NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**EVALUATION OF THE EFFECTIVENESS OF PREGNANCY PREVENTION PROGRAMME (PPP) FOR ORAL RETINOIDS (ACITRETIN, ALITRETINOIN, AND ISOTRETINOIN): AN EUROPEAN BEFORE-AFTER DRUG UTILIZATION STUDY (DUS) USING SECONDARY DATA**
ROCHE PROTOCOL NUMBER:	MX41017
VERSION NUMBER:	3.0
AUTHOR:	[redacted]
DATE FINAL:	See electronic date stamp below
EU PAS REGISTER NUMBER:	Study not yet registered
ACTIVE SUBSTANCES:	Oral retinoids: • Acitretin: D05BB02 • Alitretinoin: D11AH04 • Isotretinoin: D10BA01
MARKETING AUTHORIZATION HOLDERS (MAHs):	The joint initiative involves several companies via a consortium (a full list of all MAHs is provided in Annex 3.3). ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS LIMITED, ALMIRALL, AUROBINDO, AXXON, BAILLEUL, BAUSCH HEALTH COMPANIES, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GLAXOSMITHKLINE, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, MEDINFAR, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, STADA, SUN PHARMA, TARGET, and TEVA

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
23-Jul-2019 09:46:00	Company Signatory	[redacted]
23-Jul-2019 09:52:45	Deputy EU QPPV	[redacted]

CONFIDENTIAL

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data
PROTOCOL VERSION IDENTIFIER	Version 3.0
DATE OF LAST VERSION OF PROTOCOL	06 August 2019
EU PAS REGISTER NUMBER	Study not yet registered
ACTIVE SUBSTANCE	Oral retinoids: • Acitretin: D05BB02 • Alitretinoin: D11AH04 • Isotretinoin: D10BA01
MEDICINAL PRODUCTS	A list is provided in Annex 3.1
PRODUCT REFERENCE	Information is detailed in the cover letter's Annex.
PROCEDURE NUMBER	EMEA/H/N/PSP/J/0069.2
MARKETING AUTHORISATION HOLDERS (MAHs)	The joint initiative involves several companies via a consortium (a full list of all MAHs is provided in Annex 3.3). ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS LIMITED, ALMIRALL, AUROBINDO, AXXON, BAILLEUL, BAUSCH HEALTH COMPANIES, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GLAXOSMITHKLINE, HEXAL AG,

	IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, MEDINFAR, MYLAN, , ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, STADA, SUN PHARMA, TARGET, and TEVA
JOINT PASS	Yes

RESEARCH QUESTION AND OBJECTIVES	The aim of the DUS is to address the following 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?
	
	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:
	
	• Contraceptives* before, during, and after treatment with oral retinoids
	• Time interval between prescription dates for oral retinoids during treatment episode
	• Laboratory pregnancy tests – where available - before, during, and after treatment with oral retinoids
	
	* contraceptive methods that require prescription and which are, therefore, captured in the administrative databases
	
	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 specialty 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 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 the study
COUNTRY(-IES) OF STUDY	The study will be conducted in France, Germany, Spain, and Sweden
AUTHOR	[redacted] On behalf of the oral retinoids consortium

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification System
CI	confidence interval
DRG	diagnosis related groups
DUS	drug utilisation study
EMA	European Medicines Agency
EMR	electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
IUD	intrauterine device
MAH	marketing authorisation holder
PAS	post-authorisation study
PASS	post-authorisation safety study
PPP	pregnancy prevention programme
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	risk minimisation measure
RWES	Real World Evidence Solutions
SAP	statistical analysis plan
SHI	statutory health insurance
SIDIAP	Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària
SmPC	summary of product characteristics
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

1. TITLE

Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data

2. MARKETING AUTHORISATION HOLDERS

MARKETING AUTHORISATION HOLDER(S)	This section provides contact details of the companies involved in the consortium (all marketing authorisation holders' (MAHs) contact details are provided in Annex 3.4).
MAH CONTACT PERSON	On behalf of MAHs: [redacted]

3. RESPONSIBLE PARTIES

Responsible Party	**Name and Affiliation**
Consortium	Oral retinoids consortium of MAH (see below the list of MAHs)
Sponsors	All MAHs involved in the oral retinoids consortium
MAH responsible for submissions to HA	Roche
Contracting vendor	IQVIA Real World Evidence Solutions (RWES) [redacted]
Principal Investigator	[redacted] (Principal Investigator) Medical Director, Lead Pharmacoepidemiology and Drug Safety, IQVIA

Responsible Party	**Name and Affiliation**
IQVIA project team	• Scientific oversight: [redacted] Lead Pharmacoepidemiology and Drug Safety • Project oversight: [redacted], Principal • Project Manager: [redacted] Epidemiologist • Biostatistical Oversight: [redacted] Statistician

Marketing Authorisation Holders (MAHs) involved in the oral retinoids consortium:

ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS LIMITED, ALMIRALL, AUROBINDO, AXXON, BAILLEUL, BAUSCH HEALTH COMPANIES, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GLAXOSMITHKLINE, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, MEDINFAR, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, STADA, SUN PHARMA, TARGET, and TEVA

SIGNATURE PAGE

Reviewed and Approved by:

[redacted]			
F. Hoffmann-La Roche Ltd >	**Signature**	**Title**	**Date**
[redacted]			
IQVIA	**Signature**	**Title**	**Date**

4. ABSTRACT

Full Study Title: Evaluation of the effectiveness of PPP for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data

Protocol version 3.0 dated 06 August 2019

[redacted]

Rationale and background:

Retinoic acid analogues comprise of a group of active substances known as the retinoids and are available as topical and oral preparations. Therapeutic indications include the treatment of severe acne (such as nodular or conglobate acne) resistant to adequate courses of standard therapy, hand eczema resistant to empirical treatment measures, and severe forms of psoriasis and other skin conditions. Therapy with systemic retinoids is associated with teratogenicity. Therefore, women who are pregnant or are planning a pregnancy must not be prescribed retinoids. Strict prescription guidelines and a PPP comprising education material for patients, physicians, and pharmacists as well as strict prescription guidelines have been put in place but exposure during pregnancy still occurs.

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. After completion of the review in March 2018, the European Medicines Agency (EMA) confirmed that an update of measures of the PPP for the oral retinoids acitretin, alitretinoin and isotretinoin is needed. They, therefore, mandated the conduct of a DUS (category 1) to assess the effectiveness of these updated risk minimisation measures (RMMs). In June 2018, the decision to strengthen the recommendations for pregnancy prevention for oral retinoids was issued by the European Commission (EC).

Research question and objectives:

The aim of the DUS is to address the following 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?

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:

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

* contraceptive methods that require prescription and which are, therefore, captured in the administrative databases

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 specialty 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 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 the study

Study design:

This is a multicountry, multisource, observational cohort study in females of childbearing potential receiving oral retinoids (i.e., acitretin, alitretinoin and isotretinoin) using a pre-post design. This study will cover time periods before and after the implementation of the updated RMMs related to the PPP update. The study will be based on secondary use of data extracted from established longitudinal healthcare databases (claims, primary care database, national registries). The pre-implementation period consists of 2 distinct phases, a 2-year phase (07/2014 to 06/2016) prior to the start of the referral in July 2016 and a 2.5-year phase between the start of the referral and the distribution of EM for the updated PPP in Q4 2018. The post-implementation period captures the 2-year phase after the distribution of the EM (01/2019 to 12/2020).

Population:

The study population will consist of females of childbearing potential (13-49 years of age, inclusive) receiving oral retinoids (i.e., acitretin, alitretinoin and isotretinoin) in the outpatient setting (at office-based practices and outpatient departments at hospitals), during the pre-defined periods identified from the selected data sources in the European target countries (i.e., France, Germany, Spain, and Sweden).

Inclusion criteria

- Female gender
- Childbearing potential (13-49 years of age, inclusive)
- Received or prescribed at least one prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in either the pre-implementation or post-implementation period

Exclusion criteria

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) will be excluded.

Data for the oral retinoids acitretin, alitretinoin, and isotretinoin will only be extracted from databases in target countries where the respective active substance has been granted market authorisation.

No further exclusion criteria will be applied.

Variables*:*

The exposure is defined as one or more prescriptions of oral retinoids (i.e., acitretin, alitretinoin, or isotretinoin) during one of the study periods. The following variables will be considered (if available): patient age, oral retinoid prescribing and monitoring practice such as indication, length of prescription, treatment duration, and prescriber speciality, as well as PPP-specific variables such as prescriptions of contraceptive and – if available - laboratory pregnancy testing (before, during, and after treatment). In addition, information on exposed pregnancies and outcomes (if available) will be provided.

Data Sources:

The following established longitudinal data sources will be utilised for data extraction:

Claims databases

- France: System National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) of the Système National des Données de Santé (SNDS)
- Germany: Collective of insurants from company health insurance funds

Primary care database

- Spain: Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP)

National health registers

- Sweden: national drug-, patient-, and birth registers

Study size:

All females of childbearing potential receiving oral retinoids (i.e. acitretin, alitretinoin, isotretinoin) available in pre-defined periods of the selected databases will be included in the analysis.

The number of females of childbearing potential receiving oral retinoids was checked for a 3-year period (2015-2017) in Germany, Spain, and Sweden. The number of patients is approximately 3,700 in Germany, 4,800 in Spain, and 20,500 in Sweden.

In France, only the number of boxes that was reimbursed in France in total (without any restriction to age and gender) is available without receiving ethical approval for the study, the number of approximately 1,041,000 boxes in one year suggests that the number of female patients of childbearing potential receiving oral retinoids will be sufficient for analysis.

Data analysis:

Given the study objectives, the analyses will mainly be descriptive and will be conducted by country and study time periods (both pre-implementation periods and post-implementation period). Some comparisons will be made especially between the different study time periods.

The analyses will be provided for the overall class of oral retinoids (acitretin, alitretinoin and isotretinoin) and for the single active substances.

A meta-analytic approach will be used to pool the results of the primary outcomes from the four databases and present the results by active substance for all study countries.

Results for key variables will be presented over time where patient numbers permit to provide insights on continuous trends capturing pre- and post-implementation periods.

In addition, an interrupted time series (ITS) analysis using segmented regression to identify ongoing trends in the study's primary outcomes will be considered in case the conditions for this analysis will be met.

Milestones

Anticipated start of data extraction: 2021

Registration in the EU-Post-authorisation study (PAS) register: after approval of protocol

Final report of study results: 2022

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

The planned dates for key study milestones are:

Milestone	**Planned date**
Start of data extraction	July 2021
End of data extraction	January 2022
Registration in the EU-PAS register	After approval of protocol
Final report of study results	December 2022

7. RATIONALE AND BACKGROUND

7.1 Background

Retinoic acid analogues comprise of a group of active substances known as the retinoids and are available as topical and oral preparations. Therapeutic indications include the treatment of severe acne (such as nodular or conglobate acne) resistant to adequate courses of standard therapy, hand eczema resistant to empirical treatment measures, and severe forms of psoriasis and other skin conditions. 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 PPP comprising education material for patients, physicians, and pharmacists as well as strict prescription guidelines have been put in place, but exposure during pregnancy still occurs. A dedicated effort by women and their clinicians is required, involving patient selection, education and informed consent, detailed contraceptive counselling, and careful monitoring and management, including pregnancy testing before commencement, during, and after the end of therapy.

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 (SmPCs) for all oral retinoids in the EU'. A referral in 2003 for isotretinoin only, led to introduction of the isotretinoin PPP in the European Union (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 fore mentioned continue to occur.

In March 2018, the European Medicines Agency (EMA) completed its review of retinoid medicines and confirmed that an update of measures for pregnancy prevention is needed.

Based on 21 June 2018 EMA/261767/2018 the pregnancy prevention programme for acitretin, alitretinoin and isotretinoin includes:

- pregnancy tests before, during and after stopping treatment;
- the need to use at least one 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 to the treating physician (i.e., dermatologist or GP in some countries after first prescription). In fact, the difference between the implemented PPP before and after the implementation of the updated RMMs is relatively small (see Table 1). The measures of the of the PPP are similar in the countries of interest for this study.

The updated RMMs include updated educational material (EM), in some countries patient reminder card and pictogram on the outer package, and in addition, the redistribution of direct healthcare professional communication (DHPC).

Differences in the set of implemented tools may exist between countries due to the requirements of local authorities.

Table 1 Measures of the PPP before and after the newly implemented, updated RMMs

Active substance	**PPP**	**Contraception**			**Pregnancy test**			**Days’ supply/Length of prescription**
		Before	During	After	Before	During	After	
Acitretin	Old[1]	Yes	Yes	3yrs	Yes	Monthly	3yrs	Limited to 30d
	New[2]	1mo	Yes	3yrs	Yes	Ideally monthly	3yrs	Ideally limited to 30d
Alitretinoin	Old[1]	1mo	Yes	Yes	Yes	Monthly	5wks	Limited to 30d
	New[2]	1mo	Yes	1mo	Yes	Ideally monthly	1mo	Ideally limited to 30d
Isotretinoin	Old[1]	1mo	Yes	1mo	Yes	Monthly	5wks	Limited to 30d
	New[2]	1mo	Yes	1mo	Yes	Ideally monthly	1mo	Ideally limited to 30d

d: day(s); mo(s): month(s); yr(s): year(s)

[1] 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

[2] Annex 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 generics. 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 outcome of the Art. 31 referral on retinoids, the PRAC (endorsed by CHMP and European Commission [EC]) has requested a DUS (category 1 study) and a complementary survey (category 3 study) to assess the effectiveness of the updated RMMs. The study design should aim to evaluate and quantify the effectiveness of the updated RMM, which should include a pre- and post-implementation analysis and assessment. This protocol describes the DUS. The survey is described in a separate protocol.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of the DUS is to address the following 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?

The objectives of the DUS are:

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:

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

* contraceptive methods that require prescription and which are, therefore, captured in the administrative databases

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 specialty 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 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 the study

9. RESEARCH METHODS

9.1 Study Design

This is a multicounty, multisource, observational cohort study in females of childbearing potential receiving oral retinoids (i.e., acitretin, alitretinoin and isotretinoin) using established data sources in different European countries (i.e., France, Germany, Spain, and Sweden

The study will employ a pre-post design to evaluate the effectiveness of the implementation of the updated RMMs with respect to the PPP according to the following schedule:

- Pre-implementation period: period prior to the date of the implementation of the updated RMMs
- Post-implementation period: period after the implementation of the updated RMMs

Periods will be defined as (also see Figure 1):

Pre-implementation period: The period before the implementation of the updated RMMs. The RMM tools will be distributed in the fourth quarter 2018 (the exact date may vary depending on the country). The pre-implementation period captures two periods:

- Pre-referral: the 2-year period before referral start in July 2016. This period will be used for the before and after comparison with the post-implementation period.
- Post-referral: the 2.5-year period between the referral start date in July 2016 and the distribution of the RMM tools in the target countries (assumed until December 2018). The duration of this period may vary depending on the duration of the approval and the distribution of the RMM tools in each country.

Post-implementation period: This period captures the time starting after the distribution of EM until December 2020. The start date of the period in each country will depend on the date on which the EM is approved by the respective national competent authorities.

The final dates of the study periods depend on the final schedule of the implementation of the updated RMMs in each country.

Figure 1: Overview of study periods

A single database for all target countries is not available. Therefore, a study approach was chosen which includes multiple data sources to gather drug utilisation data for oral retinoids (acitretin, alitretinoin and isotretinoin) in the European countries of interest.

Databases with longitudinal secondary patient data collected continuously over time will be used preferably to provide the most comprehensive data for the outcomes of interest.

To gather drug utilisation data for oral retinoids (acitretin, alitretinoin and isotretinoin) before and after an update of measures for pregnancy prevention, the following types of patient-level longitudinal databases, which are commonly used for post-authorisation safety studies (PASS) with respect to drug utilisation, are considered:

- Claims data
- National registries
- Primary care databases

9.2 Setting

Oral retinoids acitretin, alitretinoin, and isotretinoin are marketed in a broad range of countries in the Europe. 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

Based on these criteria and also taking the sales data (see Table 2) into account, the following countries will be included in the DUS: France, Germany, Spain, and Sweden, the latter representing an EU country from the Northern part of Europe and a data source of national coverage which is well-established in pharmacovigilance research.

Table 2: Top countries based on volume sales (retail and hospital) for the oral retinoids acitretin, alitretinoin and isotretinoin, by country (01/2017 to 12/2017): Source: IQVIA MIDAS June 2018

Country	ACITRETIN	ALITRETINOIN	ISOTRETINOIN	Grand Total
FRANCE	2.97%	0.22%	11.97%	15.15%
UK	3.86%	0.20%	9.57%	13.63%
SPAIN	1.62%	0.02%	8.54%	10.19%
POLAND	0.81%	0.00%	9.00%	9.82%
GERMANY	0.94%	0.50%	8.11%	9.54%
NETHERLANDS	1.01%	0.37%	6.19%	7.56%
ITALY	1.65%	0.01%	3.64%	5.30%
GREECE	0.27%	0.00%	3.88%	4.15%
BELGIUM	0.47%	0.00%	3.23%	3.70%
PORTUGAL	0.41%	0.00%	2.37%	2.78%
AUSTRIA	0.17%	0.07%	2.12%	2.36%
SWEDEN	0.20%	0.00%	2.10%	2.30%
NORWAY	0.17%	0.08%	1.88%	2.13%
FINLAND	0.22%	0.01%	1.70%	1.93%
DENMARK	0.15%	0.02%	1.72%	1.89%

9.2.1 Inclusion Criteria

The following criteria must be met to be included in the study:

- Female gender
- Childbearing potential (13-49 years of age, inclusive)
- Received or was prescribed at least one prescription of the oral retinoids acitretin, alitretinoin, or isotretinoin in either the pre-implementation or post-implementation period

9.2.2 Exclusion Criteria

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) will be excluded.

Data for the oral retinoids acitretin, alitretinoin, and isotretinoin will only be extracted from databases in target countries where the respective active substance has been granted market authorisation.

No further exclusion criteria will be applied.

9.3 Variables

To meet the objectives of the DUS, the selection of variables was done with respect to the key elements requested by the PRAC as far as they are captured in established data sources.

9.3.1 Exposure Definition and Measures

Exposure will be defined as one or more prescriptions of oral retinoids (issued or dispensed) during one of the pre-defined study periods. These prescriptions will be identified using the Anatomical Therapeutic Chemical Classification System (ATC) for the target substances or the International non-proprietary name system (INN).

The exposure start date for each patient will be defined as the first prescription/dispensing record of an oral retinoids treatment episode during the pre-defined time periods. Because this study aims to assess the prescribing behaviour of HCPs, should both the prescription and the dispensing date be recorded, the prescription date would be used preferentially.

Exposure will be described by prescription length, duration of treatment and (average) daily dose and will be provided by active substance.

It will be assumed that all prescriptions and their associated dates recorded in the databases reflect actual prescription fills and subjects will start treatment at the exposure start date.

The following variables will be extracted from the data sources:

- Active substance
- Date of prescription (or dispensing)
- Pack size or days' supply
- Dosage strength
- Recommended daily dose (if available)

9.3.2 Patient age and prescribing and monitoring practices

To describe the prescribing and monitoring practices of oral retinoids before and after the dissemination of risk minimisation measures, the following variables will be considered:

- Patient age
- Specialty of prescriber (not for France)
- Records of sterilisation in the medical history
- Indication for oral retinoid prescription (only available for in-hospital prescriptions in France)
    - Diagnoses coded by International Classification of Diseases (ICD)-10 (i.e., acne, severe hand eczema, psoriasis, or other dermatological conditions oral retinoids are indicated, for code list please refer to Appendix 3)
- Contraceptives before, during and after oral retinoid treatment
    - Prescription of hormonal contraceptives (date of prescription/dispensing, type, pack size or days' supply)
    - Prescription of intrauterine devices (IUD) (date of prescription/dispensing or procedure)
- Laboratory pregnancy tests – based on availability - before, during and after oral retinoid treatment
    - Laboratory pregnancy tests (blood or urine) recorded in the databases (type, if available, and date of test)
    - Records (ICD-10 codes related to an exam) which document the performance of a laboratory pregnancy test (date of record)

9.3.3 Pregnancies and pregnancy outcome

All available records related to pregnancies and pregnancy outcomes including diagnoses (based on ICD-10 coding tests and exams usually performed during a specific trimester will be searched in databases, if available, as follows (see code list in Appendix 3).

- Pregnancies
    - Pregnancy records (date of record)
- Pregnancy outcomes
    - Outcomes of pregnancies (i.e., live births, termination, stillbirth, miscarriage, or recorded birth defect), if information is available in the data source

If information on the timing of the pregnancy is available (e.g., date of delivery, last menstrual period (LMP), trimester information), it will be considered for the estimation of the beginning of the pregnancy. The availability of such information may differ by data source.

In case no information is available permitting the analysis of the timing of the pregnancies, the method for calculating the timing of pregnancies, which is published for the specific data source, will be used. In case there is no approach published, the first pregnancy record minus 90 days, which mark the end of the first trimester and generally will be time of the pregnancy when a first check-up will have been performed, will be considered as the estimated start of the pregnancy. This approach was endorsed by the PRAC for another PASS (see for example Valproate, EUPAS11379).

9.4 Data Sources

All information on exposure and outcomes will be derived from established secondary longitudinal data sources.

Data sources are considered for the DUS based on a sufficient number of patients on oral retinoids and the availability of information relevant to describe the effectiveness of the updated PPP. Based on these criteria the following data sources will be considered (see Table 3 for more detail):

- SNIIRAM of the SNDS in France
- Collective of insurants from company health insurance funds in Germany
- SIDIAP in Spain
- National Health registers in Sweden

Table 3: Summary of various databases being considered for the DUS

Country	**France**	**Germany**	**Spain**	**Sweden**
Name and Type	***SNIIRAM of the SNDS*** Claims database	***Company Health Insurance funds*** Claims database	***SIDIAP*** Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Information System for Research in Primary Care	***National Health registers*** National Drug-, Patient- and Birth registers
Overall representativeness	~88% of French population	~6% of German population	>80% of Catalonian population	National coverage for Sweden

Size	57 million, all health insurance schemes in office-based care and hospitalization	5 million insurants	About 5 million active people and about 7 million active, transferred and dead people	10 million, specialist and hospital out and in-patient care and all drugs dispensed for the Swedish population
Data available since	2009	2004	2005	2005 (1997)
Data lag time	9 months	12 months	One year	1 - 9 months (depending on the type of registry)
Patient age	Available	Available	Available	Available
Diagnosis	Available in the hospital setting; ICD-10 codes	Available; ICD-10 codes	Available ICD-10 codes	Available; ICD-10 codes
Information on physician visits	Available	Available	Available	Available
Records of laboratory pregnancy tests (for example via ICD-10 codes)	Human chorionic gonadotropin (HCG) blood tests performed	Available	Available (mainly urine pregnancy tests)	If ICD-10 code, it could be captured
Prescriptions of oral contraceptives or IUDs	Only reimbursed contraceptives	Only reimbursed contraceptives	Available	Available
Drug information for oral retinoids (date of prescription, pack size, strength)	Available; duration approximated algorithmically	Available; duration approximated algorithmically	Available	Available; duration approximated algorithmically
Pregnancy	Available	Available	Available	Available

9.4.1 Claims data – France and Germany

9.4.1.1 France – SNDS

The SNDS (Système National des Données de Santé) 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 (PMSI databases) individualized by beneficiary.

The SNDS database is a very exhaustive option for France. It is a claims database covering all the Health Insurance schemes based on individuals' employment status in office-based care and hospitalisation and is individualized by beneficiary. The general health insurance plan covers employees in the industry, business, and service sectors; public service employees; and students, accounting for approximately 88% of the French population.

With this very large sample size (57 million beneficiaries of the French General scheme, the SNDS allows to have a comprehensive and detailed health information, relevant and very useful for epidemiological and health economic studies (Tuppin 2017). The RWES/Health Economics and Outcomes Research department of IQVIA France is now able to conduct this study, upon authorization, for SNDS access.

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 health care database (Blotière 2018).

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 (Raguideau 2015).

The data of medical services listed 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 care giver, the type of care and the monetary flows induced. However, in these files of medical services, some health consumptions cannot be seen, such as consumptions not claimed for reimbursement, not reimbursable health services or self-medication.

Now, the historical coverage of the SNDS is as large as the EGB (General sample of beneficiaries), but as the database was enriched each year, we recommend to not go further back than 2009. The choice of the study period coverage needs to be justified.

The SNIIRAM is linked to the PMSI ("Programme de médicalisation des systèmes d'information"). The PMSI is a comprehensive national database which classifies all hospital stays in all public and private health care institutions in France. PMSI access is managed by the Hospitalisation Information Technical Agency (ATIH). PMSI data covers three different types of care centers:

- 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 the PMSI, a unique identifier for each patient makes it possible to track the hospital course of patients over the years. PMSI 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 International Classification of Diseases version 10 (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 (Agence nationale de sécecurité du medicament et des produits de santé, 2017). All reimbursed contraceptives are captured in this database. Based on the results from a survey in 2016 (Rahib et al. 2017) 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 (Agostini et al. 2018; Bezin et al. 2017).

9.4.1.2 Germany – Collective of insurant from company health insurance funds

For this study, a collective of insurants from company health insurance funds will be used. The analysis will be done by Team Gesundheit, Gesellschaft für Gesundheitsmanagement GmbH, based in Germany.

Data are currently available from 2004 to 2016 (as of January 2018) and contain over 5 million insured patients representative of the entire insured German population with a coverage of about 6%. The privacy of patients in the database is protected at all times and the 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 health care services is high because all reimbursable services are comprehensively recorded in the claims data. The completeness of outcomes reporting varied depending on the type of outcome, e.g. an underreporting of induced abortions is possible (Mikolajczyk RT et al. 2013). Pregnancies will be identified in accordance with the approach published by Mikolajczyk et al.

The database also allows comparisons between patient and control groups with respect to specific utilisation of health care services.

Longitudinal pre-index and follow-up periods can also be defined according to the study requirements. Diagnoses and procedures are coded using ICD-10 (German modification), and include treatments that are reimbursed in accordance with the German law.

Among others, the following measures are available in the German database allowing demographic characteristics, treatments, healthcare utilisation and clinical outcomes to be assessed:

- Registration data including age, gender, insurance status, time insured, and region of residence
- Outpatient care data including ICD-10 diagnoses, physician specialty
- Inpatient care claim including ICD-10 diagnoses (up to 3 principal and 30 secondary diagnoses per stay), billed diagnosis related groups (DRGs, German classification), up to 30 OPS-Codes per stay, duration of hospitalizations, and medical department; drugs captured via OPS code
- Code of prescribed medications and related costs, PZN (Pharmazentralnummer) of prescribed medications, and date of prescription

German claims databases cover all reimbursed contraceptives. In 2016, 1.1 million females in the age group 13 to 49 year 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 revealed 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 had a record of contraceptives (data on file). Before the 29th 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 health care setting in Germany suitable to be used as data source for this DUS to address the study objective.

An electronic medical record (EMR) database available for Germany, Disease Analyzer, is not a suitable option in this case because patients cannot 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.

9.4.2 Primary care database – Spain

9.4.2.1 Spain – SIDIAP

SIDIAP contains data of anonymized healthcare records for nearly 5.8 million people who receive primary care in one of the primary care centers of Catalonia, representing approximately 80% of the Catalonian population. SIDIAP covers 274 centers and

approximately 3,400 GPs. SIDIAP is highly representative of the population of Catalonia in terms of geographical, age, and sex distributions (Bolibar et al., 2012). Data is collected by health professionals during routine visits in primary care:

- Electronic medical records (EMR) captured using the e-CAP platform at the center-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 2005 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. The way of calculating the beginning of a pregnancy is standardized in daily clinical practice, which includes laboratory pregnancy tests, last menstrual period and other confirmation criteria (Aliaga et al., 2018). Approximately 66% of all term pregnancies in Catalonia were recorded in SIDIAP during the period in which the study was conducted by Aliaga et al.

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 women (ages 16-29) (Carrasco-Garrido et al. 2011). 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.

To guarantee the quality of the data, a scoring system is applied. Primary care practices with ready data that is ready to be used for research can be selected based on the completeness of their records captured using the e-CAP platform. It is estimated that the data assigned to 40% of the professionals with the highest scores (coverage of 1.9 million people) is adequate to conduct high quality studies. This population sub-group is known as SIDIAP-Q. This group is representative of the Catalonian population (Garcia-Gil et al., 2011).

SIDIAP has been used extensively in medical research including DUS since 2010 across Europe and has been found to be a valid source for research (Wilson et al, 2015). A study on the association between effective disorders presenting before and during pregnancy considering the use of medication has recently been published in 2018 (Aliaga et al., 2018).

9.4.3 National registry data - Sweden

9.4.3.1 Sweden – National Registries

IQVIA suggests creating 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 health care provided in Swedish secondary care and above and drugs dispensed will be provided. This longitudinal data enables the study of historical clinical information on the subjects treated with oral retinoids. The proposed data sources will not provide 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 is collected from both in- and out-patient hospital-based specialist care across all of Sweden. The National Patient Register dates to 1964. From 1987 there is information on all completed in-patient admissions across the country. 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 include:

- Patient demographics (age, gender)
- Clinical 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.) and lifestyle (smoking, etc.) is not available through the National Patient Register, nor are laboratory and clinical measurements as blood pressure and blood lipid levels. In addition, information on drugs administered at the hospital is not available. Again, this type of data could be captured from EMRs.

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 July 1, 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 include:

- Patient demographics (age, gender, and residency)
- Prescription information (date of prescription, prescriber's specialty, 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 is only documented in free text format where available, and days' supply is not recorded.

In Sweden, the online database on prescription held by the National Board of Health and Welfare provides the following information on the annual prevalence of Swedish women aged 15-49 years who filled at least one 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. Please see below for more detailed information on the information contained in each register.

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 (National Board of Health and Welfare, Sweden 2012; Olausson PO, 2002). The register contains detailed information about mothers and new-borns. However, pregnancies are only captured after 22 weeks. The identification and timing of pregnancies will be done according to published methodology (Stephansson et al. 2018).

Records on pregnancies are also documented in the National Patient Register regardless of the duration of pregnancy, but missing information regarding early termination needs to be taken into account.

9.5 Study Sample Size

The aim of this study is to provide a description of real-life treatment patterns. The final study sample size is driven by the patient numbers available in the data sources in the target countries.
The sample size is calculated in order to ensure that the study obtains meaningful data for descriptive purposes.

9.5.1 Determination of sample size

The sample size calculation is determined by the desired accuracy/precision of the estimation by confidence interval (CI) of the observed proportions for the variables relevant to address the primary objective. As the observed percentage (p) is not known in advance, we consider it to be 50% (maximum uncertainty).

Table 4 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 proportion (p) 50 %, a sample size of 385 patients is required, for a proportion (p) 20% (80%) 246 patients. The precision for an

observed percentage with 95% CI will be 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 4: Required number of patients by acceptable precision (95% CI) or proportions (normal approximation)

	Observed percentage (accuracy): p(1-p)				
Precision	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

9.5.2 Sample Size for target countries

A feasibility count in the individual target countries showed that the data sources are able to provide a sufficient number of patients (see Table 5) for the analyses (see section 9.7 Data Analyses for details).

The numbers of females of childbearing potential receiving oral retinoids were checked for a 3-year period (2015-2017) in Germany, Spain, and Sweden. The number of patients meeting the inclusion criteria are 3,729 in Germany, 4,800 in Spain, and 20,580 in Sweden.

In France, only the number of boxes that was reimbursed in France in total (without any restriction to age and gender) is available without receiving ethical approval for the study;

the number of 1,041,500 boxes in one year suggests that the number of women of childbearing potential will be sufficient for analysis.

Table 5: Oral retinoids in target countries - number of patients or prescriptions

		France SNDS[1] 2016	**Germany Claims Data[2]** (2013 – 2015)	**Spain SIDIAP** (2015-2017)[3]	**Sweden National registry[4]** (2015-2017)
Number of patients, total		n.a.	3,729	4,842	20,580
By substance	acitretin	n.a.	153	281	442
	alitretinoin	n.a.	100	15	--
	isotretinoin	n.a.	3,492	4,546	20,138
Number of prescriptions, total		1,041,500	n.a.	n.a.	67,932
By substance	acitretin	195,417	n.a.	n.a.	1,283
	alitretinoin	15,036	n.a.	n.a.	--
	isotretinoin	831,047	n.a.	n.a.	66,225

[1] Number of boxes reimbursed; total, no restriction with respect to age and gender, [2] Unique female patients aged 13-49, [3] Female patients, 13 to 49 years, [4] Non-unique female patients aged 15-49; n.a.: not available before analysis

9.6 Data Management

The study will be conducted by IQVIA in collaboration with research partners. The processes for database management differ by data source.

Overall, routine procedures or practice will include maintaining security and data confidentiality, following statistical analysis plans, and performing quality-control checks of analysis programs. Data extracts and analysis programs will be stored to allow any necessary future analysis.

In Germany and in Spain, data management and analysis will be performed by the respective research partner (Team Gesundheit and SIDAP) according to their respective routine procedures. IQVIA will receive filled-in result tables from these external vendors. No analytical data sets will be transferred to IQVIA.

In Sweden, IQVIA will receive study specific data sets from the National Board of Health and Welfare (NBHW) generated according to routine processes at the data holder and a study-specific data application form for data extraction. The analysis will be done by data source experts at IQVIA. Storage of analytical data sets and programs will be handled by IQVIA.

In France, data will directly be extracted and stored by the CNAM (national health insurance). IQVIA has access to the study dataset via a secured portal. At IQVIA analysis will be done by data source trained statisticians. Storage of analytical programs will be handled by IQVIA.

At IQVIA, the DUS will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA's Real World & Analytics Solutions.

This study will follow relevant chapters of European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for data management.

9.7 Data Analyses

The data analyses will be described and further detailed in the Statistical Analysis Plan (SAP). The described analyses below might be revised, and adjustments might occur as needed.

9.7.1 General Considerations

Given the study objectives the analyses will be mainly descriptive and will be conducted by country, by active substance and study time periods (both pre-implementation periods and post-implementation period). To allow for analysis across all data sources used in the study, a meta-analytic approach will be used to assess and pool the results from the four study countries together for each active substance (see 9.7.3.4).

The analyses will be provided for the overall class of oral retinoids and for the single active substances. Categorical variables will be presented as counts (n), proportions (%) with CI where relevant as for parameters used to address the primary objective and for the comparison of the incidence of exposed pregnancies. Continuous variables will be presented as means with standard deviation (SD) and as medians with interquartile range (IQR), where appropriate.

Changes in the reimbursement policy for contraceptives in the healthcare systems of the study countries will be considered to discard any differential misclassification of exposure.

The statistical unit will be the oral retinoid treatment episode and patient as well as prescription where appropriate. Patients who have multiple treatment episodes of oral retinoid use will be entered the cohort for analysis more than once.

The term "use" in the context of the analysis refers to the prescription or dispensing of drugs or IUD.

In the analysis, prescriptions of patients will be followed from the exposure start date to censoring date, i.e., transfer out of the database incl. death or the end of the study period, whichever comes first.

Statistical analyses will follow the tables shells validated by the MAH consortium and will be displayed using tables, listings and/or graphs. The statistical analysis will be conducted using SAS or an equivalent statistical analysis software. A detailed statistical analysis plan (SAP) will be prepared prior to data extraction.

The statistical results of all target countries and all active substances will be presented in a single report.

9.7.2 Main analyses

The main analysis will cover the prescribing and monitoring patterns of oral retinoids during the pre- and post- implementation periods in females of childbearing age (13-49 years of age, inclusive) to meet the primary study objective. The analysis will be descriptive in nature. The first oral retinoid prescription of a treatment episode will be considered as exposure start date for the analyses of treatment episodes.

Measures related to the PPP

The following analyses will be performed:

- Laboratory pregnancy tests
    - Percentage of patients with laboratory pregnancy test performed at treatment start (up to 7 days before exposure start date)
    - Percentage of patients with laboratory pregnancy tests performed during treatment
    - Percentage of patients with laboratory pregnancy tests performed monthly according to the SmPC during treatment
    - Frequency of laboratory pregnancy tests during treatment, by month of treatment
    - Percentage of patients with laboratory pregnancy tests performed after treatment stop
    - For all retinoids: percentage of patients with laboratory pregnancy test performed within two months after treatment stop
    - 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)
- Contraceptives

  - 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)
  - Percentage of patients with use of IUDs before treatment start (up to 5 years before exposure start date)
  - Percentage of patients with concomitant use of contraceptives (hormonal contraceptives and / or IUD) during treatment
  - Percentage of patients with use of contraceptives (hormonal contraceptives and / or IUD) within two months after treatment stop
  - 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)
- Periodicity of oral retinoid prescriptions
  - Time interval between prescription dates for oral retinoid prescriptions during treatment (in days)
  - Proportion of oral retinoid users with monthly prescription intervals during treatment

It is aimed to include all patients with oral retinoid prescriptions in the analyses. However, a history of at least 3 months is necessary to cover prescriptions and laboratory pregnancy tests before treatment initiation. Analyses after treatment initiation will be performed for the following scenarios: (a) patients with a follow-up available covering the treatment episode and (b) patients with a follow-up beyond the treatment episode of at least 2 months.

9.7.3 Secondary analyses

9.7.3.1 Patient age, indication and prescriber specialty

The following analyses will be performed:

- Patient age (mean age, by age groups, 13-20 years, 21-35 years, 36-49 years)
- Indication (diagnosis related to the oral retinoid prescription at the day of oral retinoid prescription or in the last 12 months before oral retinoid initiation)
- Prescriber specialty (Germany, Spain, and Sweden; not available for France)

9.7.3.2 Exposure

The following variables of exposure will be analysed:

Prescription length

The length of prescription will be determined by the date of prescription (or prescription fill/dispensing) plus the expected number of days of supply based on the days' supply reported with this prescription or, when not available, pack size and the recommended daily dose by the physician (if available) or, by default, according to the information of strength connected with the prescription and SmPC. The length will be provided in days.

The following analyses will be performed:

- Average length of prescriptions per treatment episode
- Overall number of prescriptions per patient

Duration of treatment

The duration of treatment will be analysed through the recorded prescriptions in the databases. The date of the first prescription issued (or filled) will be considered as treatment start date. End of treatment duration will be defined by the date of the last prescription plus the number of days' supply of this last prescription. Consecutive prescriptions of oral retinoids will be considered as one treatment episode (allowed gaps between prescriptions will be provided in the statistical analysis plan). The duration of treatment episodes will be provided in days.

The following analyses will be performed:

- Duration of treatment episodes
- Number of prescriptions per treatment episode
- Number of treatment episodes per patient

Average daily dose

The average daily dose will be analysed over a treatment episode based on dosage strength, pack size or day supply and number of prescriptions per episode.

9.7.3.3 Pregnancy and pregnancy outcomes

The following analyses will be performed for the pre-implementation and the post-implementation periods:

- Number of pregnancies exposed to oral retinoids
- Incidence rate of pregnancies exposed to oral retinoids
- Information on pregnancy outcome (i.e., live births, termination, stillbirth, miscarriage, or recorded birth defect) will be provided when available in the databases

If the information on trimester, start date of pregnancy, or delivery/end of pregnancy date is available, the pregnancy will be considered exposed if at least one oral retinoid prescription was recorded in the period between the assumed dates of pregnancy start and delivery/end of pregnancy. In case information on pregnancy trimester or start date or delivery/end of pregnancy date is not available in the data source, a pregnancy will be considered as exposed to oral retinoids if at least one oral retinoid prescription was issued within 90 days before or within 180 days after the first record of a given pregnancy.

9.7.3.4 Meta-analysis

To account for any differences between the databases with regard to their format and to allow for differences in the population of patients treated with isotretinoin, acitretin, and alitretinoin, and differences in adherence to PPP measures in those populations, a meta-analytic approach will be used to combine the data. Specifically, drug- and country-specific estimates for the primary outcome measures will be assessed. In case of high heterogeneity between country-specific estimates for (a) certain active substance(s), an appropriate random-effect method will be used to derive a pooled estimate. In addition, the sensitivity of the overall pooled estimates to the inclusion or exclusion of certain country-specific estimates will be assessed. In some instances, it may not be appropriate to pool the data, and in such cases country-specific estimates will be excluded from the pooled estimate and presented separately.

9.7.3.5 Trends in the prescribing and monitoring practice of oral retinoids with respect to measures of the PPP

To identify ongoing trends in the countries of interest, ITS analysis using segmented regression will be performed in case the conditions for this analysis will be met (such as the number of time points in the pre-and post-implementation periods [at least 6 timepoints per period] and the number of observations per timepoint [at least 100] is available). Using ITS analysis, data will be evaluated at multiple time points before and after an intervention in order to detect whether or not an intervention had a significantly greater effect than any underlying trend.

The ITS analysis can assess the following key parameters:

- Proportion of episodes with contraception use for the month before treatment start
- Proportion of episodes with continuous concomitant use of contraception during the entire treatment episode
- 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 will be made based on results of analyses for primary outcomes. ITS analysis will be conducted for the outcomes only if sufficient data will be available for reliable results.

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

The definition and formula for calculation of outcome measure:

$$Concom_{Prop\_t} = \frac{\text{NEpisodes. concom\_t}}{\text{NEpisodes\_t}}$$

Where:

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

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

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

$$Concom_{Prop\_t} = \beta_0 + \beta_1 \cdot T + \beta_2 \cdot P_t + \beta_3 \cdot T \cdot P_t$$

In this model:

$Concom_{Prop\_t}$: concomitant use of oral retinoids and contraception at time t
T : time elapsed since study start in units of x-month periods
P_t : indicator variable coding pre- and post-intervention period of the RMM
β_0 : baseline level at T=0
β_1 : outcome change per unit time increase (=pre-intervention trend)
β_2 : level change following the intervention
β_3 : slope change following the intervention
For the Poisson regression, count data (i.e., $N_{Episodes.concom\_t}$) will be used directly, and 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 $N_{Episodes\_t}$ will be included in the model as an offset parameter. In case of overdispersion, quasi-Poisson will be used. Durbin-Watson (DW) test will be applied to assess the presence of autocorrelation and Newey-West standard errors will be used at the identified order if autocorrelation will be detected.

The results will be presented graphically in the results section of the report**.** Parameter estimates, standard errors and p-values will be presented in a summary table.

9.7.4 Sensitivity analyses

In order to take into account that pregnancy tests might be recorded earlier than 7 days before oral retinoid treatment start the time period before the exposure start date will be expanded to one month in a sensitivity analysis.

In order to take into account that the old and the updated RMMs may co-exist during a period a sensitivity analysis will be conducted for the post-implementation period thereby excluding the first 6 months after distribution of EMs in the target countries.

9.7.5 Exploratory Analyses (If Applicable)

Not applicable

9.7.6 Handling of Missing Data

Due to the nature of real-world data, some data points might be missing from the databases for a number of reasons. The number and type of missing values will be recorded and reported in the final study report. Statistical calculations (i.e. the denominator) will be adjusted accordingly for the analysis.

Information on recommended daily dose may be not available from all data sources. The proportion of missing values will be described. However, the degree of completeness varies between databases. The missing information will be highlighted. In case dose recommendation is missing, dose information from the SPC will be used.

9.8 Quality Control

The study will use existing databases, which are being used widely for research. The study will be 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 ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP) as well as the specific IQVIA SOPs. All study programs, log files, and output files will be stored on the secure server. Where elements of the study are being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

9.8.1 Approaches for Validating the Results

The quality control for validating the results will be conducted at three levels:

1) At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data 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.

2) At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
3) At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World & Analytics Solutions. 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 will be conducted by a person who was not in charge of their preparation.

9.8.2 Record Retention

The MAHs must maintain an adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, documentation of 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.

IQVIA will store study documentation on behalf of MAHs for 5 years, in accordance with IQVIA Standards and will transfer the documentation to the MAHs for long term archiving.

9.9 Strengths and Limitations of Research Methods

9.9.1 Study Strengths

- The data sources have readily available data for the pre-implementation period of the PPP and future data for the post-implementation period will be collected routinely.
- The data sources contain a wealth of information on patients and allow for a more complete picture to be drawn of the patients.
- The results of the study are generalizable for France, Germany and Sweden due to the comprehensive data collection and the setting in which the data is being collected, in Spain for the primary care setting.
- The data sources considered are routinely used for PASS requested by the EMA and the subject of many publications (for examples see reference section and EU-PAS register).

- The study will be conducted by an experienced team specialised in the design and conduct in such drug utilisation study in safety area. It follows IQVIA SOPs as well as the methodological guidelines on ENCePP and EMA good pharmacovigilance practices (GVP).

9.9.2 Study Limitations

- Pregnancy and pregnancy outcomes
  - The extent of available information on pregnancy, pregnancy termination and pregnancy outcomes may vary between databases and countries and might be 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 are covered, e.g. about 97% to 99.4% of deliveries have been reported in the medical birth register in Sweden (Swedish National Board of Health and Welfare 2012, Olausson PO 2002). However, the Swedish birth registry only captured pregnancies after 22 weeks. Records on pregnancies are also documented in the patient registry regardless of the duration of pregnancy, but missing information regarding early termination needs to be taken into account.
    In Germany, the coverage of pregnancies in women receiving health care 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 (Mikolajczyk RT et al. 2013).
  - Incomplete information regarding the pregnancy duration may lead to misclassification of timing of exposure during pregnancy.
- Contraceptives
  - Not all contraceptive measures are documented in databases. Therefore, the analysis will mainly focus on prescriptions for hormonal contraceptives and IUDs. It will take all contraceptives measures in the data source into account if available. An underestimation of contraceptive use and country-specific patterns has to be taken into account.
    In Germany, hormonal contraceptives are reimbursed up to the age of 22 years (20 until the 29th March 2019). In case of a medical indication (for example the treatment with drugs with teratogenic potential like oral retinoids) hormonal contraceptives are reimbursed also in females over 22 years old. However, preliminary findings indicate that the percentage for this group is low
    In Spain, not all hormonal contraceptives are reimbursed and therefore information may not be available for all patients in SIDIAP.

This limitation of a database study was addressed by the PRAC followed by the request to cover the evaluation of the use of non-prescribed, non-reimbursed contraceptive methods in female oral retinoid users in the survey. The expected underreporting of contraceptives in the data sources is going to be present in both the pre-implementation and the post-implementation period of the study.

- Laboratory pregnancy tests
  - Records of laboratory pregnancy tests may not be comprehensively captured in the databases and the extent may vary by country; the databases capture records of laboratory pregnancy tests performed within the health care setting (for example for reimbursement purposes), information on self-administered laboratory pregnancy tests at home is not available;
  - In Sweden, no lab tests are recorded in the registry data, the performance of laboratory pregnancy tests is only available when documented by ICD-10 codes like Z32 “Pregnancy examination and test”.
- For acitretin user 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 will be not available for the patients treated in the post-implementation period; however, in acitretin users the available follow-up will be checked.
- The databases used for Germany, Spain, and Sweden are updated once a year. The annual update of the German claims database is 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 SNIIRAM database does not capture the specialty of the prescribers. The indications of the oral retinoids prescriptions are not captured in either the hospital or the outpatient setting.
- External validity

  Data sources were selected based on a sufficient number of patients on oral retinoids and the availability of information relevant to describe the effectiveness of the updated PPP. The availability of suitable data sources was a limiting factor. Nonetheless, the following data sources fulfilling the criteria were identified:
  - SNIIRAM in France and the national registries Sweden are capturing near-comprehensive nation-wide data.
  - The Company Health Insurance covering 6% of the German population (approx. 5 million insurants), which is similar to the coverage of the THIN database which has been used in other DUS to assess risk minimization measures (Castellsague et al. 2018).
  - SIDIAP is representative of Catalonia which makes up approximately 16% of the overall Spanish population. The MAHs acknowledge that

Catalonia may not be representative of the Spanish population in terms of the economic status and educational levels. However, SIDIAP has routinely been used as a data source for Spain (Castellsague et al. 2018).

The four study countries may, however, differ from other European countries with regard to healthcare systems, patients' socioeconomic status, and educational materials issued with the oral retinoids treatment. A survey study will be conducted simultaneously in seven countries from different parts of Europe, three of which are also included in the DUS.

While the DUS will reveal the level of implementation of the PPP by physicians, the survey will show the physician's and patient's 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 two studies support each other's external validity.

Furthermore, in countries where only one of the study types was conducted, it can be inferred that the other would have produced similar patterns had it been conducted. Therefore, the survey can be regarded as supporting the extrapolation and generalization of the results obtained from the DUS to other European countries.

9.10 Other Aspects

9.10.1 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant independent ethics committees for approval or favourable opinion, if applicable.

9.10.2 Study Management

This study will be performed by IQVIA, with guidance, input, review and approval of the members of the MAH consortium for oral retinoids, including development of materials, data management, analysis and reporting.

10. PROTECTION OF HUMAN SUBJECTS

This DUS is non-interventional and analysis is based on secondary data use. No identifying data is collected in any of the planned approaches.

The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of

personal data and on the free movement of such data (General Data Protection Regulation, GDPR).

The execution of the study will follow the regulatory and ethical requirements of each country. The DUS will comply with the module VIII of the GVP.

Although EU Pharmacovigilance Directive (DIR 2010/84/EU) is a legal act, it does not carry the same binding force of a regulation; each Member State can determine how best to transpose the Directive into local legislation. As a result, the submission requirements for PASS vary throughout the EU, with some countries being more onerous than others. IQVIA includes experts dedicated to the review and advisement on the regulations and guidelines applicable to this study in the participating countries.

The study will be submitted to ethical review boards (ERBs) for approval wherever required by local law. Regulatory authorities will be notified, and approval will be sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

The following submissions and approvals are required in the target countries:

In France, a study using SNDS data requires the following submission:

- Submission to an expert Committee on Public Interest which examines the public interest purpose.
- The process takes around 4 to 5 months to approval.

In Germany, the study requires:

- Approval of company health insurance funds.
- The process takes 2-3 weeks.

In Spain, the study requires:

- Approval of scientific committee
- Approval of clinical research ethics committee
- The process takes 1-2 months

In Sweden, the study requires two submissions / approvals:

- In order to gain access to the linked register, an approval from the local ethical review board is necessary, wherein the research project and ethical aspects should be explained in a formal application, with attached protocol. The ethics approval is dependent on the data being made publicly available in some form.
- A standard application will subsequently be submitted to the National Board of Health with the attached approval from the local ethical review board.
- The ethical approvals process takes approximately 10-11 weeks.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The DUS study is based on the secondary use of data. According to GVP module VIII the reporting of suspected adverse reactions in the form of individual case safety reports is not required for this kind of studies. With respect to the study objectives information on adverse events/adverse reactions will be not extracted from the databases and analysed in the context of this DUS. Information on pregnancies exposed to oral retinoids will be provided in aggregated form in the final study report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The DUS will be registered in EU-PAS register (currently the ENCePP e-register of studies) by the MAH consortium and study results will be posted.

The statistical results will be discussed with and approved by the MAH consortium.

Study reports including the results for the selected target countries will be written in English, using IQVIA template (which is based on the template included in the GVP module VIII) and following STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations in MS Word format.

12.1 Final Analyses and Reporting

The final study report will be submitted to the competent authorities within 54 months after EC decision. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP.

In accordance with the 2010 EU pharmacovigilance legislation, information about this PASS will be entered in the publicly available EU PAS register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered in the register before the start of data extraction. Updates to the study protocol in case of substantial amendments and the final study report will also be entered in the register.

12.2 Publications

Any publication of the results from this study will be consistent with and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010.

All reporting will be consistent with the STROBE Initiative checklist for cohort studies (STROBE 2008).

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

Study title:

Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilization study (DUS) using secondary data

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	6
1.1.2 End of data collection[5]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				

[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[5] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☒	☐	☐	9.2.1
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☐	☒	☐	
4.2.5 Duration of follow-up?	☒	☐	☐	9.7.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

This is a database study with focus of the study is on the prescribing patterns of physicians, patients will be follow-up over the individual treatment episodes and available follow-up time in the database, if applicable

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.1

Comments: Linkage will only apply to registry data in Sweden

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.6
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5.1

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding?	☐	☒	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5.2

Comments:

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

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.2

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Annex 3.1: List of medicinal products per country being surveyed

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
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	Isoderm 10 mg, Weichkapseln	Isoderm
Dermapharm AG	Germany	Isoderm 20 mg, Weichkapseln	Isoderm
Galenpharma GmbH	Germany	IsoGalen 10 mg, Weichkapseln	IsoGalen
Galenpharma GmbH	Germany	IsoGalen 20 mg, Weichkapseln	IsoGalen
Hexal AG	Germany	Isotret-Hexal 10 mg, Weichkapseln	Isotret-Hexal
Hexal AG	Germany	Isotret-Hexal 20 mg, Weichkapseln	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
GlaxoSmithKline GmbH & Co. KG	Germany	Toctino 10 mg, Weichkapseln	Toctino
GlaxoSmithKline GmbH & Co. KG	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
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
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

Annex 3.2: List of ICD-10

Identification of indication associated with oral retinoids (lists may be subject to amendment or revision during study conduct)

Substance	Indication	ICD-10 codes
Acitretin	Extensive and severe refractory forms of **psoriasis** **Pustulous psoriasis** of the hands and feet	L40: Psoriasis L40.0: Psoriasis vulgaris L40.1: Generalized pustular psoriasis L40.3: Pustulosis palmaris et plantaris L40.9: Psoriasis unspecified
	Lichen ruber planus of skin and mucous membranes	L43: Lichen planus
	Severe congenital **ichthyosis** and ichthyosiform dermatitis	Q80: Congenital ichthyosis
	Other severe and refractory forms of **dermatitis** characterised by dyskeratosis and/or hyperkeratosis	L30: other and unspecified dermatitis
Alitretinoin	Adults who have severe **chronic hand eczema** that is unresponsive to treatment with potent topical corticosteroids	L20: Atopic dermatitis L23: Allergic contact dermatitis L24: Irritant contact dermatitis L25: Unspecified contact dermatitis L30: other and unspecified dermatitis L85.1: Acquired keratosis (keratoderma) palmaris et plantaris
Isotretinoin	**Severe forms of acne** (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy	L70: Acne

ICD-10 codes for the identification of contraceptive management, laboratory pregnancy testing and outcome of delivery (list may be subject to amendment or revision during study conduct)

Category	ICD 10 code	Description
Complications	T83.3	Mechanical complication of intrauterine contraceptive device
Health services in circumstances related to reproduction	Z30.0	General counselling and advice on contraception
	Z30.1	Insertion of (intrauterine) contraceptive device
	Z30.4	Surveillance of contraceptive drugs
	Z30.5	Surveillance of (intrauterine) contraceptive device
	Z30.8	Other contraceptive management
	Z30.9	Contraceptive management, unspecified
	Z97.5	Presence of (intrauterine) contraceptive device
	Z32.0	Pregnancy, not (yet) confirmed
	Z32.1	Pregnancy, confirmed
	Z33	Pregnant state, incidental
	Z34	Supervision of normal pregnancy
	Z35	Supervision of high-risk pregnancy
	Z36	Antenatal screening
	Z37	Outcome of delivery
	Z38	Liveborn infants according to place of birth
	Z39	Postpartum care and examination
Pregnancy and pregnancy outcomes	O00-O99	Pregnancy, childbirth and the puerperium
Certain conditions originating in the perinatal period	P00-P04	Newborn affected by maternal factors and by complications of pregnancy, labour, and delivery

Annex 3.3: List of Companies- MAHs of that are part of the oral retinoids consortium

	Name	Alias
1	ALFASIGMA ESPAÑA, S.L.	ALFASIGMA ESPAÑA
2	ALLIANCE PHARMACEUTICALS LIMITED	ALLIANCE PHARMACEUTICALS LIMITED
3	ALMIRALL S.A.	ALMIRALL
4	AUROBINDO PHARMA LIMITED	AUROBINDO
5	AXXON SP. Z O.O.	AXXON
6	BAUSCH HEALTH COMPANIES	BAUSCH HEALTH
7	DERMAPHARM AG	DERMAPHARM
8	ENNOGEN HEALTHCARE LIMITED	ENNOGEN
9	ESPECIALIDADES FARMACÉUTICAS CENTRUM S.A.	ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A.
10	F. HOFFMANN-LA ROCHE AG	ROCHE
11	FIDIA FARMACEUTICI S.P.A.	FIDIA
12	GALENPHARMA	GALENPHARMA
13	GAP S.A.	GAP
14	GLAXOSMITHKLINE PLC	GLAXOSMITHKLINE
15	HEXAL AG	HEXAL AG
16	IASIS PHARMA	IASIS PHARMA
17	INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A.	INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A.,
18	ISDIN S.A.	ISDIN
19	LABORATOIRE EXPANSCIENCE	EXPANSCIENCE
20	LABORATOIRES BAILLEUL S.A.	BAILLEUL
21	LABORATOIRES SMB S.A.	SMB
22	LABORATÓRIO MEDINFAR	MEDINFAR
23	MYLAN N.V.	MYLAN

24	ORIFARM	ORIFARM
25	PELPHARMA	PELPHARMA
26	PHARMATHEN SA	PHARMATHEN
27	PIERRE FABRE DERMATOLOGIE	PIERRE FABRE
28	STADA Arzneimittel AG	STADA
29	SUN PHARMACEUTICAL INDUSTRIES LTD.	SUN PHARMA
30	TARGET	TARGET
31	TEVA PHARMACEUTICALS EUROPE B.V.	TEVA