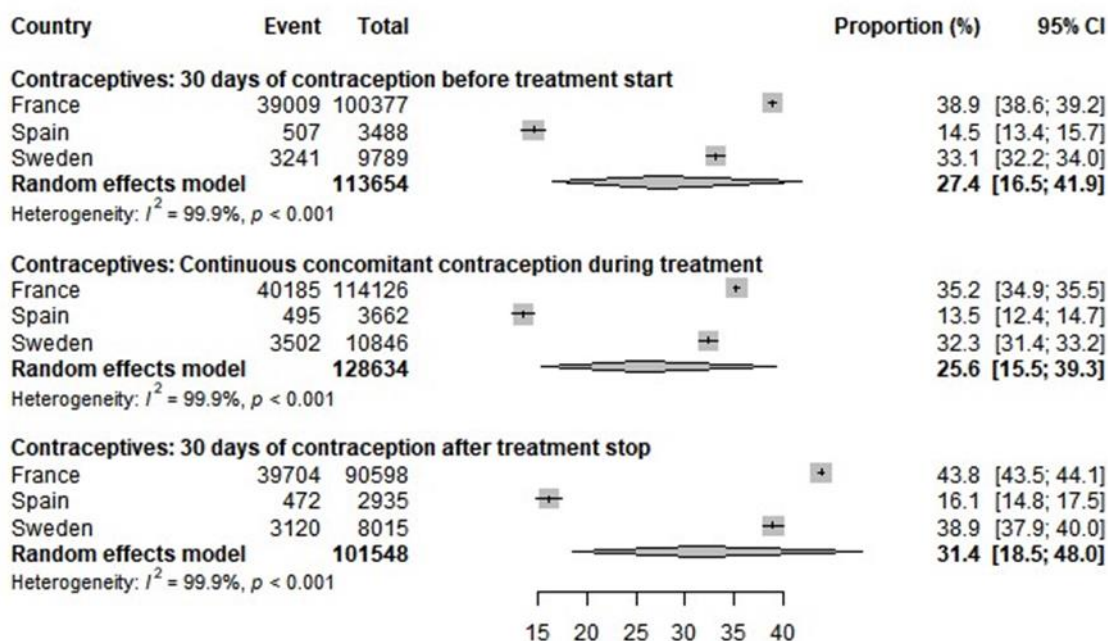


Figure 11 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the pre-referral period excluding Germany; analysis based on the episode level

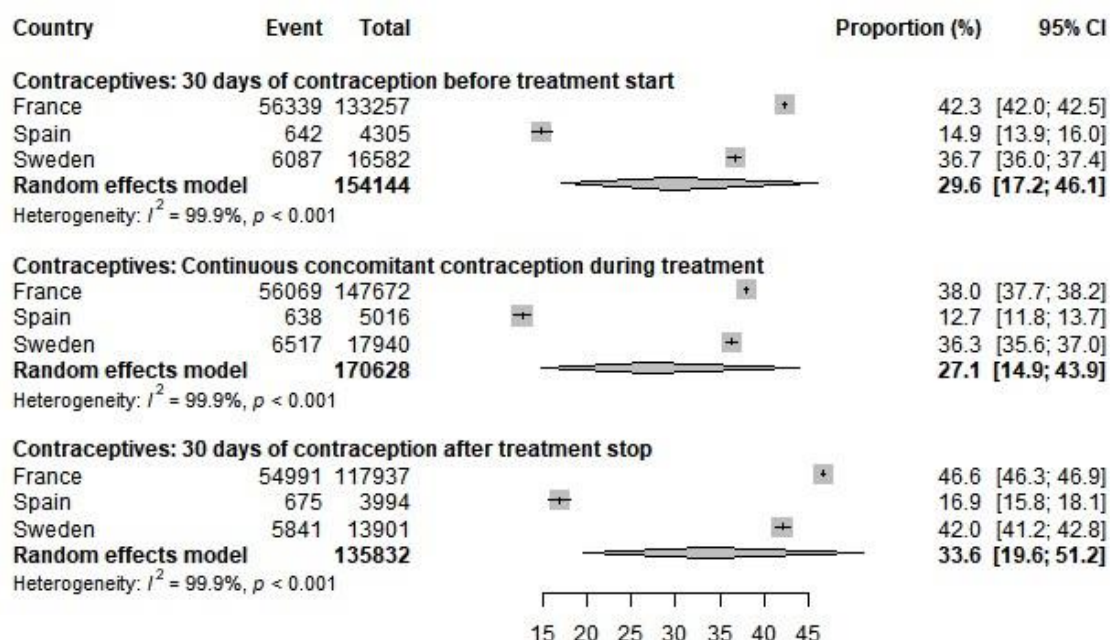


Figure 12 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-referral period excluding Germany; analysis based on the episode level

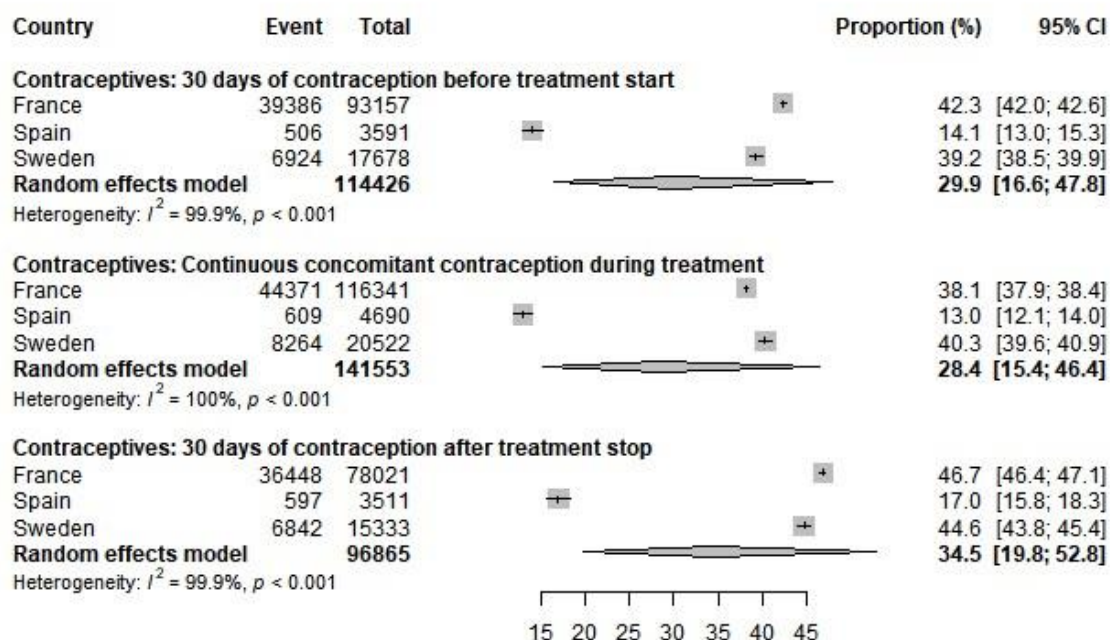


Figure 13 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-implementation period excluding Germany; analysis based on the episode level

Table 70 Meta-analysis; Prescribing patterns for contraceptives before, during and after treatment episodes excluding Spain; analysis based on the episode level

Contraceptives: n (%) [95% CI of %]	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Prior to treatment	N¹ = 112,572	χ^2, p	I²	N¹ = 154,168	χ^2, p	I²	N¹ = 112,535	χ^2, p	I²
30 days of contraception before treatment start	26,605 (23.6) [10.6 - 44.7]	795.5 <0.001	99.9	39,217 (25.4) [10.7 - 49.2]	1,575.5 <0.001	100	31,502 (28.0) [13.5 - 49.3]	571.0 <0.001	100
During treatment	N² = 127,667			N² = 170,271			N² = 138,870		
Continuous concomitant contraception during treatment	27,135 (21.3) [8.9 - 42.8]	710.9 <0.001	99.9	38,917 (22.9) [8.9 - 47.3]	1,332.6 <0.001	100	36,135 (26.0) [11.7 - 48.2]	581.4 <0.001	100
After treatment	N³ = 100,737			N³ = 135,863			N³ = 94,610		
30 days of contraception after treatment stop	26,853 (26.7) [11.1 - 51.4]	800.4 <0.001	99.9	38,209 (28.1) [11.1 - 55.0]	1,634.8 <0.001	100	29,128 (30.8) [13.8 - 55.3]	485.6 <0.001	100

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

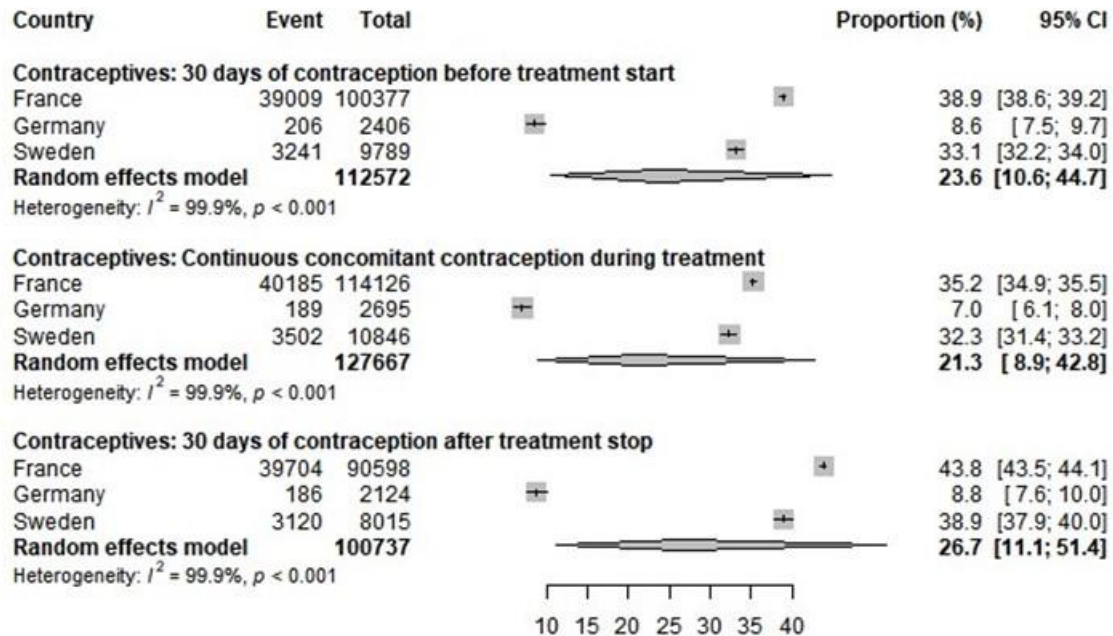


Figure 14 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the pre-referral period excluding Spain; analysis based on the episode level

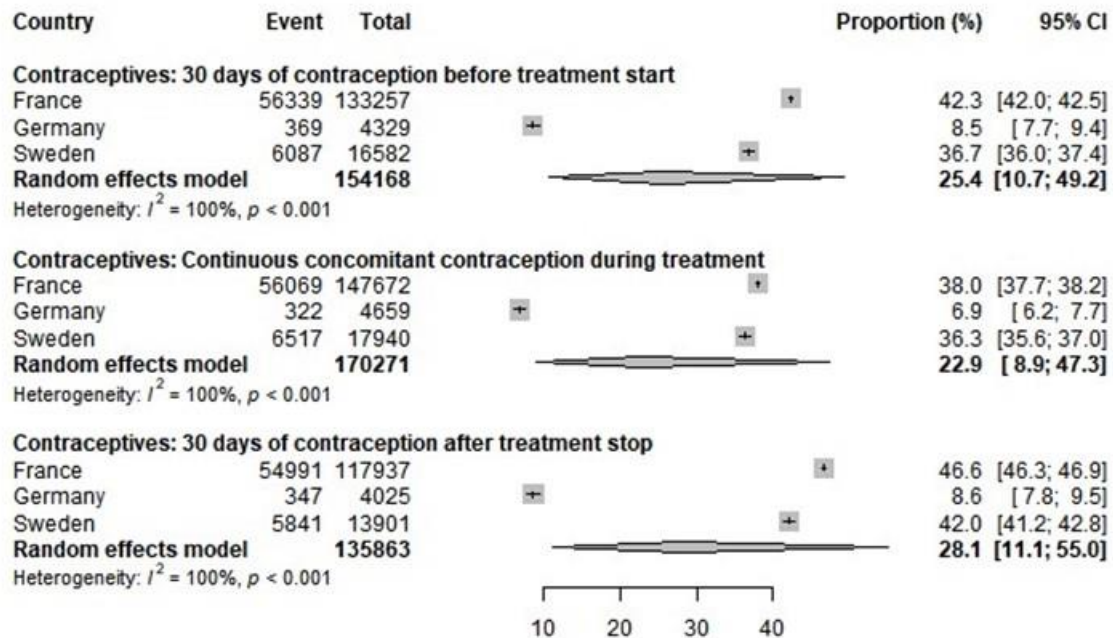


Figure 15 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-referral period excluding Spain; analysis based on the episode level

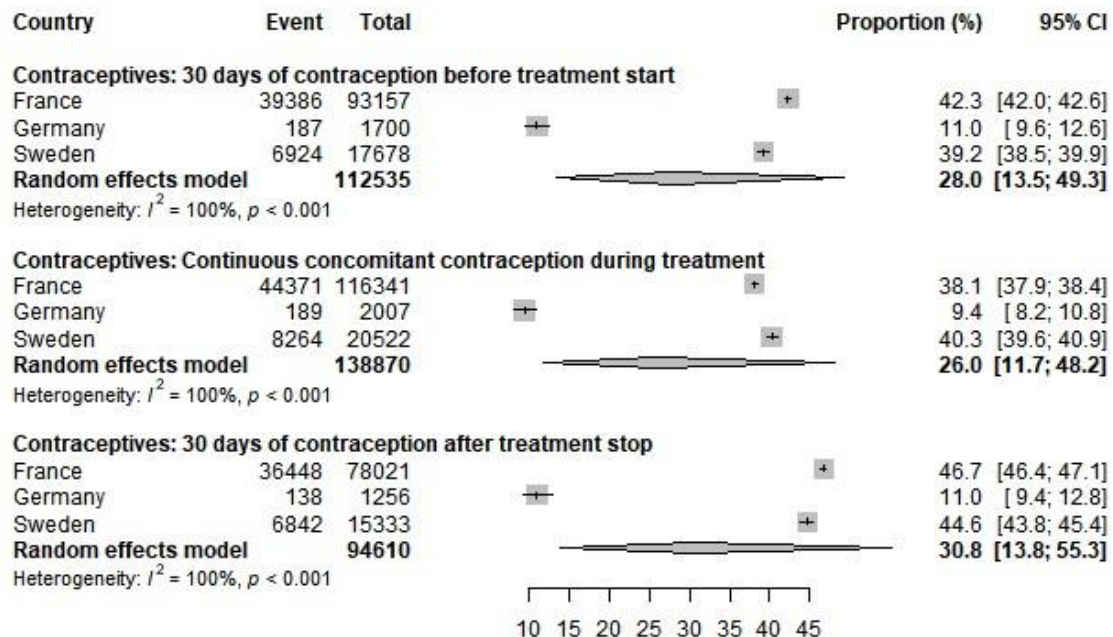


Figure 16 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-implementation period excluding Spain; analysis based on the episode level

Table 71 Meta-analysis; Prescribing patterns for contraceptives before, during and after treatment episodes excluding Sweden; analysis based on the episode level

Contraceptives: n (%) [95% CI of %]	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Prior to treatment	N¹ = 106,271	χ^2, p	I²	N¹ = 141,891	χ^2, p	I²	N¹ = 98,448	χ^2, p	I²
30 days of contraception before treatment start	18,925 (17.8)	1,408.6	99.7	26,427 (18.6)	2,486.9	99.8	19,450 (19.8)	1,462.0	99.7
	[8.0 - 34.9]	<0.001		[7.9 - 37.8]	<0.001		[9.2 - 37.4]	<0.001	
During treatment	N² = 120,483			N² = 157,347			N² = 123,038		
Continuous concomitant contraception during treatment	18,898 (15.7)	1,321.2	99.7	24,894 (15.8)	2,423.3	99.8	21,574 (17.5)	1,569.3	99.8
	[6.9 - 31.9]	<0.001		[6.5 - 33.7]	<0.001		[8.2 - 33.7]	<0.001	
After treatment	N³ = 95,657			N³ = 125,956			N³ = 82,788		
30 days of contraception after treatment stop	18,723 (19.6)	1,489.4	99.8	25,681 (20.4)	2,685.7	99.9	18,188 (22.0)	1,473.3	99.8
	[8.3 - 39.5]	<0.001		[8.3 - 42.2]	<0.001		[9.9 - 41.9]	<0.001	

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

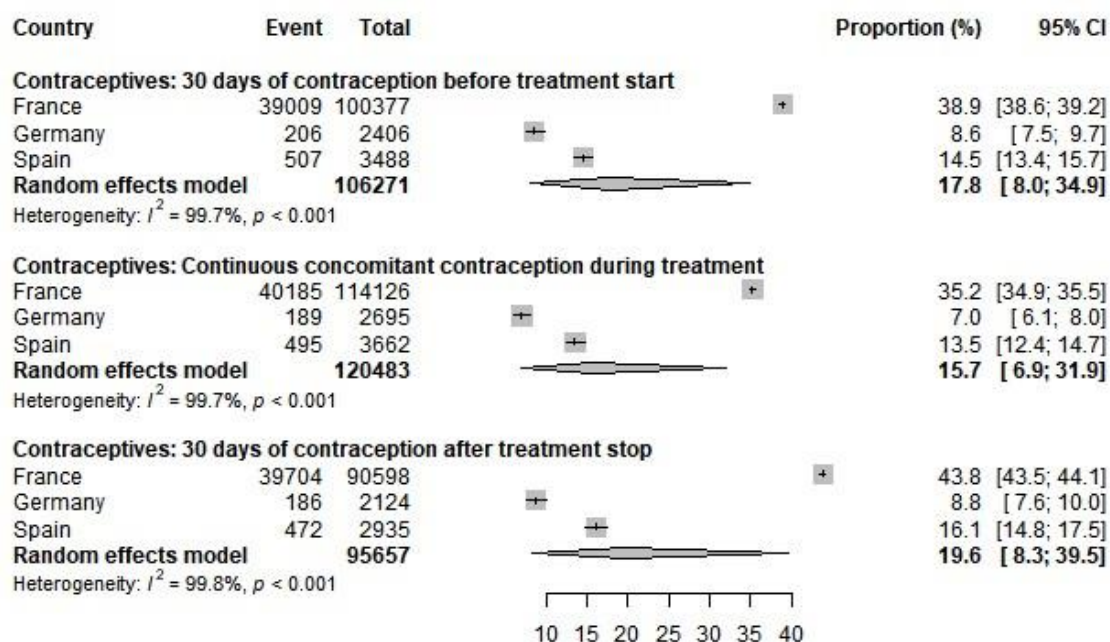


Figure 17 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the pre-referral period excluding Sweden; analysis based on the episode level

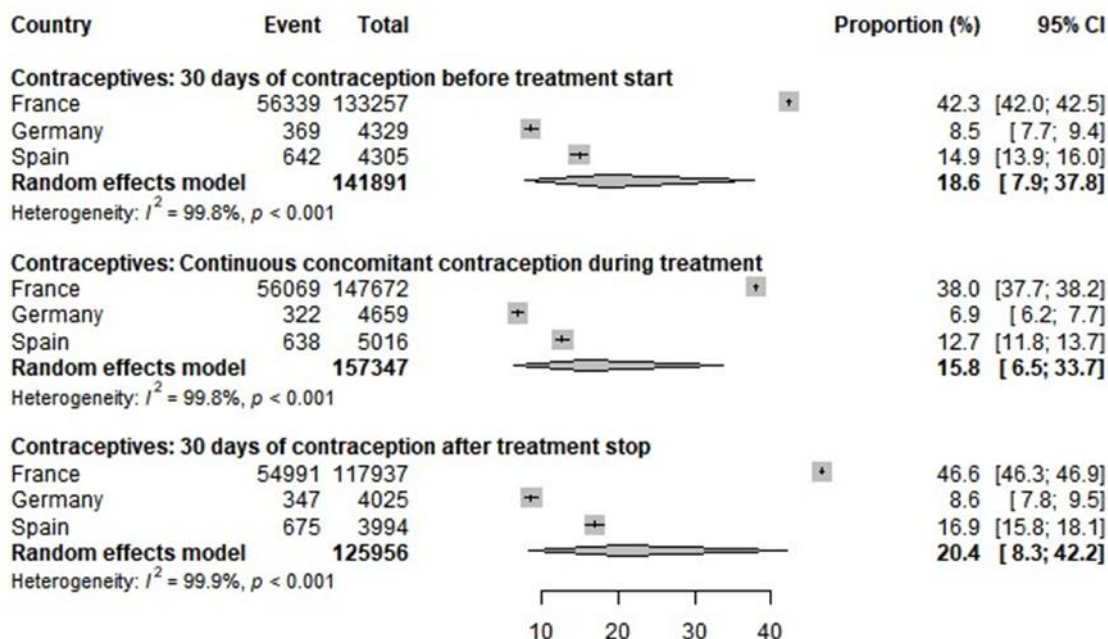


Figure 18 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-referral period excluding Sweden; analysis based on the episode level

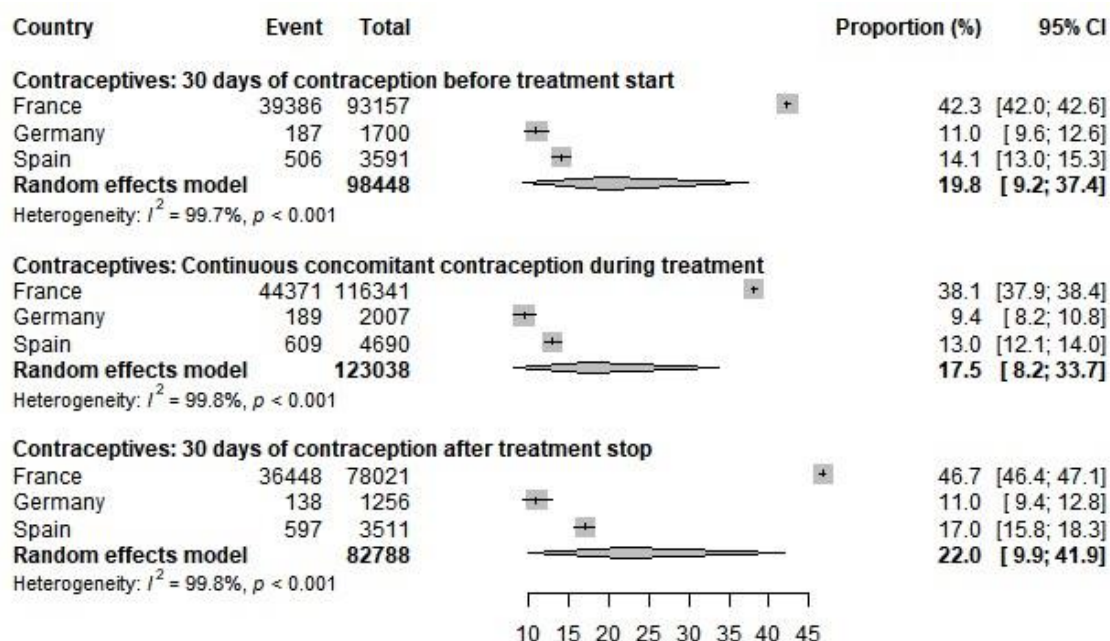


Figure 19 Forest plot for prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids for the post-implementation period excluding Sweden; analysis based on the episode level

11.4.7.2 Periodicity of Prescriptions

Meta-analysis of aggregated measures for the 4 countries together showed that the mean time interval between prescription dates for oral retinoids in the pre-referral period was 51.7 days. The proportion of episodes with monthly prescription intervals was 13.9%. During the post-referral period the mean time interval between prescription dates was 51.8 days and 14.9% of episodes had monthly prescription intervals. During the post-implementation period the mean time interval between prescription dates was 53.6 days and 17.3% of episodes had monthly prescription intervals (

Table 72). High levels of heterogeneity ($I^2 > 99\%$) were observed for both pre- and the post-implementation periods (

Table 72, Figure 20, Figure 21 and Figure 22). Excluding countries one by one from the meta-analysis (France:

Table 73, Figure 23, Figure 24 and Figure 25, Germany: Table 74, Figure 26, Figure 27 and Figure 28, Spain:

Table 75, Figure 29, Figure 30 and Figure 31, and Sweden: Table 76, Figure 32, Figure 33 and Figure 34) did not have an effect on the heterogeneity levels ($I^2 > 99\%$).

Table 72 Meta-analysis; Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
	N ¹ = 98,272	p	I ²	N ¹ = 132,399	p	I ²	N ¹ = 105,861	p	I ²
Time interval between prescription dates during episodes: days									
Mean (SE)	51.7 (14.6)			51.8 (14.5)			53.6 (16.6)		
[95% CI of %]	[5.3 - 98.1]	<0.001	99.9	[5.5 - 98]	<0.001	100	[0.8 - 106.4]	<0.001	100
Number of episodes with monthly prescription intervals during treatment: n (%)	13,674 (13.9)	2,613	99.9	19,716 (14.9)	4,468.2	99.9	18,322 (17.3)	6,030.1	99.9
[95% CI of %]	[4.7 - 34.8]	<0.001		[5.5 - 34.6]	<0.001		[5.1 - 44.7%	<0.001	

CI, confidence interval; N or n, number of episodes; SE, standard error

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model. Reported mean is the estimate of the median mean from a random effects model using the Knapp-Hartung estimate with variance correction.

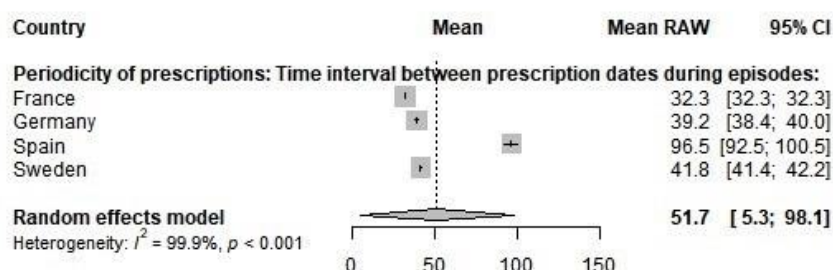
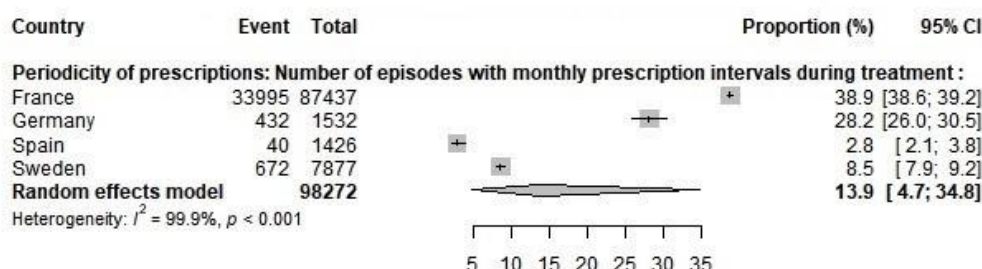


Figure 20 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the pre-referral period; analysis based on the episode level

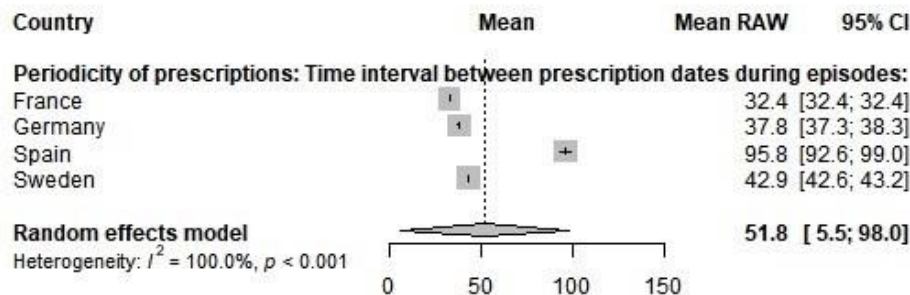
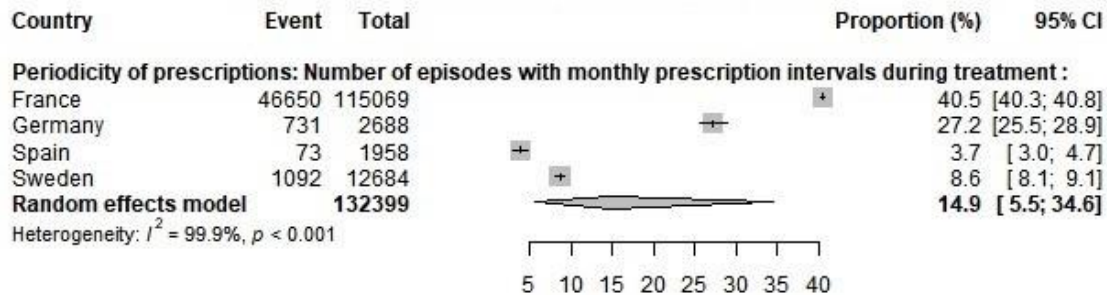


Figure 21 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-referral period; analysis based on the episode level

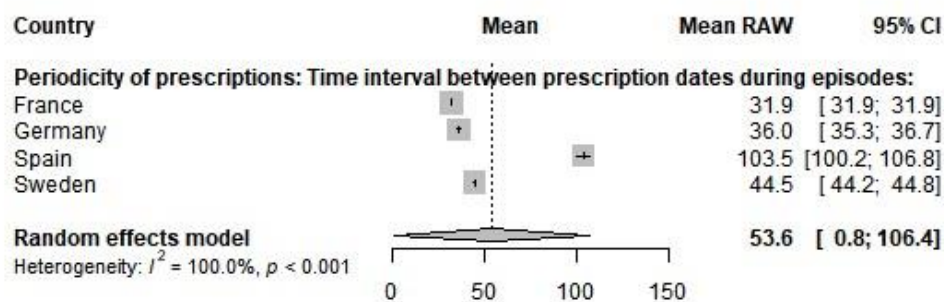
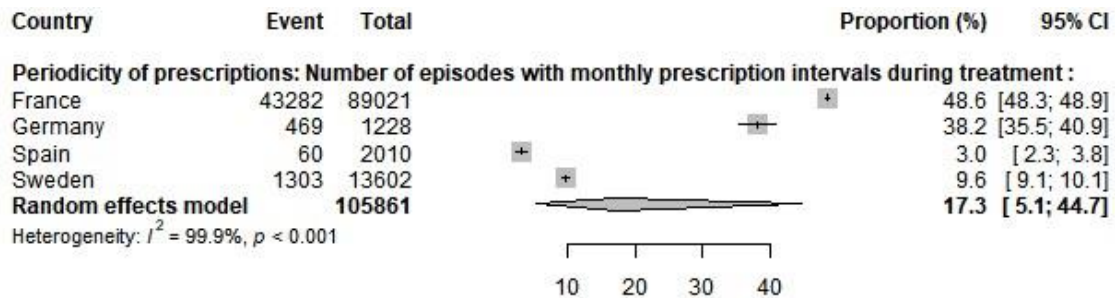


Figure 22 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-implementation period; analysis based on the episode level

Table 73 Meta-analysis; Prescribing patterns: periodicity of prescriptions within treatment episodes excluding France; analysis based on the episode level

			Pre-implementation period						Post-implementation period		
			Pre-referral			Post-referral					
			N ¹ = 10,835	p	I ²	N ¹ = 17,330	p	I ²	N ¹ = 16,840	p	I ²
Time interval between prescription dates during episodes: days	Mean (SE)		58.6 (18.5)		99.7	58.3 (18.4)		99.9	61 (21.1)		99.9
	[95% CI of %]		[-21.1 - 138.3]	<0.001		[-20.9 - 137.6]	<0.001		[-30 - 152]	<0.001	
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]			1,005 (9.3)	528.3	99.6	1,733 (10)	784.4	99.7	1,890 (11.2)	864	99.8
			[3 - 25.5]	<0.001		[3.7 - 24.2]	<0.001		[3 - 33.8]	<0.001	

CI, confidence interval; N or n, number of episodes; SE, standard error,

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model. Reported mean is the estimate of the median mean from a random effects model using the Knapp-Hartung estimate with variance correction.

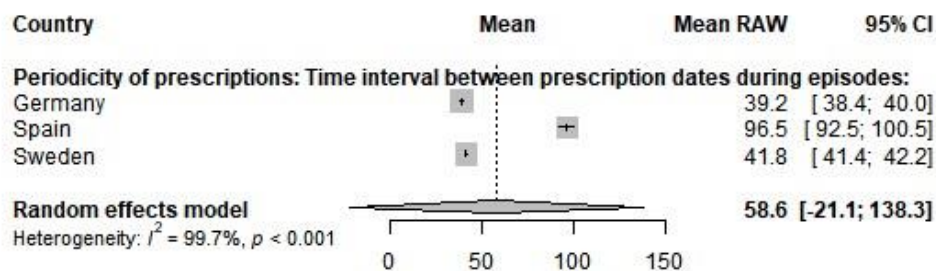
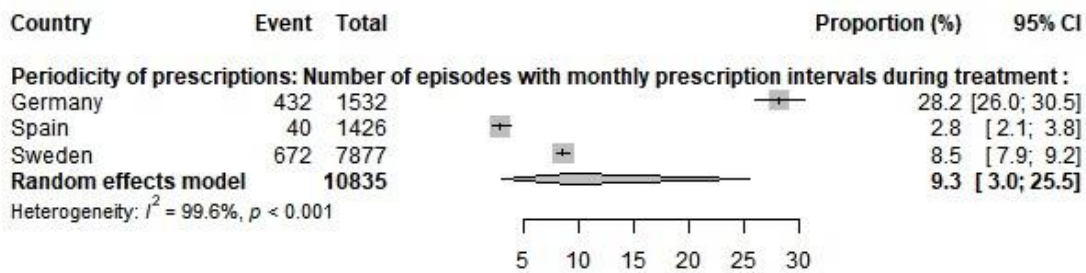


Figure 23 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the pre-referral period excluding France; analysis based on the episode level

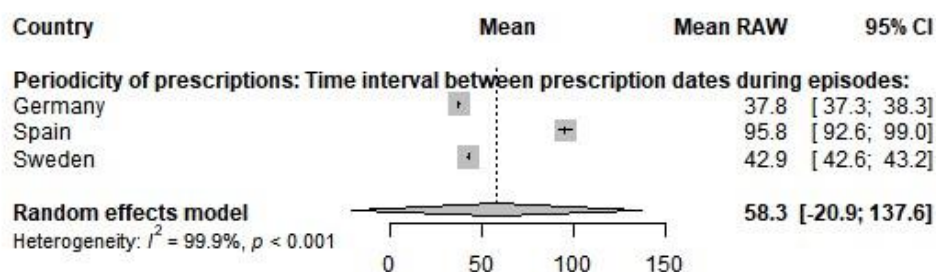
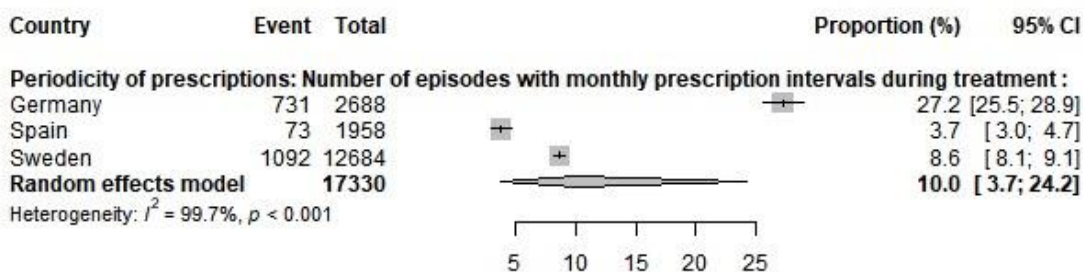


Figure 24 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-referral period excluding France; analysis based on the episode level

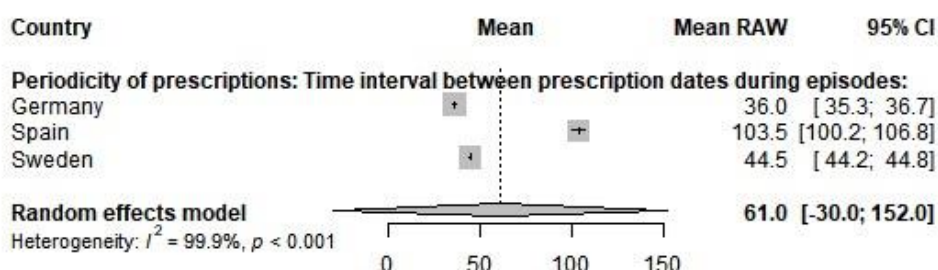
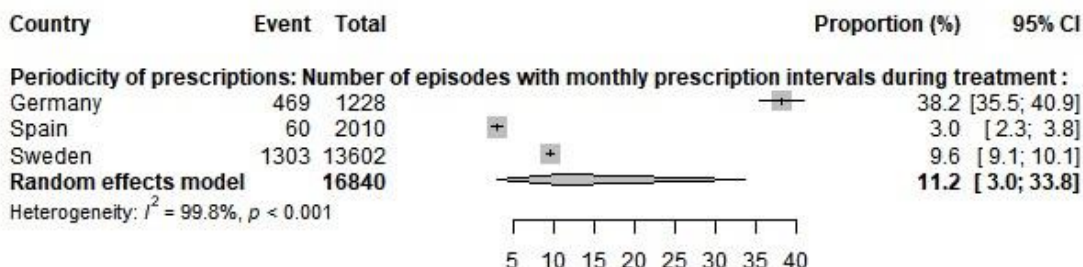


Figure 25 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-implementation period excluding France; analysis based on the episode level

Table 74 Meta-analysis; Prescribing patterns: periodicity of prescriptions within treatment episodes excluding Germany; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
	N ¹ = 96,740	p	I ²	N ¹ = 129,711	p	I ²	N ¹ = 104,633	p	I ²
Time interval between prescription dates during episodes: days									
Mean (SE)	56.1 (19.8)		99.9	56.6 (19.5)		100	59.6 (22)		100
[95% CI of %]	[-29.1 - 141.3]	<0.001		[-27.4 - 140.5]	<0.001		[-35 - 154.1]	<0.001	
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]	10,367 (10.7)	2,558.7	99.9	15,503 (12)	4,323.5	99.9	13,315 (12.7)	6,003.0	100
	[2.7 - 33.8]	<0.001		[3.4 - 34.6]	<0.001		[2.8 - 42.1]	<0.001	

CI, confidence interval; N or n, number of episodes; SE, standard error

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model. Reported mean is the estimate of the median mean from a random effects model using the Knapp-Hartung estimate with variance correction.

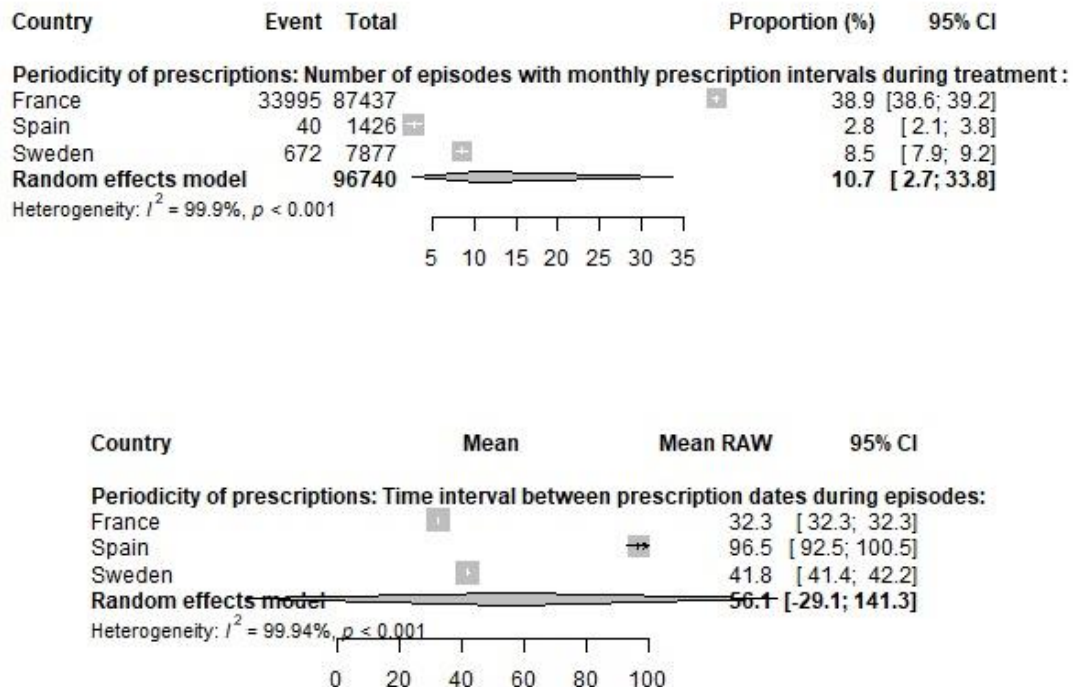


Figure 26 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the pre-referral period excluding Germany; analysis based on the episode level

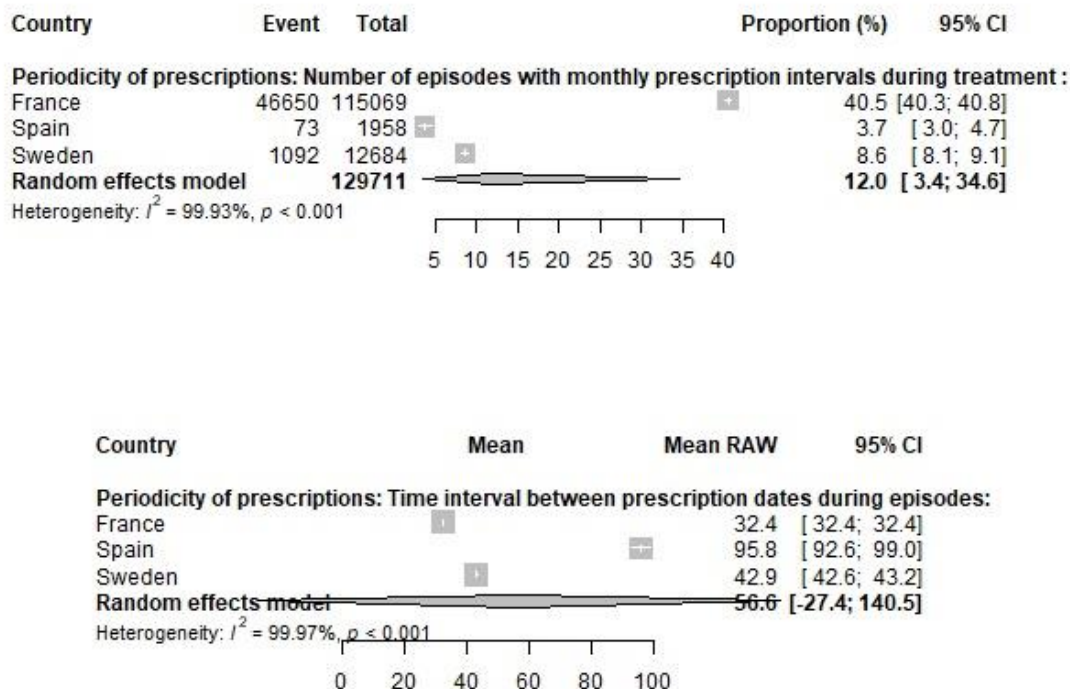


Figure 27 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-referral period excluding Germany; analysis based on the episode level

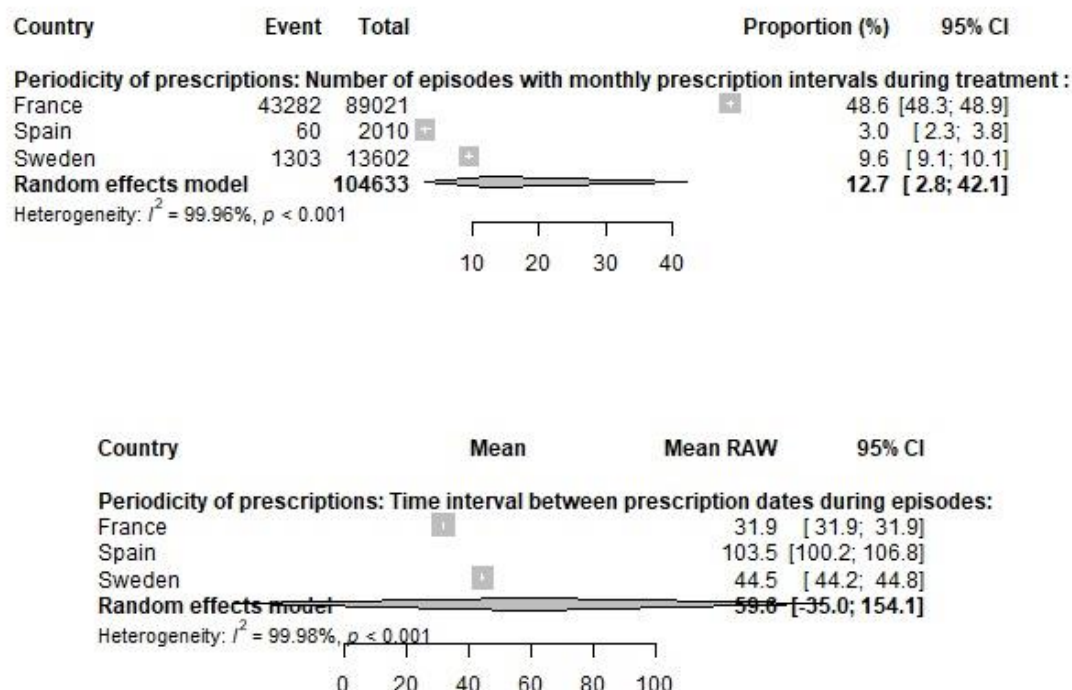


Figure 28 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-implementation period excluding Germany; analysis based on the episode level

Table 75 Meta-analysis; Prescribing patterns: periodicity of prescriptions within treatment episodes excluding Spain; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
	N ¹ = 96,846	p	I ²	N ¹ = 130,441	p	I ²	N ¹ = 103,851	p	I ²
Time interval between prescription dates during episodes: days									
Mean (SE)	37.8 (3.7)			37.7 (3.8)			37.5 (4.8)		
[95% CI of %]	[21.8 - 53.7]	<0.001	99.9	[21.1 - 54.3]	<0.001	100	[16.9 - 58.1]	<0.001	100
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]	21,514 (22.2)	2,256.3		29,200 (22.4)	3,922.5		29,433 (28.3)	5,393.2	
	[10.2 - 41.8]	<0.001	99.8	[10.1 - 42.4]	<0.001	99.9	[11.9 - 53.6]	<0.001	99.9

CI, confidence interval; N or n, number of episodes; SE, standard error

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model. Reported mean is the estimate of the median mean from a random effects model using the Knapp-Hartung estimate with variance correction.

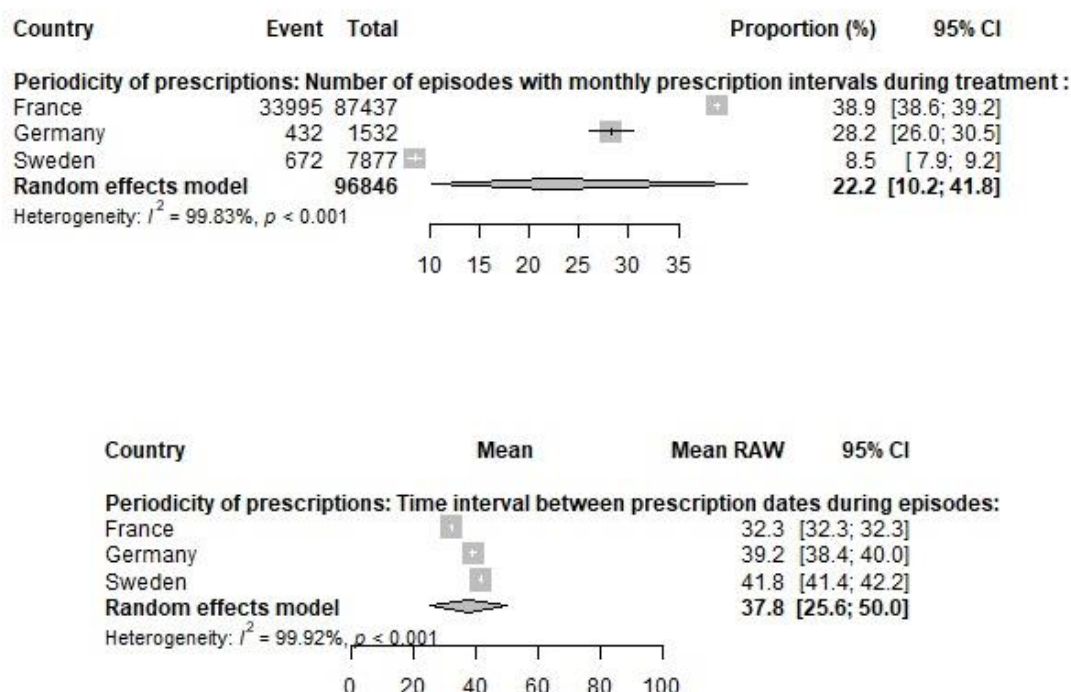


Figure 29 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the pre-referral period excluding Spain; analysis based on the episode level

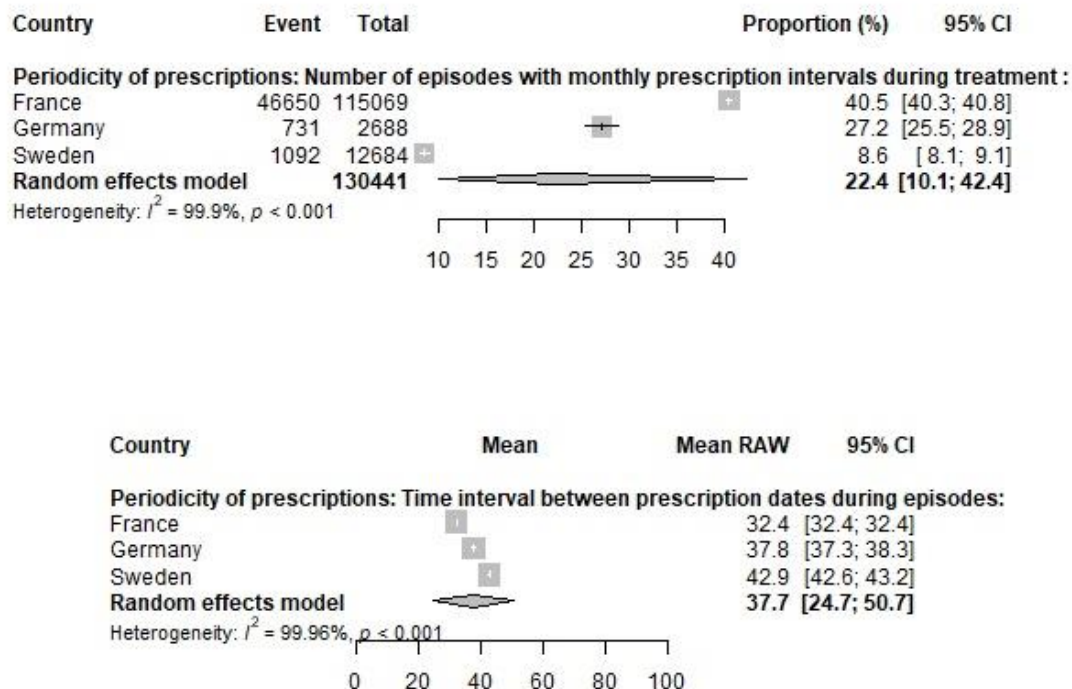


Figure 30 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-referral period excluding Spain; analysis based on the episode level

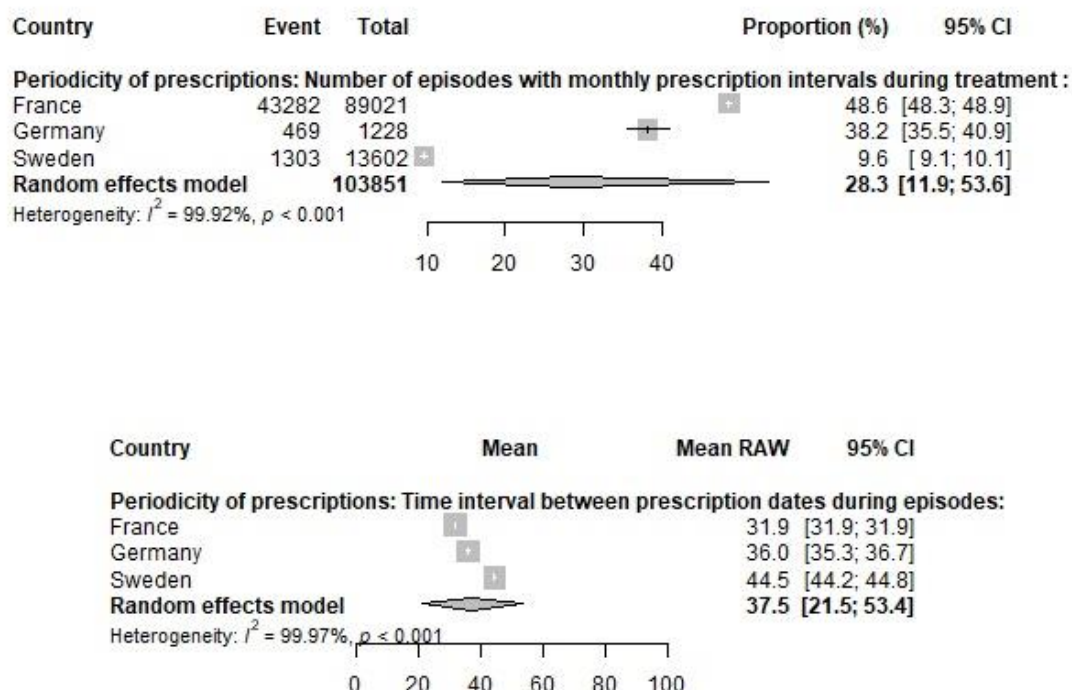


Figure 31 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-implementation period excluding Spain; analysis based on the episode level

Table 76 Meta-analysis; Prescribing patterns: periodicity of prescriptions within treatment episodes excluding Sweden; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
	N ¹ = 90,395	P	I ²	N ¹ = 119,715	P	I ²	N ¹ = 92,259	P	I ²
Time interval between prescription dates during episodes: days									
Mean (SE)	55.5 (20.2)			54.8 (20.2)			56.8 (23.1)		
[95% CI of %]	[-31.5 - 142.5]	<0.001	99.8	[-31.9 - 141.6]	<0.001	99.9	[-42.7 - 156.3]	<0.001	99.9
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]	14,687 (16.2)	440.6		21,188 (17.7)	761.3		19,186 (20.8)	731.3	
			99.8			99.9			99.9
	[4.0 - 47.4]	<0.001		[5.0 - 46.5]	<0.001		[4.5 - 59.6]	<0.001	

CI, confidence interval; N or n, number of episodes; SE, standard error,

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model. Reported mean is the estimate of the median mean from a random effects model using the Knapp-Hartung estimate with variance correction.

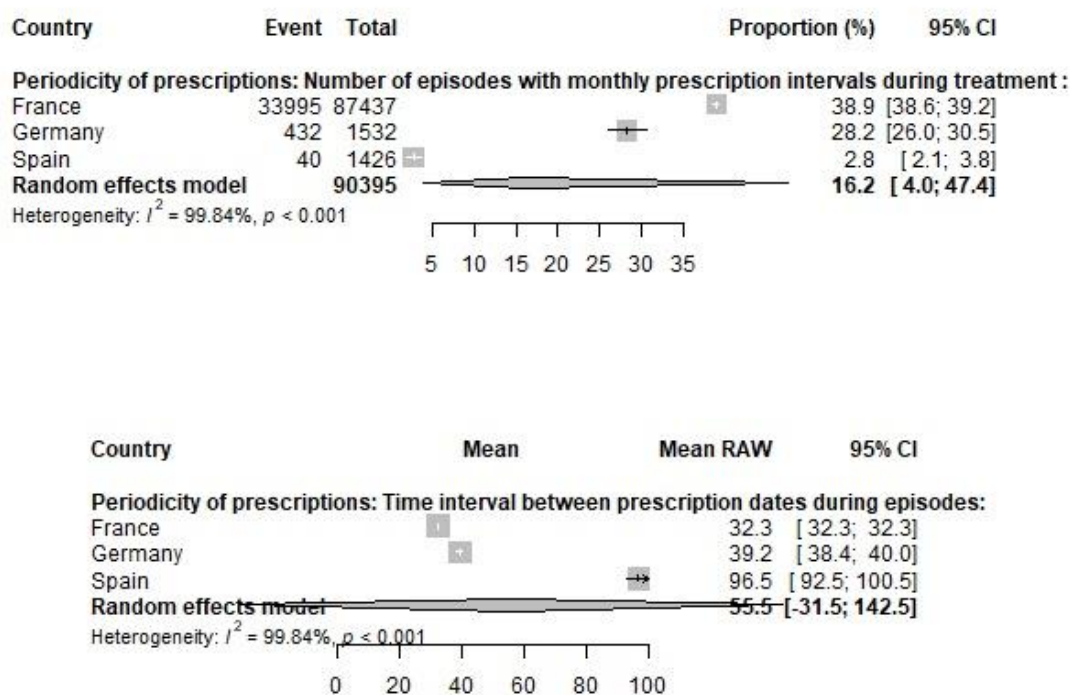


Figure 32 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the pre-referral period excluding Sweden; analysis based on the episode level

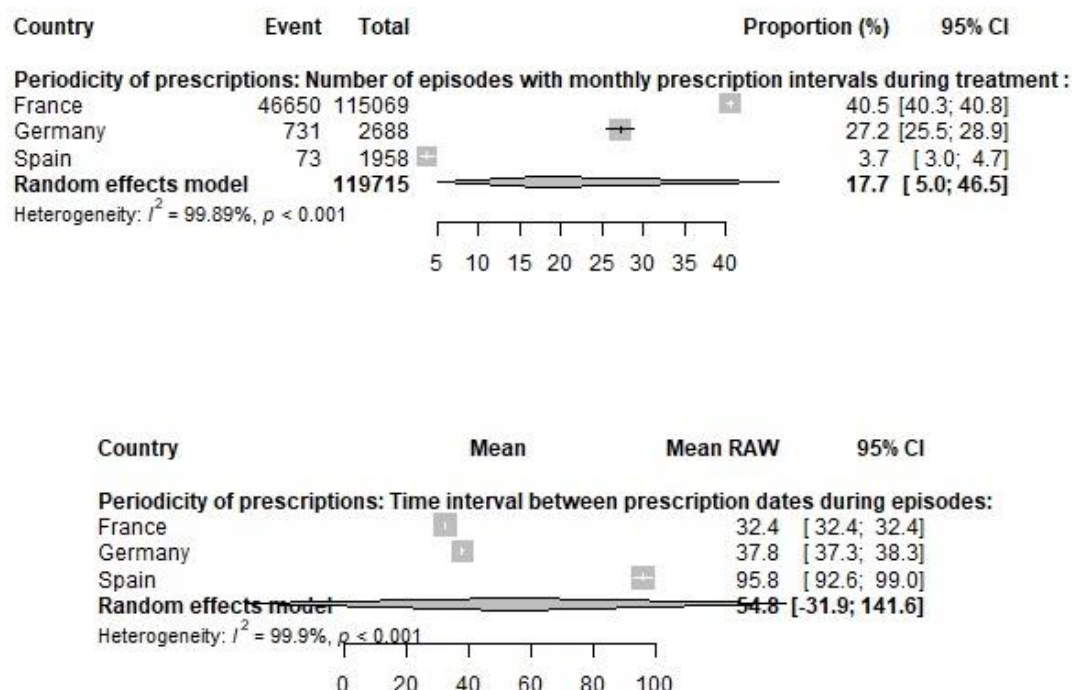


Figure 33 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-referral period excluding Sweden; analysis based on the episode level

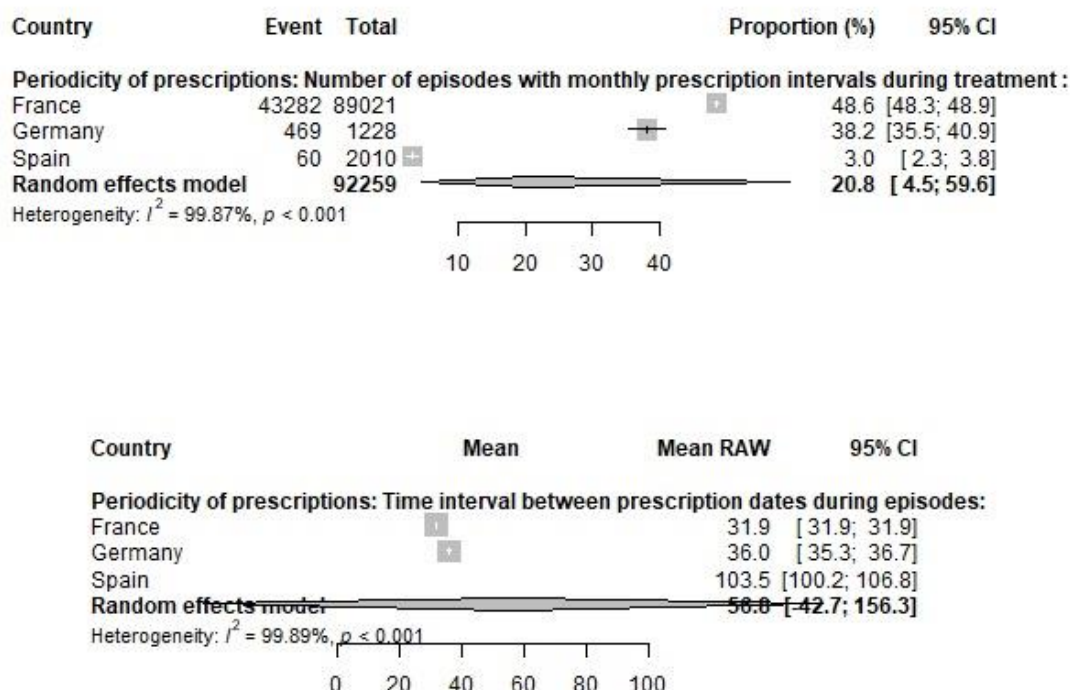


Figure 34 Forest plot for prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids for the post-implementation period excluding Sweden; analysis based on the episode level

11.4.7.3 Laboratory Pregnancy Tests

The meta-analysis was conducted including only 3 countries (France, Germany and Spain); Sweden was not included since very few laboratory pregnancy tests were recorded in the data. Meta-analysis of aggregated measures for the 3 countries (France, Germany and Spain) showed that in the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 20.6% of episodes. The proportion of treatment episode time covered by compliant monthly laboratory pregnancy testing was 2.8%. After oral retinoid treatment laboratory pregnancy testing within 30 (-/+7) days was performed in 3.7% of episodes. The corresponding proportions were 23.9%, 1.5% and 3.9% for the post-referral and 26.6%, 2.0% and 3.6% for the post-implementation period (Table 77). High levels of heterogeneity ($I^2 > 99\%$) were observed for both pre-implementation periods and the post-implementation period (Table 77, Figure 35, Figure 36 and Figure 37). Excluding countries one by one from the meta-analysis (France: Table 78, Figure 38, Figure 39 and Figure 40, Germany: **Error! Reference source not found.**,

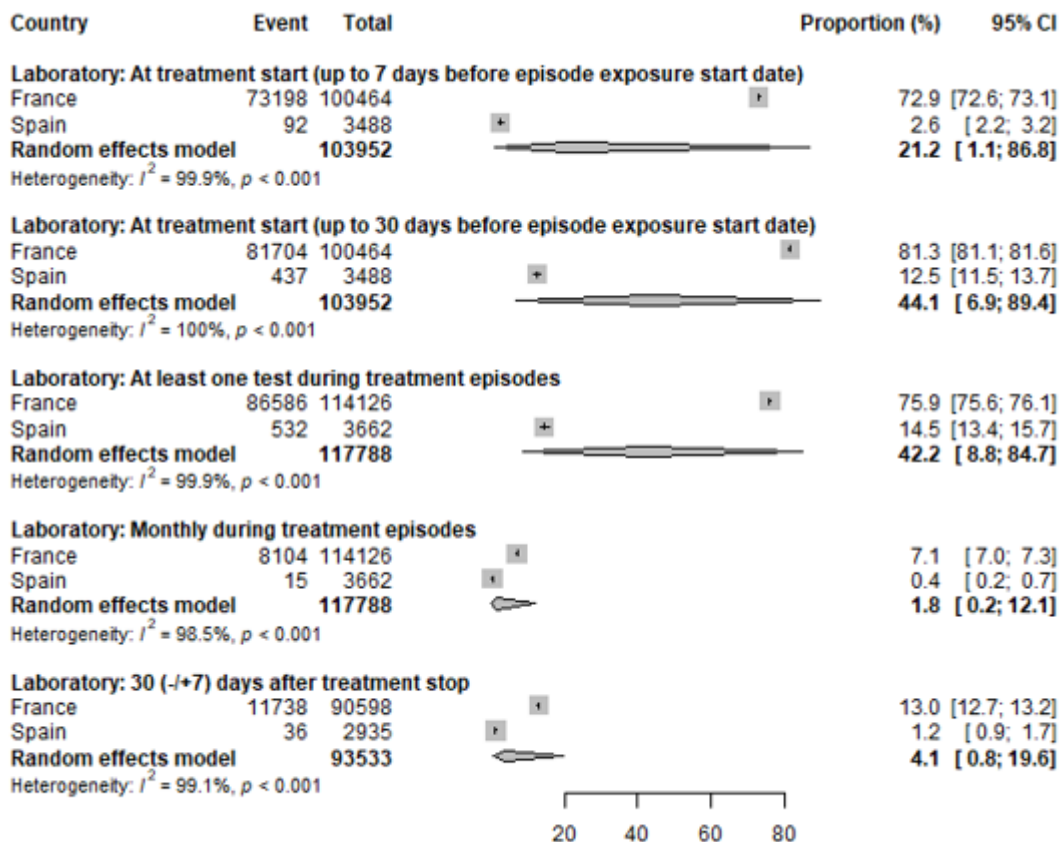


Figure 41, Figure 42 and Figure 43, and Spain: Table 80,

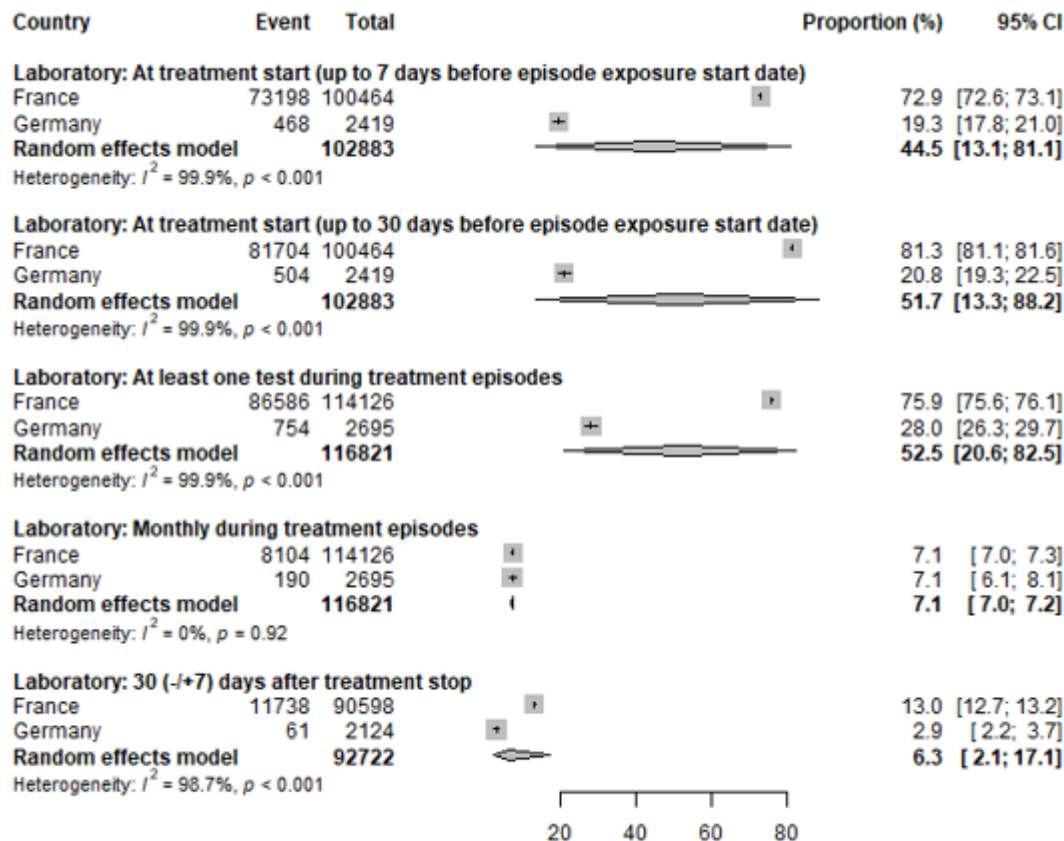


Figure 44, Figure 45, Figure 46) did generally not have an effect on the heterogeneity levels ($I^2 > 99\%$).

Table 77 Meta-analysis; Prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids; analysis based on the episode level

Laboratory pregnancy tests performed: n (%) [95% CI of %]	Pre-implementation period							Post-implementation period		
	Pre-referral			Post-referral						
	N ¹ = 106,371	χ^2 , p	I ²	N ¹ = 142,031	χ^2 , p	I ²		N ¹ = 98,516	χ^2 , p	I ²
Prior to treatment										
At treatment start (up to 7 days before episode exposure start date)	21,913 (20.6) [3.0 - 68.5]	4,007.7 <0.001	99.9	33,897 (23.9) [3.9 - 71]	6,938.8 <0.001	100		26,178 (26.6) [4.6 - 72.9]	4,164.3 <0.001	99.9

At treatment start (up to 30 days before episode exposure start date)	37,642 (35.4) [9.2 - 74.7]	7,232.5 <0.001	99.9	55,024 (38.7) [10.7 - 76.9]	11,301.7 <0.001	100	40,145 (40.8) [11.8 - 77.9]	6,980.1 <0.001	99.9
During treatment	N² = 120,483			N² = 157,347			N² = 123,038		
At least one test during treatment episodes	44,818 (37.2) [12.9 - 70.4]	5,968.4 <0.001	99.9	64,026 (40.7) [15.2 - 72.4]	9,449.4 <0.001	100	53,655 (43.6) [19.1 - 71.6]	6,102.3 <0.001	99.9
Monthly during treatment episodes	3,405 (2.8) [0.6 - 12.1]	127.3 <0.001	99.7	2,417 (1.5) [0.1 - 17.6]	71.2 <0.001	99.9	2,476 (2.0) [0.2 - 20.9]	90 <0.001	99.9
After treatment	N³ = 95,657			N³ = 125,956			N³ = 82,788		
30 (-/+7) days after treatment stop	3,511 (3.7) [1.2 - 11.0]	370.8 <0.001	99	4,974 (3.9) [1.3 - 11.2]	565.4 <0.001	99.4	2,961 (3.6) [1.1 - 11.1]	333.5 <0.001	98.8

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

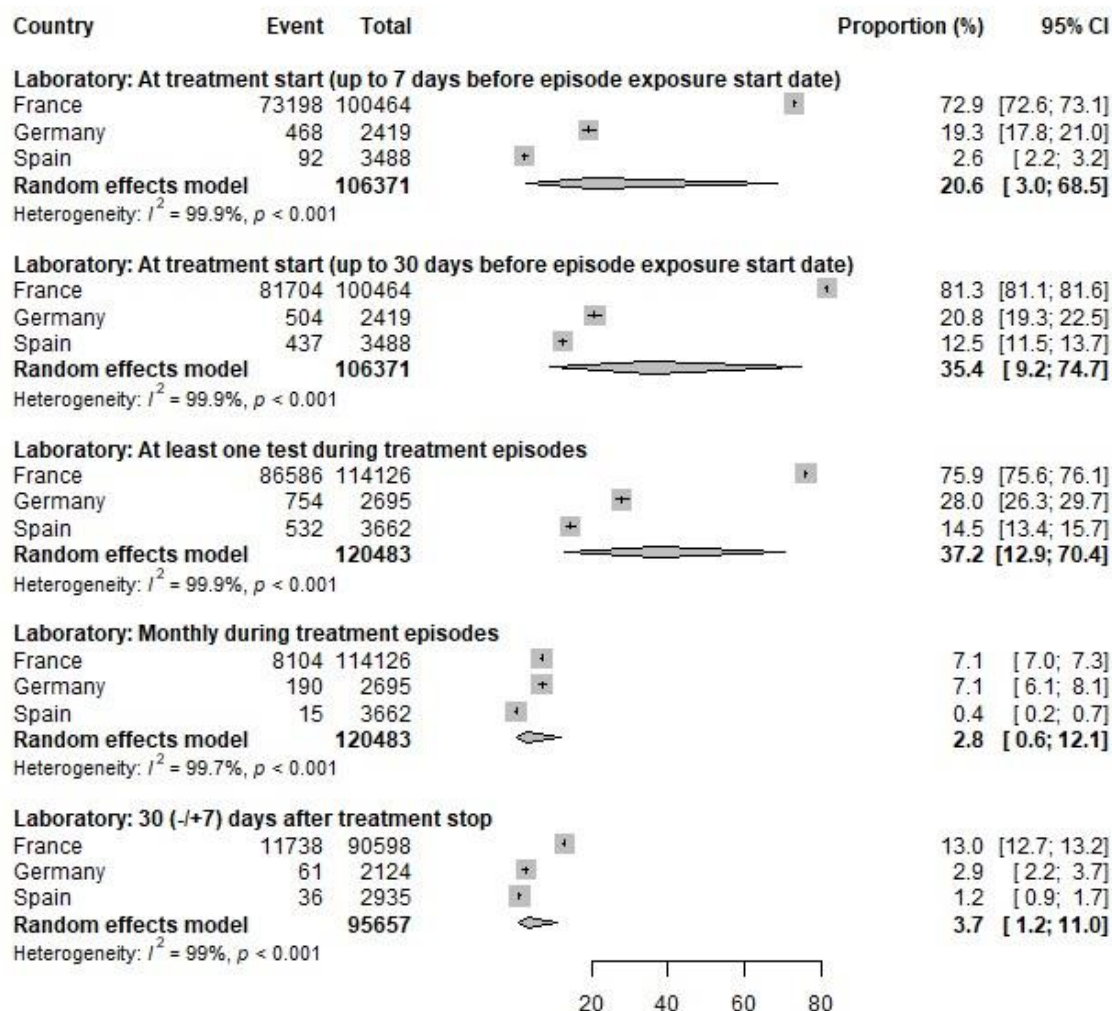


Figure 35 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the pre-referral period; analysis based on the episode level

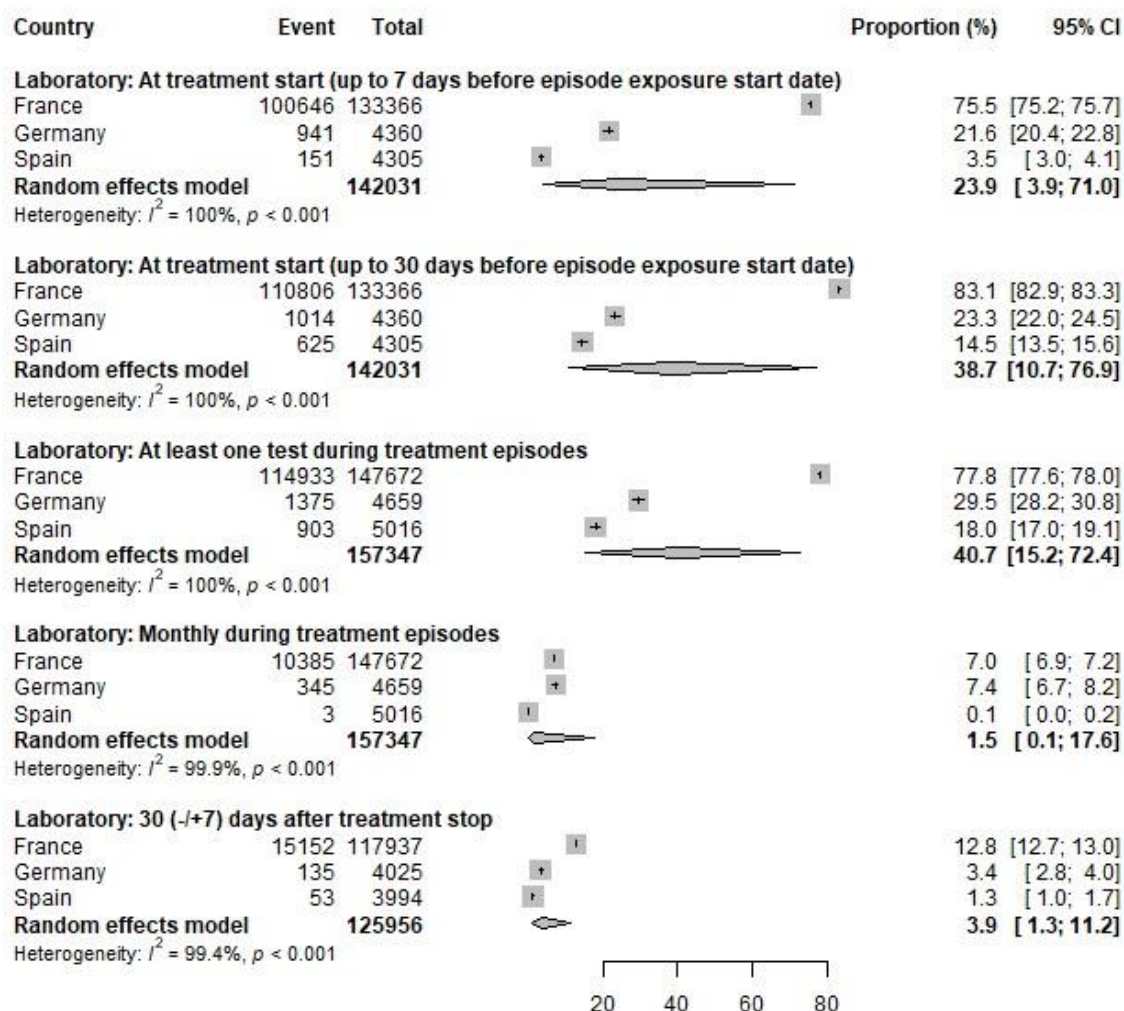


Figure 36 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-referral period; analysis based on the episode level

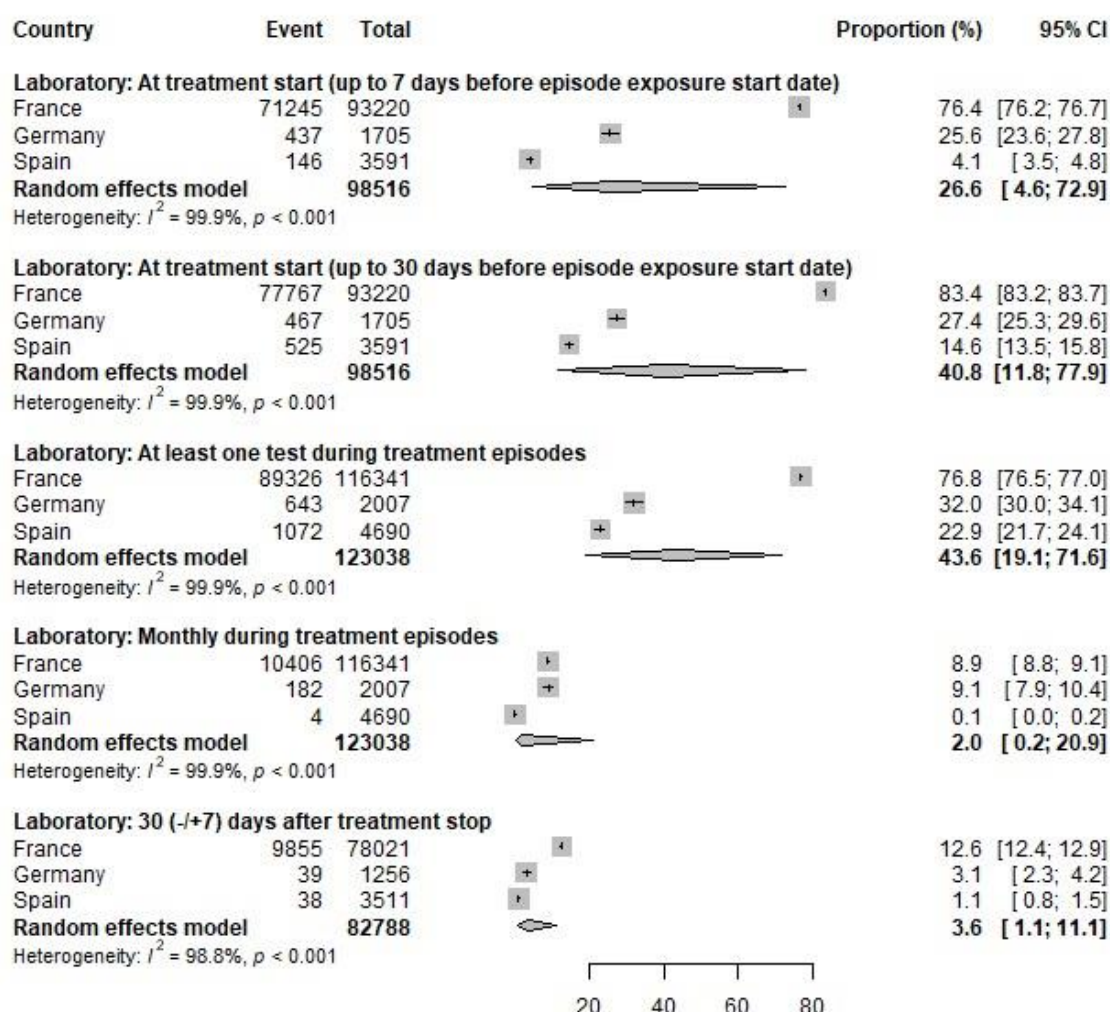


Figure 37 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-implementation period; analysis based on the episode level

Table 78 Meta-analysis; prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes excluding France; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Laboratory pregnancy tests performed: n (%) [95% CI of %]									
Prior to treatment	N¹ = 5,907	χ², p	I²	N¹ = 8,665	χ², p	I²	N¹ = 5,296	χ², p	I²
At treatment start (up to 7 days before episode exposure start date)	441 (7.5)	344.3	99.4	789 (9.1)	498.7	99.6	571 (10.8)	429.9	99.5
	[1.7 - 26.8]	<0.001		[2.4 - 29]	<0.001		[2.7 - 34.1]	<0.001	
At treatment start (up to 30 days before episode exposure start date)	960 (16.2)	72.3	97.2	1,603 (18.5)	106.2	98.1	1,072 (20.2)	120.4	98.3
	[11.3 - 22.8]	<0.001		[13.2 - 25.3]	<0.001		[12.8 - 30.5]	<0.001	
During treatment	N² = 6,357			N² = 9,675			N² = 6,697		
At least one test during treatment episodes	1,299 (20.4)	169.1	98.8	2,251 (23.3)	174.9	98.9	1,818 (27.2)	61.7	96.8
	[12.7 - 31.3]	<0.001		[16.2 - 32.2]	<0.001		[21.3 - 34]	<0.001	
Monthly during treatment episodes	111 (1.7)	117	98.3	66 (0.7)	71.2	97.4	61(0.9)	88.4	97.8
	[0.2 - 12]	<0.001		[0 - 18.4]	<0.001		[0 - 21.1]	<0.001	
After treatment	N³ = 5,059			N³ = 8,019			N³ = 4,767		
30 (-/+7) days after treatment stop	95 (1.9)	16.7	88.1	171 (2.1)	33.6	94.1	87 (1.8)	21.8	90.8
	[1 - 3.4]	<0.001		[1.1 - 4]	<0.001		[0.9 - 3.7]	<0.001	

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

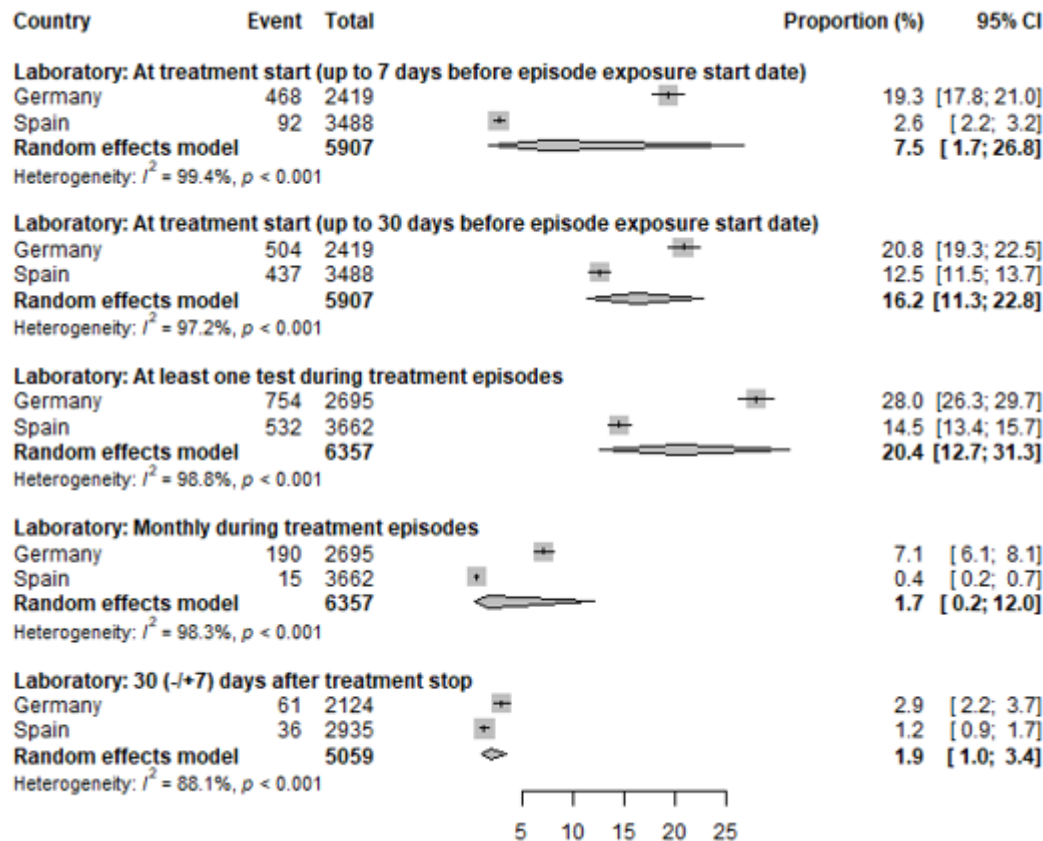


Figure 38 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the pre-referral period excluding France; analysis based on the episode level

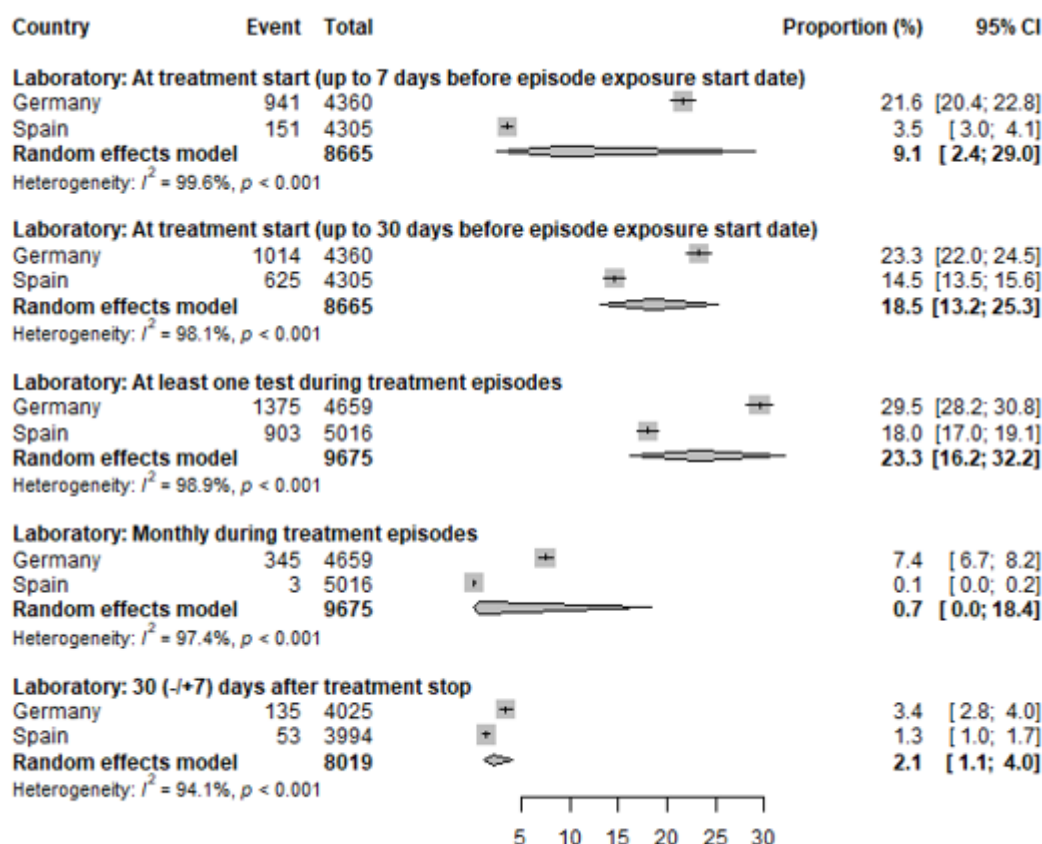


Figure 39 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-referral period excluding France; analysis based on the episode level

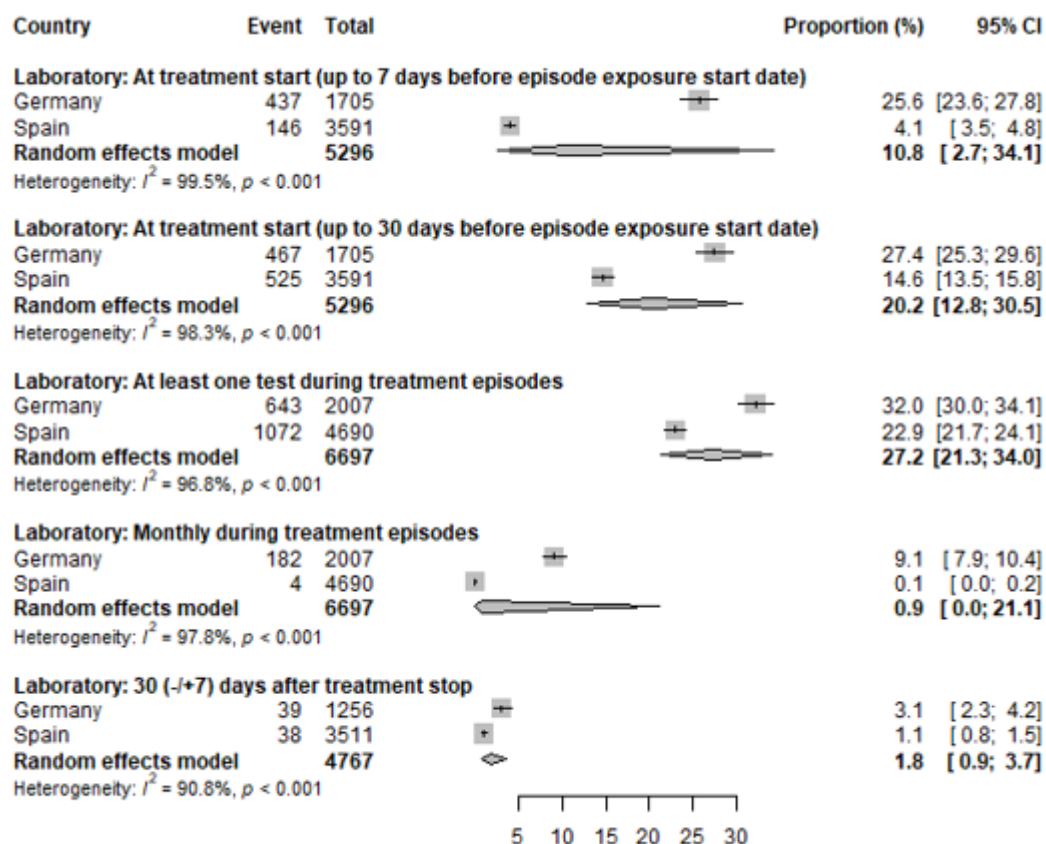


Figure 40 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-implementation period excluding France; analysis based on the episode level

Table 79 Meta-analysis; prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes excluding Germany; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Laboratory pregnancy tests performed: n (%) [95% CI of %]									
Prior to treatment	N¹ = 103,952	χ^2, p	I²	N¹ = 137,671	χ^2, p	I²	N¹ = 96,811	χ^2, p	I²
At treatment start (up to 7 days before episode exposure start date)	22,076 (21.2)	1,883.7	99.9	34,498 (25.1)	2,853.1	99.9	26,181 (27.0.0)	2,613.1	99.9
	[1.1 – 86.8]	<0.001		[1.5 – 87.9]	<0.001		[1.8 – 88.2]	<0.001	
At treatment start (up to 30 days before episode exposure start date)	45,879 (44.1)	4,348.1	100	65,725 (47.7)	5,880.2	100	46,611 (48.1)	4,950.7	100
	[6.9 – 89.4]	<0.001		[8.1 – 90.4]	<0.001		[8.2 – 90.6]	<0.001	
During treatment	N² = 117,788			N² = 152,688			N² = 121,031		
At least one test during treatment episodes	49,753 (42.2)	3,788.4	99.9	71,391 (46.8)	5,528.7	100	60,215 (49.8)	4,627.8	100
	[8.8 – 84.7]	<0.001		[11.4 – 85.7]	<0.001		[15.7 – 84.1]	<0.001	
Monthly during treatment episodes	2,065 (1.8)	127.3	98.5	1,010 (0.7)	70.2	97.3	1,090 (0.9)	90	97.9
	[0.2 – 12.1]	<0.001		[0.0 – 17.5]	<0.001		[0.0 – 20.8]	<0.001	
After treatment	N³ = 93,533			N³ = 121,931			N³ = 81,532		
30 (-/+7) days after treatment stop	3,871 (4.1)	218.6	99.1	5,214 (4.3)	298.6	99.3	3,130 (3.8)	249.4	99.2
	[0.8 – 19.6]	<0.001		[0.8 – 19.1]	<0.001		[0.7 – 19.4]	<0.001	

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

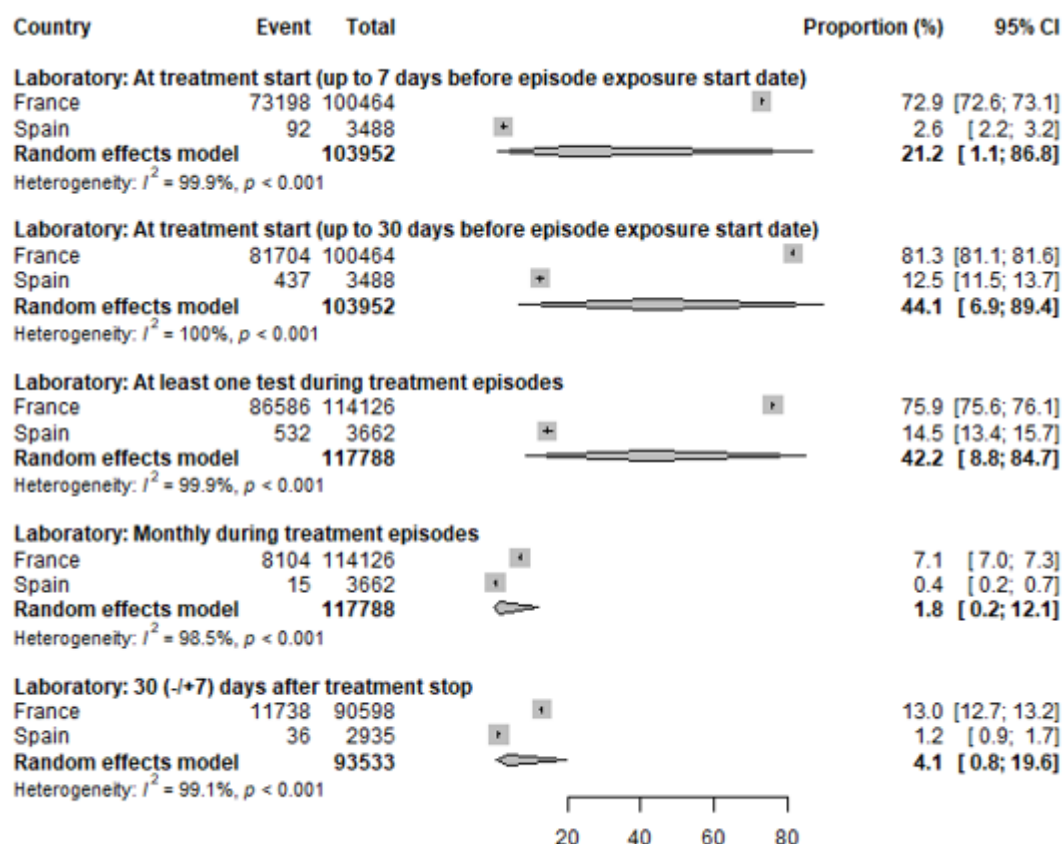


Figure 41 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the pre-referral period excluding Germany; analysis based on the episode level

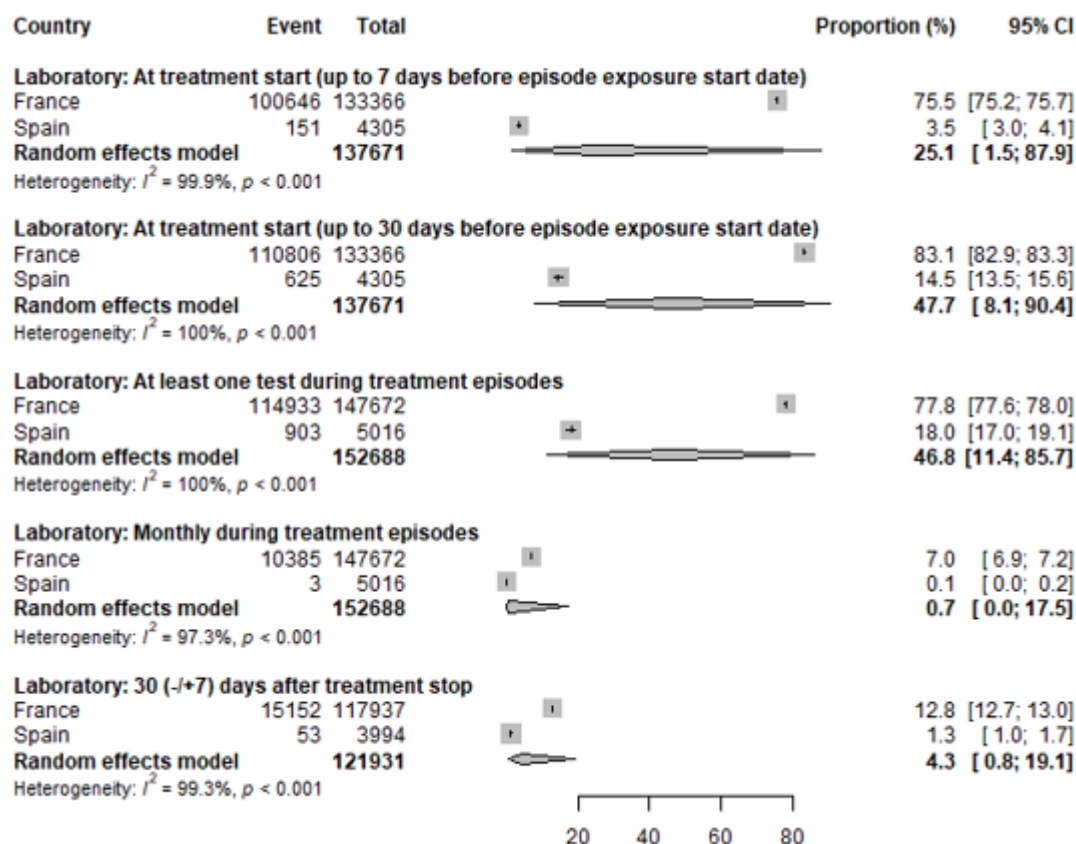


Figure 42 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-referral period excluding Germany; analysis based on the episode level

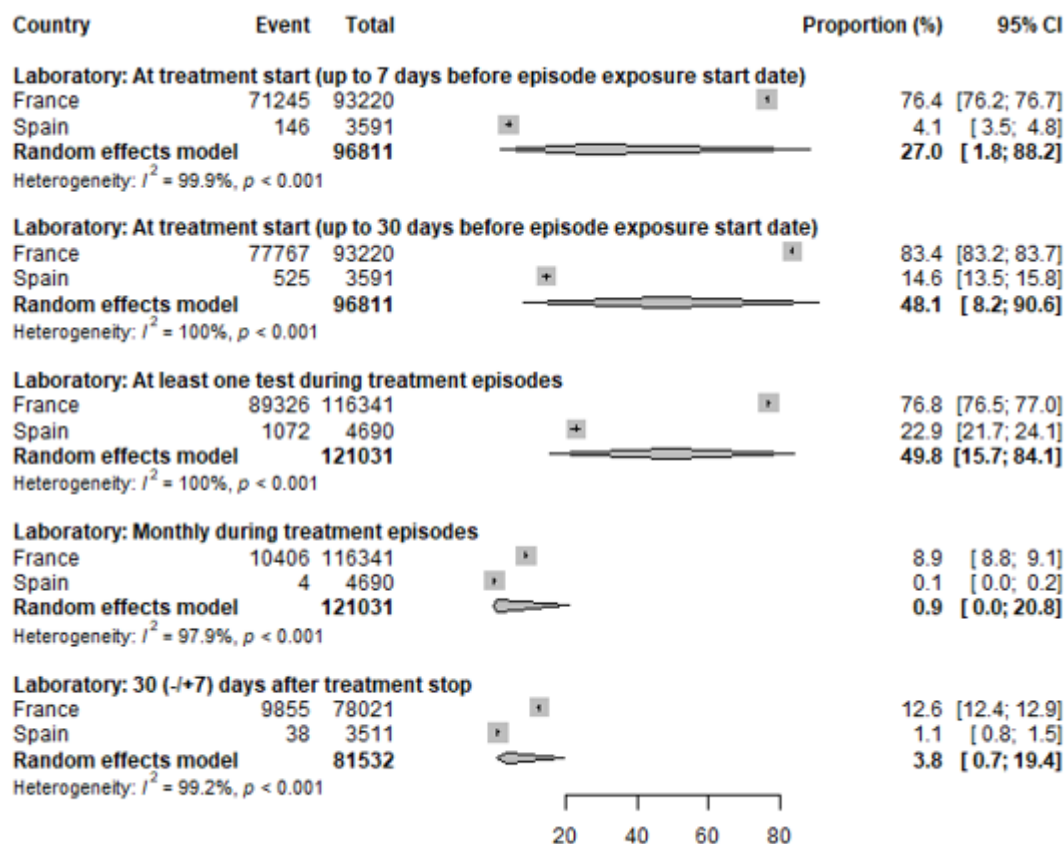


Figure 43 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-implementation period excluding Germany; analysis based on the episode level

Table 80 Meta-analysis; prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes excluding Spain; analysis based on the episode level

	Pre-implementation period						Post-implementation period		
	Pre-referral			Post-referral					
Laboratory pregnancy tests performed: n (%) [95% CI of %]									
Prior to treatment	N¹ = 102,883			N¹ = 137,726			N¹ = 94,925		
At treatment start (up to 7 days before episode exposure start date)	45,822 (44.5)	χ^2 , p	I ²	66,010 (47.9)	χ^2 , p	I ²	48,802 (51.4)	χ^2 , p	I ²
	[13.1 – 81.1]	<0.001		[14.7 – 83.1]	<0.001		[18.3 – 83.3]	<0.001	
At treatment start (up to 30 days before episode exposure start date)	53,209 (51.7)	3,062	99.9	75,697 (55.0)	5,797	100	55,022 (58.0)	2,217.8	99.9
	[13.3 – 88.2]	<0.001		[15.0 – 89.4]	<0.001		[18.6 – 89.3]	<0.001	
During treatment	N² = 116,821			N² = 152,331			N² = 118,348		
At least one test during treatment episodes	61,346 (52.5)	2,314.4	99.9	83,491 (54.8)	4,221.7	100	65,741 (55.5)	1,623.9	99.9
	[20.6 – 82.5]	<0.001		[21.7 – 84.1]	<0.001		[24.5 – 82.8]	<0.001	
Monthly during treatment episodes	8,294 (7.1)	0	0	10,730 (7)	1	0	10,588 (8.9)	0	0
	[7.0 – 7.2]	0.92		[6.9 – 7.2]	0.33		[8.8 – 9.1]	0.85	
After treatment	N³ = 92,722			N³ = 121,962			N³ = 79,277		
30 (-/+7) days after treatment stop	5,803 (6.3)	153.9	98.7	8,167 (6.7)	270.3	99.3	5,106 (6.4)	85.4	97.7
	[2.1 – 17.1]	<0.001		[2.6 – 16.4]	<0.001		[2.3 – 16.5]	<0.001	

CI, confidence interval; N or n, number of episodes

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Reported % is the maximum likelihood estimate of the median proportion from a logistic-normal random effects model.

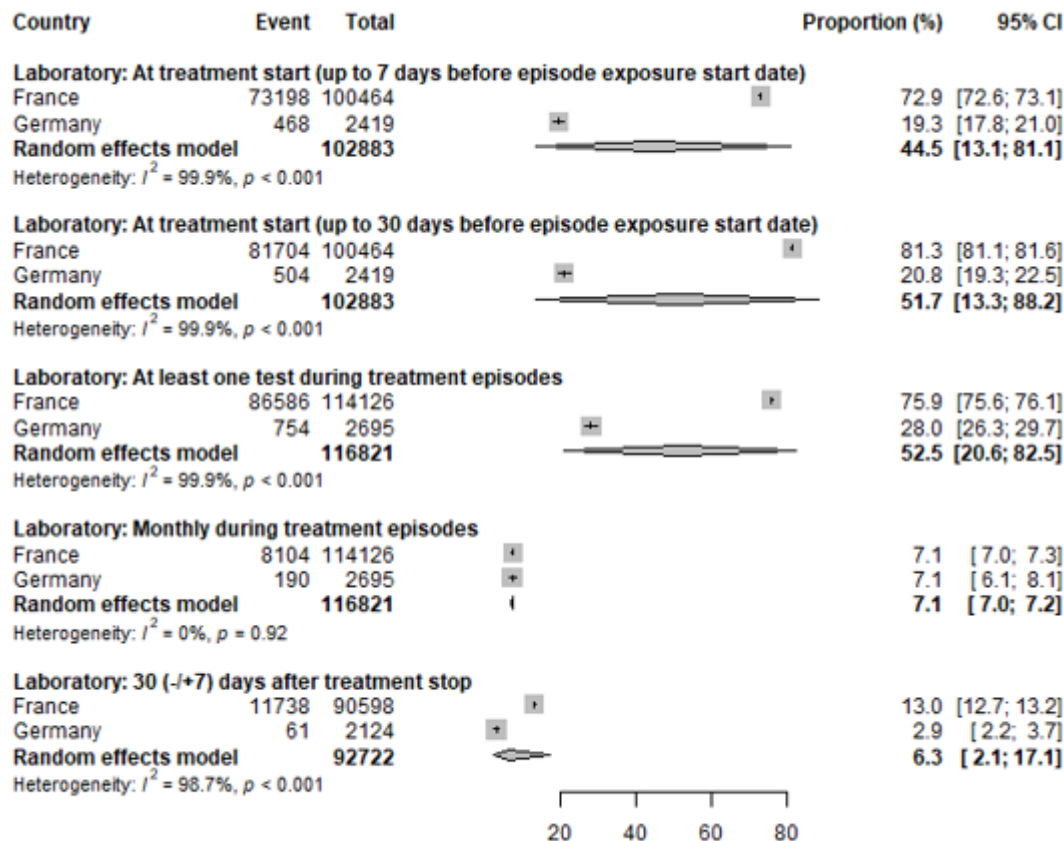


Figure 44 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the pre-referral period excluding Spain; analysis based on the episode level

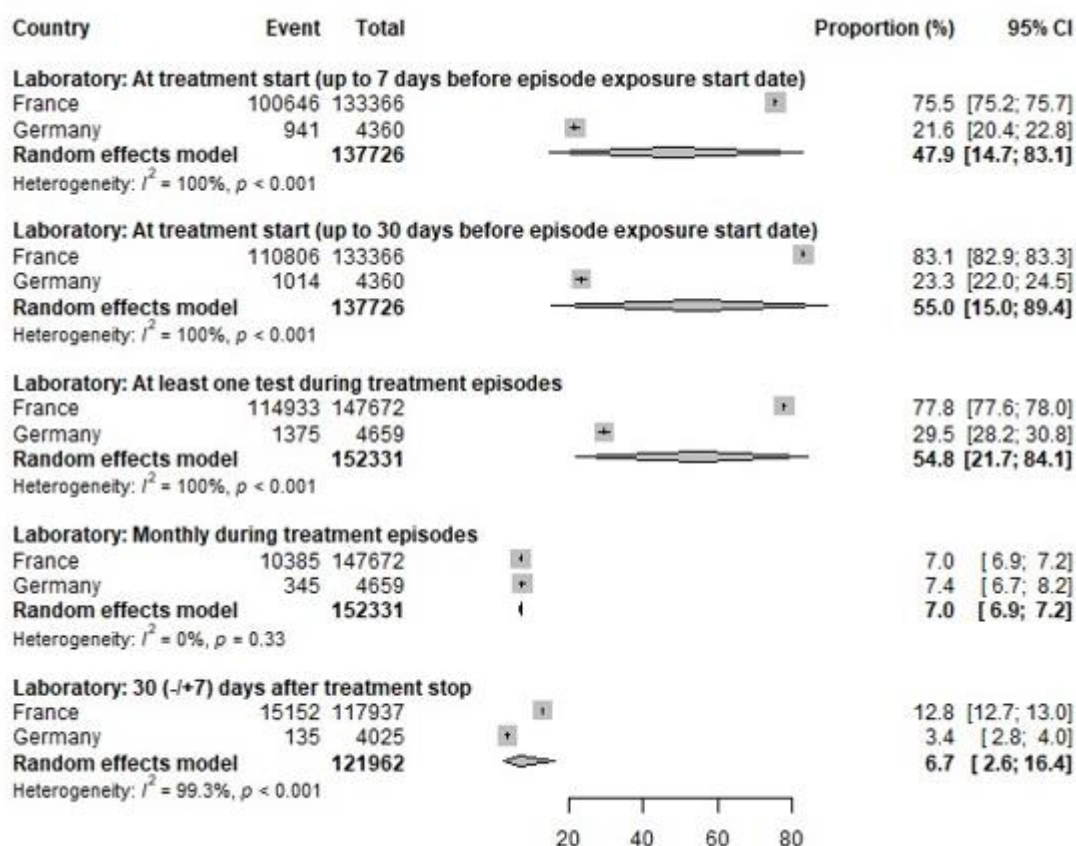


Figure 45 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-referral period excluding Spain; analysis based on the episode level

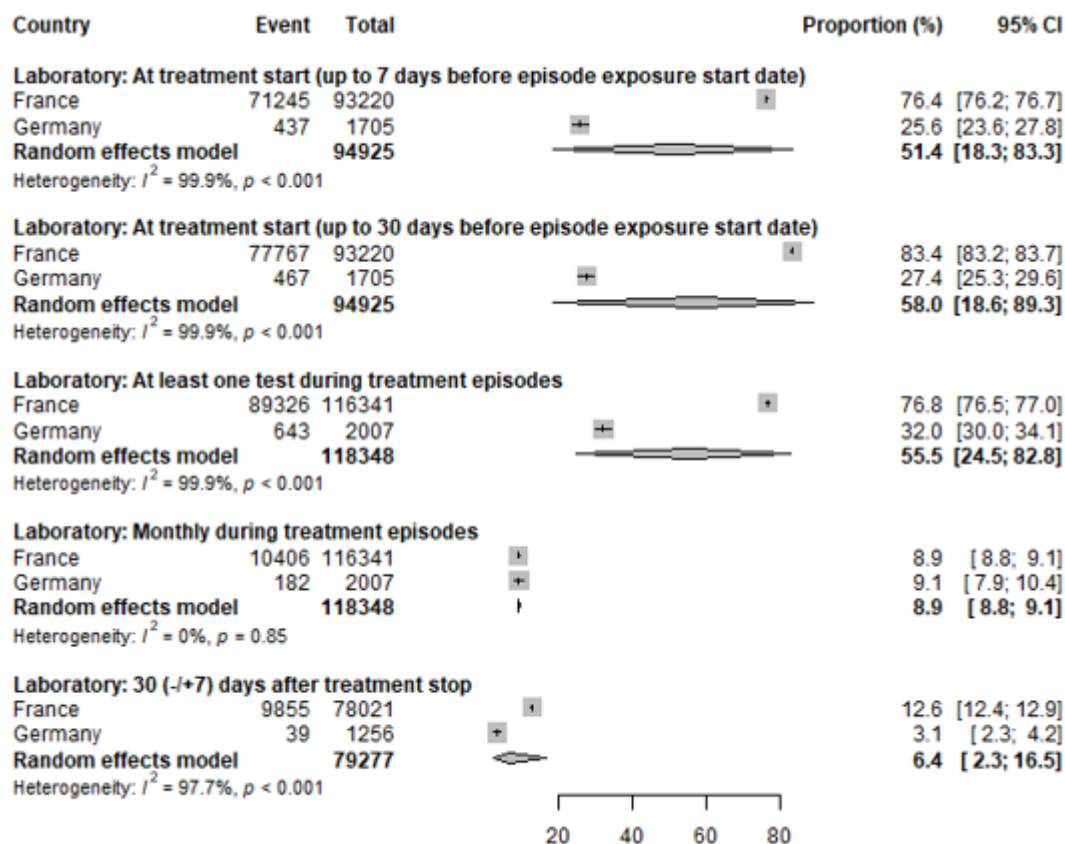


Figure 46 Forest plot for prescribing patterns: laboratory pregnancy tests before, during and after treatment episodes with oral retinoids for the post-implementation period excluding Spain; analysis based on the episode level

11.4.8 Trends in the Prescribing Practice of Oral Retinoids with Respect to Measures of the PPP - Interrupted Time Series Analysis

The ITS analysis was performed to identify trends in the prescribing patterns of contraceptives and performance of laboratory pregnancy tests before and during treatment with oral retinoids. Beta coefficients are on a logarithmic scale.

11.4.8.1 France

11.4.8.1.1 Trends in Contraceptives Use Before and During Treatment Episodes with Oral Retinoids

In the pre-referral period, there was an increasing trend in contraceptive use prior to oral retinoid treatment start ($\beta_1 = 0.009$, $p < 0.001$). After the pre-referral period, there was a statistically significant level-change, i.e. the location of the slope ($\beta_2 = -0.034$, $p = 0.007$). There was a statistically significant change in slope from the pre- to the post-referral period ($\beta_3 = -0.008$, $p < 0.001$), meaning that the proportion of treatment episodes with records of contraceptive use before treatment start increased at a slower rate over the post-referral compared to the pre-referral period. The quarterly increase in the proportion of treatment episodes with records of contraceptive use during the post-referral period was statistically significant ($\beta_1 + \beta_3 = 0.001$, $p = 0.034$). Between the end of the post-referral period and the beginning of the post-implementation period there was no significant change in the slope. The change in slope from the post-referral to the post-implementation period was significant ($\beta_5 = -0.002$, $p < 0.001$) and the slope during the post-implementation period was significant as well ($\beta_1 + \beta_3 + \beta_5 = -0.001$, $p < 0.001$). The ITS results are displayed in

Table 81. Figure 47 shows the observed point estimates and ITS fit for records of contraceptive use before treatment start with oral retinoids.

Table 81 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use before treatment start with oral retinoids; in France

Country: France			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-31.08.2014	1,583/4,475 (35.4)		
Time point 2: 01.09.2014-31.10.2014	4,739/13,329 (35.6)		
Time point 3: 01.11.2014-31.12.2014	3,840/10,388 (37.0)		
Time point 4: 01.01.2015-28.02.2015	3,594/9,585 (37.5)		
Time point 5: 01.03.2015-30.04.2015	2,856/7,639 (37.4)		
Time point 6: 01.05.2015-01.06.2015	1,952/5,167 (37.8)		
Time point 7: 01.07.2015-31.08.2015	1,766/4,383 (40.3)		
Time point 8: 01.09.2015-31.10.2015	5,370/13,336 (40.3)		
Time point 9: 01.11.2015-31.12.2015	4,227/10,207 (41.4)		
Time point 10: 01.01.2016-28.02.2016	3,707/9,030 (41.1)		
Time point 11: 01.03.2016-30.04.2016	3,108/7,526 (41.3)		
Time point 12: 01.05.2016-01.06.2016	2,267/5,312 (42.7)		
Time point 13: 01.07.2016-31.08.2016		1,787/4,410 (40.5)	
Time point 14: 01.09.2016-31.10.2016		5,224/12,609 (41.4)	
Time point 15: 01.11.2016-31.12.2016		4,309/10,112 (42.6)	
Time point 16: 01.01.2017-28.02.2017		3,823/9,063 (42.2)	
Time point 17: 01.03.2017-30.04.2017		2,950/7,059 (41.8)	
Time point 18: 01.05.2017-01.06.2017		2,162/5,006 (43.2)	
Time point 19: 01.07.2017-31.08.2017		1,924/4,504 (42.7)	
Time point 20: 01.09.2017-31.10.2017		5,409/12,964 (41.7)	
Time point 21: 01.11.2017-31.12.2017		4,163/9,742 (42.7)	
Time point 22: 01.01.2018-28.02.2018		3,878/9,245 (41.9)	
Time point 23: 01.03.2018-30.04.2018		3,071/7,034 (43.7)	
Time point 24: 01.05.2018-01.06.2018		2,080/4,979 (41.8)	
Time point 25: 01.07.2018-31.08.2018		1,951/4,479 (43.6)	
Time point 26: 01.09.2018-31.10.2018		5,317/12,696 (41.9)	
Time point 27: 01.11.2018-31.12.2018		4,253/9,792 (43.4)	
Time point 28: 01.01.2019-28.02.2019		4,038/9,563 (42.2)	
Time point 29: 01.03.2019-30.04.2019			3,120/7,319 (42.6)
Time point 30: 01.05.2019-01.06.2019			2,178/5,104 (42.7)
Time point 31: 01.07.2019-31.08.2019			2,069/4,800 (43.1)
Time point 32: 01.09.2019-31.10.2019			5,492/12,943 (42.4)
Time point 33: 01.11.2019-31.12.2019			4,210/9,826 (42.8)
Time point 34: 01.01.2020-28.02.2020			3,958/9,464 (41.8)
Time point 35: 01.03.2020-30.04.2020			2,292/5,443 (42.1)
Time point 36: 01.05.2020-01.06.2020			2,640/6,505 (40.6)
Time point 37: 01.07.2020-31.08.2020			2,275/5,225 (43.5)
Time point 38: 01.09.2020-31.10.2020			5,930/14,112 (42.0)
Time point 39: 01.11.2020-31.12.2020			5,222/12,416 (42.1)

Model parameters:

Template No.: RWI_TP_EPI0009 Revision 1
Effective Date: 15Jun2018

Reference: RWI_WI_EPI0010

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-1.049	0.005	<0.001
β_1	baseline trend	0.009	0.001	<0.001
β_2	level change by referral (between pre-referral and post-referral period)	-0.034	0.013	0.007
β_3	slope change by referral (between pre-referral and post-referral period)	-0.008	0.001	<0.001
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.001	0.004	0.748
β_5	slope change by implementation (between post-referral period and post-implementation period)	-0.002	0.000	<0.001
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.036	0.015	0.026
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	-0.010	0.001	<0.001
$\beta_1 + \beta_3$	trend within post-referral period	0.001	0.000	0.034
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	-0.001	0.000	<0.001

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020, num, numerator; den, denominator

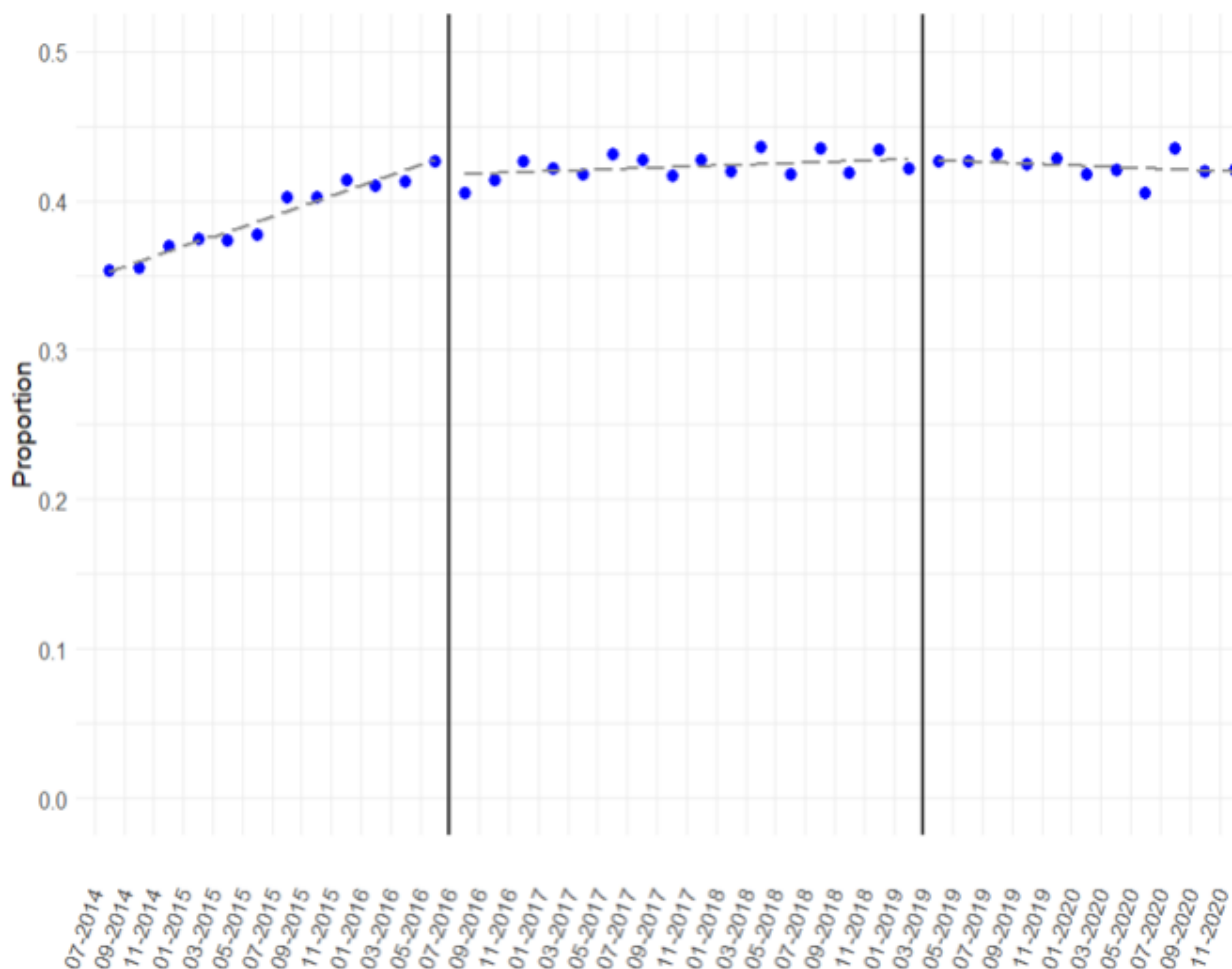


Figure 47 Observed point estimates and interrupted time series fit; for records of contraceptive use before treatment start with oral retinoids; in France

For records of contraceptive use during treatment with oral retinoids there was a significant increasing trend during pre-referral ($\beta_1 = 0.012$, $p < 0.001$). The change in slopes between pre- and post-referral period was significant ($\beta_3 = -0.010$, $p < 0.001$). During the post-referral period the slope was non-significant, as was the slope change between post-referral and post-implementation period. The slope in the post-implementation period was statistically significant with an increasing trend over the period ($\beta_1 + \beta_3 + \beta_5 = 0.006$, $p = 0.001$). In addition, there statistically significant shifts down in the slope between the pre-referral and post-referral period ($\beta_2 = -0.119$, $p = 0.004$), as well as between the post-referral and post-implementation periods ($\beta_4 = -0.090$, $p < 0.001$). The ITS results are displayed in Table 82. Figure 48 shows the observed point estimates and ITS fit for records of contraceptive use during treatment with oral retinoids.

Table 82 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use during treatment with oral retinoids; in France

Country: France			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-31.08.2014	5,121/17,959 (28.5)		
Time point 2: 01.09.2014-31.10.2014	4,469/13,357 (33.5)		
Time point 3: 01.11.2014-31.12.2014	3,496/10,422 (33.5)		
Time point 4: 01.01.2015-28.02.2015	3,297/9,616 (34.3)		
Time point 5: 01.03.2015-30.04.2015	2,826/7,654 (36.9)		
Time point 6: 01.05.2015-01.06.2015	1,958/5,181 (37.8)		
Time point 7: 01.07.2015-31.08.2015	1,741/4,394 (39.6)		
Time point 8: 01.09.2015-31.10.2015	4,978/13,368 (37.2)		
Time point 9: 01.11.2015-31.12.2015	3,838/10,246 (37.5)		
Time point 10: 01.01.2016-28.02.2016	3,366/9,062 (37.1)		
Time point 11: 01.03.2016-30.04.2016	2,905/7,542 (38.5)		
Time point 12: 01.05.2016-01.06.2016	2,190/5,325 (41.1)		
Time point 13: 01.07.2016-31.08.2016		6,415/18,558 (34.6)	
Time point 14: 01.09.2016-31.10.2016		4,743/12,639 (37.5)	
Time point 15: 01.11.2016-31.12.2016		3,821/10,153 (37.6)	
Time point 16: 01.01.2017-28.02.2017		3,417/9,098 (37.6)	
Time point 17: 01.03.2017-30.04.2017		2,741/7,083 (38.7)	
Time point 18: 01.05.2017-01.06.2017		2,068/5,022 (41.2)	
Time point 19: 01.07.2017-31.08.2017		1,821/4,514 (40.3)	
Time point 20: 01.09.2017-31.10.2017		4,916/12,989 (37.8)	
Time point 21: 01.11.2017-31.12.2017		3,701/9,747 (38.0)	
Time point 22: 01.01.2018-28.02.2018		3,531/9,261 (38.1)	
Time point 23: 01.03.2018-30.04.2018		2,856/7,048 (40.5)	

Country: France			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 24: 01.05.2018-01.06.2018		2,064/4,990 (41.4)	
Time point 25: 01.07.2018-31.08.2018		1,881/4,483 (42.0)	
Time point 26: 01.09.2018-31.10.2018		4,841/12,705 (38.1)	
Time point 27: 01.11.2018-31.12.2018		3,703/9,808 (37.8)	
Time point 28: 01.01.2019-28.02.2019		3,550/9,574 (37.1)	
Time point 29: 01.03.2019-30.04.2019			10,567/30,348 (34.8)
Time point 30: 01.05.2019-01.06.2019			2,082/5,122 (40.6)
Time point 31: 01.07.2019-31.08.2019			1,903/4,804 (39.6)
Time point 32: 01.09.2019-31.10.2019			5,057/12,957 (39.0)
Time point 33: 01.11.2019-31.12.2019			3,755/9,846 (38.1)
Time point 34: 01.01.2020-28.02.2020			3,663/9,475 (38.7)
Time point 35: 01.03.2020-30.04.2020			2,120/5,454 (38.9)
Time point 36: 01.05.2020-01.06.2020			2,521/6,521 (38.7)
Time point 37: 01.07.2020-31.08.2020			2,088/5,241 (39.8)
Time point 38: 01.09.2020-31.10.2020			5,427/14,138 (38.4)
Time point 39: 01.11.2020-31.12.2020			5,188/12,435 (41.7)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-1.176	0.022	<0.001
β_1	baseline trend	0.012	0.002	<0.001
β_2	level change by referral (between pre-referral and post-referral period)	-0.119	0.041	0.004
β_3	slope change by referral (between pre-referral and post-referral period)	-0.010	0.002	<0.001
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.090	0.021	<0.001
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.004	0.003	0.183
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.209	0.050	<0.001
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	-0.006	0.002	0.011
$\beta_1 + \beta_3$	trend within post-referral period	0.002	0.002	0.418
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.006	0.002	0.001

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020
num, numerator; den, denominator

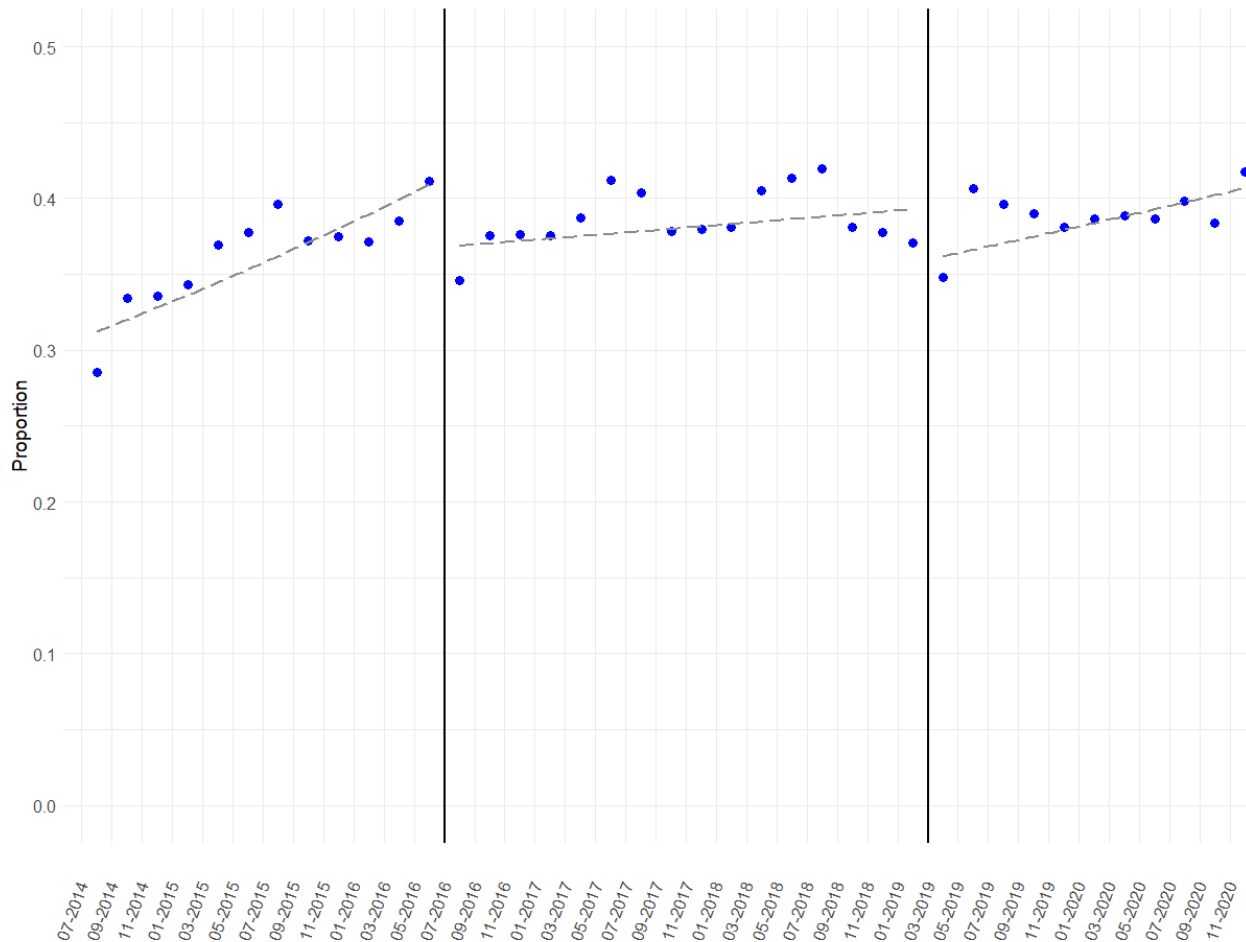


Figure 48 Observed point estimates and interrupted time series fit; for records of contraceptive use during treatment with oral retinoids; in France

11.4.8.1.2 Trends in Laboratory Pregnancy Testing Before and Monthly During Treatment Episodes with Oral Retinoids

The ITS analysis showed no significant level and slope changes for laboratory pregnancy testing before treatment start with oral retinoids from the pre- to the post-referral period. With the exception of the change in slope from post-referral to post-implementation ($\beta_5 = 0.004$, $p = 0.048$) no other level and slope changes from post-referral to post-implementation period and from pre-referral to post-implementation period were significant. In addition, the slopes during the first two study periods of the study were virtually flat and not statistically different than zero. The slope in the post-implementation period was significant ($\beta_1 + \beta_3 + \beta_5 = 0.002$, $p = 0.038$). The ITS results are displayed in Table 83. Figure 49 shows the observed point estimates and ITS fit for laboratory pregnancy tests before treatment start with oral retinoids in France.

Table 83 Interrupted time series analysis; point estimates and parameter estimates; for pregnancy testing before treatment start with oral retinoids; in France

Country: France			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-31.08.2014	2,925/4,476 (65.3)		
Time point 2: 01.09.2014-31.10.2014	10,252/13,337 (76.9)		
Time point 3: 01.11.2014-31.12.2014	7,698/10,403 (74.0)		
Time point 4: 01.01.2015-28.02.2015	6,979/9,600 (72.7)		
Time point 5: 01.03.2015-30.04.2015	5,359/7,643 (70.1)		
Time point 6: 01.05.2015-01.06.2015	3,365/5,170 (65.1)		
Time point 7: 01.07.2015-31.08.2015	3,002/4,387 (68.4)		
Time point 8: 01.09.2015-31.10.2015	10,446/13,342 (78.3)		
Time point 9: 01.11.2015-31.12.2015	7,679/10,219 (75.1)		
Time point 10: 01.01.2016-28.02.2016	6,447/9,042 (71.3)		
Time point 11: 01.03.2016-30.04.2016	5,409/7,529 (71.8)		
Time point 12: 01.05.2016-01.06.2016	3,637/5,316 (68.4)		
Time point 13: 01.07.2016-31.08.2016		3,087/4,413 (70.0)	
Time point 14: 01.09.2016-31.10.2016		9,890/12,620 (78.4)	
Time point 15: 01.11.2016-31.12.2016		7,676/10,132 (75.8)	
Time point 16: 01.01.2017-28.02.2017		6,879/9,078 (75.8)	
Time point 17: 01.03.2017-30.04.2017		5,158/7,070 (73.0)	
Time point 18: 01.05.2017-01.06.2017		3,388/5,010 (67.6)	
Time point 19: 01.07.2017-31.08.2017		3,147/4,509 (69.8)	
Time point 20: 01.09.2017-31.10.2017		10,292/12,975 (79.3)	
Time point 21: 01.11.2017-31.12.2017		7,537/9,744 (77.4)	
Time point 22: 01.01.2018-28.02.2018		7,037/9,250 (76.1)	
Time point 23: 01.03.2018-30.04.2018		5,107/7,041 (72.5)	

Country: France			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 24: 01.05.2018-01.06.2018		3,438/4,984 (69.0)	
Time point 25: 01.07.2018-31.08.2018		3,164/4,481 (70.6)	
Time point 26: 01.09.2018-31.10.2018		10,153/12,697 (80.0)	
Time point 27: 01.11.2018-31.12.2018		7,456/9,794 (76.1)	
Time point 28: 01.01.2019-28.02.2019		7,237/9,568 (75.6)	
Time point 29: 01.03.2019-30.04.2019			5,346/7,323 (73.0)
Time point 30: 01.05.2019-01.06.2019			3,558/5,110 (69.6)
Time point 31: 01.07.2019-31.08.2019			3,396/4,802 (70.7)
Time point 32: 01.09.2019-31.10.2019			10,254/12,950 (79.2)
Time point 33: 01.11.2019-31.12.2019			7,671/9,832 (78.0)
Time point 34: 01.01.2020-28.02.2020			7,302/9,466 (77.1)
Time point 35: 01.03.2020-30.04.2020			3,814/5,446 (70.0)
Time point 36: 01.05.2020-01.06.2020			4,768/6,514 (73.2)
Time point 37: 01.07.2020-31.08.2020			3,740/5,230 (71.5)
Time point 38: 01.09.2020-31.10.2020			11,428/14,124 (80.9)
Time point 39: 01.11.2020-31.12.2020			9,968/12,423 (80.2)

Model parameters:				
Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-0.310	0.022	<0.001
β_1	baseline trend	-0.001	0.002	0.736
β_2	level change by referral (between pre-referral and post-referral period)	0.035	0.033	0.294
β_3	slope change by referral (between pre-referral and post-referral period)	0.001	0.002	0.601
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.044	0.031	0.158
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.004	0.002	0.048
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.009	0.046	0.976
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	0.005	0.002	0.098
$\beta_1 + \beta_3$	trend within post-referral period	0.000	0.001	0.939
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.004	0.002	0.038

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020
num, numerator; den, denominator

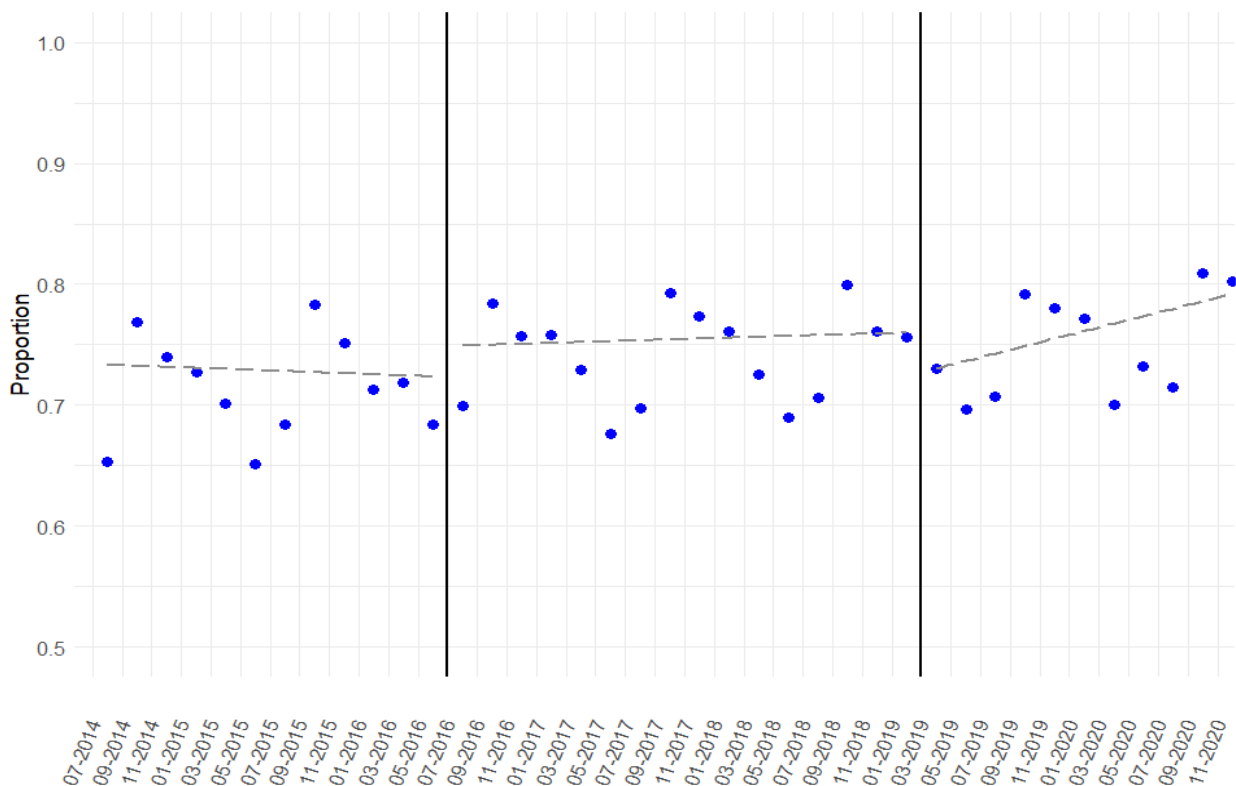


Figure 49 Observed point estimates and interrupted time series fit; for pregnancy testing before treatment start with oral retinoids (up to 7 days before start date of oral retinoid prescription); in France

With respect to monthly laboratory pregnancy testing during treatment, there was no increasing trend in testing ($\beta_1 = 0.019$ $p = 0.07$) during the pre-referral period. The level change between pre- and post-referral was marginally significant ($\beta_2 = -0.374$, $p = 0.053$). The change in slope from the pre- to the post-referral was not statistically significant, nor was the slope during the post-referral. There was a statistically significant level change from the post-referral to post-implementation period ($\beta_4 = -0.656$, $p = 0.001$). Additionally, there was a statistically significant change in the slope from the post-referral to post-implementation period ($\beta_5 = 0.058$, $p < 0.001$) and a significantly increasing slope during the post-implementation period ($\beta_1 + \beta_3 + \beta_5 = 0.066$, $p < 0.001$). The ITS results are displayed in Table 84. Figure 50 shows the observed point estimates and ITS fit for prescriptions for monthly laboratory pregnancy testing during treatment with oral retinoids.

Table 84 Interrupted time series analysis; point estimates and parameter estimates; for monthly pregnancy testing during treatment with oral retinoids; in France

Country: France			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-31.08.2014	778/17,959 (4.3)		
Time point 2: 01.09.2014-31.10.2014	902/13,357 (6.8)		
Time point 3: 01.11.2014-31.12.2014	713/10,422 (6.8)		
Time point 4: 01.01.2015-28.02.2015	726/9,616 (7.5)		
Time point 5: 01.03.2015-30.04.2015	639/7,654 (8.3)		
Time point 6: 01.05.2015-01.06.2015	512/5,181 (9.9)		
Time point 7: 01.07.2015-31.08.2015	362/4,394 (8.2)		
Time point 8: 01.09.2015-31.10.2015	957/13,368 (7.2)		
Time point 9: 01.11.2015-31.12.2015	707/10,246 (6.9)		
Time point 10: 01.01.2016-28.02.2016	689/9,062 (7.6)		
Time point 11: 01.03.2016-30.04.2016	617/7,542 (8.2)		
Time point 12: 01.05.2016-01.06.2016	502/5,325 (9.4)		
Time point 13: 01.07.2016-31.08.2016		781/18,558 (4.2)	
Time point 14: 01.09.2016-31.10.2016		861/12,639 (6.8)	
Time point 15: 01.11.2016-31.12.2016		655/10,153 (6.5)	
Time point 16: 01.01.2017-28.02.2017		696/9,098 (7.6)	
Time point 17: 01.03.2017-30.04.2017		627/7,083 (8.9)	
Time point 18: 01.05.2017-01.06.2017		519/5,022 (10.3)	
Time point 19: 01.07.2017-31.08.2017		382/4,514 (8.5)	
Time point 20: 01.09.2017-31.10.2017		845/12,989 (6.5)	
Time point 21: 01.11.2017-31.12.2017		635/9,747 (6.5)	
Time point 22: 01.01.2018-28.02.2018		706/9,261 (7.6)	
Time point 23: 01.03.2018-30.04.2018		608/7,048 (8.6)	
Time point 24: 01.05.2018-01.06.2018		491/4,990 (9.8)	
Time point 25: 01.07.2018-31.08.2018		368/4,483 (8.2)	
Time point 26: 01.09.2018-31.10.2018		865/12,705 (6.8)	
Time point 27: 01.11.2018-31.12.2018		598/9,808 (6.1)	
Time point 28: 01.01.2019-28.02.2019		748/9,574 (7.8)	
Time point 29: 01.03.2019-30.04.2019			1,258/30,348 (4.1)
Time point 30: 01.05.2019-01.06.2019			532/5,122 (10.4)
Time point 31: 01.07.2019-31.08.2019			378/4,804 (7.9)
Time point 32: 01.09.2019-31.10.2019			846/12,957 (6.5)
Time point 33: 01.11.2019-31.12.2019			667/9,846 (6.8)
Time point 34: 01.01.2020-28.02.2020			820/9,475 (8.7)
Time point 35: 01.03.2020-30.04.2020			410/5,454 (7.5)
Time point 36: 01.05.2020-01.06.2020			590/6,521 (9.0)
Time point 37: 01.07.2020-31.08.2020			430/5,241 (8.2)
Time point 38: 01.09.2020-31.10.2020			1,736/14,138 (12.3)
Time point 39: 01.11.2020-31.12.2020			2,739/12,435 (22.0)

Country: France				
		Pre-referral period	Post-referral period	Post-implementation period
		num / den (rate)	num / den (rate)	num / den (rate)
Model parameters:				
Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-2.848	0.134	<0.001
β_1	baseline trend	0.019	0.010	0.07
β_2	level change by referral (between pre-referral and post-referral period)	-0.374	0.186	0.053
β_3	slope change by referral (between pre-referral and post-referral period)	-0.011	0.012	0.37
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.656	0.182	0.001
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.058	0.011	<0.001
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-1.029	0.283	0.001
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	0.048	0.013	0.001
$\beta_1 + \beta_3$	trend within post-referral period	0.008	0.006	0.522
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.066	0.009	<0.001

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020
num, numerator; den, denominator

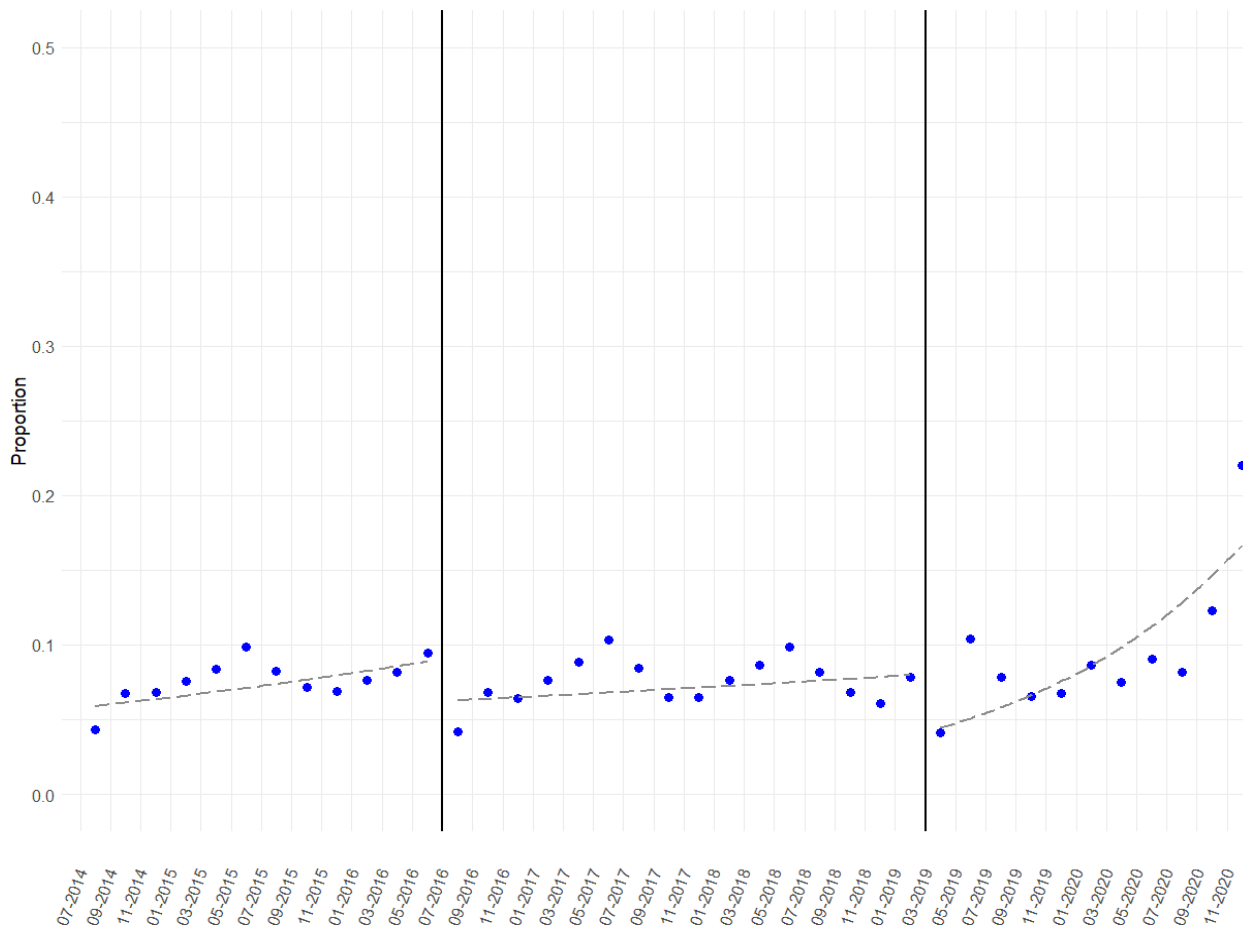


Figure 50 Observed point estimates and interrupted time series fit; for monthly pregnancy testing during treatment with oral retinoids; in France

11.4.8.2 Germany

11.4.8.2.1 Trends in Contraceptives Use Before and During Treatment Episodes with Oral Retinoids

Prior to the treatment start, there was no significant trend in contraceptive use. There was a statistically significant level-change between the pre- and post-referral period ($\beta_2 = -0.185$, $p = 0.028$). However, the change in slope between these periods was not statistically significant. There was a statistically significant increase in slope during the post-referral period ($\beta_1 + \beta_3 = 0.008$, $p = 0.02$). Between the post-referral and post-implementation period there was a significant level change, i.e. a decreasing shift in the slope ($\beta_4 = -0.368$, $p = 0.001$). The change in slope from the post-referral to the post-implementation period was statistically significant ($\beta_5 = 0.049$, $p < 0.001$) and the slope during the post-implementation phase continued on a significant upward trend ($\beta_1 + \beta_3 + \beta_5 = 0.057$, $p < 0.001$). The ITS results are displayed in Table 85. Figure 51 shows the observed point estimates and ITS fit for prescriptions for records of contraceptive use before treatment start with oral retinoids in Germany.

Table 85 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use before treatment start with oral retinoids; in Germany

Country: Germany			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	22/283 (7.8)		
Time point 2: 01.10.2014-31.12.2014	24/326 (7.4)		
Time point 3: 01.01.2015-31.03.2015	38/326 (11.7)		
Time point 4: 01.04.2015-30.06.2015	22/272 (8.1)		
Time point 5: 01.07.2015-30.09.2015	19/270 (7.0)		
Time point 6: 01.10.2015-31.12.2015	31/312 (9.9)		
Time point 7: 01.01.2016-31.03.2016	21/306 (6.9)		
Time point 8: 01.04.2016-30.06.2016	29/311 (9.3)		
Time point 9: 01.07.2016-30.09.2016		18/286 (6.3)	
Time point 10: 01.10.2016-31.12.2016		31/345 (9.0)	
Time point 11: 01.01.2017-31.03.2017		26/359 (7.2)	
Time point 12: 01.04.2017-30.06.2017		24/297 (8.1)	
Time point 13: 01.07.2017-30.09.2017		22/320 (6.9)	
Time point 14: 01.10.2017-31.12.2017		31/371 (8.4)	
Time point 15: 01.01.2018-31.03.2018		31/359 (8.6)	

Time point 16: 01.04.2018-30.06.2018	27/301 (9.0)	
Time point 17: 01.07.2018-30.09.2018	29/310 (9.4)	
Time point 18: 01.10.2018-31.12.2018	29/375 (7.7)	
Time point 19: 01.01.2019-31.03.2019	44/391 (11.3)	
Time point 20: 01.04.2019-30.06.2019	31/309 (10.0)	
Time point 21: 01.07.2019-30.09.2019	26/306 (8.5)	
Time point 22: 01.10.2019-31.12.2019		30/358 (8.4)
Time point 23: 01.01.2020-31.03.2020		29/337 (8.6)
Time point 24: 01.04.2020-30.06.2020		31/305 (10.2)
Time point 25: 01.07.2020-30.09.2020		34/315 (10.8)
Time point 26: 01.10.2020-31.12.2020		63/385 (16.4)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-2.468	0.107	<0.001
β_1	baseline trend	0.001	0.006	0.885
β_2	level change by referral (between pre-referral and post-referral period)	-0.185	0.084	0.028
β_3	slope change by referral (between pre-referral and post-referral period)	0.008	0.006	0.222
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.368	0.113	0.001
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.049	0.008	<0.001
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.553	0.162	0.001
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	0.056	0.010	<0.001
$\beta_1 + \beta_3$	trend within post-referral period	0.008	0.003	0.002
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.057	0.009	<0.001

Pre-implementation period = pre-referral period 07/2014-06/2016 + post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

num, numerator; den, denominator

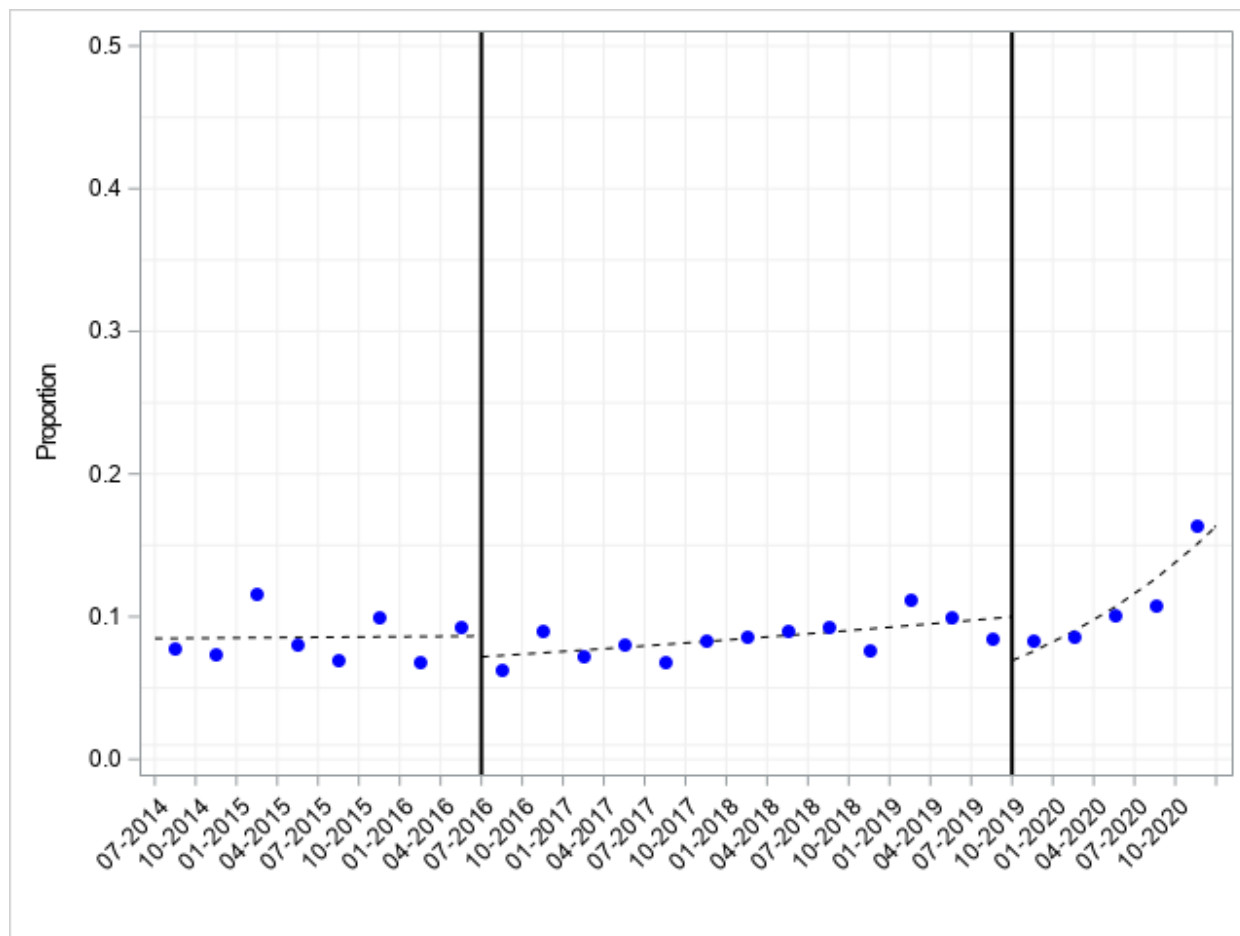


Figure 51 Observed point estimates and interrupted time series fit; for records of contraceptive use before treatment start with oral retinoids; in Germany

For records of contraceptive use during treatment with oral retinoids there was no significant trend during the pre-referral period. The change in slope between pre- and post-referral period was not significant. During the post-referral period the slope showed a marginally significant increase ($\beta_1 + \beta_3 = 0.011$, $p = 0.054$). There was a statistically significant change in the slope between the post-referral and post-implementation period ($\beta_5 = 0.046$, $p = 0.035$). The slope increase in the post-implementation period was statistically significant as well ($\beta_1 + \beta_3 + \beta_5 = 0.057$, $p = 0.003$). The change in levels was marginally significant between the pre-referral to post-referral period ($\beta_2 = -0.445$, $p = 0.057$) and not significant between post-referral and post-implementation period. The ITS results are displayed in Table 86. Figure 52 shows the observed point estimates and ITS fit for records of contraceptive use during treatment with oral retinoids.

Table 86 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use during treatment with oral retinoids; in Germany

Country: Germany			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	38/552 (6.9)		
Time point 2: 01.10.2014-31.12.2014	15/328 (4.6)		
Time point 3: 01.01.2015-31.03.2015	27/327 (8.3)		
Time point 4: 01.04.2015-30.06.2015	15/274 (5.5)		
Time point 5: 01.07.2015-30.09.2015	14/271 (5.2)		
Time point 6: 01.10.2015-31.12.2015	28/314 (8.9)		
Time point 7: 01.01.2016-31.03.2016	18/313 (5.8)		
Time point 8: 01.04.2016-30.06.2016	34/316 (10.8)		
Time point 9: 01.07.2016-30.09.2016		37/573 (6.5)	
Time point 10: 01.10.2016-31.12.2016		24/346 (6.9)	
Time point 11: 01.01.2017-31.03.2017		21/369 (5.7)	
Time point 12: 01.04.2017-30.06.2017		18/301 (6.0)	
Time point 13: 01.07.2017-30.09.2017		19/321 (5.9)	
Time point 14: 01.10.2017-31.12.2017		21/372 (5.7)	
Time point 15: 01.01.2018-31.03.2018		26/364 (7.1)	
Time point 16: 01.04.2018-30.06.2018		19/303 (6.3)	
Time point 17: 01.07.2018-30.09.2018		23/311 (7.4)	
Time point 18: 01.10.2018-31.12.2018		19/377 (5.0)	
Time point 19: 01.01.2019-31.03.2019		31/401 (7.7)	
Time point 20: 01.04.2019-30.06.2019		30/314 (9.6)	
Time point 21: 01.07.2019-30.09.2019		34/307 (11.1)	
Time point 22: 01.10.2019-31.12.2019			52/658 (7.9)
Time point 23: 01.01.2020-31.03.2020			26/339 (7.7)
Time point 24: 01.04.2020-30.06.2020			22/305 (7.2)

Time point 25: 01.07.2020-30.09.2020 24/317 (7.6)
Time point 26: 01.10.2020-31.12.2020 65/388 (16.8)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-2.850	0.171	< 0.001
β_1	baseline trend	0.017	0.012	0.184
β_2	level change by referral (between pre-referral and post-referral period)	-0.445	0.220	0.057
β_3	slope change by referral (between pre-referral and post-referral period)	-0.005	0.014	0.697
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.332	0.220	0.148
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.046	0.020	0.035
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.777	0.338	0.022
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	0.040	0.023	0.077
$\beta_1 + \beta_3$	trend within post-referral period	0.011	0.006	0.054
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.057	0.019	0.003

Pre-implementation period = pre-referral period 07/2014-06/2016 + post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

num, numerator; den, denominator

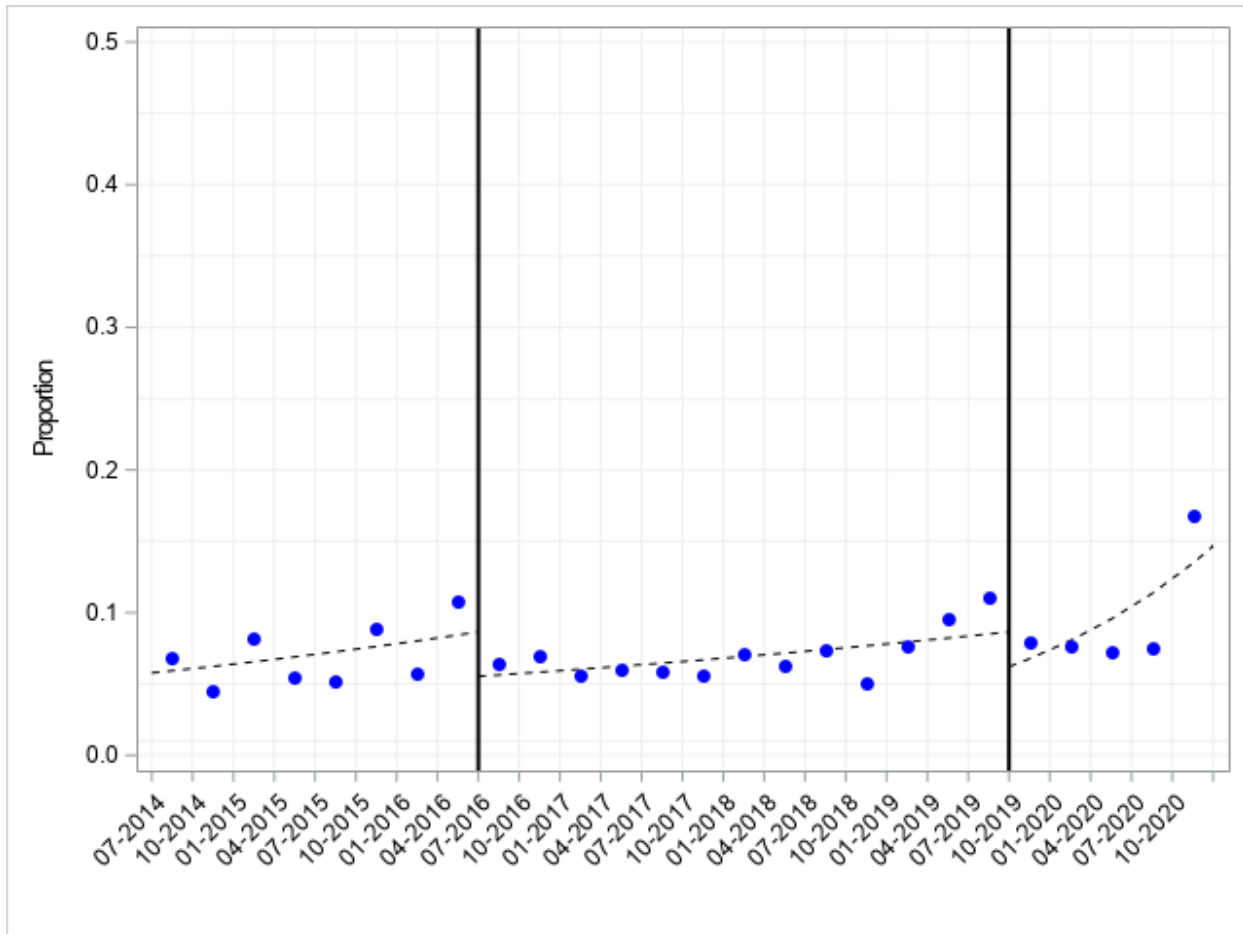


Figure 52 Observed point estimates and interrupted time series fit; for records of contraceptive use during treatment with oral retinoids; in Germany

11.4.8.2.2 Trends in Laboratory Pregnancy Testing Before and Monthly During Treatment Episodes with Oral Retinoids

The ITS analysis showed no significant level and slope changes for laboratory pregnancy testing before treatment start with oral retinoids from the pre- to the post-referral period. Furthermore, no other level and slope changes from post-referral to post-implementation period and from pre-referral to post-implementation period were significant. In addition, the slopes during all 3 periods of the study were virtually flat and not significantly different from zero. The ITS results are displayed in Table 87. Figure 53 shows the observed point estimates and ITS fit for laboratory pregnancy tests before treatment start with oral retinoids.

Table 87 Interrupted time series analysis; point estimates and parameter estimates; for pregnancy testing before treatment start with oral retinoids; in Germany

Country: Germany			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num/ den (rate)	num/ den (rate)
Time point 1: 01.07.2014-30.09.2014	45/283 (15.9)		
Time point 2: 01.10.2014-31.12.2014	65/327 (19.9)		
Time point 3: 01.01.2015-31.03.2015	58/327 (17.7)		
Time point 4: 01.04.2015-30.06.2015	57/272 (21.0)		
Time point 5: 01.07.2015-30.09.2015	59/271 (21.8)		
Time point 6: 01.10.2015-31.12.2015	64/313 (20.5)		
Time point 7: 01.01.2016-31.03.2016	63/311 (20.3)		
Time point 8: 01.04.2016-30.06.2016	57/315 (18.1)		
Time point 9: 01.07.2016-30.09.2016		61/286 (21.3)	
Time point 10: 01.10.2016-31.12.2016		73/346 (21.1)	
Time point 11: 01.01.2017-31.03.2017		73/366 (20.0)	
Time point 12: 01.04.2017-30.06.2017		65/299 (21.7)	
Time point 13: 01.07.2017-30.09.2017		61/321 (19.0)	
Time point 14: 01.10.2017-31.12.2017		75/372 (20.2)	
Time point 15: 01.01.2018-31.03.2018		95/362 (26.2)	
Time point 16: 01.04.2018-30.06.2018		66/303 (21.8)	
Time point 17: 01.07.2018-30.09.2018		72/310 (23.2)	
Time point 18: 01.10.2018-31.12.2018		77/376 (20.5)	
Time point 19: 01.01.2019-31.03.2019		94/399 (23.6)	
Time point 20: 01.04.2019-30.06.2019		67/313 (21.4)	
Time point 21: 01.07.2019-30.09.2019		62/307 (20.2)	
Time point 22: 01.10.2019-31.12.2019			94/359 (26.2)
Time point 23: 01.01.2020-31.03.2020			91/337 (27.0)
Time point 24: 01.04.2020-30.06.2020			65/305 (21.3)
Time point 25: 01.07.2020-30.09.2020			85/317 (26.8)
Time point 26: 01.10.2020-31.12.2020			102/387 (26.4)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-1.703	0.094	<0.001
β_1	baseline trend	0.005	0.007	0.456
β_2	level change by referral (between pre-referral and post-referral period)	0.020	0.113	0.857
β_3	slope change by referral (between pre-referral and post-referral period)	-0.003	0.007	0.637
β_4	level change by implementation (between post-referral period and post-implementation period)	0.140	0.116	0.225
β_5	slope change by implementation (between post-referral period and post-implementation period)	-0.001	0.011	0.912
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	0.161	0.175	0.358
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	-0.005	0.013	0.713
$\beta_1 + \beta_3$	trend within post-referral period	0.002	0.003	0.604
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.000	0.011	0.980

Pre-implementation period = pre-referral period 07/2014-06/2016 + post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

num, numerator; den, denominator

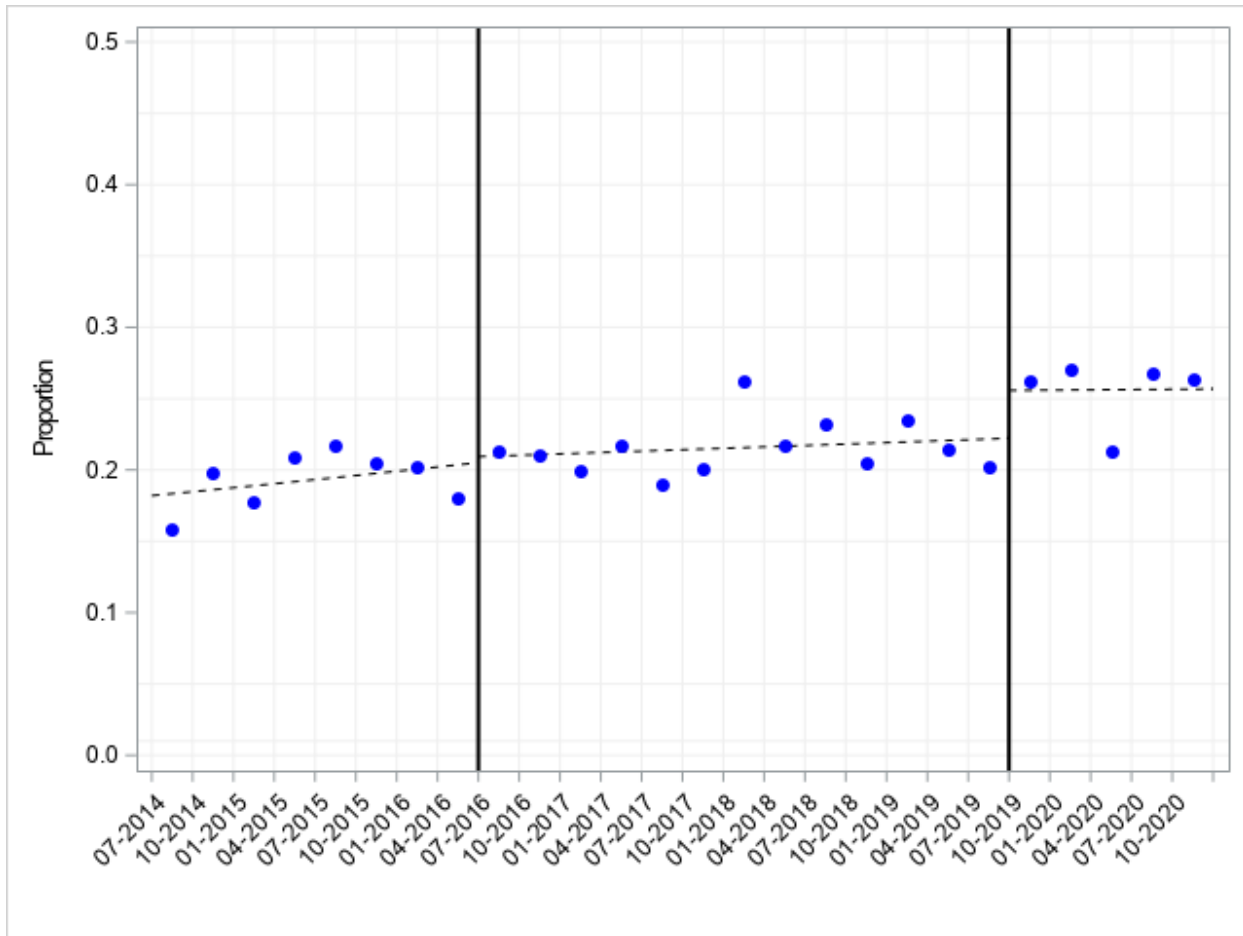


Figure 53 Observed point estimates and interrupted time series fit; for pregnancy testing before treatment start with oral retinoids; in Germany

With respect to monthly laboratory pregnancy testing during treatment, there was an increasing trend in testing during the pre-referral period ($\beta_1 = 0.034$, $p = 0.027$), as well as a level change between pre- and post-referral ($\beta_2 = -0.615$, $p = 0.02$). The change in slope from the pre- to the post-referral period was not statistically significant, however, the slope during the post-referral period was increasing significantly ($\beta_1 + \beta_3 = 0.013$, $p = 0.044$). There was a statistically significant level change from the post-referral to post-implementation period ($\beta_4 = -0.822$, $p = 0.007$). Additionally there was a statistically significant change in the slope from the post-referral to post-implementation period ($\beta_5 = 0.086$, $p = 0.002$) and a significantly increasing slope during the post-implementation period ($\beta_1 + \beta_3 + \beta_5 = 0.099$, $p < 0.001$). The ITS results are displayed in Table 88. Figure 54 shows the observed point estimates and ITS fit for monthly laboratory pregnancy testing during treatment with oral retinoids.

Table 88 Interrupted time series analysis; point estimates and parameter estimates; for monthly pregnancy testing during treatment with oral retinoids; in Germany

Country: Germany			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	33/552 (6.0)		
Time point 2: 01.10.2014-31.12.2014	19/328 (5.8)		
Time point 3: 01.01.2015-31.03.2015	18/327 (5.5)		
Time point 4: 01.04.2015-30.06.2015	19/274 (6.9)		
Time point 5: 01.07.2015-30.09.2015	12/271 (4.4)		
Time point 6: 01.10.2015-31.12.2015	22/314 (7.0)		
Time point 7: 01.01.2016-31.03.2016	23/313 (7.4)		
Time point 8: 01.04.2016-30.06.2016	44/316 (13.9)		
Time point 9: 01.07.2016-30.09.2016		41/573 (7.2)	
Time point 10: 01.10.2016-31.12.2016		19/346 (5.5)	
Time point 11: 01.01.2017-31.03.2017		19/369 (5.2)	
Time point 12: 01.04.2017-30.06.2017		24/301 (8.0)	
Time point 13: 01.07.2017-30.09.2017		20/321 (6.2)	
Time point 14: 01.10.2017-31.12.2017		27/372 (7.3)	
Time point 15: 01.01.2018-31.03.2018		23/364 (6.3)	
Time point 16: 01.04.2018-30.06.2018		22/303 (7.3)	
Time point 17: 01.07.2018-30.09.2018		27/311 (8.7)	
Time point 18: 01.10.2018-31.12.2018		26/377 (6.9)	
Time point 19: 01.01.2019-31.03.2019		30/401 (7.5)	
Time point 20: 01.04.2019-30.06.2019		26/314 (8.3)	
Time point 21: 01.07.2019-30.09.2019		41/307 (13.4)	

Country: Germany

	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 22: 01.10.2019-31.12.2019			35/658 (5.3)
Time point 23: 01.01.2020-31.03.2020			31/339 (9.1)
Time point 24: 01.04.2020-30.06.2020			16/305 (5.3)
Time point 25: 01.07.2020-30.09.2020			23/317 (7.3)
Time point 26: 01.10.2020-31.12.2020			77/388 (19.9)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-3.052	0.208	<0.001
β_1	baseline trend	0.034	0.014	0.027
β_2	level change by referral (between pre-referral and post-referral period)	-0.615	0.243	0.020
β_3	slope change by referral (between pre-referral and post-referral period)	-0.020	0.016	0.208
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.822	0.271	0.007
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.086	0.024	0.002
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-1.437	0.393	<0.001
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	0.066	0.027	0.016
$\beta_1 + \beta_3$	trend within post-referral period	0.013	0.007	0.044
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.099	0.023	<0.001

Pre-implementation period = pre-referral period 07/2014-06/2016 + post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

num, numerator; den, denominator

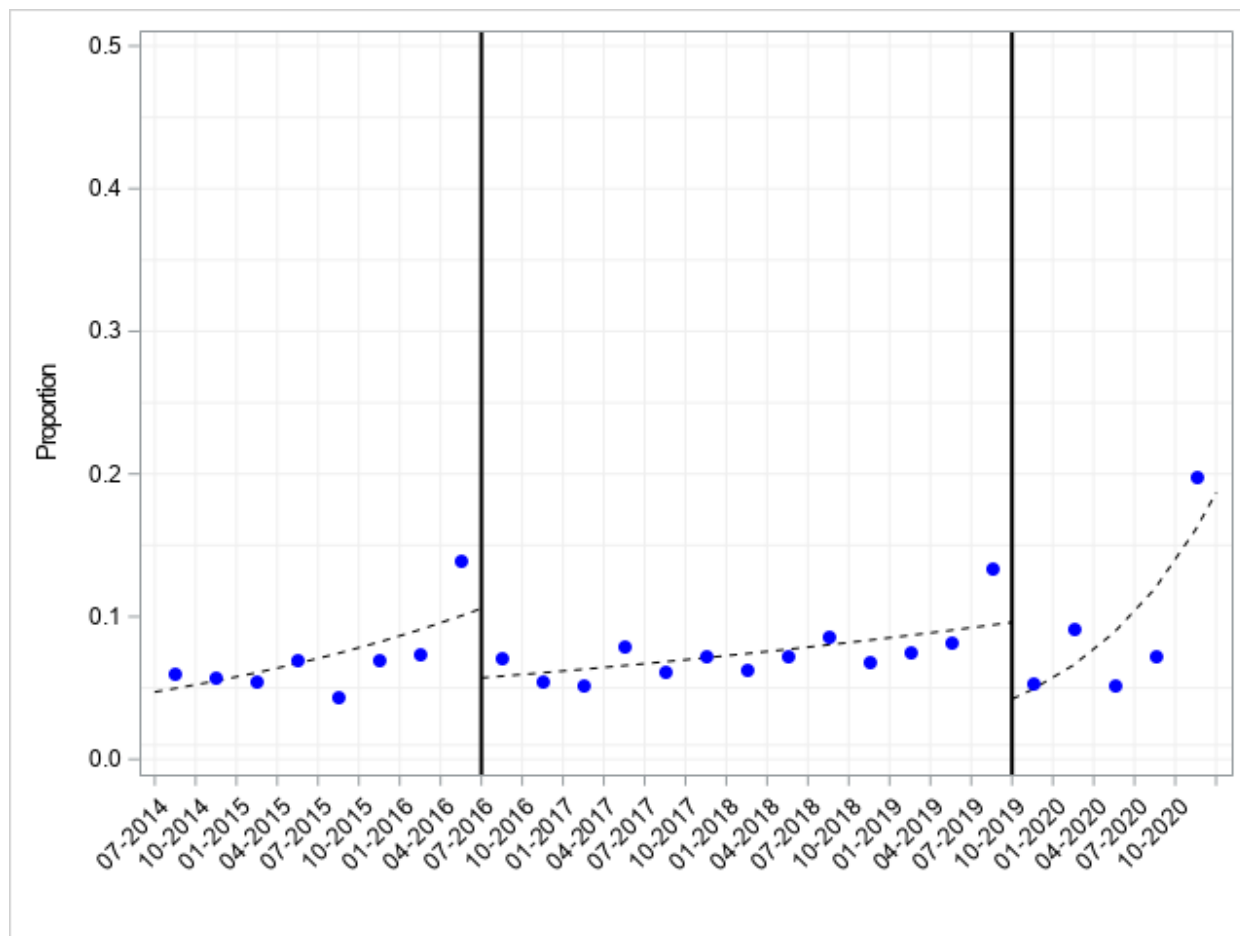


Figure 54 Observed point estimates and interrupted time series fit; for monthly pregnancy testing during treatment with oral retinoids; in Germany

11.4.8.3 Spain

11.4.8.3.1 Trends in Contraceptives Use Before and During Treatment Episodes with Oral Retinoids

With respect to contraceptive use before treatment start, there were no statistically significant trends (slopes) during the pre-referral, or post-implantation periods. However, there was a statistically significant decrease in slope during the post-referral period ($\beta_1 + \beta_3 = -0.005$, $p = 0.044$). Between time intervals, there were no significant changes in slopes between the pre-referral and post-referral period nor between post-referral and post-implementation periods. However, between the pre-referral period and the post-referral period there was a statistically significant level-change ($\beta_2 = 0.151$, $p = 0.029$) while there was no statistically significant level change between the post-referral and post-implementation period. The ITS results are displayed in

Table

89.

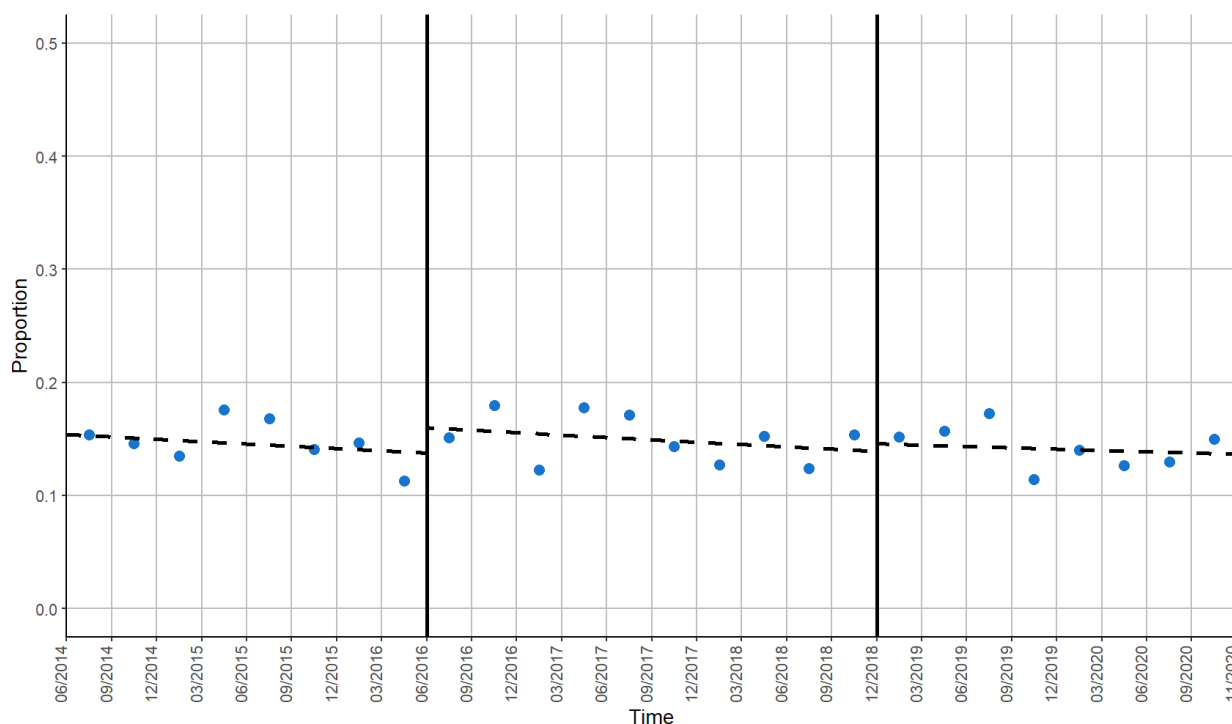


Figure 55 shows the observed point estimates and ITS fit for prescriptions for records of contraceptive use before treatment start with oral retinoids in Spain.

Table 89 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use before treatment start with oral retinoids; in Spain

Country: Spain			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 2014-07-01 to 2014-09-30	32/208 (15.4)		
Time point 2: 2014-10-01 to 2014-12-31	91/625 (14.6)		
Time point 3: 2015-01-01 to 2015-03-31	70/520 (13.5)		
Time point 4: 2015-04-01 to 2015-06-30	49/279 (17.6)		
Time point 5: 2015-07-01 to 2015-09-30	49/292 (16.8)		
Time point 6: 2015-10-01 to 2015-12-31	99/702 (14.1)		
Time point 7: 2016-01-01 to 2016-03-31	85/579 (14.7)		
Time point 8: 2016-04-01 to 2016-06-30	32/283 (11.3)		
Time point 9: 2016-07-01 to 2016-09-30		42/278 (15.1)	
Time point 10: 2016-10-01 to 2016-12-31		107/596 (18.0)	
Time point 11: 2017-01-01 to 2017-03-31		64/522 (12.3)	
Time point 12: 2017-04-01 to 2017-06-30		49/276 (17.8)	
Time point 13: 2017-07-01 to 2017-09-30		49/286 (17.1)	
Time point 14: 2017-10-01 to 2017-12-31		91/636 (14.3)	
Time point 15: 2018-01-01 to 2018-03-31		70/551 (12.7)	
Time point 16: 2018-04-01 to 2018-06-30		40/263 (15.2)	
Time point 17: 2018-07-01 to 2018-09-30		33/266 (12.4)	
Time point 18: 2018-10-01 to 2018-12-31		97/631 (15.4)	
Time point 19: 2019-01-01 to 2019-03-31			85/561 (15.2)
Time point 20: 2019-04-01 to 2019-06-30			39/249 (15.7)
Time point 21: 2019-07-01 to 2019-09-30			51/296 (17.2)
Time point 22: 2019-10-01 to 2019-12-31			82/720 (11.4)
Time point 23: 2020-01-01 to 2020-03-31			79/565 (14.0)
Time point 24: 2020-04-01 to 2020-06-30			20/158 (12.7)
Time point 25: 2020-07-01 to 2020-09-30			39/300 (13.0)
Time point 26: 2020-10-01 to 2020-12-31			111/742 (15.0)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-1.871	0.045	<0.001
β_1	baseline trend	-0.005	0.004	0.186
β_2	level change by referral (between pre-referral and post-referral period)	0.151	0.069	0.029
β_3	slope change by referral (between pre-referral and post-referral period)	0.000	0.004	0.992
β_4	level change by implementation (between post-referral period and post-implementation period)	0.047	0.058	0.419
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.002	0.006	0.733
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	0.198	0.094	0.036
$\beta_3 + \beta_5$	slope change	0.002	0.006	0.730

Country: Spain

	Pre-referral period	Post-referral period	Post-implementation period	
	num / den (rate)	num / den (rate)	num / den (rate)	
	(between pre-referral period and post-implementation period)			
$\beta_1 + \beta_3$	trend within post-referral period	-0.005	0.002	0.044
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	-0.003	0.004	0.505

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020
num, numerator; den, denominator

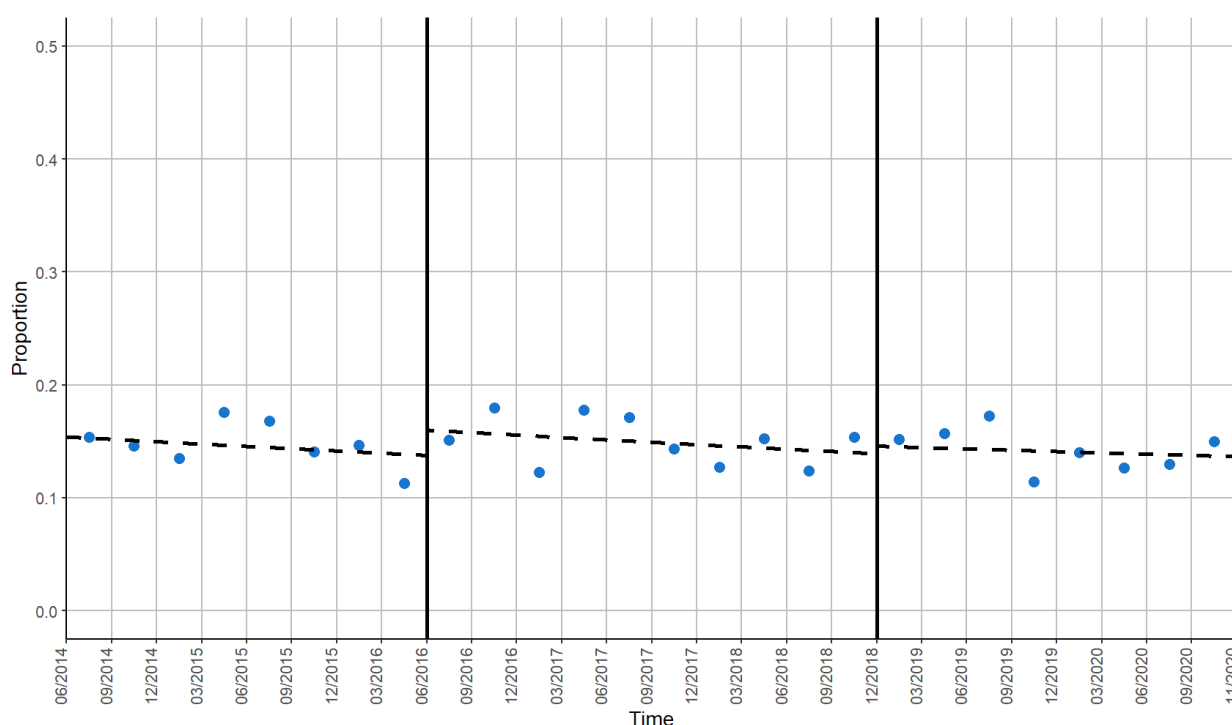


Figure 55 Observed point estimates and interrupted time series fit; for records of contraceptive use before treatment start with oral retinoids; in Spain

For records of contraceptive use during treatment with oral retinoids there was a marginally significant trend during the pre-referral period ($\beta_1 = 0.006$, $p = 0.074$). The change in slope between pre- and post-referral period was statistically significant ($\beta_3 = -0.019$, $p < 0.001$). During the post-referral period the slope did change significantly ($\beta_1 + \beta_3 = -0.013$, $p < 0.001$). There was a statistically significant change in the slope between the pre-referral and post-implementation period ($\beta_3 + \beta_5 = -0.010$, $p = 0.006$) and between the post-referral and post-implementation period

($\beta_5 = 0.008$, $p = 0.007$). The slope increase in the post-implementation period was statistically significant ($\beta_1 + \beta_3 + \beta_5 = -0.005$, $p = 0.026$). The level changes between the pre-referral to post-referral period ($\beta_2 + \beta_4 = 0.332$, < 0.001) and between post-referral and post-implementation period were statistically significant ($\beta_4 = 0.261$, $p < 0.001$). The ITS results are displayed in Table 90. Figure 56 shows the observed point estimates and ITS fit for prescriptions for records of contraceptive use during treatment start with oral retinoids.

Table 90 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use during treatment with oral retinoids; in Spain

Country: Spain				
	Pre-referral period	Post-referral period	Post-implementation period	
	num / den (rate)	num / den (rate)	num / den (rate)	
Time point 1: 01.07.2014-30.09.2014	46/382 (12.0)			
Time point 2: 01.10.2014-31.12.2014	86/625 (13.8)			
Time point 3: 01.01.2015-30.03.2015	59/520 (11.3)			
Time point 4: 01.04.2015-30.06.2015	44/279 (15.8)			
Time point 5: 01.07.2015-30.09.2015	44/292 (15.1)			
Time point 6: 01.10.2015-31.12.2015	90/702 (12.8)			
Time point 7: 01.01.2016-30.03.2016	94/579 (16.2)			
Time point 8: 01.04.2016-30.06.2016	32/283 (11.3)			
Time point 9: 01.07.2016-30.09.2016		44/290 (15.2)		
Time point 10: 01.10.2016-31.12.2016		97/613 (15.8)		
Time point 11: 01.01.2017-30.03.2017		66/543 (12.2)		
Time point 12: 01.04.2017-30.06.2017		39/293 (13.3)		
Time point 13: 01.07.2017-30.09.2017		40/324 (12.3)		
Time point 14: 01.10.2017-31.12.2017		100/780 (12.8)		
Time point 15: 01.01.2018-30.03.2018		107/814 (13.1)		
Time point 16: 01.04.2018-30.06.2018		53/462 (11.5)		
Time point 17: 01.07.2018-30.09.2018		24/266 (9.0)		
Time point 18: 01.10.2018-31.12.2018		68/631 (10.8)		
Time point 19: 01.01.2019-30.03.2019			215/1660 (13.0)	
Time point 20: 01.04.2019-30.06.2019			36/249 (14.5)	
Time point 21: 01.07.2019-30.09.2019			49/296 (16.6)	
Time point 22: 01.10.2019-31.12.2019			92/720 (12.8)	
Time point 23: 01.01.2020-30.03.2020			77/565 (13.6)	
Time point 24: 01.04.2020-30.06.2020			15/158 (9.5)	
Time point 25: 01.07.2020-30.09.2020			33/300 (11.0)	
Time point 26: 01.10.2020-31.12.2020			92/742 (12.4)	
Model parameters:				
Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-2.068	0.035	< 0.001
β_1	baseline trend	0.006	0.003	0.074
β_2	level change by referral (between pre-referral and post-referral period)	0.071	0.055	0.196
β_3	slope change by referral (between pre-referral and post-referral period)	-0.019	0.004	< 0.001
β_4	level change by implementation (between post-referral period and post-implementation period)	0.261	0.037	< 0.001
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.008	0.003	0.007
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	0.332	0.074	<0.001
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	-0.010	0.004	0.006
$\beta_1 + \beta_3$	trend within post-referral period	-0.013	0.002	<0.001

$\beta_1 + \beta_3 + \beta_5$ trend within post-implementation period -0.005 0.002 0.026
Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020
num, numerator; den, denominator

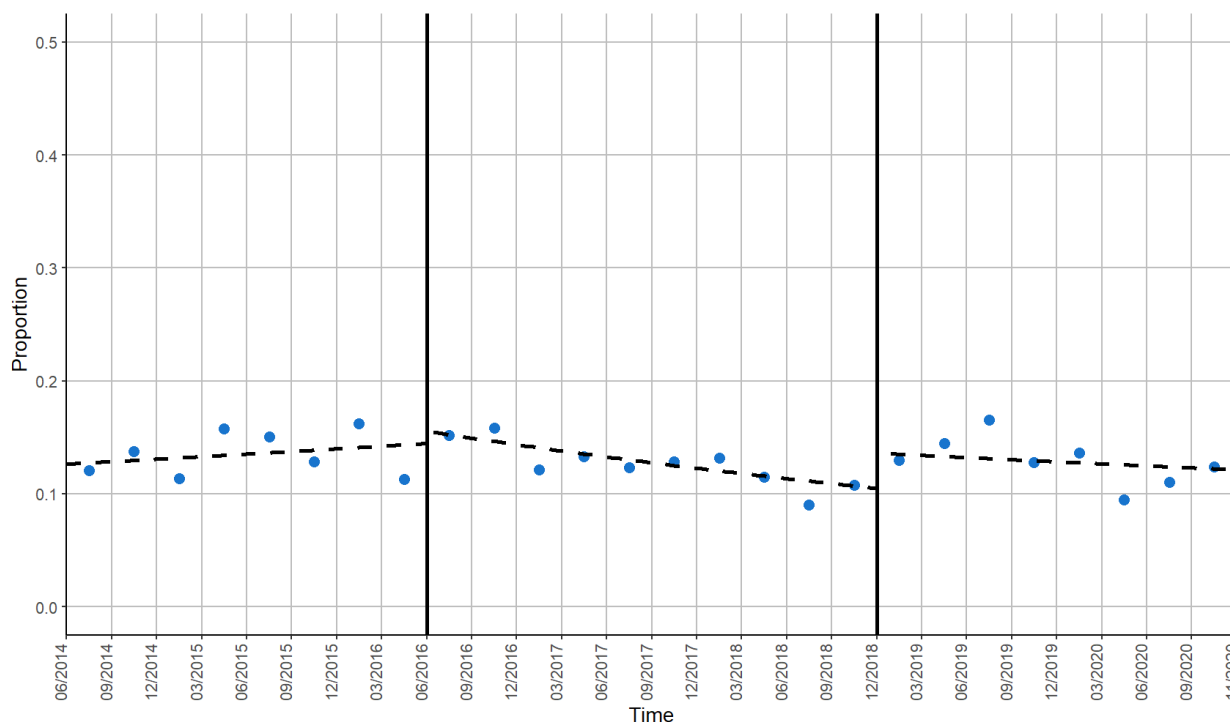


Figure 56 Observed point estimates and interrupted time series fit; for records of contraceptive use during treatment with oral retinoids; in Spain

11.4.8.3.2 Trends in Laboratory Pregnancy Testing Before and Monthly During Treatment Episodes with Oral Retinoids

With respect to laboratory pregnancy testing before treatment start, the ITS analysis showed a significant decreasing trend during the pre-referral period ($\beta_1 = -0.017$, $p < 0.001$). There was a significant level change after the pre-referral period ($\beta_2 = 0.473$, $p < 0.001$) and a significant change in slope between the pre-referral and post-referral period ($\beta_3 = 0.018$, $p < 0.001$). During the post-referral period the slope was not statistically significant and there was no significant level change between post-referral and post-implementation period. The slope changed significantly between the post-referral and post-implementation period ($\beta_5 = 0.014$, $p = 0.001$) and increased during the post-implementation period ($\beta_1 + \beta_3 + \beta_5 = 0.015$, $p < 0.001$). The ITS results are

displayed in Table 91. Figure 57 shows the observed point estimates and ITS fit for laboratory pregnancy testing before treatment start with oral retinoids.

Table 91 Interrupted time series analysis; point estimates and parameter estimates; for pregnancy testing before treatment start with oral retinoids; in Spain

Country: Spain			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	4/208 (1.9)		
Time point 2: 01.10.2014-31.12.2014	26/625 (4.2)		
Time point 3: 01.01.2015-30.03.2015	10/520 (1.9)		
Time point 4: 01.04.2015-30.06.2015	6/279 (2.2)		
Time point 5: 01.07.2015-30.09.2015	6/292 (2.1)		
Time point 6: 01.10.2015-31.12.2015	22/702 (3.1)		
Time point 7: 01.01.2016-30.03.2016	13/579 (2.2)		
Time point 8: 01.04.2016-30.06.2016	5/283 (1.8)		
Time point 9: 01.07.2016-30.09.2016		12/278 (4.3)	
Time point 10: 01.10.2016-31.12.2016		19/596 (3.2)	
Time point 11: 01.01.2017-30.03.2017		23/522 (4.4)	
Time point 12: 01.04.2017-30.06.2017		5/276 (1.8)	
Time point 13: 01.07.2017-30.09.2017		8/286 (2.8)	
Time point 14: 01.10.2017-31.12.2017		21/636 (3.3)	
Time point 15: 01.01.2018-30.03.2018		23/551 (4.2)	
Time point 16: 01.04.2018-30.06.2018		4/263 (1.5)	
Time point 17: 01.07.2018-30.09.2018		10/266 (3.8)	
Time point 18: 01.10.2018-31.12.2018		26/631 (4.1)	
Time point 19: 01.01.2019-30.03.2019			20/561 (3.6)
Time point 20: 01.04.2019-30.06.2019			6/249 (2.4)
Time point 21: 01.07.2019-30.09.2019			7/296 (2.4)
Time point 22: 01.10.2019-31.12.2019			36/720 (5.0)
Time point 23: 01.01.2020-30.03.2020			27/565 (4.8)
Time point 24: 01.04.2020-30.06.2020			5/158 (3.2)
Time point 25: 01.07.2020-30.09.2020			8/300 (2.7)
Time point 26: 01.10.2020-31.12.2020			37/742 (5.0)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-3.429	0.058	< 0.001
β_1	baseline trend	-0.017	0.004	< 0.001
β_2	level change by referral (between pre-referral and post-referral period)	0.473	0.068	< 0.001
β_3	slope change by referral (between pre-referral and post-referral period)	0.018	0.005	< 0.001
β_4	level change by implementation	-0.061	0.067	0.363

	(between post-referral period and post-implementation period)			
	slope change by implementation			
β_5	(between post-referral period and post-implementation period)	0.014	0.004	0.001
	level change			
$\beta_2 + \beta_4$	(between pre-referral period and post-implementation period)	0.412	0.117	1.000
	slope change			
$\beta_3 + \beta_5$	(between pre-referral period and post-implementation period)	0.032	0.004	1.000
$\beta_1 + \beta_3$	trend within post-referral period	0.001	0.003	0.716
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.015	0.003	<0.001

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020
 num, numerator; den, denominator

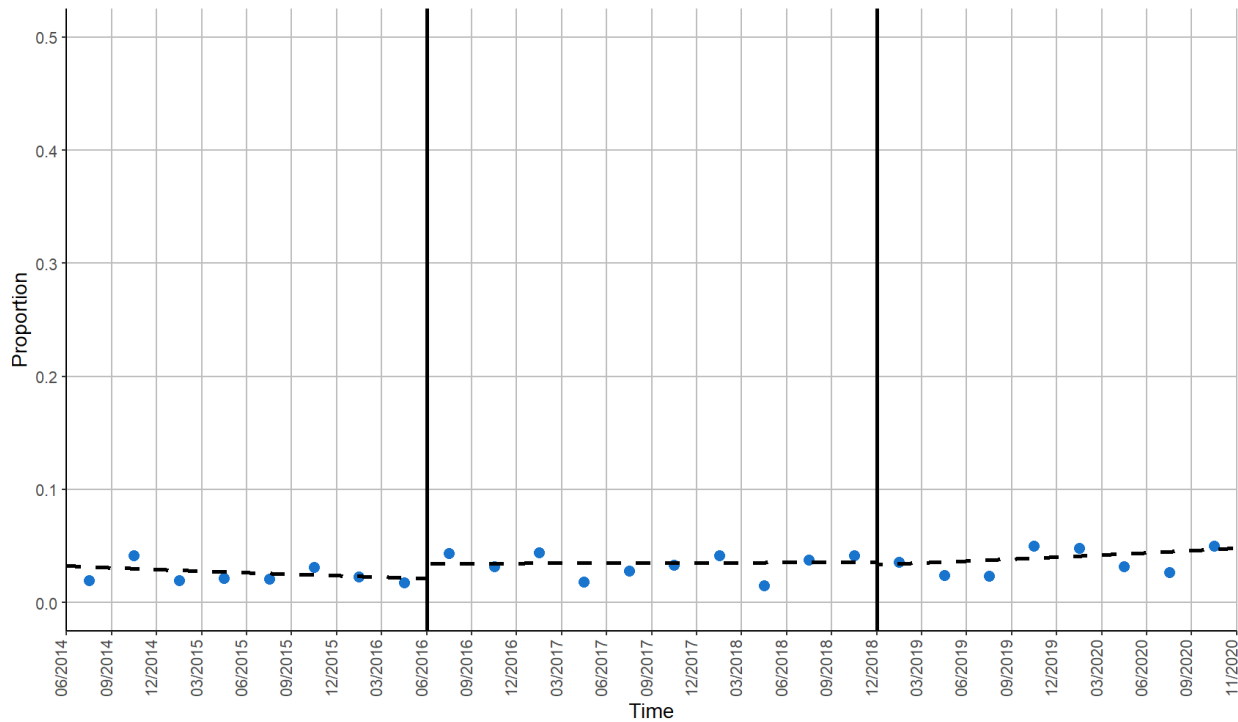


Figure 57 Observed point estimates and interrupted time series fit; for pregnancy testing before treatment start with oral retinoids; in Spain

The ITS analysis showed no significant level and slope changes for monthly laboratory pregnancy testing during treatment. Furthermore, the slopes during all 3 periods of the study were virtually flat and not statistically different than zero. The ITS results are displayed in Table 92. Figure 58 shows the observed point estimates and ITS fit for monthly laboratory pregnancy tests during treatment with oral retinoids.

Table 92 Interrupted time series analysis; point estimates and parameter estimates; for monthly pregnancy testing during treatment with oral retinoids; in Spain

Country: Spain			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	0/382 (0.0)		
Time point 2: 01.10.2014-31.12.2014	5/625 (0.8)		
Time point 3: 01.01.2015-30.03.2015	2/520 (0.4)		
Time point 4: 01.04.2015-30.06.2015	1/279 (0.4)		
Time point 5: 01.07.2015-30.09.2015	5/292 (1.7)		
Time point 6: 01.10.2015-31.12.2015	1/702 (0.1)		
Time point 7: 01.01.2016-30.03.2016	1/579 (0.2)		
Time point 8: 01.04.2016-30.06.2016	0/283 (0.0)		
Time point 9: 01.07.2016-30.09.2016		0/290 (0.0)	
Time point 10: 01.10.2016-31.12.2016		0/613 (0.0)	
Time point 11: 01.01.2017-30.03.2017		0/543 (0.0)	
Time point 12: 01.04.2017-30.06.2017		1/293 (0.3)	
Time point 13: 01.07.2017-30.09.2017		1/324 (0.3)	
Time point 14: 01.10.2017-31.12.2017		0/780 (0.0)	
Time point 15: 01.01.2018-30.03.2018		0/814 (0.0)	
Time point 16: 01.04.2018-30.06.2018		1/462 (0.2)	
Time point 17: 01.07.2018-30.09.2018		0/266 (0.0)	
Time point 18: 01.10.2018-31.12.2018		0/631 (0.0)	
Time point 19: 01.01.2019-30.03.2019			2/1660 (0.1)
Time point 20: 01.04.2019-30.06.2019			0/249 (0.0)
Time point 21: 01.07.2019-30.09.2019			0/296 (0.0)
Time point 22: 01.10.2019-31.12.2019			1/720 (0.1)
Time point 23: 01.01.2020-30.03.2020			0/565 (0.0)
Time point 24: 01.04.2020-30.06.2020			0/158 (0.0)
Time point 25: 01.07.2020-30.09.2020			0/300 (0.0)
Time point 26: 01.10.2020-31.12.2020			1/742 (0.1)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-5.072	0.602	< 0.001
β_1	baseline trend	-0.039	0.050	0.445
β_2	level change by referral	-1.379	1.744	0.438

	(between pre-referral and post-referral period)			
β_3	slope change by referral (between pre-referral and post-referral period)	0.036	0.102	0.726
β_4	level change by implementation (between post-referral period and post- implementation period)	0.525	1.787	0.772
β_5	slope change by implementation (between post-referral period and post- implementation period)	-0.012	0.122	0.925
$\beta_2 + \beta_4$	level change (between pre-referral period and post- implementation period)	-0.854	2.952	0.772
$\beta_3 + \beta_5$	slope change (between pre-referral period and post- implementation period)	0.025	0.098	0.801
$\beta_1 + \beta_3$	trend within post-referral period	-0.003	0.089	0.977
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	-0.014	0.084	0.866

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020
num, numerator; den, denominator

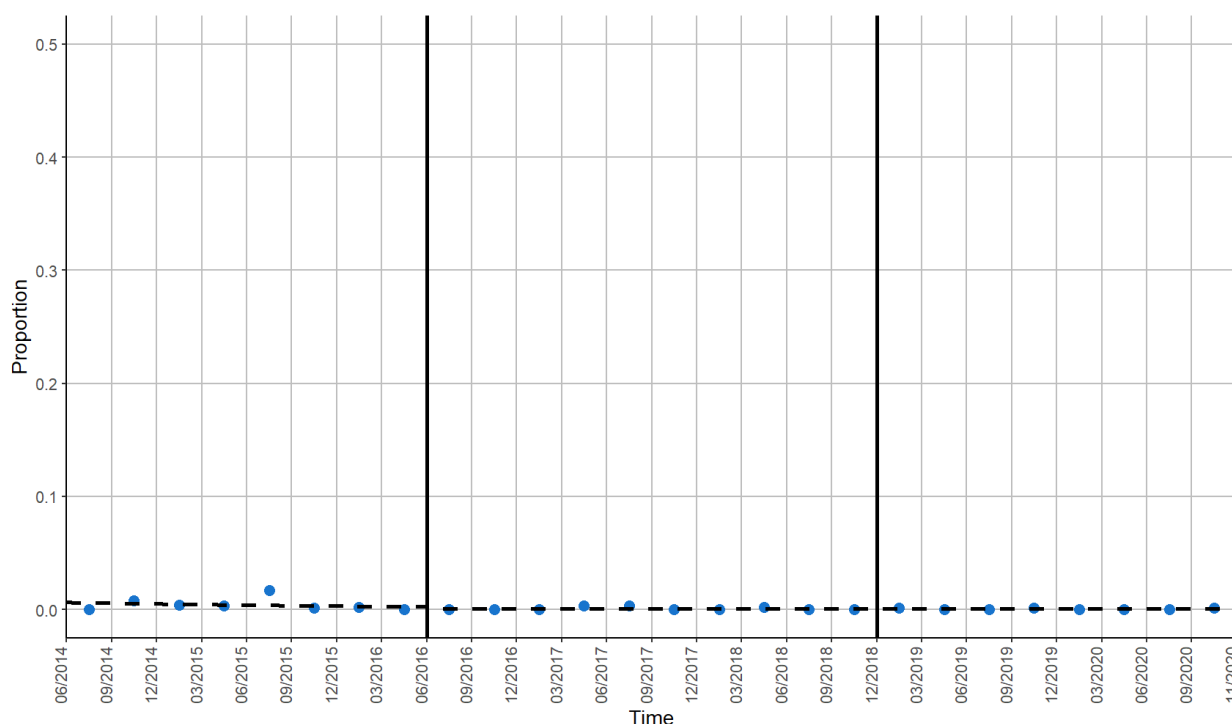


Figure 58 Observed point estimates and interrupted time series fit; for monthly pregnancy testing during treatment with oral retinoids; in Spain

11.4.8.4 Sweden

11.4.8.4.1 Trends in Contraceptives use Before and During Treatment Episodes with Oral Retinoids

Prior to the start of treatment, there was an increasing trend in contraceptive use during the pre-referral period ($\beta_1 = 0.006$, $p < 0.001$). After the pre-referral period, there was a marginally significant level-change, i.e. the location of the slope ($\beta_2 = -0.024$, $p = 0.051$) and a statistically significant change in slope to the post-referral period ($\beta_3 = -0.003$, $p = 0.015$), i.e. the proportion of treatment episodes with records of contraceptive use before treatment start increased at a slower rate over the post-referral compared to the pre-referral period. There was a significant slope for treatment episodes with records of contraceptive use during the post-referral period ($\beta_1 + \beta_3 = -0.003$, $p < 0.001$). There was a significant level change between post-referral and post-implementation period ($\beta_4 = -0.029$, $p = 0.006$). The change in slope was non-significant. The slope in the post-implementation phase remained virtually unchanged and was also significant ($\beta_1 + \beta_3 + \beta_5 = -0.003$, $p < 0.001$). The ITS results are displayed in Table 93. Figure 59 shows the observed point estimates and ITS fit for prescriptions for records or contraceptive use before treatment start with oral retinoids.

Table 93 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use before treatment start with oral retinoids; in Sweden

Country: Sweden			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	278/948 (29.3)		
Time point 2: 01.10.2014-31.12.2014	474/1,469 (32.3)		
Time point 3: 01.01.2015-30.03.2015	432/1,328 (32.5)		
Time point 4: 01.04.2015-30.06.2015	291/862 (33.8)		
Time point 5: 01.07.2015-30.09.2015	359/1,058 (33.9)		
Time point 6: 01.10.2015-31.12.2015	520/1,592 (32.7)		
Time point 7: 01.01.2016-30.03.2016	525/1,511 (34.7)		
Time point 8: 01.04.2016-30.06.2016	362/1,021 (35.5)		
Time point 9: 01.07.2016-30.09.2016		473/1,392 (34.0)	
Time point 10: 01.10.2016-31.12.2016		699/1,950 (35.8)	
Time point 11: 01.01.2017-30.03.2017		601/1,650 (36.4)	
Time point 12: 01.04.2017-30.06.2017		376/1,040 (36.2)	

Country: Sweden			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 13: 01.07.2017-30.09.2017		563/1,506 (37.4)	
Time point 14: 01.10.2017-31.12.2017		683/1,973 (34.6)	
Time point 15: 01.01.2018-30.03.2018		675/1,770 (38.1)	
Time point 16: 01.04.2018-30.06.2018		463/1,250 (37.0)	
Time point 17: 01.07.2018-30.09.2018		631/1,675 (37.7)	
Time point 18: 01.10.2018-31.12.2018		923/2,376 (38.8)	
Time point 19: 01.01.2019-30.03.2019			802/2,118 (37.9)
Time point 20: 01.04.2019-30.06.2019			551/1,414 (39.0)
Time point 21: 01.07.2019-30.09.2019			721/1,875 (38.5)
Time point 22: 01.10.2019-31.12.2019			989/2,592 (38.2)
Time point 23: 01.01.2020-30.03.2020			995/2,521 (39.5)
Time point 24: 01.04.2020-30.06.2020			678/1,734 (39.1)
Time point 25: 01.07.2020-30.09.2020			836/2,190 (38.2)
Time point 26: 01.10.2020-31.12.2020			1352/3234 (41.8)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-1.182	0.014	< 0.001
β_1	baseline trend	0.006	0.001	< 0.001
β_2	level change by referral (between pre-referral and post-referral period)	-0.024	0.012	0.051
β_3	slope change by referral (between pre-referral and post-referral period)	-0.003	0.001	0.015
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.029	0.011	0.006
β_5	slope change by implementation (between post-referral period and post-implementation period)	0.000	0.001	0.936
$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.053	0.017	0.002
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	-0.003	0.001	0.033
$\beta_1 + \beta_3$	trend within post-referral period	0.003	0.000	<0.001
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.003	0.001	<0.001

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

num, numerator; den, denominator

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

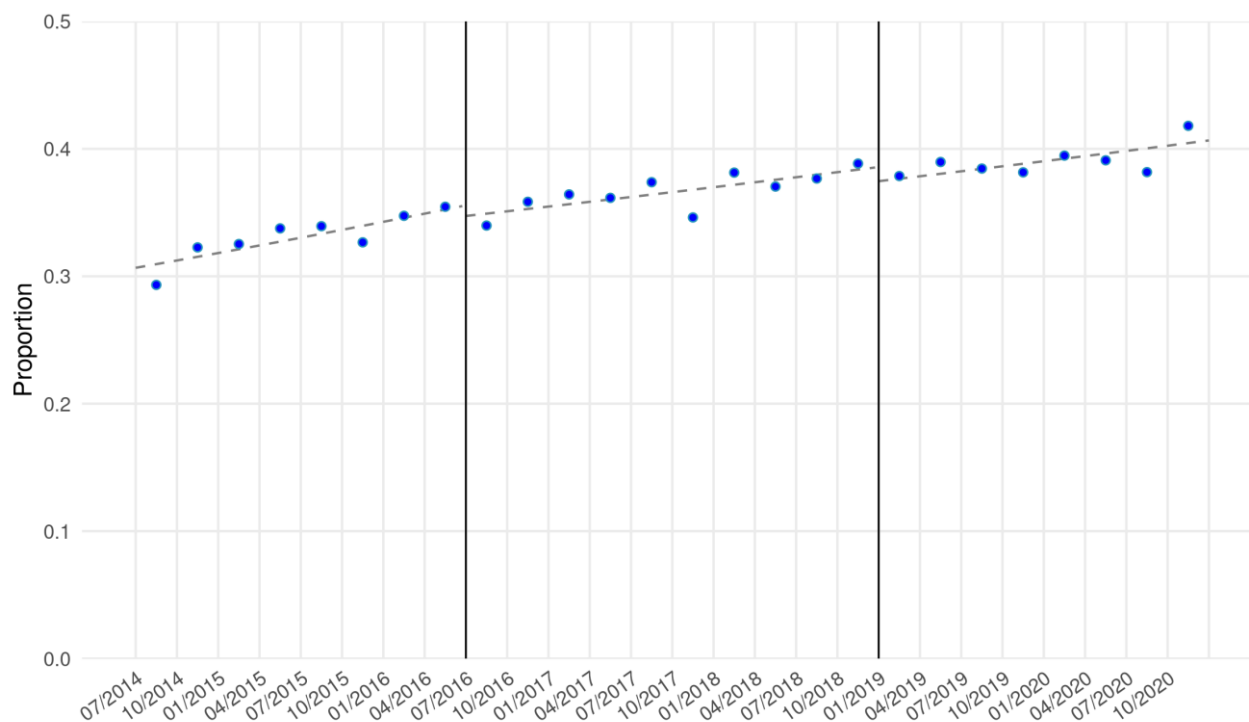


Figure 59 Observed point estimates and interrupted time series fit; for records of contraceptive use before treatment start with oral retinoids; in Sweden

During treatment with oral retinoids, the quarterly change for records of contraceptive use was remarkably similar. There were statistically significant positive slopes (i.e. trend) within each period (pre-referral: $\beta_1 = 0.011$, $p = 0.025$; post-referral: $\beta_1 + \beta_3 = 0.010$, $p < 0.001$; post-implementation: $\beta_1 + \beta_3 + \beta_5 = 0.007$, $p = 0.012$). There were no statistically significant changes in slopes between the post-referral period and pre-referral period, between post-referral period and post-implementation period and between pre-referral and post-implementation period. However, there were statistically significant level changes between the pre-referral and post-referral periods ($\beta_2 = -0.181$, $p = 0.04$), as well as between the post-referral and post-implementation periods ($\beta_4 = -0.135$, $p = 0.04$) and between the pre-referral and post-implementation periods ($\beta_2 + \beta_4 = -0.317$, $p = 0.005$). The ITS results are displayed in Table 94. Figure 60 shows the observed point estimates and ITS fit for prescriptions for records or contraceptive use before treatment start with oral retinoids.

Table 94 Interrupted time series analysis; point estimates and parameter estimates; for records of contraceptive use during treatment with oral retinoids; in Sweden

Country: Sweden			
	Pre-referral period	Post-referral period	Post-implementation period
	num / den (rate)	num / den (rate)	num / den (rate)
Time point 1: 01.07.2014-30.09.2014	597/1,964 (30.4)		
Time point 2: 01.10.2014-31.12.2014	460/1,496 (30.7)		
Time point 3: 01.01.2015-30.03.2015	379/1,330 (28.5)		
Time point 4: 01.04.2015-30.06.2015	262/867 (30.2)		
Time point 5: 01.07.2015-30.09.2015	338/1,060 (31.9)		
Time point 6: 01.10.2015-31.12.2015	512/1,594 (32.1)		
Time point 7: 01.01.2016-30.03.2016	542/1,514 (35.8)		
Time point 8: 01.04.2016-30.06.2016	412/1,021 (40.4)		
Time point 9: 01.07.2016-30.09.2016		903/2,688 (33.6)	
Time point 10: 01.10.2016-31.12.2016		650/1,979 (32.8)	
Time point 11: 01.01.2017-30.03.2017		544/1,655 (32.9)	
Time point 12: 01.04.2017-30.06.2017		369/1,044 (35.3)	
Time point 13: 01.07.2017-30.09.2017		536/1,509 (35.5)	
Time point 14: 01.10.2017-31.12.2017		665/1,976 (33.7)	
Time point 15: 01.01.2018-30.03.2018		631/1,773 (35.6)	
Time point 16: 01.04.2018-30.06.2018		456/1,253 (36.4)	
Time point 17: 01.07.2018-30.09.2018		651/1,679 (38.8)	
Time point 18: 01.10.2018-31.12.2018		1,112/2,384 (46.6)	
Time point 19: 01.01.2019-30.03.2019			1,940/4,916 (39.5)
Time point 20: 01.04.2019-30.06.2019			554/1,438 (38.5)
Time point 21: 01.07.2019-30.09.2019			692/1,878 (36.8)
Time point 22: 01.10.2019-31.12.2019			994/2,597 (38.3)
Time point 23: 01.01.2020-30.03.2020			969/2,528 (38.3)
Time point 24: 01.04.2020-30.06.2020			684/1,736 (39.4)
Time point 25: 01.07.2020-30.09.2020			863/2,193 (39.4)
Time point 26: 01.10.2020-31.12.2020			1,568/3,236 (48.5)

Model parameters:

Parameter	Interpretation	Estimate	SE	p-value
β_0	baseline level	-1.263	0.065	< 0.001
β_1	baseline trend	0.011	0.005	0.025
β_2	level change by referral (between pre-referral and post-referral period)	-0.181	0.083	0.040
β_3	slope change by referral (between pre-referral and post-referral period)	-0.001	0.005	0.835
β_4	level change by implementation (between post-referral period and post-implementation period)	-0.135	0.061	0.040
β_5	slope change by implementation (between post-referral period and post-implementation period)	-0.003	0.004	0.448

$\beta_2 + \beta_4$	level change (between pre-referral period and post-implementation period)	-0.317	0.112	0.005
$\beta_3 + \beta_5$	slope change (between pre-referral period and post-implementation period)	-0.004	0.006	0.449
$\beta_1 + \beta_3$	trend within post-referral period	0.010	0.003	<0.001
$\beta_1 + \beta_3 + \beta_5$	trend within post-implementation period	0.007	0.003	0.012

Pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

num, numerator; den, denominator

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

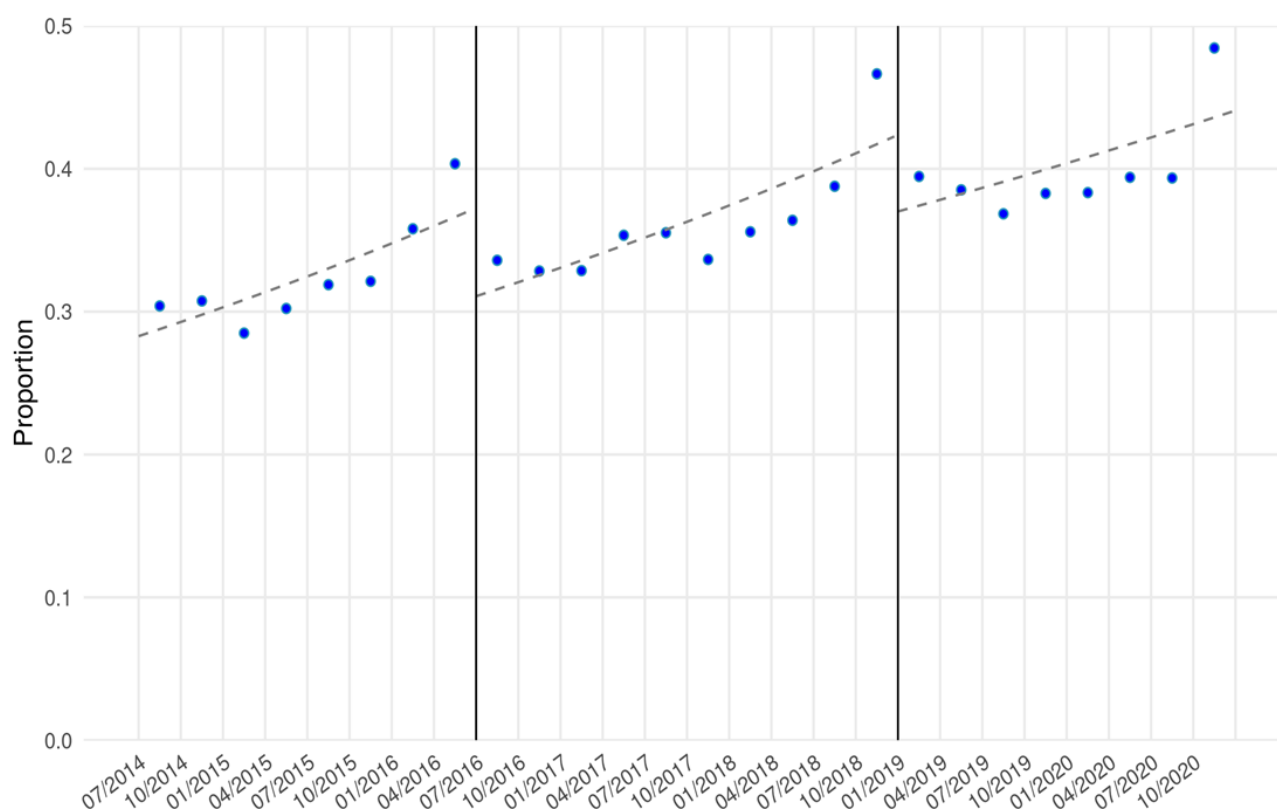


Figure 60 Observed point estimates and interrupted time series fit; for records of contraceptive use during treatment with oral retinoids; in Sweden

For pregnancy testing before treatment start with oral retinoids and during treatment with oral retinoids in Sweden there were no records available, therefore no Tables and Figures are reported.

11.5 Other Analyses

11.5.1 Sensitivity Analysis 1

11.5.1.1 France

Laboratory Pregnancy Tests

In the pre-referral period, 81.3% of oral retinoid treatment episodes had a laboratory pregnancy test performed when the pre-exposure time period was extended from 7 to 30 days. In the post-referral and post-implementation periods this was the case for 83.1% and 83.4% of oral retinoid treatment episodes, respectively (Table 95).

Table 95 Prescribing patterns for laboratory pregnancy tests before treatment start with oral retinoids in France; time period before the exposure date extended to 30 days; analysis based on the episode level

Country: France	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed:			
n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 100,464	N¹ = 133,366	N¹ = 93,220
At treatment start (up to 30 days before episode exposure start date)	81,704 (81.3) [81.1-81.6]	110,806 (83.1) [82.9-83.3]	77,767 (83.4) [83.2-83.7]

CI, confidence interval; N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

Confidence intervals were calculated using the Wilson method.

11.5.1.2 Germany

In the pre-referral period, 20.8% of oral retinoid treatment episodes had a laboratory pregnancy test performed when the pre-exposure time period was extended from 7 to 30 days. In the post-referral and post-implementation periods this was the case for 23.3% and 27.4% of oral retinoid treatment episodes, respectively (Table 96).

Laboratory Pregnancy Tests

Table 96 Prescribing patterns for laboratory pregnancy tests before treatment start with oral retinoids in Germany; time period before the exposure date extended to 30 days; analysis based on the episode level

Country: Germany

	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed:			
n (%) [95% CI of %]			
Prior to treatment ¹	N ¹ = 2,419	N ¹ = 4,360	N ¹ = 1,705
At treatment start (up to 30 days before episode exposure start date)	504 (20.8) [19.3 - 22.5]	1,014 (23.3) [22.0 - 24.5]	467 (27.4) [25.3 - 29.6]

CI, confidence interval, N or n, number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

Confidence intervals were calculated using the Wilson method.

11.5.1.3 Spain

Laboratory Pregnancy Tests

In the pre-referral period, 12.5% of oral retinoid treatment episodes had a laboratory pregnancy test performed when the pre-exposure time period was extended from 7 to 30 days. In the post-referral period this was the case for 14.5% of oral retinoid treatment episodes and in the post-implementation period for 14.6% of oral retinoid treatment episodes (Table 97).

Table 97 Prescribing patterns for laboratory pregnancy tests before treatment start with oral retinoids in Spain; time period before the exposure date extended to 30 days; analysis based on the episode level

Country: Spain

	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed:			
n (%) [95% CI of %]			
Prior to treatment ¹	N ¹ = 3,488	N ¹ = 4,305	N ¹ = 3,591
At treatment start (up to 30 days before episode exposure start date)	437 (12.5) [11.5 - 13.7]	625 (14.5) [13.5 - 15.6]	525 (14.6) [13.5 - 15.8]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

Confidence intervals were calculated using the Wilson method.

11.5.1.4 Sweden

Laboratory Pregnancy Tests

The number of available pregnancy tests was too low for meaningful analysis. The proportion of treatment episodes with pregnancy test performed before treatment start remained around 0.0% in both pre-implementation periods and in post-implementation period when the pre-exposure time period was extended from 7 to 30 days (Table 98).

Table 98 Prescribing patterns for laboratory pregnancy tests before treatment start with oral retinoids in Sweden; time period before the exposure date extended to 30 days; analysis based on the episode level

Country: Sweden	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed:			
n (%) [95% CI of %]			
Prior to treatment^{1,2}	N¹ = 9,789	N¹ = 16,582	N¹ = 17,678
At treatment start (up to 30 days before episode exposure start date)	0 (0.0) [0.0-0.0]	2 (0.01) [0.0-0.0]	0 (0.0) [0.0-0.0]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SEStesting)

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

11.5.2 Sensitivity Analysis 2

A sensitivity analysis was conducted on prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids, the periodicity of prescriptions within treatment episodes with oral retinoids and the prescribing patterns for laboratory pregnancy tests before, during and after treatment with oral retinoids; excluding the first 6 months after implementation of the updated RMM.

11.5.2.1 France

Contraceptives Use

During the pre-referral period, the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 38.9%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 35.2%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 43.8%. In the post-referral period, the respective proportions were 42.3%, 38.0%, and 46.6%. In the post-implementation period, the respective proportions were 42.1%, 38.1%, and 47.3% (Table 99).

Table 99 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in France; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment	N¹ = 100,377	N¹ = 133,257	N¹ = 74,006
30 days of contraception before treatment start	39,009 (38.9) [38.6-39.2]	56,339 (42.3) [42.0-42.5]	31,176 (42.1) [41.8-42.5]
During treatment	N² = 114,126	N² = 147,672	N² = 92,510
Continuous concomitant contraception during treatment	40,185 (35.2) [34.9-35.5]	56,069 (38.0) [37.7-38.2]	35,287 (38.1) [37.8-38.5]
After treatment	N³ = 90,598	N³ = 117,937	N³ = 49,576
30 days of contraception after treatment stop	39,704 (43.8) [43.5-44.1]	54,991 (46.6) [46.3-46.9]	23,428 (47.3) [46.8-47.7]

CI, confidence interval; N or n: number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated based on were calculated using the Wilson method.

Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 32.3 days. The proportion of episodes with monthly prescription intervals was 38.9%. During the post-referral period the mean time interval between prescription dates was 32.4 days and 40.5%

of episodes had monthly prescription intervals. During the post-implementation period, the mean time interval between prescription dates was 31.8 days and 49.6% of episodes had monthly prescription intervals (Table 100).

Table 100 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in France; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 87,437	Post-referral N ¹ = 115,069	N ¹ = 70,521
Time interval between prescription dates during episodes (days):			
Mean (SD)	32.3 (6.4)	32.4 (6.2)	31.8 (6.0)
Median (Q1 – Q3)	31.0 (29.4 – 34.0)	31.0 (29.4 – 33.8)	30.6 (29.0 – 33.0)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]			
	33,995 (38.9) [38.6-39.2]	46,650 (40.5) [40.3-40.8]	34,963 (49.6) [49.2-49.9]

CI, confidence interval; N or n, number of episodes; Q1, first quartile; Q3, third quartile, SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Confidence intervals were calculated using the Wilson method.

Laboratory Pregnancy Tests

In the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 72.9% of episodes. Fifty-point-eight percent of the treatment episode time was covered by compliant pregnancy testing. Pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 13.0% of episodes. The corresponding proportions were 75.5%, 52.5% and 12.8% for the post-referral and 77.6%, 49.6% and 13.2% for the post-implementation period (Table 101).

Table 101 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in France; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed:			
n (%) [95% CI of %]			
Prior to treatment	N¹ = 100,464	N¹ = 133,366	N¹ = 75,985
At treatment start (up to 7 days before episode exposure start date)	73,198 (72.9) [72.6-73.1]	100,646 (75.5) [75.2-75.7]	58,945 (77.6) [77.3-77.9]
During treatment	N² = 114,126	N² = 147,672	N² = 92,510
At least one test during treatment episodes	86,586 (75.9) [75.6-76.1]	114,933 (77.8) [77.6-78.0]	70,906 (76.6) [76.4-76.9]
Monthly during treatment episodes	8,104 (7.1) [7.0-7.3]	10,385 (7.0) [6.9-7.2]	8,519 (9.2) [9.0-9.4]
Percentage of treatment episode time covered by compliant pregnancy tests (SD)	50.8% (32.79%) [50.6%-50.9%]	52.5% (32.28%) [52.4%-52.7%]	49.6% (31.83%) [49.4%-49.8%]
After treatment	N³ = 90,598	N³ = 117,937	N³ = 49,576
30 (-/+7) days after treatment stop	11,738 (13.0) [12.7-13.2]	15,152 (12.8) [12.7-13.0]	6,547 (13.2) [12.9-13.5]

CI, confidence interval; N or n, number of episodes; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.5.2.2 Germany

Contraceptives Use

During the pre-referral period, the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 8.6%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 7.0%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 8.8%. In the post-referral period, the respective proportions were 8.5%, 6.9%, and 8.6%. In the post-implementation period, the respective proportions were 12.5%, 11.1%, and 11.4% (Table 102).

Table 102 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in Germany; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Germany		
	Pre-implementation period	Post-implementation period

	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment	N¹=2,406	N¹=4,329	N¹=1,020
30 days of contraception before treatment start	206 (8.6) [7.5 - 9.7]	369 (8.5) [7.7 - 9.4]	128 (12.5) [10.7 - 14.7]
During treatment	N¹=2,695	N¹=4,659	N¹=1,356
Continuous concomitant contraception during treatment	189 (7.0) [6.1 - 8.0]	322 (6.9) [6.2 - 7.7]	150 (11.1) [9.5 - 12.8]
After treatment	N=2,124	N=4,025	N=632
30 days of contraception after treatment stop	186 (8.8) [7.6 - 10.0]	347 (8.6) [7.8 - 9.5]	72 (11.4) [9.1 - 14.1]

CI, confidence interval; N or n: number of episodes, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated based using the Wilson method.

Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 39.2 days. The proportion of episodes with monthly prescription intervals was 28.2%. During the post-referral period the mean time interval between prescription dates was 37.8 days and 27.2% of episodes had monthly prescription intervals. During the post-implementation period, the mean time interval between prescription dates was 36.0 days and 43.5% of episodes had monthly prescription intervals (

Table 103).

Table 103 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in Germany; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N¹ = 1,532	N¹ = 2,688	N¹ = 837
Time interval between prescription dates during episodes (days):			
Mean (SD)	39.2 (16.4)	37.8 (13.4)	36.0 (12.8)
Median (Q1 – Q3)	33.8 (29.7 - 44.0)	33.4 (29.6 - 42.0)	31.7 (28.4 - 38.8)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]	432 (28.2) [26.0 - 30.5]	731 (27.2) [25.5 - 28.9]	364 (43.5) [40.2 - 46.9]

CI, confidence interval; N or n, number of episodes; Q1, first quartile; Q3, third quartile; SD: standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

Confidence intervals were calculated using the Wilson method.

Laboratory Pregnancy Tests

In the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 19.3% of episodes. The proportion of treatment episode time covered by compliant pregnancy testing was 19.3%. Pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 2.9% of episodes. The corresponding proportions were 21.6%, 21.4%, and 3.4% for the post-referral and 24.8%, 25.3%, and 3.0% for the post-implementation period (Table 104).

Table 104 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in Germany; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Germany	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed:			
n (%) [95% CI of %]			
Prior to treatment	N¹ = 2,419	N¹ = 4,360	N¹ = 1,024
At treatment start (up to 7 days before episode exposure start date)	468 (19.3) [17.8 - 21.0]	941 (21.6) [20.4 - 22.8]	254 (24.8) [22.3 - 27.5]
During treatment	N² = 2,695	N² = 4,659	N² = 1,356
At least one test during treatment episodes	754 (28.0) [26.3 - 29.7]	1,375 (29.5) [28.2 - 30.8]	433 (31.9) [29.5 - 34.5]
Monthly during treatment episodes	190 (7.1) [6.1 - 8.1]	345 (7.4) [6.7 - 8.2]	145 (10.7) [9.2 - 12.5]
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	19.3% (34.6%) [18.0% - 20.6%]	21.4% (36.2%) [20.4% - 22.4%]	25.3% (39.6%) [23.2% - 27.4%]
After treatment	N³ = 2,124	N³ = 4,025	N³ = 632
30 (-/+7) days after treatment stop	61 (2.9) [2.2 - 3.7]	135 (3.4) [2.8 - 4.0]	19 (3.0) [1.9 - 4.6]

CI, confidence interval; N or n, number of episodes, SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.5.2.3 Spain

Contraceptives Use

During the pre-referral period, the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 14.5%. The proportion of episodes

with continuous concomitant contraception during oral retinoid treatment was 13.5%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 16.1%. In the post-referral period, the respective proportions were 14.9%, 12.7%, and 16.9%. In the post-implementation period, the respective proportions were 12.4%, 12.0%, and 14.8% (Table 105).

Table 105 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in Spain; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 3,488	N¹ = 4,305	N¹ = 2,781
30 days of contraception before treatment start	507 (14.5) [13.4 - 15.7]	642 (14.9) [13.9 - 16.0]	345 (12.4) [11.2 - 13.7]
During treatment²	N² = 3,662	N² = 5,016	N² = 2,781
Continuous concomitant contraception during treatment	495 (13.5) [12.4 - 14.7]	638 (12.7) [11.8 - 13.7]	335 (12.0) [10.9 - 13.3]
After treatment³	N³ = 2,935	N³ = 3,994	N³ = 1,657
30 days of contraception after treatment stop	472 (16.1) [14.8 - 17.5]	675 (16.9) [15.8 - 18.1]	246 (14.8) [13.2 - 16.6]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – contraception (SES_{contraception})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 96.5 days. The proportion of episodes with monthly prescription intervals was 2.8%. During the post-referral period the mean time interval between prescription dates was 95.8 days and 3.7% of episodes had monthly prescription intervals. During the post-implementation period, the mean time interval between prescription dates was 93.2 days and 3.2% of episodes had monthly prescription intervals (Table 106).

Table 106 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in Spain; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
	N¹ = 1,426	N¹ = 1,958	N¹ = 1,089

**Time interval between
prescription dates during
episodes (days):**

Mean (SD)	96.5 (76.4)	95.8 (71.4)	93.2 (58.1)
Median (Q1 – Q3)	74.0 (55.0 - 108.0)	77.0 (56.0 - 112.0)	79.0 (56.0 - 113.0)

**Number of episodes with
monthly prescription intervals
during treatment: n (%) [95%
CI of %]**

40 (2.8%)	73 (3.7%)	35 (3.2)
[2.1 - 3.8]	[3.0 - 4.7]	[2.3 - 4.4]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription
Confidence intervals were calculated using the Wilson method.

Laboratory Pregnancy Tests

In the pre-referral period, laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 12.5% of episodes. The proportion of treatment episode time covered by compliant pregnancy testing was 38.4%. Pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 1.2% of episodes. The corresponding proportions were 14.5%, 33.9%, and 1.3% for the post-referral and 4.3%, 25.0%, and 1.0% for the post-implementation period (Table 107).

Table 107 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in Spain; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Spain

	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 3,488	N¹ = 4,305	N¹ = 2,781
At treatment start (up to 7 days before episode exposure start date)	437 (12.5) [11.5 - 13.7]	625 (14.5) [13.5 - 15.6]	120 (4.3) [3.6 - 5.1]
During treatment²	N² = 3,662	N² = 5,016	N² = 2,781
At least one test during treatment episodes	532 (14.5) [13.4 - 15.7]	903 (18.0) [17.0 - 19.1]	579 (20.8) [19.4 - 22.4]
Monthly during treatment episodes	15 (0.4) [0.2 - 0.7]	3 (0.1) [0.0 - 0.2]	2 (0.1) [0.0 - 0.3]
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	38.4% (21.0%) [37.2% - 39.6%]	33.9% (16.5%) [33.0% - 34.9%]	25.0% (18.0%) [23.9% - 26.2%]
After treatment³	N³ = 2,935	N³ = 3,994	N³ = 1,657
30 (-/+7) days after treatment stop	36 (1.2) [0.9 - 1.7]	53 (1.3) [1.0 - 1.7]	16 (1.0) [0.6 - 1.6]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SES_{testing})

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

Confidence intervals were calculated using the Wilson method.

11.5.2.4 Sweden

Contraceptives Use

During the pre-referral period, the proportion of oral retinoid treatment episodes with 30 days of contraceptive prescriptions prior to oral retinoid treatment was 33.1%. The proportion of episodes with continuous concomitant contraception during oral retinoid treatment was 32.3%. The proportion of episodes with 30 days of contraceptive prescriptions after oral retinoid treatment was 38.9%. In the post-referral period, the respective proportions were 36.7%, 36.3% and 42.0%. In the post-implementation period, the respective proportions were 39.4%, 40.9% and 44.3% (

Table 108).

Table 108 Prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids in Sweden; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Contraceptives: n (%) [95% CI of %]			
Prior to treatment¹	N¹ = 9,789	N¹ = 16,582	N¹ = 14,141
30 days of contraception before treatment start	3,241 (33.1) [32.2-34.0]	6,087 (36.7) [36.0-37.4]	5,569 (39.4) [38.6-40.2]
During treatment²	N² = 10,846	N² = 17,940	N² = 16,068
Continuous concomitant contraception during treatment	3,502 (32.3) [31.4-33.2]	6,517 (36.3) [35.6-37.0]	6,567 (40.9) [40.1-41.6]
After treatment³	N³ = 8,015	N³ = 13,901	N³ = 10,888
30 days of contraception after treatment stop	3,120 (38.9) [37.9-40.0]	5,841 (42.0) [41.2-42.8]	4,823 (44.3) [43.4-45.2]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – contraception (SEScontraception)

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

Periodicity of Prescriptions

The mean time interval between prescription dates for oral retinoids in the pre-referral period was 41.8 days. The proportion of episodes with monthly prescription intervals was 8.5%. During the post-referral period the mean time interval between prescription dates was 42.9 days and 8.6% of episodes had monthly prescription intervals. During the post-implementation period the mean time interval between prescription dates was 44.8 days and 9.9% of episodes had monthly prescription intervals (

Table 109).

Table 109 Prescribing patterns: periodicity of prescriptions within treatment episodes with oral retinoids in Sweden; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral N ¹ = 7,877	Post-referral N ¹ = 12,684	N ¹ = 10,187
Time interval between prescription dates during episodes (days):			
Mean (SD)	41.8 (17.6)	42.9 (17.3)	44.8 (17.7)
Median (Q1 – Q3)	38.6 (30.0-50.8)	40.0 (31.0-51.7)	42.0 (32.3-54.0)
Number of episodes with monthly prescription intervals during treatment: n (%) [95% CI of %]			
	672 (8.5) [7.9-9.2]	1,092 (8.6) [8.1-9.1]	1,005 (9.9) [9.3-10.5]

CI, confidence interval; SD, standard deviation; Q1, first quartile; Q3, third quartile; N or n, number of episodes; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS) and excluding episodes consisting of 1 prescription

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

Laboratory Pregnancy Tests

No laboratory pregnancy tests were recorded in the registry data. Data were only available when documented by ICD-10 codes. The number of laboratory pregnancy observed prior, during and after treatment was therefore close to or 0.0% in the pre-implementation and the post-implementation period (Table 110).

Table 110 Prescribing patterns for laboratory pregnancy tests before, during and after treatment episodes with oral retinoids in Sweden; excluding the first 6 months after implementation of the updated risk minimisation measures; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Laboratory pregnancy tests performed: n (%) [95% CI of %]			
Prior to treatment¹	N ¹ = 9,789	N ¹ = 16,582	N ¹ = 14,141
At treatment start (up to 7 days before episode exposure start date)	0 (0.0) [0.0-0.0]	0 (0.0) [0.0-0.0]	0 (0.0) [0.0-0.0]
During treatment²	N ² = 10,846	N ² = 17,940	N ² = 16,068
At least one test during treatment episodes	9 (0.1) [0.0-0.2]	7 (0.0) [0.0-0.1]	9 (0.1) [0.0-0.1]
Monthly during treatment episodes	0 (0.0) [0.0-0.0]	1 (0.0) [0.0-0.0]	2 (0.0) [0.0-0.1]
Percentage of treatment episodes time covered by compliant pregnancy tests (SD)	0.0% (0.0%) [0.0% - 0.0%]	0.0% (0.0%) [0.0% - 0.0%]	0.0% (0.0%) [0.0% - 0.0%]
After treatment³	N ³ = 8,015	N ³ = 13,901	N ³ = 10,888

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
30 (-/+7) days after treatment stop	1 (0.0) [0.0-0.1]	2 (0.0) [0.0-0.1]	2 (0.0) [0.0-0.1]

CI, confidence interval; N or n, number of episodes; SD, standard deviation; NA, not applicable; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the starting episodes set – pregnancy testing (SEStesting)

² Based on the full analysis set (FAS)

³ Based on the ending episodes set (EES)

In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Confidence intervals were calculated using the Wilson method.

11.6 Adverse Events/Adverse Reactions

The DUS study is based on the secondary use of anonymised data. According to the guidelines of the International Society for Pharmacoepidemiology (ISPE) (2007, Section VI) and the EMA Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2013, Section VI: C.1.2.1), noninterventional studies which are based on secondary use of data do not require reporting of adverse events and adverse drug reactions (36, 37). With respect to the study objectives, information on adverse events/adverse reactions were not extracted from the databases and analysed in the context of this DUS.

12 DISCUSSION

This section discusses the key results of the multi-country, multisource, observational DUS open cohort study in females of childbearing potential receiving oral retinoids. The study aimed to investigate whether there are differences in physicians' prescribing and monitoring practices in the periods before and after the update of the PPP and RMM for oral retinoids when treating women of childbearing potential. The pre-implementation included the (1) *pre-referral period*: capturing the 2-year period before referral start in July 2016 and the (2) *post-referral period*: capturing the time between the referral start date in July 2016 and the distribution of the new RMM tools, the post-implementation period varied between countries and covered 14 to 24 months after the implementation of the RMM (Table 4). During the post-implementation period the world was affected by a pandemic of the coronavirus disease (COVID-19), an infectious disease caused by the SARS-CoV-2 virus. The emergency response of the majority of governments in Europe,

including 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 (38), which impacted profoundly on care as usual (39). COVID-19 priority care and safety measures lead to a drastic reduction in face-to-face scheduled physician visits for chronic disease detection and monitoring (40, 41).

12.1 Key Results

12.1.1 Number of Patients and Oral Retinoid Prescriptions

The study included the following numbers of women treated with oral retinoid in the pre-referral period: 87,818 in France, 1,953 in Germany, 3,004 in Spain and 9,182 in Sweden. The post-referral study sample was slightly larger and included the following numbers: 111,897 in France, 3,100 in Germany, 4,211 in Spain, and 14,594 in Sweden. The post-implementation study sample comprised the following numbers of women treated with oral retinoids: 92,582 in France, 1,598 in Germany, 4,100 in Spain and 16,709 in Sweden. In both pre-implementation periods, the majority of included women received isotretinoin (range 92.9% to 98.6%). In comparison, acitretin and alitretinoin were prescribed relatively rarely (range 1.5% to 7.0%, and 0.4% to 2.5%, respectively). During the pre-implementation period alitretinoin did not hold marketing authorisation in Sweden. In the post-implementation period most of the included women received isotretinoin (range 94.7% to 98.8%). In comparison, acitretin and alitretinoin were prescribed relatively rarely (range 1.1% to 5.1% and 0.1% to 2.2%, respectively).

12.1.2 Primary Objectives

The primary objectives of this study were to describe prescribing and monitoring practices, i.e., for contraceptives, oral retinoids and laboratory pregnancy tests during the pre-implementation and post-implementation period to assess the effectiveness of the updated RMMs.

12.1.2.1 Contraceptives Use

The PPP requires the use of at least 1 effective contraceptive before oral retinoid treatment start (specified as 1 month for alitretinoin and isotretinoin), during treatment, and after treatment (specified as 3 years for acitretin and 1 month for isotretinoin) (42).

In France, the proportions of oral retinoid treatment episodes with a 30-day contraceptive prescription prior to treatment were 38.9% and 42.3% in the pre- and post-referral periods, and 42.3% during the post-implementation period. Thus, while contraceptive prescriptions 30 days before oral retinoid use were approximately 3% higher in the post- than the pre-referral period, there was no change from the post-referral to the post-implementation period. During the pre- and post-referral and post-implementation periods, 35.2%, 38.0% and 38.1% of oral retinoid treatment episodes were covered by concomitant contraception use, again showing an increase of approximately 3% from pre- to post-referral, but not thereafter. In the pre- and post-referral periods 43.8% and 46.6% of episodes showed the required 30-day contraceptive prescriptions after oral retinoid treatment, again showing an increase of approximately 3%. Similar to the post-referral period, 46.7% of episodes showed the required 30-day contraceptive prescriptions after oral retinoid treatment stop in the post-implementation period, i.e. not suggesting any further improvements.

In Germany, the proportions of oral retinoid treatment episodes with a 30-day contraceptive prescription prior to treatment were 8.6% and 8.5% in the pre- and post-referral periods, and 11.0% during the post-implementation period. During the pre- and post-referral periods, 7.0% and 6.9% of episodes were covered by continuous concomitant contraceptive prescriptions. During the post-implementation period this was observed in 9.4% of episodes. During the pre-implementation periods 8.8% and 8.6% of episodes showed the required 30-day contraceptive prescriptions after oral retinoid treatment. This was observed for 11.0% of episodes in the post-implementation period. Overall, the German data showed little change from the pre- to post-referral period, and a slight increase in the proportions of oral retinoid treatment episodes with PPP conform prescriptions of contraceptives during the post-implementation period.

In Spain, the proportions of oral retinoid treatment episodes with a 30-day contraceptive prescription prior to treatment were 14.5% and 14.9% in the pre- and post-referral periods, and 14.1% in the post-implementation period. In the pre- and post-referral and post-implementation periods 13.5%, 12.7% and 13.0% of episodes were covered by continuous concomitant contraceptive prescriptions. In the pre- and post-referral and post-implementation periods 16.1%,

16.9% and 17.0% of episodes showed the required 30-day contraceptive prescriptions after oral retinoid treatment. Overall, the Spanish data showed little change in the prescribing patterns of contraceptives.

In Sweden, the proportions of oral retinoid treatment episodes with a 30-day contraceptive prescription prior to treatment were 33.1% and 36.7% in the pre- and post-referral periods, and 39.2% in the post-implementation period. In the pre-, post-referral and post-implementation periods 32.3%, 36.3% and 40.3% of episodes were covered by continuous concomitant contraceptive prescriptions. In the pre-, post-referral and post-implementation periods 38.9%, 42.0% and 44.6% of episodes, respectively, showed the required 30-day contraceptive prescriptions after oral retinoid treatment. Overall, the Swedish data showed an increasing trend of approximately 6%-8% in terms of prescribing patterns of contraceptives before, during and after treatment episodes with oral retinoids over the 3 study periods.

The proportions of oral retinoid treatment episodes with contraceptive prescriptions were smaller in Germany and Spain than in France and Sweden, which could point to lower compliance with the PPP in the 2 countries. However, the findings need to be considered carefully, given that not all contraceptives are reimbursed (Supplement 1.2) and/or captured by the databases (Table 8). For example, in Spain condoms, which are typically not captured in the primary care database, are the most frequently used contraceptive (17), and may have been the only used contraceptive, although using a single measure to prevent pregnancy would not be in line with the PPP requirements. Moreover, while for France, for example, records for contraceptives in SNIIRAM are present for over 50.0% of women of childbearing potential age (12, 13), in the German data only 2.0% of patients above the age of 20 had a record of contraceptives.

12.1.2.2 Periodicity of Prescriptions

The PPP ideally requires a 30-day prescription interval for oral retinoids and that prescriptions must be dispensed within 7 days of issuance (3). Overall, the periodicity of prescriptions in France was in line with this requirement, with about 32 days in all 3 study periods. In Germany the periodicity was 39.2 and 37.8 days in the pre- and post-referral periods and 36.0 days in the post-

implementation period. In Spain the periodicity of prescriptions was 96.5 days in the pre-referral, 95.8 days in the post-referral period and 103.5 days in the post-implementation period, potentially suggesting lower PPP compliance. However, observed periodicity of prescription intervals is in line with clinical practice for oral retinoid treatment in Spain where physicians issue a prescription with a 3-month duration and give the patient instructions for dose increase if the oral retinoid is well tolerated. Only after 3 months the patient typically goes back to see their physician (internal communication with data holders). In Sweden the intervals between prescriptions were 41.8, 42.9 and 44.5 days in the pre-, post-referral and post-implementation periods, i.e. slightly longer than the required monthly interval. Overall, little change in the periodicity of prescriptions was observed over the 3 study periods in the 4 study countries.

12.1.2.1 Laboratory Pregnancy Tests

The PPP requires that pregnancy must be excluded before oral retinoid treatment and the pregnancy test results are documented within 3 days before prescriptions are issued. Moreover, it states that during oral retinoid treatment females should undergo pregnancy testing at monthly follow-up assessments (3). Specifically, the *Assessment report Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data* (p. 8) states that: ‘The first pregnancy test, prior to the first prescription needs to be medically supervised. Thereafter, where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber. This allows for appropriate clinical discretion but guarantees that patients will get their prescription in a timely way in order that the results of the pregnancy test remain valid.’ This suggests that follow-up tests at home test might be suitable.

Overall, the proportions of treatment episodes with PPP compliant laboratory pregnancy testing observed in the French data were larger than in the other 2 countries with available data. In the pre- and post-referral periods, 72.9% and 75.5% of oral retinoid treatment episodes were associated with laboratory pregnancy testing prior to treatment start. This was observed for 76.4% of treatment episodes in the post-implementation period. The respective proportions were 19.3%, 21.6% and 25.6% in Germany, and 2.6%, 3.5% and 4.1% in Spain. Suggesting a slight positive change in all 3 countries with respect to compliance in terms of laboratory pregnancy testing prior to treatment. In France, approximately half of the treatment episodes in the pre- and post-referral

and post-implementation periods were covered by compliant laboratory pregnancy testing during a treatment episode. This was the case for 19.3%, 21.4% and 24.4% of treatment episode time in Germany and 38.4%, 33.9% and 25.9% of treatment episode time in Spain in the pre- and post-referral and post-implementation periods, suggesting a positive trend in Germany and a negative trend in Spain. Prescribing patterns of laboratory pregnancy tests after treatment in the pre- and post-referral and post-implementation periods showed little change in the 3 countries. Observed were 13.0%, 12.8% and 12.6% in France, 2.9%, 3.4% and 3.1% in Germany and 1.2%, 1.3% and 1.1% in Spain.

Overall, the referral and implementation of the updated PPP were associated with relatively little change in prescribing patterns of laboratory pregnancy test before, during and after oral retinoid treatment. The results could suggest a potential need for better compliance with the PPP with respect to medically supervised pregnancy testing, particularly during and after oral retinoid treatment, even though alternative explanations are also possible. Importantly, the overall low rates for pregnancy testing, particularly in Spain are likely partly explained by the fact that point-of-care quick urine pregnancy tests, which are performed by the physician during the medical consultation, are not captured in the databases (as suggested by the data provider). However, some of these types of pregnancy tests may not always have the required minimum sensitivity of 25 mUI/mL for hCG (Human Chorionic Gonadotropin), and therefore may not always be compliant with the PPP. Furthermore, tests might have been underreported or might not have taken place, in cases where the risk for pregnancy was deemed negligible (e.g., in case of sexually inactive patients, patients with regular menstrual cycles, or patients who have used various forms of contraception).

12.1.3 Secondary Objectives

12.1.3.1 Patient Age

The average patient age in the pre-referral period ranged between 24.5 and 25.4 years and was similar in France, Spain and Sweden. The average age of the German patients was 26.9 years. In all countries the average age was about 1 year higher in the pre- compared to the post-referral and post-implementation periods. In line with the respective oral retinoid indication, patients who were

prescribed acitretin (range 39.0 to 42.2 years) and alitretinoin were older (range 35.0 to 40.5 years) than those who were prescribed isotretinoin (range 23.1 to 26.1 years, Supplement 2.2.1). The results were comparable for the episode level data.

12.1.3.2 Indication for Oral Retinoids

In all 3 countries with available data, acne was the most commonly observed indication for oral retinoid prescriptions. Across the pre-, post-referral and post-implementation periods the proportions ranged from 89.4% to 92.5% in Germany, 83.0% to 85.0% in Spain and 63.4% to 67.7% in Sweden. The second most commonly observed indication group was dermatitis and eczema, which accounted for 13.8% to 15.3% of prescriptions in Germany, 10.4% to 19.1% of prescriptions in Spain and 3.8% to 4.4% of prescriptions in Sweden. Psoriasis was the third most commonly observed indication, with proportions ranging from about 0.9% to 6.8% across all countries and study periods. The indications of lichen planus and ichthyosis were rare across all countries and study periods (equal or less than 0.8%). There was a relatively high frequency of missing data for Sweden (30.2% to 35.0% of prescriptions vs. 2.2% to 4.8% in Germany and Spain). No data on oral retinoid indication was available for France. The results were comparable for the episode level data. There was a discrepancy between the rates with which particular oral retinoids were prescribed and the respective indications. This is most likely due to the fact that diagnosis codes could not be directly linked to prescriptions (e.g., in Spain) or are missing for the prescriptions (e.g., from 2.2% to 35.0%). We also found a small number of prescriptions that were linked to some diagnostic ICD codes that were out of scope for the study (e.g., L66.2 - Folliculitis decalvans, L71.9 - Rosacea, unspecified, L73 - Other follicular disorders), which may have contributed to the discrepancy.

12.1.3.3 Speciality of Oral Retinoid-Prescribing Physicians

Oral retinoids were mostly prescribed by dermatologists, who across study periods made between 81.1% to 83.9% of the prescriptions in France, 89.7% to 90.1% in Germany and 88.0% to 87.4% in Sweden. In Spain dermatologists made 16.8% to 27.6% of oral retinoid prescriptions across study periods. GP's were the second most common prescriber group, accounting for between 14.2% to 16.7% of prescriptions in France across study periods. The respective proportions were

around 6% in Germany, around 21% in Spain and between 1.1% and 2.0% in Sweden. Data for prescriber speciality in the 3 study periods was missing for 44.1% to 50.5% of prescriptions in Spain and 9.4% to 10.7% of prescriptions in Sweden. Therefore, the data from the 2 countries needs to be considered with caution. Overall, the pattern of prescriber speciality was largely consistent across study periods. The results were comparable for the episode level data.

12.1.3.4 Treatment Characteristics: Prescription Count, Prescription Length, Duration of Treatment and Average Daily Dose

The treatment characteristics varied considerably between the 4 countries. The *average prescription count* ranged from 1.6 to 5.3 in the pre-referral period, from 1.6 to 5.5 in the post-referral period and from 1.7 to 4.8 in the post-implementation period. Overall, the lowest counts were observed in Spain and the highest in France. In line with PPP recommendations, the *average prescription length* in France was approximately 28 days in both pre-implementation periods and 27.4 days in the post-implementation period. In Germany, the average prescription length was slightly longer than a month, with 43.2 and 42.5 days in the pre- and post-referral periods, and 38.2 days in the post-implementation period. In Sweden, the average prescription length was approximately 55 days in all 3 study periods. Spain showed the longest prescription lengths with 94.1, 117.0 and 125.9 days, respectively, that were not in line with the PPP recommendation. However, this finding could be related to local prescribing practice (see section 12.1.2.2). The average treatment duration observed in Germany was the shortest with 114.6 and 129.8 days in the pre- and post-referral period, and 102.2 days in the post-implementation period. The French and Spanish data showed a similar average treatment duration of 135.3, 150.7 and 133.8 days and 133.7, 166.2 and 169.9 days across the 3 study periods, respectively. The Swedish data showed overall the longest treatment duration with 173.9, 181.8 and 162.9 days in the 3 study periods. Across the 3 study periods, the average treatment durations varied widely by the type of oral retinoid and country (APPENDIX 3 RESULTS FOR TREATMENT CHARACTERISTICS BY ORAL RETINOID MOLECULE AND BY COUNTRY). For acitretin the treatment durations ranged from 55.7 days in France to 173.6 days in Spain (~8-25 weeks) across countries and study periods. For alitretinoin they ranged from 39.0 days in Sweden to 126.7 days in France (~5.5-18

weeks) and for isotretinoin from 102.3 days in Germany to 186.3 days in Sweden (~14.5-26.5 weeks) across the study periods.

The results on the average daily dose prescribed varied across countries but were similar for the 3 study periods. The averages observed were around 27.0 mg to 27.3 mg for France, 17.1 mg to 17.6 mg for Germany, 26.8 mg to 28.8 mg for Spain and 30.5 mg to 31.4 mg for Sweden. Different oral retinoids that have different dosage recommendations (Table 12) have been grouped together for this analysis. The observed differences may reflect the country specific differences in indications, recommended dosages and/or possibly local practice with respect to oral retinoid prescriptions. In the interpretation it is also important to note that data on dosage was unavailable in the German and Swedish databases. Here the average daily dose was estimated according to the procedure described in the SAP section 16.2.3.6. The average daily dose varied by oral retinoid. For acitretin the dosages ranged from 20.8 mg to 32.6 mg across countries and the two implementation periods. For alitretinoin the range was between 19.1 mg and 30.0 mg. For isotretinoin the range was between 16.7 mg and 31.3 mg. APPENDIX 3 RESULTS FOR TREATMENT CHARACTERISTICS BY ORAL RETINOID MOLECULE AND BY COUNTRY shows the results for the average dosage stratified by country and oral retinoid.

12.1.3.5 Pregnancies Exposed to Oral Retinoids and Outcomes

The number of *exposed pregnancies* identified in the pre-, post-referral and post-implementation period were 958 (13.4%), 1,164 (10.4%) and 730 (16.6%) in France, 13 (12.1%), 14 (6.1%) and 11 (36.7%) in Germany, 21 (20.2%), 27 (14.6%) and 31 (19.0%) in Spain and 7 (5.9%), 31 (7.8%) and 38 (15.1%) in Sweden.

The *incidence rates* per 1000 patient years for the pre-, post-referral and post-implementation periods were 18.6, 17.7 and 14.1 for France, 5.4, 4.1 and 7.9 for Germany, 11.3, 9.5 and 10.2 for Spain, and 1.1, 1.9 and 2.7 for Sweden.. Further, the numbers presented in our study may not be directly comparable with other studies conducted in France or other study countries due to differences in the study design and exposure assessment methods.

With respect to *pregnancy outcomes* of exposed pregnancies, termination was generally the most frequently observed among pregnancies exposed with available information on outcome in the pre-, post-referral and post-implementation periods with proportions of 56.7%, 57.8% and 68.0% in France, 77.8%, 66.7% and 71.4% in Germany, 50.0%, 56.2% and 0.0% in Spain, and 0.0%, 82.6% and 65.7% in Sweden. In the respective study periods, live births were observed in 39.6%, 38.7% and 26.9% of exposed pregnancies in France, 11.1%, 33.3% and 14.3% in Germany, 38.9%, 18.8% and 83.3% in Spain, and 25.0%, 0.0% and 0.0% in Sweden. Miscarriages were observed in <1.7%, <1.3% and <2.7% of exposed pregnancies in France, 11.1%, 0.0% and 14.3% in Germany, and 11.1%, 25.0% and 16.7% in Spain and 75.0%, 17.4% and 34.3% in Sweden. Stillbirths were not observed in France, Germany, Spain and Sweden. Although France reported non-live births, which may have included stillbirths. There were no recorded birth defects in Germany, Spain and Sweden and recorded birth defects were very rare in France (less than 1.7% of exposed pregnancies) in the pre-implementation periods and not observed in the post-implementation period. In France terminations were comparatively higher in the post-implementation than pre-implementation periods, however it needs to be noted that the incidence rate of exposed pregnancies declined. The proportions varied more for the countries with smaller samples and the findings need to be interpreted very cautiously.

12.1.3.6 Multi-Country Meta-Analysis

All meta-analyses were characterised by substantial heterogeneity. Below we therefore focus on the discussion of change in contraceptive use before, during and after oral retinoid treatment, periodicity of oral retinoid prescriptions, and laboratory pregnancy testing before, during and after oral retinoid treatment, rather than aggregated proportions per study period.

12.1.3.6.1 Contraceptives Use

The meta-analysis for prescribing patterns of contraceptives showed a 1.4% increase in oral retinoid treatment episodes with contraceptive use within 30 days before treatment start from the pre-referral to the post-referral period and a 2.9% increase to the post-implementation period. A gradual increase of 3.0% over the 3 study periods was observed for concomitant contraceptive use during oral retinoid treatment and a gradual increase of 3.1% over the 3 study periods was

observed for contraceptive use within 30 days after oral retinoid treatment. The proportions were similar when France or Germany were removed from the analysis. Slightly smaller increases in the proportions of contraceptive use before, during and after oral retinoid treatment of around 2.0% were observed when Sweden was removed from the analysis and slightly larger increases of the proportions of around 4% were observed when Spain was removed from the analysis.

12.1.3.6.2 Periodicity of Prescriptions

The meta-analysis of the periodicity of oral retinoids prescriptions for the 4 countries showed no change in the time interval of approximately 50 days between prescription dates during the pre-implementation periods. However, an increase of approximately 2 days was observed during the post-implementation period. Over the 3 study periods, there was a more gradual increase of 3.4% in treatment episodes with monthly prescription intervals. The results were similar when France, Germany or Sweden were removed from the analysis. Removing Spain from the analysis led to a substantially shorter average observed time interval between prescription dates, which was overall more in line with the PPP requirements, as well as an increase of approximately 6% was observed with respect to treatment episodes with monthly prescription intervals.

12.1.3.6.3 Laboratory Pregnancy Tests

The meta-analysis for laboratory pregnancy testing before, during and after oral retinoid treatment was conducted for the 3 countries with available data (i.e. France, Germany, and Spain); Sweden was excluded due to very low counts. A gradual increase in proportions of treatment episodes with laboratory pregnancy testing before treatment start was observed over the 3 study periods. The overall change in proportions amounted to approximately 5% when a period up to 30 days before treatment start was considered and to approximately 6% when a period up to 7 days was considered. Also, with regard to treatment episodes with at least one monthly test during treatment, an overall increase of approximately 5% over the 3 study periods was observed. The proportions of treatment episode time covered by compliant monthly laboratory pregnancy testing, as well as laboratory pregnancy testing after oral retinoid treatment stop remained low and relatively stable over the 3 study periods (1.5% to 2.8% and 3.6% to 3.9%, respectively).

12.1.3.7 Trends in the Prescribing Practice of Oral Retinoids with Respect to Measures of the PPP - Interrupted Time Series Analysis

ITS analyses were performed to identify ongoing trends in contraceptive use and laboratory pregnancy testing before and during oral retinoid treatment during the pre-, post-referral and post-implementation periods.

12.1.3.7.1 Contraceptives Use

12.1.3.7.1.1 Trends in Contraceptives Use Before Treatment Episodes with Oral Retinoids

During the *pre-referral period* there were significant increasing trends in the proportion of treatment episodes with contraceptive use before oral retinoid treatment start in France and Sweden. For Germany and Spain, in contrast, no significant trends were observed. During the *post-referral period* significant increasing trends were again observed for France and Sweden. For France, the trend was less pronounced and almost flat compared to pre-referral, but for Sweden the trend remained unchanged. A significant increasing trend in the proportions was also observed for Germany. France, Germany and Sweden showed small negative but significant level changes, i.e. a decrease in proportions, from the pre-referral to the post-implementation period. Spain showed a significantly decreasing trend in the proportion of treatment episodes with contraceptive use before oral retinoid treatment from the pre-referral to the post-implementation period. During the *post-implementation period* significantly increasing trends were observed for Germany and Sweden. For Germany there was now an accelerated increase compared to the post-referral period. For Sweden the previously observed increasing trend remained unchanged and continued increasing on the same trajectory. However, a slight negative trend was now observed for France. No significant trend was observed for Spain. Although here, significant positive level changes occurred between the pre- and post-implementation periods.

Overall, the ITS analyses suggest slight improvements in the adherence to the PPP with respect to contraceptive use before treatment start with oral retinoids from the pre-referral to the post-

implementation period for Germany and Sweden. However, only for Germany this trend accelerated significantly after the implementation of the updated PPP. Although it needs to be noted that this pattern appeared to be mainly influenced by the data captured during the last quarter in the study period. For France the observed positive trend levelled off during the post-referral period, possibly suggesting changes in clinical practice already occurred with the announcement of the updated PPP. It needs to be noted that the current data suggests that PPP compliance in France was already higher than in the other 3 countries that were included in this study. Some of the level changes are difficult to explain in the light of referral and/or implementation of the updated PPP. It is important to consider that other factors might account for the observed changes. In some cases the level changes appear to be related to seasonality patterns in the data. Level changes should only be interpreted with caution, particularly with respect to pre-referral and post-implementation period that are separated by a longer time period. The level changes observed in Spain could suggest that referral and implementation of the updated PPP may have led to a slight improvement with regard to clinical practice around contraceptive use before oral retinoid treatment, however no sustained positive trend occurred over time.

12.1.3.7.1.2 Trends in Contraceptives Use During Treatment Episodes with Oral Retinoids

France and Sweden showed significant increasing trends in the proportion of oral retinoid treatment episodes with concomitant contraceptive use in all 3 study periods. For France, the trend was most pronounced during the pre-referral period compared to the post-referral and post-implementation periods. For Germany, a significant increasing trend was observed during the post-implementation period. However, the trend was small and only differed significantly from the trend observed in the pre- but not post-referral period. France, Germany and Sweden showed small negative level changes between pre-referral and post-implementation periods (i.e. a decrease in proportions at the start of the period compared to the end of the previous period). For Spain no significant trend was observed during the pre-referral period, but slight significant decreasing trends were observed during the post-referral and post-implementation periods. There was a significant level change, i.e. increase in proportions, from the end of the post-referral to the start of the post-implementation period.

Overall, the ITS analyses suggest slight improvements in the adherence to the PPP with respect to contraceptive use during treatment with oral retinoids in France and Sweden. However, the trends did not increase with referral or implementation of the updated PPP. Only for Germany the trend accelerated significantly after the implementation of the updated PPP. Although it needs to be noted that this pattern appears to be driven by the data of the last quarter in the study period. The negative level changes for France and Germany from the pre-referral to the post-implementation period are difficult to explain in the light of referral and/or implementation of the updated PPP. In part, these effects appear to be caused by the high proportions observed at the end of the previous study period. The high proportions are likely due to the fact that episodes that start in the last 3 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. The level changes observed in Spain could suggest that referral and implementation of the updated PPP may have led to a slight improvement with regard to clinical practice around contraceptive use during oral retinoid treatment, however no sustained positive trend occurred over time.

12.1.3.7.2 Laboratory Pregnancy Tests

12.1.3.7.2.1 Trends in Laboratory Pregnancy Testing Before Treatment Episodes with Oral Retinoids

For France there were no significant trends in the proportions of oral retinoid treatment episodes with prior laboratory pregnancy testing in the two pre-implementation periods. There were no significant level and trend changes for pregnancy testing before oral retinoid treatment start during any of the study periods, with the exception of a positive change in slope from post-referral to post-implementation. Here a significant increasing trend in the proportions over time was observed. For Germany no significant trends or changes in trends or levels between study periods were observed. For Spain a significant decreasing trend in the proportions of oral retinoid treatment episodes with prior laboratory pregnancy testing was observed during the pre-referral period. There was a significant level change from the pre- to the post-referral period and also a significant change in trend from negative to flat. This trend changed again significantly during the post-implementation period, where it became positive.

Overall the ITS analysis results suggest that the implementation of the updated PPP was associated with small and statistically significant improvements in the proportions of oral retinoid treatment episodes with prior laboratory pregnancy testing, possibly suggesting improved clinical practice with respect to pregnancy testing in 2 of the 3 countries with available data.

12.1.3.7.2.2 Trends in Monthly Laboratory Pregnancy Testing During Treatment Episodes with Oral Retinoids

With respect to the proportions of oral retinoid treatment episodes covered with monthly laboratory pregnancy tests, there were no significant trends during the pre- or post-referral periods in France. There were (marginally) significant level changes from the pre- to the post-referral and from the post-referral to the post-implementation period, which appeared to be due to the seasonal patterns in the proportions of treatment episodes that were covered with pregnancy tests. A significant trend change occurred from the post-referral to the post-implementation period. During the post-implementation period a significant increasing trend was observed. However, here the change in trend appeared to be largely driven by the data of the last four months of the post-implementation period. For Germany there was a significant 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 laboratory pregnancy tests observed in the shorter last quarter of the pre-referral period. A further significant change in the trend occurred from the post-referral to the post-implementation period. This trend during post-referral showed an accelerated increase in the proportion of oral retinoid treatment episodes that were covered with laboratory pregnancy tests. The increased proportion in the last four months is likely at least partially due to the fact that episodes starting near the end of the period have less episode time for analysis in the study period and therefore less time for a monthly test to be missed per episode. Visual inspection of the trend excluding the last four months suggests at best a marginal increase in laboratory pregnancy testing over the study periods. No significant trends or changes in trends were observed for Spain.

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 laboratory pregnancy testing during oral retinoid treatment in 2 of the 3 countries with available data, but 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.

12.1.3.8 Other analyses

12.1.3.8.1 Key Elements of the PPP Described in the Primary Objective by Oral Retinoid Substance

The results of the stratified analyses for the primary and secondary objectives (except for treatment characteristics) are presented in the Supplement 2.

12.1.3.8.1.1 Contraceptives Use

Across the 4 countries there was no clear pattern of contraceptive prescriptions associated with the different oral retinoids 30 days prior to-, continuous concomitant during- and 30 days after treatment.

In France, the proportions of episodes with PPP conform contraceptive prescriptions prior to oral retinoid treatment in the pre- and post-referral and post-implementation periods were 40.6%, 47.1% and 43.9% for acitretin, 53.7%, 63.9% and 67.3% for alitretinoin, and 38.6%, 41.9% and 42.1% for isotretinoin. In Germany, the respective proportions were 6.7%, 2.2% and 0.0% for acitretin, 4.9%, 3.2% and 2.9% for alitretinoin, and 8.7%, 8.8% and 11.4% for isotretinoin. In Spain, the proportions were 8.1%, 9.1% and 4.6% for acitretin, 26.7%, 8.3% and 0.0% for alitretinoin, and 14.9%, 15.3% and 14.6% for isotretinoin. In Sweden, the proportions were 33.3%, 28.6% and 33.2% for acitretin and 33.1%, 37.0% and 39.3% for isotretinoin. Alitretinoin did not have marketing authorisation during the pre-implementation period in Sweden. The proportion of episodes with 30 days of contraception before treatment start with alitretinoin in the post-implementation period was 37.5%.

In France, the proportion of treatment episodes with concomitant contraceptive prescriptions were lower in the pre- than in the post-referral period and intermediate in the post-implementation period for acitretin (39.9%, 46.6% and 43.1%, respectively). For alitretinoin an increasing pattern was observed (47.6%, 56.7% and 59.0%, respectively) and for isotretinoin there was little change over the 3 study periods (34.8%, 37.4% and 37.9%, respectively). In Germany, the proportions were lower for acitretin (4.3%, 4.6% and 2.0%, respectively) for the respective study periods. For alitretinoin the proportions fluctuated (4.7%, 1.9% and 4.9%, respectively) and for isotretinoin there was an increase from the pre-implementation to the post-implementation period (7.2%, 7.1% and 9.7%, respectively). In Spain, the proportions of treatment episodes with PPP compliant contraceptive prescriptions during oral retinoid treatment showed a decreasing pattern from the pre- to the post-implementation periods. For acitretin the proportions remained relatively stable from pre- to post-referral and decreased thereafter to the post-implementation period (6.6%, 6.9% and 2.9%, respectively). For alitretinoin a decreasing pattern over the study periods was observed (20.0%, 11.8% and 0.0%, respectively). For isotretinoin the proportion of compliant prescriptions was relatively stable across the study periods (14.0%, 13.1% and 13.6%, respectively). The Spanish alitretinoin data came from less than or equal to 17 individuals and does therefore not allow for firm conclusions. The Swedish data showed little change in terms of the proportions of treatment episodes with compliant contraceptive prescriptions for acitretin (32.7%, 28.9% and 33.0%), whereas for isotretinoin the proportions increased from the pre- to the post-referral and the post-implementation period (32.3%, 36.6% and 40.4%, respectively). For alitretinoin the proportion of episodes with continuous concomitant contraception was 45.8%.

In France, the proportions of episodes with PPP conform contraceptive prescriptions after oral retinoid treatment increased from pre- to post-referral and a decreased thereafter during the post-implementation period for acitretin (42.4%, 49.5% and 45.5%, respectively). For alitretinoin an increasing pattern was observed (54.5%, 64.5% and 66.3%, respectively). For isotretinoin the proportion increased from pre- to post-referral and remained relatively stable thereafter (43.8%, 46.3% and 46.6%, respectively). In Germany, the respective proportions fluctuated for acitretin (3.8%, 5.0% and 0.0%, respectively), and alitretinoin (5.8%, 2.2% and 4.2%), and there was a

slight increase for isotretinoin (9.0%, 8.9% and 11.4%, respectively). In Spain, the proportions fluctuated for acitretin (7.6%, 10.8% and 3.6%, respectively). Across study periods, a decreasing pattern was observed for alitretinoin (20.0%, 16.7% and 0.0%, respectively), and an increasing pattern for isotretinoin (16.6%, 17.3% and 17.7%, respectively). In Sweden, the proportions remained relatively stable from pre- referral to post-implementation period for acitretin (34.2%, 29.8% and 32.7%, respectively), while an increasing pattern was observed for isotretinoin across study periods (39.2%, 42.4% and 44.9%, respectively). Alitretinoin did not have marketing authorisation during the pre-implementation period in Sweden. The proportion of episodes with 30 days of contraception after treatment with alitretinoin in the post-implementation period was 20.0%.

12.1.3.8.1.2 Periodicity of Prescriptions

In line with PPP recommendation of prescriptions that are ideally limited to 30 days, the French data showed a mean interval between prescriptions that was around 1 month (31.9 to 34.2 days) for all 3 oral retinoids and across the pre- and post-implementation periods. The German data showed intervals between 29.7 and 35.1 days for alitretinoin and 36.0 and 38.8 days for isotretinoin prescriptions, that were in line with or close to PPP recommendations. However, with 55.5, 53.2 and 41.3 days, in the pre-, post-referral and post-implementation periods respectively the interval between prescriptions was slightly longer than recommended for acitretin. The Spanish data also showed longer than recommended intervals between prescriptions with 147.4, 152.8 and 164.2 days for the pre- and post-referral and post-implementation period for acitretin, 256.0, 278.5 and 137.1 days for alitretinoin and 91.0, 91.0 and 100.0 days for isotretinoin, respectively. The results for alitretinoin were based on less than or equal to 6 observations and need to be considered with caution. In Sweden the interval between prescriptions was also longer than recommended with 50.9, 45.8 and 46.4 days for acitretin and 41.7, 42.8 and 44.5 days for isotretinoin, in the pre-and post-referral and post-implementation periods, respectively. For alitretinoin it was 40.0 days in the post-implementation period.

The proportion of treatment episodes with monthly prescription intervals in France was relatively stable and ranged between 35.5% and 48.9% over the 3 study periods for all oral retinoids. The proportions ranged from 11.1% to 43.5% in Germany, 0.0% to 16.7% in Spain (the n of alitretinoin

was less than or equal to 6), and 8.5% to 9.9% for acitretin and isotretinoin in Sweden. The proportion for alitretinoin in the post-implementation period in Sweden was 40.0% but based on $n = 4$.

12.1.3.8.1.3 Laboratory Pregnancy Tests

The French data showed the highest proportion of episodes with laboratory pregnancy testing conform PPP recommendations before treatment start for isotretinoin, with 75.1, 77.3% and 77.8% in the pre-and post-referral and post-implementation periods. Across the 3 study periods, between 51.3% and 53.9% of treatment episode time was covered by compliant laboratory pregnancy testing and the proportion of treatment episodes with laboratory pregnancy tests performed after treatment was around 13% in all study periods. For alitretinoin the proportions of episodes with prior laboratory pregnancy testing were 66.2%, 62.9% and 64.1% in the pre- and post-referral and post-implementation periods. Between 41.5% and 43.0% of treatment episode time across the study periods was covered by compliant laboratory pregnancy testing and the proportion of episodes with laboratory pregnancy tests performed after treatment was around 6% in both pre-implementation periods and 10.8% in the post implementation period. For acitretin the proportion of treatment episodes with laboratory pregnancy tests performed prior to treatment start was around 30% in all 3 study periods. In all 3 study periods, about 20% of treatment episode time was covered by compliant laboratory pregnancy testing and the proportion of treatment episodes with laboratory pregnancy tests performed after treatment was around 12%.

In Germany, the proportion of episodes with laboratory pregnancy tests before isotretinoin treatment start was 20.0%, 22.1% and 26.3% in the pre- and post-referral and post-implementation periods. Compliant laboratory pregnancy testing was observed in 20.0%, 22.0% and 25.2% of treatment episode time, respectively, and the proportion of treatment episodes with laboratory pregnancy tests performed after treatment was 2.9%, 3.4% and 3.2% in the respective study periods. For alitretinoin and acitretin the proportions of treatment episodes with compliant laboratory pregnancy testing before treatment start were 6.6%, 13.5% and 8.8% and 10.5%, 5.5% and 12.2% in the pre- and post-referral and post-implementation periods, respectively. Compliant laboratory pregnancy testing was observed in 8.9%, 13.0% and 10.2% and 6.6%, 6.5% and 6.5% of treatment episode time, respectively. After treatment 3.8%, 1.1% and 0.0% of alitretinoin and 0.0%, 2.5% and 0.0% of acitretin treatment episodes were covered by laboratory pregnancy tests, respectively.

In Spain, the proportion of episodes with laboratory pregnancy testing prior to isotretinoin treatment start was between 2.8% and 4.3% across the study periods. Compliant testing was observed in 38.7%, 34.2% and 26.3% of treatment episode time in the pre-, post-referral and post-implementation periods and the proportion of treatment episodes with laboratory pregnancy tests performed after treatment was between 1.1% and 1.4% across study periods. For alitretinoin less than or equal to 17 oral retinoid treatment episodes were observed, and no laboratory pregnancy testing was observed for these episodes before or after treatment. In the pre-implementation periods 20.8% of treatment episode time was covered by compliant laboratory pregnancy testing. This was 0.0% in the post-implementation period. For acitretin the proportions of oral retinoid treatment episodes with PPP compliant laboratory pregnancy testing prior to treatment were between 0.0% and 0.4% in all study periods. Compliant laboratory pregnancy testing was observed in 30.6%, 24.4% and 8.9% of treatment episode time in the pre-, post-referral and post-implementation periods and the proportion of treatment episodes with laboratory pregnancy tests performed after treatment was between 0.0% and 0.6% across study periods.

For Sweden no laboratory pregnancy tests were recorded in the registry data. Data was only available when documented by ICD-10 codes. The number of laboratory pregnancy observed prior, during and after treatment was therefore close to or 0%.

Overall, the French data showed higher proportions of oral retinoid treatment episodes with compliant laboratory pregnancy testing compared to the other 2 countries with available data, suggesting better PPP compliance. The findings show that isotretinoin treatment is associated with higher PPP compliance with respect to laboratory pregnancy testing, possibly because patients who are treated with isotretinoin are overall younger and of reproductive age (Supplement 2.2.1).

12.1.3.8.2 Sensitivity analyses

The first sensitivity analysis showed that in France the proportions of episodes with laboratory pregnancy testing before treatment start, as per PPP, were about 10% higher when laboratory pregnancy tests were considered over a 30-day (81.3%, 83.1% and 83.4%, respectively) rather than a 7-day period (72.9%, 75.5% and 76.4%, respectively) in the pre-, post-referral and post-implementation period, respectively. In Germany the proportion of episodes with compliant laboratory pregnancy testing before oral retinoid treatment start was similar when calculated over

a 30-day (20.8%, 23.3% and 27.4%, respectively) and a 7 day period (19.3%, 21.6% and 25.6%, respectively), respectively. In Spain the proportion of episodes with compliant laboratory pregnancy testing was approximately 10% higher when considered over a 30 day (12.5%, 14.5% and 14.6%, respectively) rather than a 7 day period (2.6%, 3.5% and 4.1%, respectively). Data on laboratory pregnancy testing was unavailable for Sweden.

The second sensitivity analysis was conducted excluding the first 6 months after implementation of the updated RMM. For all countries the results of the sensitivity analysis for laboratory pregnancy testing were comparable to the results of the main analysis.

For prescribing patterns for contraceptives before, during and after treatment episodes with oral retinoids the respective proportions in France excluding and including the 6 months after RMM implementation were 42.1%, 38.1%, and 47.3% vs. 42.3%, 38.1% and 46.7%. The mean time intervals between prescription dates and episodes with monthly prescription intervals were comparable with 31.8 days and 49.6% vs. 31.9 days and 48.6%. Laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 77.6% vs. 76.4% of episodes. The proportions of treatment episode time covered by compliant laboratory pregnancy testing were 49.6% vs. 50.4% and laboratory pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 13.2% vs. 12.6% of episodes.

In Germany, the respective proportions were also similar excluding and including the 6 months after RMM implementation with 12.5%, 11.1%, and 11.4% vs. 11.0%, 9.4% and 11.0%. The mean time intervals between prescription dates and episodes with monthly prescription intervals were comparable with 36 days and 43.5% vs. 36 days and 38.2%. Laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 24.8% vs. 25.6% of episodes. Treatment episode time was covered by compliant laboratory pregnancy testing was 25.3% vs. 24.4%. Laboratory pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 3.0% vs. 3.1% of episodes.

In Spain, the respective proportions were also similar excluding and including the 6 months after RMM implementation with 12.4%, 12.0%, and 14.8% vs. 14.1%, 13.0% and 17.0%. The mean time intervals between prescription dates and episodes with monthly prescription intervals were comparable with 93.2 days and 3.2% vs. 103.5 days and 3.0%. Laboratory pregnancy tests were performed within 7 days prior to oral retinoid treatment in 4.3% vs. 4.1% of episodes. Treatment episode time was covered by compliant laboratory pregnancy testing was 25.0% vs. 22.9%. Laboratory pregnancy testing within 30 (-/+7) days after oral retinoid treatment was performed in 1.0% vs. 1.1% of episodes.

In Sweden, the respective proportions were similar excluding and including the 6 months after RMM implementation with 39.4%, 40.9% and 44.3% vs. 39.2%, 40.3% and 44.6%. The mean time intervals between prescription dates and episodes with monthly prescription intervals were comparable with 44.8 days and 9.9% vs. 44.5 days and 9.6%. No laboratory pregnancy tests were recorded in the registry data. The number of laboratory pregnancy observed prior, during and after treatment was therefore close to or 0.0% in the pre- and post-implementation periods.

12.2 Strengths and Limitations

12.2.1 Study Strengths

- The data sources contain a wealth of readily available information from routine clinical practice which contribute to a comprehensive understanding of real-world clinical practice and outcomes with respect to oral retinoid treatment in France, Germany, Spain and Sweden.
- The results of the study are highly generalisable for France (e.g., database covers ~99% of the population) and Sweden (e.g., database has full national cover; all medicines are electronically prescribed). Coverage of data collected in Germany and Spain was lower, due to the nature of the data sources. However, the German data had high coverage of pregnancies in women receiving healthcare services as all reimbursable services were comprehensively recorded. The Spanish database covered Catalonia only (~16% of the Spanish population), however here coverage of the population was high (~80%).
- The included data sources have continuously provided reliable insights for various PASS (14), including PASS requested by the EMA (e.g., EUPAS18510, EUPAS19610, EUPAS14852,

EUPAS34255), as well as are routinely used in peer reviewed publications (8, 15, 43, 18, 44, 7, 45, 10, 12, 46, 20, 47–49).

- The study was conducted by an experienced team specialised in the design and conduct of such drug utilisation studies in the safety area. It followed IQVIA SOPs as well as the methodological guidelines on ENCePP and EMA GVP Module VIII – PASS (1).

12.2.2 Study Limitations

- The use of secondary data, data that has not been primarily collected for research purposes comes with specific limitations. For instance, when data is not available assumptions are made to approximate values for e.g. daily dosage, prescription length and/or treatment length. Such issues were addressed by the PRAC and followed by the request to cover the evaluation of the use of non-prescribed, non-reimbursed contraceptive methods in female oral retinoid users in an accompanying multi-country patient survey. This multi-country patient survey has been conducted by the MAHs to gain further insights into PPP compliance and potential barriers and facilitators of compliance. The results are reported in a separate report.
- Contraceptives
 - Not all contraceptive measures that may have been used by women on oral retinoid treatment were documented in databases, i.e. in France, Germany and Spain only reimbursed contraceptives were captured. Therefore, the present analysis mainly focussed on prescriptions for hormonal contraceptives and IUDs. While all contraceptive measures that were available in the data were considered, the current results on contraceptive use likely reflect an underestimation of actual contraceptive use. However, this concerns both the pre-implementation and the post-implementation periods of the study. Thus estimates of change are still meaningful.
 - The German claims database contained information about all reimbursed contraceptives in the outpatient setting (including prescriptions by all physician specialties like GPs and gynaecologists). Contraceptives are not prescribed outside of this setting in Germany. Contraceptive use in Germany might be underestimated, as contraceptives were only reimbursed up to the 20th birthday until 29-Mar-2019 and until the 22nd birthday thereafter (42). However, contraceptives have always been

reimbursed when medically indicated, as is the case with oral retinoids treatment (50, 51). Accordingly, it is expected that the analysis reflects accurate data that is representative of the wider German female population between the ages of 13 and 49. Nevertheless, the percentage of females on oral retinoid treatment over the age of 20 years with records of contraceptives seems low. As for all countries, in Germany not all contraceptives that would have been used by the women would have been prescribed and reimbursed.

- In Spain, not all hormonal contraceptives are reimbursed and therefore reported information in SIDIAP may reflect an underestimation. However, if the physician issued a prescription for contraceptives, or the gynaecologist/midwife registers in the ASSIR database module that the patient is on contraceptive treatment, the contraception was captured. The ASSIR are the primary care centres for women's sexual and reproductive healthcare, where approximately 50%-60% of the pregnancies in Catalonia are followed by gynaecologists and midwives.
- The study aimed to detect prescriber practice, yet, due to the nature of the databases used (e.g. claims) it is more reflective of patient practice (e.g., prescription refill rather than issuance).
- Laboratory pregnancy tests
 - Records of laboratory pregnancy tests performed within the healthcare setting (e.g., for reimbursement purposes) were not comprehensively captured in the databases and the extent varied across countries.
 - In Spain point-of-care quick urine tests which are performed by the physician during the medical consultation might be captured, yet, inconsistently and as free text. Hence, such tests were not included in the analysis to avoid introducing bias.
 - In Sweden, no laboratory pregnancy tests were recorded in the registry data, the performance of laboratory pregnancy tests was only available when documented by ICD-10 codes like Z32 "Pregnancy examination and test".
 - For acitretin users contraception and laboratory pregnancy tests should be continued until 3 years after completion of therapy; as the post-implementation period is limited to 2 years in order to provide a final report in December 2022 this follow-up time was

not available for patients treated in the post-implementation period; however, in acitretin users the available follow-up was checked.

- Pregnancy and pregnancy outcomes
 - The extent of available information on pregnancy, pregnancy termination and pregnancy outcomes varied between databases and countries, thus the information was likely not captured for all patients. In France SNIIRAM (administrative claims data) and in Sweden (Medical Birth Register) the vast majority of pregnancies and pregnancy outcomes were covered, e.g. about 97% to 99% of deliveries have been reported in the medical birth register in Sweden (21). However, the Swedish birth registry only captured pregnancies after 22 weeks. Records on pregnancies were also documented in the patient registry regardless of the duration of pregnancy, but missing information regarding early termination needs to be considered. Further, it is likely that overestimating pregnancy length, as there is an undocumented loss, could have led to misclassification of exposure in pregnancy.
 - In France, a previously published algorithm was used to identify pregnancies in SNDS (8). The basic algorithm was based on the pregnancy outcomes as a source to identify the pregnancies. Additionally, this study considered pregnancies based on reimbursed events related to the management of a pregnancy (e.g., ultrasound of the 2nd trimester of pregnancy) that did not have an associated outcome. For this safety study, a more conservative approach was chosen. A larger pregnancy period was considered when the pregnancy start date could not be determined clearly in the data and pregnancies were counted in all periods that they overlapped. Thus, it is possible that the same pregnancies were counted multiple times across periods. As a result, the number of exposed pregnancies may have been overestimated.
 - In Germany, the coverage of pregnancies in women receiving healthcare services is generally high because all reimbursable services are comprehensively recorded in administrative claims data. The completeness of outcomes' reporting varied depending on the type of outcome, e.g., an underreporting of induced abortions is possible (52).
 - For Spain, pregnancy related diagnoses in SIDIAP were captured from two ambulatory modules existing in the electronic records. The primary care ICD-10 registers (which

record diagnoses coded by GPs and nurses as Z30-Z39 and O00-O99) may have had a pregnancy end date that is not the true date of pregnancy termination, as in some cases it might have been the date of the visit in the primary care centre or the date of a diagnosis related to pregnancy (Z30-Z39). The sexual and reproductive health care (ASSIR) registers have information reported by gynaecologists and midwives. Approximately 50%-60% of pregnant women in Catalonia visit these centres, where pregnancy related information is thoroughly recorded. If the patient is registered in ASSIR, the date of last menstruation and the date of predicted delivery/date of termination of pregnancy were used, but for other patients less reliable primary care register data was used.

- In Spain, with the information available on the follow-up of pregnant women, it was not known whether labour and caesarean sections were live births.
- In Spain, pregnancy outcomes of about 68% (estimate from 2005 to 2018) of newborns can be linked to their mothers in SIDIAP (15, 18), thus the current results reflect only available data.
- Incomplete information regarding the pregnancy duration may have led to misclassification of timing of exposure during pregnancy.
- For Sweden data on the indication for oral retinoid treatment was only available in the hospital setting (no primary care data), which may have led to underestimated results.
- The databases used for Germany, Spain, and Sweden are updated once a year and data availability differed due to the differences in the timepoints for updates. The annual update of the German claims database was available at the beginning of the year adding data for an entire calendar year (for example: 2016 data is available at the beginning of 2018). The Swedish National Patient Register annual update is completed in Q3 of the following year.
- The French SNIIRAM database does not capture the speciality of the prescribers in the inpatient setting. Moreover, the indications of the oral retinoid prescriptions were neither captured in the hospital nor the outpatient setting.
- The post-implementation period coincided largely with the COVID-19 pandemic, during which lockdowns frequently precluded physician visits and thus mandated procedures for the PPP. Furthermore, safety concerns around possible COVID-19 infection might have led

women to avoid physician visits and to conduct pregnancy testing at home, even in absence of or after the official lockdown periods.

12.3 Interpretation

This study report provides results on the pre-implementation period before the update of PPP (i.e., pre- and post-referral period) and the post-implementation period, for the 4 target countries France, Germany, Spain, and Sweden.

The proportion of oral retinoid treatment episodes with fully compliant contraceptive prescriptions ranged from approximately 30% to 40% in France and Sweden and were below 10.0% in Germany and around 13.0% in Spain. While this result might indicate lower compliance with strict PPP criteria in Germany and Spain, the findings need to be interpreted cautiously in the light of the different data availability and reimbursement of contraceptives in the 4 countries. Moreover, the proportions may underestimate actual PPP compliance due to the exclusion of nonpharmacological and over the counter contraception (53).

The periodicity of prescriptions of oral retinoids in France, Germany and Sweden was mostly in line with PPP requirements in both pre-implementation periods and the post-implementation period, whereas the periodicity was about twice as long as required in Spain. This finding is in line with local clinical practice, possibly indicating the need of better PPP adherence in Spain. While there are no publications on electronic prescriptions, the Spanish data provider also specified that chronic prescriptions, which in the Spanish system have a default duration of 1 year, may have automatically extended during part of the year 2020, due to the impact of the COVID-19 pandemic. This may explain the relatively longer interval between prescription dates that was observed for the post-implementation period.

Data on laboratory pregnancy testing was available for France, Germany and Spain. However, for Sweden this was largely not the case. French oral retinoid prescription records indicated that laboratory pregnancy testing was conducted approximately $\frac{3}{4}$ of the time prior to initiating

treatment with oral retinoids, indicating overall a relatively good compliance with the PPP recommendations over the 3 study periods. This is in contrast to a report by others for French data (9), but similar results have been recently reported elsewhere (54). Overall, the German and Spanish cohorts, showed lower rates of laboratory pregnancy testing before oral retinoid treatment start than France. However, an increase of 6.3% over study periods was observed in Germany, and a 1.5% increase was observed Spain. These findings for Germany and Spain might reflect lower compliance, however may also be partly explained by local clinical practice and the data availability in the 2 countries.

In France, approximately half of the treatment episode time in all 3 study periods was covered by compliant laboratory pregnancy testing, and there was little change over the study periods. Over the 3 study periods, a slight increasing trend in terms of compliant laboratory pregnancy testing during oral retinoid treatment was observed for Germany. For Spain, in contrast, a declining trend was observed. It is likely that the need for medically supervised pregnancy testing is determined according to local practice, including consideration of the patient's sexual activity and recent menstrual history, leaving some clinical discretion for further testing which should be considered in the interpretation of the current results (3). While particularly the Spanish results with the declining trend may raise concerns, the data from the post-implementation period needs to be interpreted with particular caution, given that this period was heavily impacted by the COVID-19 pandemic. For example, due to the pandemic the face-to-face attendance in primary care was often not possible. Research has shown that there was a decline in diagnoses in Spain, which would have normally been made during face-to-face physician visits that could not take place due to strict lockdown measures (55, 39, 56).

Finally, laboratory pregnancy testing after treatment with oral retinoids was comparatively low in the 3 countries with available data and relatively stable across the study periods, suggesting lower PPP compliance, which may be related to patient disengagement after the treatment with oral retinoids has ended. Overall, this study seems to indicate that compliance with pregnancy testing could be improved. A recent study, which was conducted in Belgium reported similar findings (57).

There was a lot of variability in the number of exposed pregnancies, especially in countries with low data availability, and no clear trend occurred over the study periods. In line with the findings of a previous review (58), the current study showed that generally the majority of the oral retinoid exposed pregnancies resulted in pregnancy terminations. Importantly, with the exception of the French cohort, cohort sizes were small. The number of (exposed) pregnancies with available information on outcomes was overall very low in Germany, Spain and Sweden, and the French data can be considered as most informative but after considering the limitations related to exposure and pregnancies assessment in the study. The findings pertaining to pregnancy outcomes in the German, Spanish and Swedish cohort need to be interpreted very cautiously.

Overall, the current results appear in line with the findings of Crijns et al.'s (2013) systematic review of PPP compliance in Europe, supporting the updated RMM (59). This study detected some positive changes in terms of PPP compliance over the 3 study periods, however overall these changes were relatively small and possibly further reduced due to COVID-19 lockdown measures that coincided with the post-implementation period. Additional, important cohort specific considerations with respect to the interpretation of the results are discussed in section 12.2.2 and in the following section 12.4.

12.4 Generalisability

The data sources were selected based on a sufficient number of patients taking oral retinoids and the availability of information relevant to describe the effectiveness of the updated PPP within these countries (see section 10.5.1). SNIIRAM in France and the national registries Sweden capture near-comprehensive nation-wide data. These databases are the most comprehensive data sources for prescribed /dispensed contraceptives in the 2 countries and the best reflection of current clinical practice with high generalisability within countries.

The Company Health Insurance covering about 3% of the German population (~3.5 million insurants), is slightly lower than the coverage of the THIN database which has been used in other DUS to assess effectiveness of the RMMs (60). For SIDIAP, one should be mindful that this data is representative of Catalonia, which makes up approximately 16% of the overall Spanish population. SIDIAP has routinely been used as a data source representative for Spain (60). It

captures the prescription of hormonal contraceptives that are reimbursed (i.e., levonorgestrel plus ethinylestradiol) and captures dates of prescription of IUDs. However, information on other hormonal contraceptives including over-the-counter sales are not recorded.

Finally, it bears mentioning that the 4 study countries which capture north, mid and south-western Europe differ from other European countries with regard to healthcare systems, socioeconomic conditions (61), contraceptive use (62) and EM issued along with oral retinoid treatment. While the findings are in line with previous reports from the Netherlands (63), generalisability of the current results across Europe might be limited in particular with respect to eastern or south-eastern European countries. In order to get further insights across other European countries a survey study has been conducted simultaneously in 7 countries in different parts of Europe, 3 of which are also included in the DUS. While the DUS reveals the level of implementation of the PPP by physicians, the survey shows the physicians' and patients' level of understanding of the PPP. If both studies were to demonstrate similar levels of knowledge, understanding, and implementation/adherence, it could be argued that the 2 studies support each other, thereby providing some external validity. Thus, the survey may give a supplementary reference to the extrapolation and generalisation of the results obtained from the DUS to other European countries.

13 OTHER INFORMATION

NA

14 CONCLUSION

This study report provides insights on treatment patterns, PPP compliance and patient characteristics associated with oral retinoid treatment in 4 European countries for the pre- and post-referral (pre-implementation) and post-implementation periods of the updated PPP. Overall, the results seem to support concerns about PPP compliance raised by the 2016 PRAC review. Some positive trends in compliance from the pre- to the post-implementation period were observed, yet overall the changes were of relatively small magnitude. Importantly, given that the findings overestimate the occurrence of exposed pregnancies and underestimate contraceptive use and pregnancy testing, they may potentially represent an underestimation of overall PPP compliance. Studies that use primary data collection could give more exact estimates. Furthermore, the implementation of possible changes in clinical practice in response to the updated

PPP has likely been impacted negatively by the effects of the COVID-19 pandemic and associated lockdown measures or patient safety behaviours (64, 39, 65, 56, 41, 55).

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16 APPENDICES

APPENDIX 1 LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	NA	21 November 2022	Oral Retinoids DUS Final Report V1.0_Supplement

APPENDIX 2 ADDITIONAL INFORMATION

Appendix 2.1 List of Medicinal Products Marketed by the Oral Retinoids Consortium Per Country Included in the Study

MAH of product in the member state	Member State	Product Name (in authorisation country)	Brand
Arrow Génériques	France	Acnetrait 10 mg, capsule molle	Acnetrait
Arrow Génériques	France	Acnetrait 20 mg, capsule molle	Acnetrait
Arrow Génériques	France	Acnetrait 40 mg, capsule molle	Acnetrait
Arrow Génériques	France	Acnetrait 5 mg, capsule molle	Acnetrait
Arrow Génériques	France	Soriatane 10 mg, gélule	Soriatane
Arrow Génériques	France	Soriatane 25 mg, gélule	Soriatane
Laboratoires Bailleul S.A.	France	Contracne 10 mg, capsule molle	Contracne
Laboratoires Bailleul S.A.	France	Contracne 20 mg, capsule molle	Contracne
Laboratoires Bailleul S.A.	France	Contracne 40 mg, capsule molle	Contracne
Laboratoires Bailleul S.A.	France	Contracne 5 mg, capsule molle	Contracne
Laboratoires Expanscience	France	Procuta 5 mg, capsule molle	Procuta
Laboratoires Expanscience	France	Procuta 10 mg, capsule molle	Procuta
Laboratoires Expanscience	France	Procuta 20 mg, capsule molle	Procuta
Laboratoires Expanscience	France	Procuta 40 mg, capsule molle	Procuta
Stiefel laboratories legacy (Ireland) Ltd	France	Toctino 10 mg, capsule molle	Toctino
Stiefel laboratories legacy (Ireland) Ltd	France	Toctino 30 mg, capsule molle	Toctino
Pierre Fabre Dermatologie	France	Curacné 10 mg, soft capsule	Curacné
Pierre Fabre Dermatologie	France	Curacné 20 mg, soft capsule	Curacné
Pierre Fabre Dermatologie	France	Curacné 40 mg, soft capsule	Curacné

MAH of product in the member state	Member State	Product Name (in authorisation country)	Brand
Pierre Fabre Dermatologie	France	Curacné 5 mg, soft capsule	Curacné
Pierre Fabre Dermatologie	France	Alizem 10 mg, capsule molle	Alizem
Pierre Fabre Dermatologie	France	Alizem 30 mg, capsule molle	Alizem
Almirall Hermal GmbH	Germany	Aknenormin (isotretinoin) 10 mg, soft capsule	Aknenormin
Almirall Hermal GmbH	Germany	Aknenormin (isotretinoin) 20 mg, soft capsule	Aknenormin
Puren Pharma GmbH & Co. KG	Germany	Isotretinoin Puren 10 mg, Weichkapseln	Isotretinoin
Puren Pharma GmbH & Co. KG	Germany	Isotretinoin Puren 20 mg, Weichkapseln	Isotretinoin
Puren Pharma GmbH & Co. KG	Germany	Neotigason 10 10mg, Hartkapseln	Neotigason
Puren Pharma GmbH & Co. KG	Germany	Neotigason 25 25mg, Hartkapseln	Neotigason
Dermapharm AG	Germany	Acicutan 10 mg, Hartkapseln	Acicutan
Dermapharm AG	Germany	Acicutan 25 mg, Hartkapseln	Acicutan
Dermapharm AG	Germany	Alitrederm 10 mg, Weichkapseln	Alitrederm
Dermapharm AG	Germany	Alitrederm 30 mg, Weichkapseln	Alitrederm
Galenpharma GmbH	Germany	IsoGalen 10 mg, Weichkapseln	IsoGalen
Galenpharma GmbH	Germany	IsoGalen 20 mg, Kapseln	IsoGalen
Hexal AG	Germany	Isotret-Hexal 10 mg, Kapseln	Isotret-Hexal
Hexal AG	Germany	Isotret-Hexal 20 mg, Kapseln	Isotret-Hexal
Basics GmbH	Germany	Isotretinoin Basics 10 mg, Weichkapseln	Isotretinoin
Basics GmbH	Germany	Isotretinoin Basics 20 mg, Weichkapseln	Isotretinoin
Ratiopharm GmbH	Germany	Isotretinoin-ratiopharm 10 mg, Weichkapseln	Isotretinoin-ratiopharm
Ratiopharm GmbH	Germany	Isotretinoin-ratiopharm 20 mg, Weichkapseln	Isotretinoin-ratiopharm
GAP S.A.	Germany	Isotretinoin GAP 10 mg Weichkapseln	Isotretinoin GAP

MAH of product in the member state	Member State	Product Name (in authorisation country)	Brand
GAP S.A.	Germany	Isotretinoin GAP 20 mg Weichkapseln	Isotretinoin GAP
GSK	Germany	Toctino 10 mg, Weichkapseln	Toctino
GSK	Germany	Toctino 30 mg, Weichkapseln	Toctino
Alfasigma España, S.L.	Spain	Mayesta 10 mg, cápsulas blandas	Mayesta
Alfasigma España, S.L.	Spain	Mayesta 20 mg, cápsulas blandas	Mayesta
Aurovitas Spain, S.A.U.	Spain	Neotigason 10 mg, cápsulas duras	Neotigason
Aurovitas Spain, S.A.U.	Spain	Neotigason 25 mg, cápsulas duras	Neotigason
Especialidades Farmacéuticas Centrum, S.A.	Spain	Flexresan 10 mg, cápsulas blandas	Flexresan
Especialidades Farmacéuticas Centrum, S.A.	Spain	Flexresan 20 mg, cápsulas blandas	Flexresan
Stiefel Farma, S.A.	Spain	Toctino 10 mg, cápsulas blandas	Toctino
Stiefel Farma, S.A.	Spain	Toctino 30 mg, cápsulas blandas	Toctino
Industrial Farmacéutica Cantabria, S.A.	Spain	Alitretinoína IFC 10 mg, cápsulas blandas EFG	Alitretinoína
Industrial Farmacéutica Cantabria, S.A.	Spain	Alitretinoína IFC 30 mg, cápsulas blandas EFG	Alitretinoína
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 5 mg, cápsulas blandas	Dercutane
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 10 mg, cápsulas blandas	Dercutane
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 20 mg, cápsulas blandas	Dercutane
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 30 mg, cápsulas blandas	Dercutane
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 40 mg, cápsulas blandas	Dercutane
ISDIN SA	Spain	Isdiben 10 mg, cápsulas blandas	Isdiben
ISDIN SA	Spain	Isdiben 20 mg, cápsulas blandas	Isdiben
ISDIN SA	Spain	Isdiben 40 mg, cápsulas blandas	Isdiben

MAH of product in the member state	Member State	Product Name (in authorisation country)	Brand
Pierre Fabre Iberica SA	Spain	Isoacne 10 mg, cápsulas blandas	Isoacne
Pierre Fabre Iberica SA	Spain	Isoacne 20 mg, cápsulas blandas	Isoacne
Pierre Fabre Iberica SA	Spain	Isoacne 40 mg, cápsulas blandas	Isoacne
Pierre Fabre Iberica SA	Spain	Isoacne 5 mg, cápsulas blandas	Isoacne
Sun Pharmaceutical Industries Europe B.V.	Spain	Isotretinoína Sun 10 mg, cápsulas blandas	Isotretinoína
Sun Pharmaceutical Industries Europe B.V.	Spain	Isotretinoína Sun 20 mg, cápsulas blandas	Isotretinoína
Industrial Farmacéutica Cantabria, S.A.	Spain	Acitretina IFC 10 mg, cápsulas duras	Acitretina
Industrial Farmacéutica Cantabria, S.A.	Spain	Acitretina IFC 25 mg, cápsulas duras	Acitretina
Laboratoires Bailleul S.A.	Spain	Isotretinoína Bailleul 20 mg cápsulas blandas	Isotretinoína Bailleul
Laboratoires Bailleul S.A.	Spain	Isotretinoína Bailleul 40 mg cápsulas blandas	Isotretinoína Bailleul
Orifarm Generics A/S	Sweden	Acitretin Orifarm 10 mg, capsules hard	Acitretin
Orifarm Generics A/S	Sweden	Acitretin Orifarm 25 mg, capsules hard	Acitretin
Orifarm Generics A/S	Sweden	Isotretinoin Orifarm 10 mg, capsules soft	Isotretinoin
Orifarm Generics A/S	Sweden	Isotretinoin Orifarm 20 mg, capsules soft	Isotretinoin
Actavis Group PTC ehf	Sweden	Isotretinoin Actavis 10mg, capsules soft	Isotretinoin
Actavis Group PTC ehf	Sweden	Isotretinoin Actavis 20mg, capsules soft	Isotretinoin
Actavis Group PTC ehf	Sweden	Neotigason 10 mg capsules hard	Neotigason
Actavis Group PTC ehf	Sweden	Neotigason 25 mg capsules hard	Neotigason
SANDOZ A/S	Sweden	Isotretinoin Sandoz 5 mg mjuka kapslar	Isotretinoin Sandoz
SANDOZ A/S	Sweden	Isotretinoin Sandoz 10 mg mjuka kapslar	Isotretinoin Sandoz
SANDOZ A/S	Sweden	Isotretinoin Sandoz 20 mg mjuka kapslar	Isotretinoin Sandoz

Appendix 2.2 List of Companies - MAHs that constitute the oral retinoids consortium

Name	Alias
2CARE4GENERIC	2CARE4GENERIC
ALFASIGMA ESPAÑA S.L.	ALFASIGMA ESPAÑA
ALMIRALL S.A.	ALMIRALL
ARISTO PHARMA SP. Z O.O.	ARISTO PHARMA
AUROBINDO PHARMA LIMITED	AUROBINDO
BAUSCH HEALTH COMPANIES	BAUSCH HEALTH IRELAND LIMITED
DERMAPHARM AG	DERMAPHARM
ENNOGEN HEALTHCARE LIMITED	ENNOGEN HEALTHCARE
ESPECIALIDADES FARMACÉUTICAS CENTRUM S.A.	ESPECIALIDADES FARMACÉUTICAS CENTRUM
F. HOFFMANN-LA ROCHE AG	ROCHE
FIDIA FARMACEUTICI S.P.A.	FIDIA
GALENPHARMA	GALENPHARMA
GAP S.A.	GAP
GLAXOSMITHKLINE PLC	GSK
HEXAL AG	HEXAL
IASIS PHARMA	IASIS PHARMA
INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A.	INDUSTRIAL FARMACÉUTICA CANTABRIA
ISDIN S.A.	ISDIN
LABORATOIRE EXPANSCIENCE	EXPANSCIENCE
LABORATOIRES BAILLEUL S.A.	BAILLEUL
LABORATOIRES SMB S.A.	SMB
LABORATÓRIO MEDINFAR	MEDINFAR
MORNINGSIDE HEALTHCARE LTD	MORNINGSIDE HEALTHCARE
MYLAN N.V.	MYLAN
ORIFARM	ORIFARM
PELPHARMA	PELPHARMA
PHARMATHEN S.A.	PHARMATHEN
PIERRE FABRE DERMATOLOGIE	PIERRE FABRE
SANOSWISS UAB	SANOSWISS
STADA Arzneimittel AG	STADA
SUN PHARMACEUTICAL INDUSTRIES LTD.	SUN PHARMA
TARGET	TARGET
TEVA PHARMACEUTICALS EUROPE B.V.	TEVA

Appendix 2.3 List of Represented MAHs Contact Details

MAH identified as contact for PASS	Represented Affiliates
2CARE4GENERICs Stenhuggervej 12-14, DK-6710 Esbjerg, Denmark	N/A
Alfasigma España, S.L. Avenida Diagonal 490, 4º 08006 Barcelona Spain	N/A
Almirall, S.A. Laureà Miró, 408 - 410 08980 Sant Feliu de Llobregat Spain	Almirall Sp. z o.o. ul. Pileckiego 63 02-781 Warszawa Poland Phone number: +48 22 330 02 57 LSO email: agnieszka.raczewska@almirall.com Almirall Germany (Reinbek) Scholtzstrasse 3 21465 Reinbek Germany Phone: +49 40 727 040 LSO email: marit.stieglitz@almirall.com PharmAZet Group s.r.o. Trtinová 260/1 196 00 Prague Czech Republic Tereza Rajdlova, rajdlova@pharmazet.com; Tereza Lunackova, lunackova@pharmazet.com
Laboratoire Arrow 26, avenue Tony Garnier 69007 Lyon France	Puren Pharma GmbH & Co. KG Willy-Brandt-Allee 2 81829 Munich Germany Aurovitas Spain Sau 5ª Planta Avda de Burgos 16 D 28036 Madrid Spain Laboratoire Arrow 26, avenue Tony Garnier

MAH identified as contact for PASS	Represented Affiliates
	69007 Lyon France Aurobindo Pharma (Italia) Srl. Via San Giuseppe,102 21047 Saronno (VA) Italy Aurobindo Pharma B.V. Baarnsche Dijk 1 3741 LN Baarn Netherlands Iprac sprl Holstheide 18 – 3040 Huldenberg Belgium Generis Farmaceutica, S.A. Rua João de Deus, 19 2700-487 Amadora Portugal
ARISTO PHARMA Sp. z o.o. Baletowa 30 02-867 Warsaw Poland	N/A
Bausch Health Ireland Limited 3013 Lake Drive Citywest Business Campus, Dublin 24 D24 PPT3, Ireland Formerly: Pharmaswiss Ceska Republika S.R.O., Jankovcova 1569/2c 170 00 Prague 7 Czech Republic	N/A
mibe GmbH Arzneimittel Münchener Str.15 06796 Brehna Germany	Dermapharm AG Lil-Dagover-Ring 7 82031 Grünwald Germany Sun-Farm Sp. z o.o. ul. Dolna 21 05-092 Łomianki Poland
Ennogen Healthcare Limited	N/A

MAH identified as contact for PASS	Represented Affiliates
Unit G4, Riverside Industrial Estate Riverside Way Dartford, DA1 5BS United Kingdom	
Especialidades Farmacéuticas Centrum S.A. Calle Sagitario 14 03006 Alicante Spain	N/A
F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel Switzerland	N.V. Roche S.A.,Bruxelles Rue Dante 75 Bruxelles, 1070 Belgium Roche Bulgaria EOOD 16, Bialo pole Str. Sofia, 1618 Bulgaria Roche d.o.o. Ulica grada Vukovara 269a Zagreb, 10000 Croatia Roche Eesti OÜ Lõõtsa 2 Tallinn, 11415 Estonia Roche (Magyarország) Kft Edison u. 1. Budaörs, 2040 Hungary Roche Products (Ireland) Limited 3004 Lake Drive, Citywest Naas Road Dublin 24 Ireland Roche Latvija SIA G. Astras iela 8B Rīga, 1082 Latvia UAB Roche Lietuva

MAH identified as contact for PASS	Represented Affiliates
	J.Jasinskio 16b Vilnius, 01112 Lithuania Roche Romania SRL Piața Presei Libere Nr. 3-5 City Gate - South Tower Bucharest, 13702 Romania
Fidia Farmaceutici S.p.A., Via Ponte della Fabbrica 3/a 35031 Abano Terme (PD) Italy	N/A
Galenpharma GmbH Wittland 13 24109 Kiel Germany	N/A
GAP S.A. 46, Agissilaou str. 17341 Agios Dimitrios Greece	N/A
GlaxoSmithKline R&D Limited 1-3 Iron Bridge Road Stockley Park West, Uxbridge Middlesex, UB11 1BT United Kingdom	Glaxosmithkline Pharma GmbH - Vienna Wienerbergstraße 7 1100 Wien Austria CMS: Austria Stiefel Laboratories Legacy (Ireland) Limited - Cork Unit 2 Building 2500, Avenue 2000 Cork Airport Business Park Cork, Ireland CMS: Denmark, France, Iceland, Italy, Netherlands, Norway, Poland GlaxoSmithKline Oy The Piispansilta 9A, P.O. Box 24 Espoo, 02230 Finland CMS: Finland

MAH identified as contact for PASS	Represented Affiliates
	GlaxoSmithKline GmbH & Co. KG Prinzregentenplatz 9, Munchen 81675, Germany CMS: Germany GlaxoSmithKline Trading Services Limited - Dublin 12 Riverwalk Citywest Business Campus 24 Dublin, Ireland CMS: Slovakia GlaxoSmithKline Trading Services Limited - Dublin 12 Riverwalk Citywest Business Campus 24 Dublin, Ireland CMS: Slovenia Spain - Stiefel Farma, S.A. Severo Ochoa, 2 Parque Tecnologico de Madrid, Tres Cantos, Madrid 28760 Spain CMS: Spain GlaxoSmithKline UK Ltd. 980 Great West Road, Brentford, Middlesex TW8 9GS CMS: United Kingdom
Hexal AG Stella Boehmert Industriestrasse 25 83607 Holzkirchen Germany	Sandoz A/S Edvard Thomsens Vej 14 2300 Copenhagen Denmark Hexal AG Industriestrasse 25 83607 Holzkirchen Germany Sandoz B.V. Veluwezoom 22,

MAH identified as contact for PASS	Represented Affiliates
	1327 AH Almere The Netherlands Sandoz Pharmaceuticals d.d. Verovškova ulica 57 1000 Ljubljana Slovenia Rowex Ltd. Bantry Co. Cork P75 V009 Ireland.
Iasis Pharmaceuticals Hellas S.A. 137 Filis Ave 13451 Kamatero Greece	N/A
Industrial Farmacéutica Cantabria S.A. Calle Arequipa 1 28043 Madrid Spain	Difa Cooper S.p.A. Via Milano 160 21042 Caronno Pertusella Italy
Isdin S.A. Provençals 33 08019 Barcelona Spain	Isdin S.r.l. Via Tito Speri, 8 20154 Milano Italy
Laboratoires Expanscience 1 place des Saisons 92 048 Paris La Défense cedex France	N/A
Laboratoires Bailleul S.A. 10 12 Avenue Pasteur 2310 Luxembourg Luxembourg	N/A
Laboratoires SMB S.A. Rue de la Pastorale 26-28 1080 Brussels Belgium	N/A
Laboratório Medinfar - Produtos Farmaceuticos S.A. Rua Henrique de Paiva Couceiro, N° 29 Venda Nova 2700-451 Amadora Portugal	N/A
Generics (UK) Limited Station Close,	Generics (UK) Limited Station Close,

MAH identified as contact for PASS	Represented Affiliates
Potters Bar, Hertfordshire EN6 1TL United Kingdom Correspondence Address: Generics (UK) Limited t/a Mylan Building 4, Trident Place, Mosquito Way, Hatfield, Hertfordshire, AL10 9UL United Kingdom	Potters Bar, Hertfordshire EN6 1TL United Kingdom Mylan B.V. Dieselweg 25 3752 LB Bunschoten Netherlands
Morningside Healthcare Ltd. Morningside House Unit C Harcourt Way Leicester LE19 1WP United Kingdom	N/A
Orifarm Generics A/S Energivej 15 5260 Odense S Denmark	N/A
Pelpharma Handels GmbH Wohndorfweg 36 3001 Tulbing Austria	N/A
Pharmathen S.A. 6, Dervenakion street 153 51 Pallini Greece	Pharmathen Investments Group Limited 32, Kritis, Papachristoforou Building 3087 Limassol Cyprus
Pierre Fabre Dermatologie 45 place Abel Gance 92100 Boulogne France	Pierre Fabre Benelux S.A. Rue Henri-Joseph Genesse 1 B - 1070 Bruxelles Belgium Pierre Fabre Italia SpA con Unico Azionista Via G. Washington, 70 20146 Milano Italy Pierre Fabre Iberica S.A. C/Ramon Trias Fargas, 7-11 Edificio Marina Village 08005 Barcelona

MAH identified as contact for PASS	Represented Affiliates
	Spain
SanoSwiss UAB Aukstaiciu str. 26A LT-44169 Kaunas Lithuania	SanoSwiss UAB Lvovo str. 25 LT-09320 Vilnius Lithuania
Stada Arzneimittel AG Stadastraße 2-18 61118 Bad Vilbel Germany	Eurogenerics N.V./S.A. Heizel Esplanade B22 1020 Bruxelles Belgium Centrafarm B.V. van de Reijtstraat 31-E 4814 NE BredaNetherlands Genus Pharmaceuticals Limited Linthwaite, Huddersfield West Yorkshire, HD7 5QH United Kingdom
Sun Pharmaceutical Industries Europe B.V. Polarisavenue 87 2132JH Hoofddorp Netherlands	Basics GmbH Hemmelrather Weg 201 51377 Leverkusen Germany SC Terapia S.A. 124 Fabricii str. Cluj-Napoca 400 632 Romania SUN PHARMA UK 6-9 The Square ,Stockley Park, Uxbridge UB11 1FWLondon, United Kingdom
Target Pharma Ltd. 54, Menandrou Str. 104 31 Athens Greece	N/A
Teva Pharmaceuticals Europe B.V. Piet Heinkade 107: P.O. Box 16416 1001 RM Amsterdam Netherlands	Teva B.V Swensweg 5 2031GA Haarlem Netherlands Actavis Group PTC ehf Reyklavikurvegi 76-78

MAH identified as contact for PASS	Represented Affiliates
	220 Hafnarfjordur Iceland Ratiopharm GmbH Graf-Arco-Str. 3 89079 Ulm Germany Teva Gyógyszergyár Zrt Pallagi ut 13 4042 Debrecen Hungary

APPENDIX 3 RESULTS FOR TREATMENT CHARACTERISTICS BY ORAL RETINOID MOLECULE AND BY COUNTRY

Please note that the same tables in this Appendix 3 are repeated in **Supplement 2.2.4** of the stand-alone final report Supplement file (see Appendix 1).

Appendix 3.1 France

Table 111 Treatment characteristics of patients on acitretin in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	5,443	5,353	2,822
Number of episodes (CES): n	4,343	4,573	2,334
Number of prescriptions (FAS): n	15,045	14,508	7,745
Number of prescriptions (CES): n	9,450	10,279	5,190
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	5.6 (6.9)	5.5 (6.8)	5.2 (5.6)
Median (Q1 – Q3)	3.0 (1.0 – 7.0)	3.0 (1.0 – 6.0)	3.0 (1.0 – 7.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	18.5 (9.2)	18.8 (9.1)	18.8 (9.6)
Median (Q1 – Q3)	17.0 (9.0 – 21.0)	17.0 (9.0 – 21.0)	17.0 (9.0 – 21.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	55.7 (72.0)	58.1 (77.1)	57.2 (71.3)
Median (Q1 – Q3)	26.0 (17.0 – 66.0)	26.0 (17.0 – 70.0)	26.0 (17.0 – 71.0)
Number of prescriptions per treatment episode			
Mean (SD)	2.2 (2.3)	2.2 (2.5)	2.2 (2.3)
Median (Q1 – Q3)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 3.0)
Number of treatment episodes per patient			
Mean (SD)	2.4 (2.3)	3.1 (3.8)	4.0 (5.3)
Median (Q1 – Q3)	1.0 (1.0 – 3.0)	1.0 (1.0 – 3.0)	1.0 (1.0 – 4.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	30.2 (7.2)	30.3 (7.1)	30.2 (7.3)
Median (Q1 – Q3)	35.0 (25.0 – 35.0)	35.0 (25.0 – 35.0)	35.0 (25.0 – 35.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Table 112 Treatment characteristics of patients on alitretinoin in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	1,498	1,562	731
Number of episodes (CES): n	1,056	1,157	489
Number of prescriptions (FAS): n	5,138	5,664	2,361
Number of prescriptions (CES): n	3,293	3,692	1,311
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	4.0 (3.4)	4.4 (4.3)	3.8 (3.5)
Median (Q1 – Q3)	3.0 (1.0 – 5.0)	3.0 (2.0 – 6.0)	3.0 (1.0 – 5.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	38.6 (11.7)	37.7 (12.6)	36.3 (12.9)
Median (Q1 – Q3)	45.0 (33.0 – 45.0)	45.0 (30.0 – 45.0)	45.0 (25.0 – 45.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	125.3 (95.7)	126.7 (103.7)	106.1 (93.0)
Median (Q1 – Q3)	90.0 (45.0 – 180.0)	92.0 (45.0 – 180.0)	74.0 (45.0 – 148.0)
Number of prescriptions per treatment episode			
Mean (SD)	3.1 (2.7)	3.2 (2.6)	2.7 (2.2)
Median (Q1 – Q3)	2.0 (1.0 – 5.0)	3.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)
Number of treatment episodes per patient			
Mean (SD)	1.2 (0.6)	1.3 (1.1)	1.5 (1.5)
Median (Q1 – Q3)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	19.3 (2.5)	19.3 (2.5)	19.1 (2.9)
Median (Q1 – Q3)	20.0 (20.0 – 20.0)	20.0 (20.0 – 20.0)	20.0 (20.0 – 20.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹Based on the full analysis set (FAS)

²Based on the complete episodes set (CES)

Table 113 Treatment characteristics of patients on isotretinoin in France; analysis based on the episode level

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	107,185	140,757	112,788
Number of episodes (CES): n	74,067	101,152	65,853
Number of prescriptions (FAS): n	446,942	595,672	435,903
Number of prescriptions (CES): n	304,909	451,359	266,047
Oral retinoid prescription count¹			

Country: France			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of prescriptions per patient			
Mean (SD)	5.3 (2.9)	5.5 (3.1)	4.8 (3.0)
Median (Q1 – Q3)	6.0 (3.0 – 7.0)	6.0 (3.0 – 7.0)	4.0 (2.0 – 7.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	28.5 (11.7)	29.2 (11.9)	27.7 (11.9)
Median (Q1 – Q3)	29.4 (20.0 – 35.0)	30.0 (20.0 – 36.7)	28.0 (20.0 – 35.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	140.1 (109.7)	155.1 (116.8)	136.7 (113.5)
Median (Q1 – Q3)	120.0 (31.0 – 234.0)	147.0 (40.0 – 252.0)	102.0 (30.0 – 237.0)
Number of prescriptions per treatment episode			
Mean (SD)	4.1 (2.9)	4.5 (3.1)	4.0 (3.0)
Median (Q1 – Q3)	4.0 (1.0 – 6.0)	4.0 (1.0 – 7.0)	3.0 (1.0 – 7.0)
Number of treatment episodes per patient			
Mean (SD)	1.4 (1.0)	1.6 (1.3)	1.8 (1.7)
Median (Q1 – Q3)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	27.3 (4.5)	27.2 (4.6)	26.9 (4.8)
Median (Q1 – Q3)	30.0 (25.0 – 35.0)	30.0 (25.0 – 35.0)	30.0 (25.0 – 35.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-02/2019, post-implementation period 03/2019-12/2020

¹Based on the full analysis set (FAS)

²Based on the complete episodes set (CES)

Appendix 3.2 Germany

Table 114 Treatment characteristics of patients on acitretin in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	94	109	51
Number of episodes (CES): n	56	73	34
Number of prescriptions (FAS): n	307	382	148
Number of prescriptions (CES): n	122	150	64
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	3.9 (3.6)	4.6 (5.4)	3.7 (3.1)
Median (Q1 – Q3)	3.0 (1.0 - 5.0)	2.0 (1.0 - 5.0)	3.0 (1.0 - 5.5)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	66.8 (32.0)	66.9 (35.3)	55.1 (24.8)
Median (Q1 – Q3)	53.3 (50.0 - 95.0)	50.0 (50.0 - 100.0)	50.0 (30.0 - 63.5)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	139.6 (111.7)	127.4 (146.6)	99.8 (79.7)
Median (Q1 – Q3)	100.0 (54.5 - 170.0)	100.0 (50.0 - 150.0)	70.5 (50.0 - 127.0)
Number of prescriptions per treatment episode			
Mean (SD)	2.2 (2.0)	2.1 (3.1)	1.9 (1.5)
Median (Q1 – Q3)	2.0 (1.0 - 3.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Number of treatment episodes per patient			
Mean (SD)	0.7 (0.7)	0.9 (0.8)	0.9 (0.8)
Median (Q1 – Q3)	1.0 (0.0 - 1.0)	1.0 (0.0 - 1.0)	1.0 (0.0 - 1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	30.6 (20.5)	31.5 (19.4)	27.6 (14.7)
Median (Q1 – Q3)	25.0 (17.0 - 42.0)	25.0 (17.0 - 42.0)	25.0 (17.0 - 42.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Table 115 Treatment characteristics of patients on alitretinoin in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	64	103	41

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (CES): n	50	85	30
Number of prescriptions (FAS): n	204	380	116
Number of prescriptions (CES): n	137	271	91
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	4.2 (2.7)	5.1 (4.7)	3.3 (2.4)
Median (Q1 – Q3)	4.0 (2.0 - 5.0)	4.0 (2.0 - 6.0)	3.0 (1.0 - 5.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	32.8 (6.0)	32.8 (5.0)	30.2 (6.5)
Median (Q1 – Q3)	30.0 (30.0 - 32.5)	30.0 (30.0 - 34.3)	30.0 (30.0 - 32.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	91.8 (67.2)	106.4 (109.6)	97.6 (88.3)
Median (Q1 – Q3)	62.5 (30.0 - 135.0)	68.0 (30.0 - 150.0)	61.0 (30.0 - 147.0)
Number of prescriptions per treatment episode			
Mean (SD)	2.7 (1.8)	3.2 (3.1)	3.0 (2.5)
Median (Q1 – Q3)	2.0 (1.0 - 4.0)	2.0 (1.0 - 4.0)	2.0 (1.0 - 4.0)
Number of treatment episodes per patient			
Mean (SD)	1.0 (0.7)	1.1 (0.9)	0.9 (0.7)
Median (Q1 – Q3)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (0.0 - 1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	24.9 (7.4)	23.8 (7.9)	25.5 (6.5)
Median (Q1 – Q3)	30.0 (23.0 - 30.0)	29.0 (16.0 - 30.0)	29.0 (23.0 - 30.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-09/2019, post-implementation period 10/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Table 116 Treatment characteristics of patients on isotretinoin in Germany; analysis based on the episode level

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	2 537	4 447	1 915
Number of episodes (CES): n	1 929	3 755	1 479
Number of prescriptions (FAS): n	7 820	14 935	5 977
Number of prescriptions (CES): n	5 308	12 023	4 095
Oral retinoid prescription count¹			
Number of prescriptions per patient			

Country: Germany			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Mean (SD)	4.3 (3.1)	5.1 (3.8)	3.9 (2.8)
Median (Q1 – Q3)	4.0 (2.0 - 6.0)	4.0 (2.0 - 7.0)	3.0 (2.0 - 5.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	42.8 (19.7)	42.3 (18.1)	37.9 (16.8)
Median (Q1 – Q3)	33.5 (30.0 - 50.7)	32.9 (30.0 - 50.0)	30.3 (30.0 - 43.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	114.5 (104.8)	130.4 (117.7)	102.3 (87.9)
Median (Q1 – Q3)	71.0 (30.0 - 166.0)	90.0 (30.0 - 193.0)	66.0 (30.0 - 150.0)
Number of prescriptions per treatment episode			
Mean (SD)	2.8 (2.5)	3.2 (3.0)	2.8 (2.3)
Median (Q1 – Q3)	1.0 (1.0 - 4.0)	2.0 (1.0 - 5.0)	2.0 (1.0 - 4.0)
Number of treatment episodes per patient			
Mean (SD)	1.1 (1.1)	1.3 (1.2)	1.0 (0.8)
Median (Q1 – Q3)	1.0 (0.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	17.1 (10.0)	16.7 (9.4)	16.7 (8.7)
Median (Q1 – Q3)	16.0 (10.0 - 20.0)	16.0 (10.0 - 20.0)	16.0 (10.0 - 20.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period, post-referral period, post-implementation period

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Appendix 3.3 Spain

Table 117 Treatment characteristics of patients on acitretin in Spain; analysis based on the episode level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	271	318	243
Number of episodes (CES): n	142	166	110
Number of prescriptions (FAS): n	437	521	362
Number of prescriptions (CES): n	297	352	209
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	2.1 (1.7)	1.9 (1.5)	1.9 (1.5)
Median (Q1 – Q3)	1.0 (1.0 - 2.5)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	110.0 (91.0)	123.5 (117.2)	136.1 (99.8)
Median (Q1 – Q3)	85.5 (58.0 - 151.5)	88.5 (59.0 - 145.2)	98.5 (61.2 - 185.5)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	146.6 (120.8)	173.6 (152.2)	171.1 (120.0)
Median (Q1 – Q3)	97.0 (59.2 - 190.5)	122.0 (75.2 - 225.8)	148.0 (69.8 - 255.8)
Number of prescriptions per treatment episode			
Mean (SD)	1.4 (0.7)	1.4 (0.8)	1.3 (0.7)
Median	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 1.0)
Number of treatment episodes per patient			
Mean (SD)	1.7 (1.3)	1.8 (1.1)	1.3 (0.5)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	21.3 (12.0)	21.4 (14.6)	20.8 (10.3)
Median (Q1 – Q3)	25.0 (10.0 - 25.0)	25.0 (10.0 - 25.0)	25.0 (10.0 - 25.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Table 118 Treatment characteristics of patients on alitretinoin in Spain; analysis based on the episode level

Country: Spain	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	15	17	10
Number of episodes (CES): n	10	7	3
Number of prescriptions (FAS): n	21	21	14

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of prescriptions (CES): n	17	11	4
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	1.5 (0.8)	1.4 (0.8)	1.6 (1.6)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 1.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	84.5 (70.0)	94.6 (107.0)	74.0 (76.0)
Median (Q1 – Q3)	60.2 (33.4 - 153.1)	61.0 (44.2 - 91.5)	60.0 (33.0 - 108.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	118.5 (89.4)	104.9 (104.9)	75.0 (76.0)
Median (Q1 – Q3)	118.0 (37.2 - 182.5)	92.0 (52.5 - 102.5)	61.0 (34.0 - 109.0)
Number of prescriptions per treatment episode			
Mean (SD)	1.5 (1.0)	1.1 (0.4)	1.0 (0.0)
Median (Q1 – Q3)	1.0 (1.0 - 1.8)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)
Number of treatment episodes per patient			
Mean (SD)	1.6 (0.8)	1.0 (0.0)	1.3 (0.6)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.5)
Average oral retinoid daily dose (mg)²			
Mean (SD)	30.0 (23.1)	24.3 (9.8)	30.0 (0.0)
Median (Q1 – Q3)	30.0 (15.0 - 30.0)	30.0 (20.0 - 30.0)	30.0 (30.0 - 30.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Table 119 Treatment characteristics of patients on isotretinoin in Spain; analysis based on the episode level

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	3,376	4,681	4,437
Number of episodes (CES): n	2,620	3,129	2,329
Number of prescriptions (FAS): n	4,997	7,152	6,608
Number of prescriptions (CES): n	4,217	5,526	4,431
Oral retinoid prescription count¹			
Number of prescriptions per patient			

Country: Spain			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Mean (SD)	1.6 (0.9)	1.6 (1.0)	1.7 (1.0)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	93.3 (72.7)	116.7 (85.6)	125.5 (89.3)
Median (Q1 – Q3)	71.0 (50.0 - 119.7)	90.0 (59.5 - 158.0)	97.0 (60.0 - 178.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	133.1 (94.2)	165.9 (109.5)	170.0 (109.2)
Median (Q1 – Q3)	110.0 (56.0 - 184.0)	154.0 (78.0 - 222.0)	156.0 (90.0 - 232.0)
Number of prescriptions per treatment episode			
Mean (SD)	1.5 (0.8)	1.6 (0.9)	1.5 (0.9)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Number of treatment episodes per patient			
Mean (SD)	1.5 (0.8)	1.4 (0.7)	1.4 (0.6)
Median (Q1 – Q3)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	27.1 (17.6)	29.1 (19.6)	27.7 (16.1)
Median (Q1 – Q3)	20.0 (20.0 - 30.0)	20.0 (20.0 - 30.0)	20.0 (20.0 - 30.0)

CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation, pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Appendix 3.4 Sweden

Table 120 Treatment characteristics of patients on acitretin in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	440	526	421
Number of episodes (CES): n	360	454	359
Number of prescriptions (FAS): n	679	912	738
Number of prescriptions (CES): n	511	678	560
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	3.3 (2.7)	4.2 (4.0)	4.1 (3.9)
Median (Q1 – Q3)	2.0 (1.0-5.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	42.3 (19.2)	37.2 (15.8)	37.1 (16.5)
Median (Q1 – Q3)	29.0 (29.0-58.0)	29.0 (29.0-29.0)	29.0 (29.0-29.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	64.2 (53.1)	60.7 (59.6)	62.6 (62.8)
Median (Q1 – Q3)	29.0 (29.0-72.0)	29.0 (29.0-72.0)	29.0 (29.0-72.0)
Number of prescriptions per treatment episode			
Mean (SD)	1.4 (1.0)	1.5 (1.2)	1.6 (1.4)
Median (Q1 – Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Number of treatment episodes per patient			
Mean (SD)	2.1 (1.5)	2.4 (1.8)	2.2 (1.5)
Median (Q1 – Q3)	1.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	32.6 (6.0)	32.4 (4.9)	32.3 (5.0)
Median (Q1 – Q3)	34.5 (34.5-34.5)	34.5 (34.5-34.5)	34.5 (34.5-34.5)

NA, not applicable; CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

Table 121 Treatment characteristics of patients on alitretinoin in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period ³
	Pre-referral	Post-referral	
Number of episodes (FAS): n	0	0	24
Number of episodes (CES): n	0	0	5
Number of prescriptions (FAS): n	0	0	46

Country: Sweden			
	Pre-implementation period		Post-implementation period ³
	Pre-referral	Post-referral	
Number of prescriptions (CES): n	0	0	5
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	NA	NA	1.9 (1.3)
Median	NA	NA	1.0 (1.0-2.2)
Oral retinoid prescription length²			
Average length of prescriptions per treatment episode (days)			
Mean (SD)	NA	NA	39.0 (13.4)
Median	NA	NA	45.0 (45.0-45.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	NA	NA	39.0 (13.4)
Median (Q1 – Q3)	NA	NA	45.0 (45.0-45.0)
Number of prescriptions per treatment episode			
Mean (SD)	NA	NA	1.0 (0.0)
Median (Q1 – Q3)	NA	NA	1.0 (1.0-1.0)
Number of treatment episodes per patient			
Mean (SD)	NA	NA	1.0 (0.0)
Median (Q1 – Q3)	NA	NA	1.0 (1.0-1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	NA	NA	20.0 (0.0)
Median (Q1 – Q3)	NA	NA	20.0 (20.0-20.0)

NA, not applicable; CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

³ In Sweden, oral alitretinoin was granted a marketing authorisation in April 2020.

Table 122 Treatment characteristics of patients on isotretinoin in Sweden; analysis based on the episode level

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Number of episodes (FAS): n	10,407	17,419	20,078
Number of episodes (CES): n	6,609	12,112	12,138
Number of prescriptions (FAS): n	37,029	60,847	63,742
Number of prescriptions (CES): n	23,960	45,015	39,365
Oral retinoid prescription count¹			
Number of prescriptions per patient			
Mean (SD)	4.1 (2.3)	4.2 (2.6)	3.9 (2.5)
Median (Q1 – Q3)	4.0 (2.0-5.0)	4.0 (2.0-6.0)	3.0 (2.0-5.0)
Oral retinoid prescription length²			

Country: Sweden			
	Pre-implementation period		Post-implementation period
	Pre-referral	Post-referral	
Average length of prescriptions per treatment episode (days)			
Mean (SD)	55.9 (24.5)	56.1 (22.2)	55.4 (20.7)
Median (Q1 – Q3)	53.8 (34.0-67.0)	57.6 (34.0-67.0)	58.8 (34.0-67.0)
Duration of oral retinoid treatment²			
Duration of treatment episodes (days)			
Mean (SD)	179.9 (103.1)	186.3 (108.8)	165.9 (109.7)
Median (Q1 – Q3)	201.0 (67.0-262.0)	201.0 (67.0-268.0)	158.0 (67.0-261.0)
Number of prescriptions per treatment episode			
Mean (SD)	3.6 (2.4)	3.7 (2.5)	3.2 (2.5)
Median (Q1 – Q3)	3.0 (1.0-5.0)	3.0 (1.0-5.0)	3.0 (1.0-5.0)
Number of treatment episodes per patient			
Mean (SD)	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)
Median (Q1 – Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Average oral retinoid daily dose (mg)²			
Mean (SD)	31.3 (6.8)	31.3 (6.3)	30.4 (5.6)
Median (Q1 – Q3)	29.9 (29.4-31.5)	29.9 (29.4-31.9)	29.9 (29.4-29.9)

NA, not applicable; CES, complete episodes set; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation; pre-referral period 07/2014-06/2016, post-referral period 07/2016-12/2018, post-implementation period 01/2019-12/2020

¹ Based on the full analysis set (FAS)

² Based on the complete episodes set (CES)

APPENDIX 4 SUMMARY REPORT

The summary report below describes the key findings of two studies that were conducted in response to the EMA Referral EMEA/H/A-31/1446 Retinoid-containing medicinal products:

- *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)*
- *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*

1. 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 the Pregnancy Prevention Programme (PPP) have been put in place since 2003.

In July 2016, the United Kingdom (UK) initiated an *Article 31 referral* requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to review the benefit-risk profile of oral and topical retinoids. The PRAC completed the review in 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 for pregnancy testing and the use of contraception. After the review, the PRAC recommended to amend the product information for acitretin, alitretinoin, and isotretinoin, update the PPP, and the associated educational materials. In June 2018, the decision to strengthen the recommendations for pregnancy prevention for oral retinoids was endorsed by the European Commission. In addition to an update of the Risk Minimisation Measures (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 (*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)*) and a drug utilisation study (*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*) described in this current summary report, were conducted to assess healthcare professionals' (HCPs') and patients'/caregivers' awareness, knowledge, and adherence to the PPP, as well as to assess the effectiveness of the updated RMMs. This report will first discuss the survey and then the DUS. In this summary report only primary objectives of the survey and the DUS are described and discussed. At the end of the report a general discussion and conclusions are provided.

2. 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

2.1 Study objectives

The primary objectives of the survey were to assess the effectiveness of the PPP based on the pre-defined success thresholds for PPP awareness, knowledge, and adherence among HCPs and patients/caregivers. Additional secondary objectives included the assessment of HCPs' and patients'/caregivers' awareness of and adherence to the updated PPP, as well as knowledge of the risks and RMMs associated with the use of oral retinoids.

2.2 Study designs and Settings

The 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 due to long regulatory timelines]). The HCP survey was initiated first, followed by the

patient/caregiver survey, where the participants were invited by the HCPs. 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 so that respondents could participate only once.

2.3 Results

Out of 14,996 reachable and eligible HCPs, 3.2% (n = 477) submitted the completed questionnaire and were included in the analysis. 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 (categories were not mutually exclusive). 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 were not mutually exclusive).

Of the 116 participating patients/caregivers, 85.3% (n = 99) were 18 to 49 years old. 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. 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.

Analysis of success in HCPs

Success of the PPP for HCPs in all three domains was not met in the survey. However, the success of the awareness domain, which had a pre-defined threshold of 75%, was met.

HCPs: Analysis of success in awareness domain

Overall, 93.3% of HCPs had access to the Summary of Product Characteristics (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

For questions concerning risk of oral retinoid use, >95% HCPs agreed with most of the statements including that treatment with oral retinoids is contraindicated during pregnancy and poses a risk of teratogenicity. In general, a lower proportion (~70%) of HCPs agreed with the statements regarding prescribing restrictions including limiting the prescriptions to 30 days' supply and requiring a new prescription every month.

HCPs: Analysis of success in adherence domain among HCPs

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. However, only 18.7% (95% CI: 15.1%, 23.0%) correctly indicated requiring supervised pregnancy test within a maximum of seven days before the first dose. Further, among the prescribers of acitretin in the previous six months, 29.6% (95% CI: 24.1%, 35.8%) correctly indicated requiring supervised pregnancy test regularly for three years after treatment discontinuation. 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 (68.4% [95% CI: 63.3%, 73.1%]) always prescribed/recommended contraception for their patients or referred them to a gynaecologist for contraception. Overall, 70.6% of HCPs had monthly or every two weeks follow-up visits with their female oral retinoid patients who are of childbearing potential, which were the options considered for answering the question correctly. Finally, another finding was that the adherence of HCPs to both conduct medically supervised pregnancy testing and to prescribe contraceptives seemed to decrease once the treatment with oral retinoids had stopped.

Analysis of success in patients/caregivers

Success of the PPP for patients/caregivers in all three domains was not met in this survey. However, the success of the awareness domain, which had a pre-defined threshold of 60%, was met.

Patients/Caregivers: Analysis of Success in Awareness Domain

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 questions 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 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. Further, 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 and 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. Also, 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. 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.

3. DUS: Evaluation of the effectiveness of Pregnancy Prevention Programme (PPP) for oral retinoids

3.1 Study objectives

The primary objectives of the DUS were to evaluate possible changes in oral retinoid prescribing and monitoring practices for females of childbearing age receiving oral retinoid prescriptions of acitretin, alitretinoin, or isotretinoin before and after the referral and implementation of the updated PPP (i.e., pre- and post-implementation period). Specifically, contraceptive use and pregnancy testing were examined before, during, and after treatment with oral retinoids. Additionally, changes in the adherence to the recommended time interval between oral retinoid prescription dates were examined. The DUS also had a number of secondary objectives related to describing patient characteristics (e.g., age, indication for treatment), prescriber characteristics (e.g., specialty), and pregnancy outcomes during the pre- and the post-implementation period.

In this summary report only primary objectives of the survey and the DUS are described and discussed.

3.2 Study designs and Settings

The DUS data was obtained from established secondary longitudinal data sources. Claims data were used for France and Germany (France: Système National des Données de Santé (SNDS) and Germany: Collective of insurants from company health insurance funds), a primary care data source was used for Spain (Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP), and the National health registers data for Sweden (national drug-, patient-, and birth registers).

The DUS employed a multi-country, multisource, observational cohort design and presented the results of the analysis for three time periods: pre-implementation period which included 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 period: month of implementing the RMMs in each country to December 2020. The study was mainly descriptive.

3.3 Results

The DUS sample in the pre, post-referral and post-implementation periods comprised of 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. Overall, most patients (>92%) were on isotretinoin during the pre-referral, post-referral and post-implementation period in France, Germany, Spain and Sweden.

Contraceptives use

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

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 compliant pregnancy tests was 50.8%. After treatment, 13.0% of episodes showed compliance to 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 tests was not available in the national registers.

4. General Discussion

4.1 Interpretation

The survey generated important insights about awareness, knowledge, and adherence to the RMMs of the PPP for oral retinoids among HCPs and patients/caregivers. Two of the three success criteria (awareness, knowledge, and adherence) of the PPP for HCPs and patients/caregivers were not met. Success criteria were achieved only for the awareness domain, where HCPs and patients/caregivers were well aware about the RMMs of the PPP. Both, HCPs and patients/caregivers 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, suggesting a general awareness of the RMM. However, a lower percentage (~70%) of patients were actually adherent to contraception use. Similarly, the DUS showed that 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. Overall, small, positive trends with respect to PPP compliant contraception use before and during oral retinoid treatment after the referral and implementation of the new RMMs were observed in France and Sweden and to a lesser degree also in 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 sources included in DUS study. Thus, the proportions might underestimate the actual use of contraceptives of women who receive oral retinoid treatment.

For pregnancy testing, the survey showed that the pre-defined threshold for success in the adherence domain was neither met by HCPs nor patients/caregivers. The adherence among patients/caregivers who are the ultimate users of oral retinoids was higher than HCPs in the survey sample, but results cannot be directly compared as the questions related to pregnancy testing were different for HCPs and patients (e.g., pregnancy testing for HCPs referred to "medically supervised pregnancy testing" whereas patients could have complied by conducting home pregnancy tests). The DUS results also showed a relatively low proportion of PPP compliant laboratory pregnancy testing across the three study periods. During 50% of oral retinoid treatment episode time, individuals were fully compliant with laboratory pregnancy testing in France during the treatment. In Germany the proportion was about 20% across the three time periods, and the proportion varied (25%-38%) across the three study time periods in Spain. No laboratory pregnancy tests were recorded in the national registers in Sweden. Thus, overall, the data suggest that the compliance with respect to laboratory pregnancy testing was low. However, the results need to be interpreted cautiously, particularly as at home pregnancy testing might have been considered sufficient, as suggested by the survey results.

4.2 Limitations

Both studies had specific limitations, the findings of these studies should therefore be interpreted cautiously.

In the survey, a success in the knowledge domain for HCPs was conditioned on strict criteria for assessing days' supply/length of prescription. The 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 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”* (Article 31 of Directive 2001/83/EC, pg. 7/29). A possible explanation for why the knowledge criteria were not met is that the majority of patients responded that they have taken pregnancy tests at home and thus did not consider that medically supervised pregnancy tests were needed. This reasoning might have been amplified by the COVID-19 pandemic when countries were in lockdown and physician visits were not possible or might have been perceived as a health risk for COVID-19 by patients. Further, the criteria for HCPs to correctly answer the questions regarding medically supervised pregnancy testing were restrictive as they warranted specific timing and frequency. In addition, despite the questions referring 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 have been relevant. Finally, it is of importance to highlight that the desired sample size for patients/caregivers was not achieved, decreasing power of the results.

The DUS post-implementation study period coincided with the 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 utilisation. It is likely that these changes influenced the implementation of the updated PPP in clinical practice negatively. Furthermore, the DUS used secondary data that was not collected primarily for research purposes and therefore information

on certain parameters, such as PPP compliant laboratory pregnancy testing, and contraceptive use may reflect an underestimation of actual PPP compliance.

Finally, findings of both, the survey and the DUS, may not generalise to all individuals in the respective study countries or other countries.

5. Conclusion

The survey, conducted during 2021, gave important insights about the effectiveness of the revised PPP for oral retinoids, implemented in 2018/2019, by assessing awareness, knowledge and adherence to the PPP among HCPs and patients/caregivers in seven European countries. For both HCPs and patients/caregivers, the pre-defined success threshold for awareness was met, while it was nearly met for knowledge and not met for adherence. HCPs and patients/caregivers acknowledged that oral retinoids should not be taken during pregnancy, posed a risk of teratogenicity and that contraception should be used before, during, and after treatment with oral retinoids (>80% respondents). The finding complements the results from the DUS, which showed small, positive trends with respect to PPP compliant contraceptive use before and during oral retinoid treatment in some countries. The low overall rate of adherence to pregnancy testing as seen from the survey results were in line with the DUS findings, where, across study periods, during 20% to 50% of oral retinoid treatment episode time, individuals were fully compliant with laboratory pregnancy testing (20% in Germany, 25-38% in Spain, 50% in France). The results of the two studies were likely impacted by safety measures associated with the COVID-19 pandemic.

Although small increases with respect to PPP compliance were observed in some countries, this report highlights that measures which can improve PPP compliance can be implemented. The current studies were unable to accurately assess PPP compliance due to lack of data on certain characteristics such as proportion of sexually active women, over the counter contraceptive use and at home pregnancy testing.

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