Study Report

P3-C1-021

DARWIN EU® - Characterisation of exposure to acitretin and purpura and related conditions

08/04/2025

Version 3.0

Contents

Study title	DARWIN EU® - Characterisation of exposure to acitretin and purpura and related conditions
Study report version	V3.0
Date	08/04/2025
EU PAS number	EUPAS1000000429
Active substance	Acitretin (ATC D05BB02)
Research question and objectives	1. To characterise patients initiating treatment with acitretin in terms of: a. Demographics b. Treatment indications c. Risk factors for purpura and related conditions d. Comorbidities 2. To describe patient-level utilisation of acitretin in a cohort of new users including: a. Duration of treatment b. Concomitant medications taken/prescribed at index date 3. To estimate crude and age-sex standardised incidence rates of purpura and related conditions (and stratified by thrombocytopenic purpura vs non-thrombocytopenic purpura) in patients with common indications for acitretin and/or treatment groups, namely: a. Treatment: acitretin, methotrexate, cyclosporine, azathioprine-containing immunosuppressants; TNF alpha inhibitors; interleukin inhibitors b. Indication: (psoriasis, severe disorders of keratinization) c. Treatment-indication combination: Acitretin-psoriasis, Acitretin-keratinization, Acitretin-unknown/other, Methotrexate-psoriasis, Azathioprine/cyclosporine immunosuppressants-psoriasis, TNF alpha inhibitors-psoriasis, Interleukin inhibitors-psoriasis.
Countries of study	Spain, Netherlands, Denmark, United Kingdom
Author(s)	W. Wang

TITLE

DARWIN EU® - Characterisation of exposure to acitretin and purpura and related conditions

1. DESCRIPTION OF STUDY TEAM

Study team role(s)	Name(s)	Organisation(s)
Study Project Manager/Principal Investigator	Wanning Wang Daniel Prieto-Alhambra	University of Oxford
Data Scientist	Yuchen Guo Xihang Chen Marti Catala	University of Oxford
Epidemiologist	Annika Jodicke	University of Oxford
Clinical Domain Expert	Daniel Prieto-Alhambra	University of Oxford and Erasmus MC University
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
CPRD GOLD	Antonella Delmestri	University of Oxford
DK-DHR	Claus Møldrup, Elvira Bräuner Susanne Bruun	Danish Medicines Agency
IPCI	Katia Verhamme	Erasmus MC
SIDIAP	Agustina Giuliodori Anna Palomar Talita Duarte Salles	IDIAPJGol

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

2. DATA SOURCES

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source
Spain	SIDIAP	Primary Care	EHR	5.8 million	01/01/2010 to 01/06/2023
Netherlands	IPCI	Primary Care	EHR	2.9 million	01/01/2010 to 31/12/2023
Denmark	DK-DHR	Secondary Care and Hospital in-patient care	EHR, registries	5.8 million	01/01/2010 to 31/12/2023
UK	CPRD Gold	Primary Care	EHR	17 million	01/01/2010 to 15/12/2023

3. ABSTRACT

Title

DARWIN EU® –Characterisation of exposure to acitretin and purpura and related conditions

Rationale and background

The Marketing Authorisation Holders (MAHs) that hold Marketing Authorisations (MAs) for acitretin in Canada and the US have included purpura in their label. The Pharmacovigilance Risk Assessment Committee (PRAC) requested additional real-world evidence (RWE) to assess the association between certain purpura and related conditions and acitretin before deciding whether to include selected purpura and related conditions in section 4.4 (or 4.8) of the Summary of product characteristics (SmPC) of acitretin.

Acitretin (D05BB02) is a synthetic aromatic analogue of retinoic acid. Retinol (a derivative of Vitamin A) is known to be essential for normal epithelial growth and differentiation. Acitretin is a Nationally Authorised Product (NAP) with approved indications including severe forms of psoriasis (erythrodermic psoriasis and local or generalized pustular psoriasis); severe disorders of keratinization (such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease); and other disorders of keratinization which may be resistant to other therapies. It is authorised in the majority of European Union (EU) countries (not in Bulgaria, Cyprus, Greece, Malta, or Romania).

This study aimed to characterise patients treated with acitretin, estimate the incidence rate of purpura and related conditions in patients with common indications for acitretin and/or related treatment groups, as detailed below.

Research question and objectives

1. To characterise patients initiating treatment of acitretin in terms of:
    a. Demographics
    b. Treatment indications
    c. Risk factors for purpura and related conditions

   d. Comorbidities
2. To describe patient-level acitretin utilisation in a cohort of new users including:
   a. Duration of treatment
   b. Concomitant medications prescribed at/before/after index date
3. To estimate crude and age-sex standardised incidence rates of purpura and related conditions (and stratified by thrombocytopenic purpura vs non-thrombocytopenic purpura) in patients with common indications for acitretin and/or treatment groups, namely:
   a. Treatment: methotrexate, cyclosporine, azathioprine-containing immunosuppressants; acitretin; TNF alpha inhibitors; interleukin inhibitors
   b. Indication (psoriasis vs other)
   c. Treatment-indication combination: Acitretin-psoriasis, Acitretin-keratinization, Acitretin-unknown/other, Methotrexate-psoriasis, Azathioprine/cyclosporine immunosuppressants-psoriasis, TNF alpha inhibitors-psoriasis, Interleukin inhibitors-psoriasis

Methods

Study design

- New drug user cohort (Objectives 1-2)
- Population-level descriptive epidemiology (Objective 3)

Population

Patient-level characterisations (Objectives 1-2): New users of acitretin in the study period between 01/01/2010 and 31/12/2023 (or the latest date of data availability of the respective databases), with at least 365 days of visibility prior to the date of their first prescription and no prior use of acitretin.

Population-level descriptive epidemiology (Objective 3): New users of acitretin, alternative treatments, and/or diagnosis of a condition of interest in the study period between 01/01/2010 and 31/12/2023 (or the latest date of data availability of the respective databases), with at least 365 days of visibility prior to the date of their first prescription and no prior use of the respective drug/s, comprised the denominator population based on the respective treatment and indication groups.

Variables

Condition of interest

Indications of interest were psoriasis and severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease.

Exposure of interest was acitretin.

Outcomes of interest for the new-user cohort study were purpura and related conditions.

Co-variates for Objective 3

Treatment groups: methotrexate, cyclosporine/azathioprine-containing immunosuppressants; acitretin; TNF alpha inhibitors; interleukin inhibitors

Data sources

1. SIDIAP (Spain, Primary Care Database)
2. IPCI (Netherlands, Primary Care Database)
3. DK-DHR (Denmark, National Registry)
4. CPRD GOLD (United Kingdom [UK], Primary Care Database)

Statistical analysis

Analytical methods:

Patient level characterisation was conducted any time before or on index date (date of first prescription of acitretin), including patient demographics, treatment indications, comorbidities pre-specified as known risk factors for purpura and related conditions. For drug utilisation, duration of treatment and concomitant medications at index date, 90 days before and 90 days after index date was reported.

Incidence rates (IRs) were calculated for purpura and related conditions in acitretin users, those of other major treatment groups and those indicated for treatment with acitretin. Incidence rates per 100,000 person years were estimated crude and age-sex standardised using the European Standard Population. Results were reported for overall purpura and related conditions, and for thrombocytopenic purpura vs non-thrombocytopenic purpura.

For all analyses a minimum cell counts of 5 was used when reporting results, with any smaller counts noted as <5.

Results

Among new users of acitretin, median age was similar across the four databases ranging between 56 and 60 years of age. There were consistently more males than females with new acitretin prescriptions. The most common indication was psoriasis (68% in CPRD GOLD, 20% in IPCI, 21% in DK-DHR and 59% in SIDIAP). The most common recorded risk factor for purpura and related conditions was infectious disease (69% in CPRD GOLD, 89% in IPCI, 21% in DK-DHR and 76% in SIDIAP), while the most common comorbidities were malignant neoplastic disease (12% in CPRD GOLD, 14% in IPCI, 11% in DK-DHR and 10% in SIDIAP), anxiety (15% in CPRD GOLD, 18% in IPCI, 5% in DK-DHR and 23% in SIDIAP) and hypertension (23% in CPRD GOLD, 19% in IPCI, 1% in DK-DHR and 22% in SIDIAP).

Across the four databases analysed for drug utilisation, the median number of days exposed (equals to the duration of the first treatment episode) ranged between 30 days (CPRD GOLD) and 159 days (SIDIAP).

Common medications recorded within 90 days or less before the first prescription of acitretin were systemic antibacterials (25% in CPRD GOLD, 14% in IPCI, 21% in DK-DHR and 17% in SIDIAP) , antidepressants (24% in CPRD GOLD, 11% in IPCI, 11% in DK-DHR and 17% in SIDIAP) and anti-inflammatory/anti-rheumatics (17% in CPRD GOLD, 20% in IPCI, 18% in DK-DHR and 31% in SIDIAP). This was consistent across the four databases. Prescriptions of these drugs appeared among the most common medications observed in the 90 days after index date.

Due to low number of events (n<5) of purpura and related conditions in IPCI, IRs could not be calculated. Among the other three databases, age-sex standardised IRs for purpura and related conditions in patients with psoriasis was highest in CPRD GOLD (189 cases per 100,000 person years [95% CI: 169-209]) and lower in DK-DHR (71 [48-94]), and SIDIAP (85 [56-114]). In the psoriasis treatment group, non-thrombocytopenic purpura showed consistently higher standardised IRs than thrombocytopenic purpura (16 [10-23] vs 9[4-14], respectively in CPRD GOLD). In CPRD GOLD, the methotrexate treatment group had the highest standardised IR for purpura and related conditions at 295 [200-390], while in SIDIAP IR was 107 [49-165]. Across all databases, the number of acitretin users with outcomes of interest was too low (n<5) for IRs to be calculated.

Conclusions

Broadly, our study aimed to characterise acitretin use and purpura and related conditions across four routinely-collected healthcare databases in Denmark, Netherlands, Spain, and the UK. New users of acitretin were generally in their mid-50s to 60s and predominantly male. Psoriasis was the most common

indication, and the most common risk factor of acitretin new use recorded in the data was infectious disease.

Across the four databases for drug utilisation, the median treatment duration ranged from 30 to 159 days. Most frequent comedications were systemic antibacterials, antidepressants and anti-inflammatory/anti-rheumatics.

Due to low number of events of purpura and related conditions overall in IPCI, IRs were not calculated for this database. Among the other three databases, age-sex standardised IRs for purpura and related conditions showed that events were uncommon (<1/100 to > 1/1000) to very rare (<1/10 000). Non-thrombocytopenic purpura showed consistently higher standardised rates than thrombocytopenic purpura. The psoriasis treatment group had the highest number of events. In this treatment group, the outcome of overall purpura and related conditions were uncommon in CPRD GOLD and rare (<1/1000 to ≥ 1/10 000) in SIDIAP and DK-DHR. Moreover, the outcome of non-thrombocytopenic purpura among patients with psoriasis was rare for all three databases and thrombocytopenic purpura was very rare. Across all databases, the treatment group of acitretin did not have enough outcomes for IRs to be calculated.

Taken together, our results suggest that acitretin is most commonly used for psoriasis, and the outcome of purpura was rare in our populations of interest.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CHI	Catalan Health Institute
CI	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disorder
CPRD	Clinical Practice Research Datalink
DARWIN EU	Data Analysis And Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
HIV	Human Immunodeficiency Virus
ID	Index Date
IPCI	Integrated Primary Care Information Project
IQR	Interquartile Range
IRs	Incidence Rates
IRRs	Incidence Rate Ratios
MAs	Marketing Authorisations
MAHs	Marketing Authorisation Holders
NAJS	Croatian National Public Health Information System
NAP	Nationally Authorised Product
OHDSI	Observational Health Data Sciences And Informatics
OMOP	Observational Medical Outcomes Partnership
PRAC	Pharmacovigilance Risk Assessment Committee
RWE	Real-World Evidence
SIDIAP	Sistema d'Informació Per Al Desenvolupament De La Investigació En Atenció Primària
SmPC	Summary Of Product Characteristics
UK	United Kingdom (UK)

5. AMENDMENTS AND UPDATES

Updated *9.6.3 Other covariates..* to include infectious disease as a risk factor for purpura and related conditions.

Updated *17 Annexes Table 2. Purpura and related conditions concept IDs and names for descendants of SNOMED terms associated with MedDRA Terms*, to include the most up to date code list and classification of purpura.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	November 2024	November 26, 2024
Final Study Protocol	November 2024	December 12, 2024
Creation of Analytical code	December 2024- January 2025	January 27, 2025
Execution of Analytical Code on the data	January- February 2025	February 17, 2025
Draft Study Report	February 28, 2025	February 28, 2025
Final Study Report	March 31, 2025	April 8, 2025

7. RATIONALE AND BACKGROUND

The Marketing Authorisation Holders (MAHs) that hold Marketing Authorisations (MAs) for acitretin in Canada and the US have included purpura in their label. The Pharmacovigilance Risk Assessment Committee (PRAC) requested additional real-world evidence (RWE) to assess the association between certain purpura and related conditions and acitretin before deciding whether to include selected purpura and related conditions in section 4.4 (or 4.8) of the Summary of product characteristics (SmPC) of acitretin.

Acitretin (D05BB02) is a synthetic aromatic analogue of retinoic acid. Retinol (a derivative of Vitamin A) is known to be essential for normal epithelial growth and differentiation. Acitretin is a Nationally Authorised Product (NAP) with approved indications including severe forms of psoriasis (erythrodermic psoriasis and local or generalized pustular psoriasis); severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease. And other disorders of keratinization which may be resistant to other therapies. It is authorised in the majority of EU countries (not in Bulgaria, Cyprus, Greece, Malta, Romania).

This study aimed to characterise patients treated with acitretin, estimate the incidence rate of purpura and related conditions in patients with treatment indications for acitretin.

8. RESEARCH QUESTION AND OBJECTIVES

Description of the proposed objectives to be achieved in the study (**Table 1**).

Table 1. Research questions and objectives.

A. Objectives 1 & 2.

Objective:	To characterise patients initiating treatment with acitretin in terms of demographics, treatment indications, risk factors for purpura and related conditions any time before or on date of first prescription of acitretin (index date), duration of treatment, and concomitant prescribed at index date, 90 days before index date, and 90 days after index date.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users were defined as having prescription of acitretin in the period between 1/1/2010 and 31/12/2023 (or the latest date of data availability of the respective databases), with 1 year of prior data availability and no prior use of acitretin.
Exposure:	acitretin (D05BB02)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on the date of incident acitretin prescription and/or dispensation (index date). End of follow-up was defined as the earliest of loss to follow-up, end of data availability, or death.
Setting:	Inpatient and outpatient setting using data from the following 4 data sources: SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark], CPRD [UK]
Main measure of effect:	We described demographic characteristics including age, sex, comorbidities, indication, duration of treatment, concomitant treatment.

B. Objective 3

Objective:	To estimate crude and age-sex standardised incidence rates of purpura and related conditions in patients with common indications for acitretin and/or treatment groups, overall and stratified by thrombocytopenic purpura vs non-thrombocytopenic purpura
Hypothesis:	Not applicable

Population ***(mention key inclusion-exclusion criteria):***	**New user cohorts** New users of acitretin or alternative treatments in the period between 1/1/2010 and 31/12/2023 (or the latest date of data availability of the respective databases), with at least 365 days of data availability and no prior use of that same drug since the start of the patient's observation period. **New diagnosis cohorts** A first diagnosis of an indication of interest between 1/1/2010 and 31/12/2023 (or the latest date of data availability of the respective databases), with at least 365 days of data availability **New user cohorts with indication** New users of acitretin or alternative treatments in the period between 1/1/2010 and 31/12/2023 (or the latest date of data availability of the respective databases), with at least 365 days of data availability and no prior use of that same drug since the start of the patient's observation period. With a diagnosis of an indication of interest any time before drug initiation.

Exposure:	Common indication for acitretin
	- Major treatment groups (acitretin; methotrexate, cyclosporine or azathioprine-containing immunosuppressants; TNF alpha inhibitors; interleukin inhibitors)
	- Indication
	  ○ Psoriasis
	  ○ Severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease
	- Treatment and indication combination groups of:
	  ○ Acitretin-psoriasis
	  ○ Acitretin-keratinization
	  ○ Acitretin-unknown/other
	  ○ Methotrexate-psoriasis
	  ○ Azathioprine/cyclosporine immunosuppressants-psoriasis
	  ○ TNF alpha inhibitors-psoriasis
	  ○ Interleukin inhibitors-psoriasis

Comparator:	none
Outcome:	Purpura and related conditions

Time *(when follow up begins and ends):*	Follow-up started on the index date (date of first drug prescription or diagnosis of a condition of interest), for the calculation of incidence rate. End of follow-up was defined as the earliest of outcome of interest, loss to follow-up, end of data availability, or death.
Setting:	Inpatient and outpatient setting using data from the following 4 data sources: SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark], CPRD [UK]
Main measure of effect:	Crude and age-sex standardised incidence rates of purpura and related conditions

9. RESEARCH METHODS

9.1 Study type and study design

New drug user cohort study was conducted using routinely collected health data from 4 databases. **Table 2** describes study types and related study designs for each of the 4 proposed objectives.

Table 2. Description of potential study types and related study designs.

Objective	Study type	Study design	Study classification
Objectives 1	Patient-level characterisation	New drug user/s cohort	Off the shelf
Objective 2	Patient-level drug utilisation study (DUS)	New drug/s user cohort	Off the shelf
Objective 3	Population-level descriptive epidemiology	New drug/s user cohort	Off the shelf

9.2 Study setting and data sources

This study was conducted using routinely collected data from 4 databases from 4 European countries. All databases were previously mapped to the OMOP CDM.

1. SIDIAP (Spain, Primary Care Database)
2. IPCI (Netherlands, Primary Care Database)
3. DK-DHR (Denmark, National Registry)
4. CPRD GOLD (United Kingdom [UK], Primary Care Database)

Information on the data source(s) used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 3**. These proposed data sources include patients from Northern, Central and Southern Europe, and cover databases that include both primary and secondary care, which is essential for the characterisation of patients with chronic conditions (e.g. psoriasis) and for drug utilisation (Objectives 1-3).

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure	Feasibility count of outcome (Person counts)*	Data lock for the last update
Spain	SIDIAP	Exposure and outcome of interest are documented in the patient records, as identified in the feasibility request Contribute to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients contained	Primary Care	EHR	5.8 million	15500 (Record count)	Non-thrombocytopenic purpura: 8400	10/10/2023
Netherlands	IPCI	Exposure and outcome of interest are documented in the patient records, as identified in the feasibility request Contribute to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients contained	Primary Care	EHR	2.9 million	1400 (Person count)	Thrombocytopenic purpura: 1300	30/04/2024
Denmark	DK-DHR	Exposure and outcome of interest are documented in the patient records, as identified in	Secondary Care and Hospital in-	EHR, registries	5.8 million	12100 (Person count)	Non-thrombocytopenic	21/5/2024

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure	Feasibility count of outcome (Person counts)*	Data lock for the last update
		the feasibility request Contribute to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients contained	patient care				purpura: 1500	
UK	CPRD Gold	Exposure and outcome of interest are documented in the patient records, as identified in the feasibility request Contribute to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients contained	Primary Care	EHR	17 million	2400 (Person count)	Purpuric disorder: 11800	04/03/2024

EHR: electronic health records

* Person counts for the most common concept code for the outcome of purpura is presented for each database

1) Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] (Spain, Primary Care Database)

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymised patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymised patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

2) Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of GPs throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardized to the Observational Medical Outcomes Partnership common data model (OMOP CDM), enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the European Medicines Agency (EMA) ENCePP resources database (http://www.encepp.eu).

3) Danish Data Health Registries [DK-DHR] (Denmark, National Registry)

Danish health data is collected, stored and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age and geography in Danish health data due to mandatory reporting on all patients from birth to death, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so we have data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use.

In the present data base, we have access to the following registries for the entire Danish population of 5.9 million persons from 1.1.1995: The central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Clinical Laboratory Information Register, COVID-19 test and vaccination Registries, The complete Vaccination registry. All data registered from 1.1.1995 will be included.

4) Clinical Practice Research Datalink GOLD [CPRD] (United Kingdom, Primary Care Database)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[20] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data is available for 20 million patients, including 3.2 million currently registered patients. Access to CPRD GOLD data requires approval via the Research Data Governance Process.

9.3 Study period

The study period was from 1st January 2010 until 31st December 2023 or the latest date of data availability of the respective databases (see **Table 3** for details). The study period beginning after 2010 allowed for sufficient and consistent follow up and to preserve data quality among the databases (IPCI had limited patients before 2010, SIDIAP started recording patients in 2006).

9.4 Follow-up

For Objectives 1-2, follow up started with the first prescription (index date) of acitretin, and patients were followed until the earliest of discontinuation of study drug (greater than 30 days between prescriptions), loss to follow up, lack of data availability, or death.

For Objective 3, index dates differed based on the cohort of treatment group, indication group or treatment-indication group. For treatment groups, the index date is the first prescription of acitretin or other treatments of interest. For indication groups, the index date is the first diagnosis of a condition that is indicated for acitretin (psoriasis, severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease). For the treatment-indication combination groups, the index date is the first prescription of treatment of interest with a diagnosis of the condition before or on treatment initiation. Participants started contributing person-time in the denominator population at index date given that they have reached 365 days of sufficient prior history (to ensure adequate length of time to ascertain new use of acitretin and other treatment groups and incident purpura, and to capture baseline characteristics), and the index date is within the study period. Participants stopped contributing person time at the earliest date of the following: 1) outcome of interest, 2) date at which the observation period of the specific person ends (due to loss to follow up or death), or 3) end of available data in each of the data sources. The follow up of treatment cohort was censored at treatment discontinuation (intention to treat approach), to allow for comparability of incidence rates with the indication groups.

An example of entry and exit into the denominator population for incidence rates for treatment groups of interest is shown in **Figure 1.** In this example, person ID 1, and 3 were included as denominators after the study start date at date of drug initiation as all were being observed in the database from a prior date.

Person ID 2 and 4 entered the study after the study at drug initiation, when they had reached sufficient prior history of 365 days. Person ID 1, 2 and 4 was followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 left when exiting the database (the end of observation period). Lastly, person ID 5 had two observation periods in the database. The first period did not contribute time as the treatment was not initiated, the second started contributing time from drug initiation and exited at study end date.

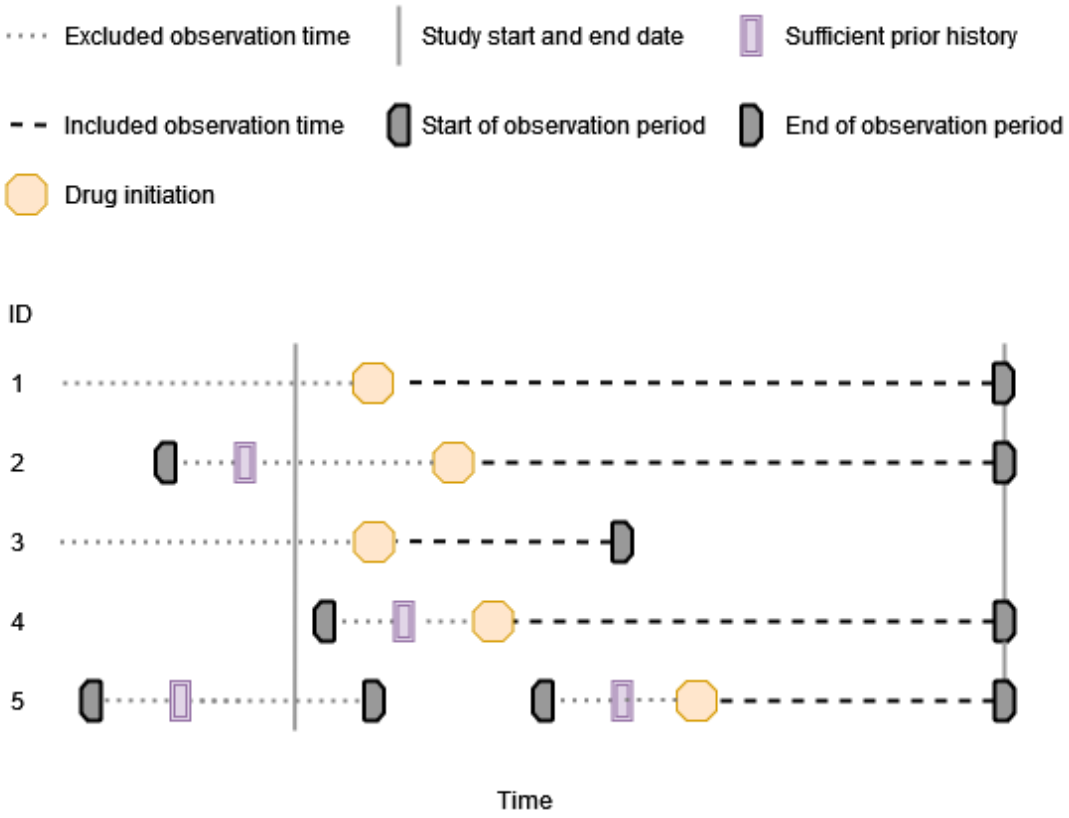

Figure 1. Incidence rate denominator visualisation for treatment groups of interest.

An example of entry and exit into the denominator population for incidence rates for indications of interest is shown in **Figure 2**. In this example, person ID 1, and 3 were included as denominators after the study start date at date of diagnosis of a condition of interest all were being observed in the database from a prior date. Person ID 2 and 4 enter the study after the study at date of diagnosis, when they had reached sufficient prior history of 365 days. Person ID 1, 2 and 4 was followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 left when exiting the database (the end of observation period). Lastly, person ID 5 had two observation periods in the database. The first period did not contribute time as there was no diagnosis for the condition of interest, the second started contributing time from date of diagnosis and exited at study end date.

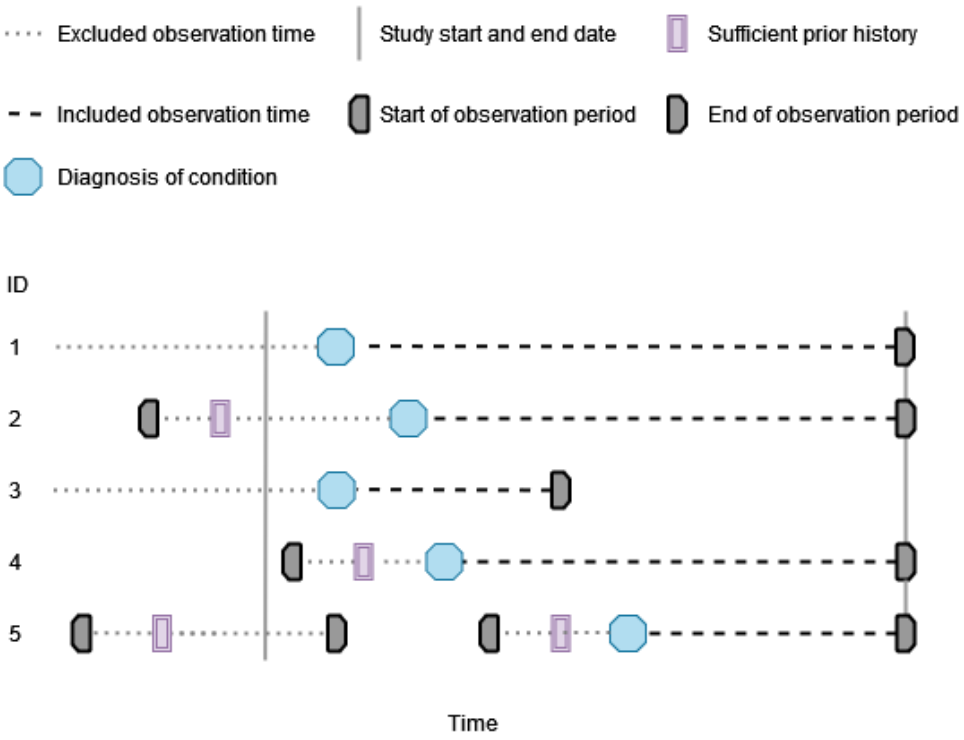

Figure 2. Incidence rate denominator visualisation for diagnosis of condition of interest.

An example of entry and exit into the denominator population for incidence rates for treatment-indication groups is shown in **Figure 3**. Diagnosis of condition could be any time before drug initiation. In this example, person ID 1, and 3 were included as denominators after the study start date and after date of diagnosis of a condition of interest at date of drug initiation as all were being observed in the database from a prior date. Person ID 2 and 4 entered the study after the study, when they had reached sufficient prior history of 365 days and after date of diagnosis at date of drug initiation. Person ID 1, 2 and 4 were followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 left when exiting the database (the end of observation period). Lastly, person ID 5 had two observation periods in the database. The first period did not contribute time as there was no diagnosis for the condition of interest, the second started contributing time from drug initiation and exited at study end date.

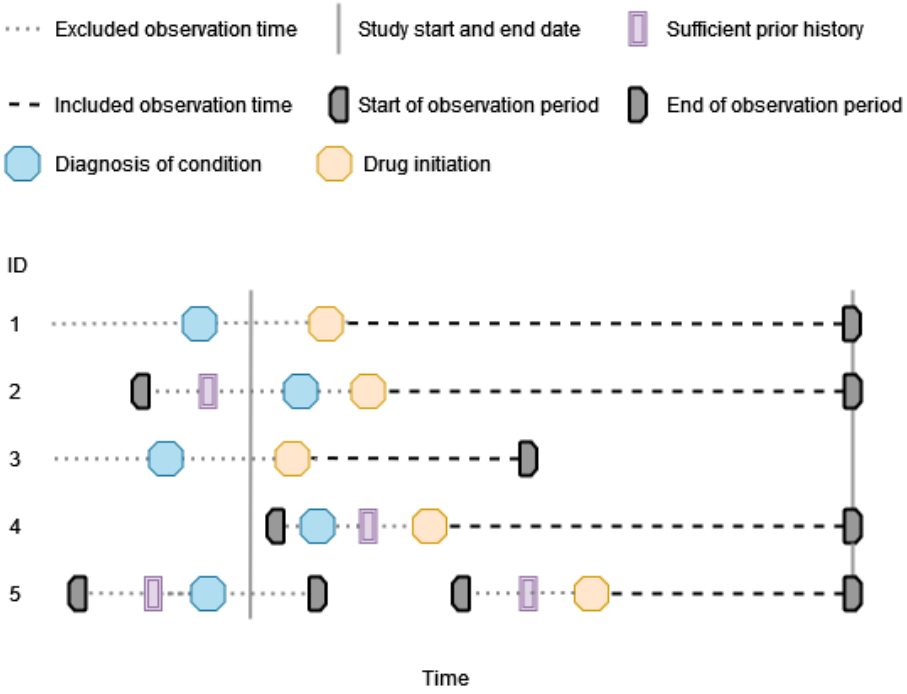

Figure 3. Incidence rate denominator visualisation for treatment-condition groups of interest.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window (days)	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
All patients with incident use of acitretin	Date of first prescription of acitretin (first drug era)	Single	Incident	[-inf, -1]	IP, OP	RxNorm	n/a	Acitretin use	n/a	n/a
All patients with incident use of treatments of interest	Date of first prescription of treatment of interest	Single	Incident	[-inf, -1]	IP, OP	RxNorm	n/a	Specific medicine of interest	n/a	n/a
All patients with diagnosis of condition of interest	Date of first diagnosis of condition of interest	Single	Incident	[-inf, -1]	IP, OP	SNOMED	n/a	Specific condition of interest	n/a	n/a

1 IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

9.5 Study population with in and exclusion criteria

Patient-level characterisations (Objectives 1-2)

New acitretin user cohort

- No previous use of acitretin
- 365 days of data availability before treatment initiation
- First use of acitretin within study period

Population-level descriptive epidemiology (Objective 3)

New user cohorts

- No previous use of treatment of interest in patient's observation period
- At least 365 days of data availability before treatment initiation
- First use of treatment of interest within study period

New diagnosis cohorts

- A diagnosis of an indication of interest
- At least 365 days of data availability before diagnosis
- First diagnosis within study period

New user cohorts with indication

- No previous use of drug on interest
- At least 365 days of data availability before treatment initiation
- First use of drug of interest within study period
- Initiation of drug of interest after diagnosis of indication of interest

The operational definitions of the inclusion and exclusion criteria are presented in **Table 5**.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Valid prior database history	Study participants were required to have a year of prior history observed before contributing observation time in incidence calculations, and for characterisation of new users	After	[-365, -1]	IP,OP	N/A	N/A	New users of the drugs of interest within selected databases	N/A	N/A
Study period	Patient present in the database during the study period (2010-2023)	After	N/A	IP,OP	N/A	N/A	All populations	N/A	N/A
Washout period	New users were required to not have used acitretin/other treatment of interest before	After	[-Inf, -1]	IP,OP	N/A	N/A	New users of the drugs of interest	N/A	N/A
Diagnosis of indication of interest	New diagnosis cohort with first diagnosis of an indication of interest	After	[-Inf, -1]	IP, OP	N/A	N/A	Indication groups for incidence rate calculations	N/A	N/A
Diagnosis of indication of interest	A diagnosis of an indication of interest was required before index date	After	[-Inf, -1]	IP, OP	N/A	N/A	Treatment-indication groups for incidence rate calculations	N/A	N/A

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

1 Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6 Variables

9.6.1 Exposure

The exposure of interest for this study was acitretin (D05BB02). For Objective 3, alternative treatments were also studied including: methotrexate, cyclosporine/azathioprine-containing immunosuppressants; TNF alpha inhibitors; and interleukin inhibitors.

Acitretin exposure consisted of a prescription record of acitretin for systemic use, accounting for the first prescription in the study period with no prior prescription in the patient's observation period. Treatment episodes of sequential prescriptions were estimated, where a maximum of 30 days between the end date of one prescription and the start date of the next prescription. Treatment discontinuation was defined as the prescription end date where there was no further prescription within the subsequent 30 days. The exposed risk window therefore accounted for all periods when the patient was likely to be using the drug. The operational definition of exposure is described in **Table 6.**

Table 6. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Acitretin	Prescription record of acitretin	[-Inf, -1]	Study period	IP, OP	RxNorm	n/a	New drug user cohort	Acitretin	n/a	n/a
Treatment groups	Preliminary code list in Appendix 1 Table 1	[-Inf, -1]	Study period	IP, OP	RxNorm	n/a	New drug user cohort	Specific treatment	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter

9.6.2 Outcome/s

The outcome for this study was first occurrence of purpura and related conditions. Outcomes were presented by purpura and related conditions (overall) and by grouping of thrombocytopenic purpura vs non-thrombocytopenic purpura.

While purpura is known to have acute presentation, it may also relapse and become chronic. Given the nature of real-world data, it may be difficult to differentiate relapses/reoccurrences from documentation of the same event. Thus, only the first outcome event was included in our analysis.

Purpura and related conditions were defined based on the MedDRA terms and their associated SNOMED codes, and phenotyped with consultation from clinical experts in the field.

The operational definition of the outcomes is presented in the **Table 7**. A preliminary list of the outcomes is provided in **Appendix 1 Table 2**.

Table 7. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Purpura	Purpura and related conditions	Yes	binary	First ever occurrence	IP, OP	N/A	N/A	Treatment group: All patients with incident use of acitretin or treatments of interest Indication group: All patients with first diagnosis of psoriasis/keratinization disorder Treatment-indication group: All patients with incident use of acitretin or treatments of interest and prior diagnosis of psoriasis/keratinization disorder	N/A	N/A

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6.3 Other covariates, including confounders, effect modifiers and other variables

Stratifications were only conducted if sufficient sample size was achieved (each strata had a minimum cell count of 5).

9.6.3.1 Objective 1:

Characterisation of patients treated with acitretin (new user cohort):

- Age
- Sex
- Treatment indications (**Appendix 1 Table 3**)
    - Psoriasis
    - Severe disorders of keratinization such as congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease
- Comorbidities prespecified as known risk factors for purpura and related conditions (1–3):
    - Blood clotting disorders
    - Nutrient deficiencies (e.g. Vitamin deficiencies, Iron deficiency anaemia)
    - Connective tissue hereditary disorder
    - Certain cancers and diseases of the bone marrow (e.g leukaemia, aplastic anaemia, multiple myeloma)
    - Infectious disease
- Comorbidities
    - Anxiety, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disorder (COPD), dementia, gastroesophageal reflux disease (GERD), heart failure, human immunodeficiency virus (HIV), hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism

9.6.3.2 Objective 2:

Characterisation of treatment with acitretin in a cohort of new users including:

- Duration of use of first continuous treatment era (gap of ≤30 days between repeated prescriptions)
- Preliminary list of concomitant medications taken at index date and (≤90 days before index date and after index date):
    - Other anti-psoriatic medications
        - methotrexate, cyclosporine /azathioprine-containing immunosuppressants; TNF alpha inhibitors; interleukin inhibitors
    - Antidepressants
    - Anti-inflammatory and anti-rheumatic agents (non-steroids)
    - Antineoplastic agents
    - Anti-thrombotic agents
    - Corticosteroids
    - Immunosuppressants
    - Systemic antibacterials
    - Systemic hormonal contraceptives

9.6.3.3 Objective 3:

Crude and age-sex standardised [based on European Standard Population 2013 (4)] incidence rates of purpura and related conditions among patients in major treatment groups, indications groups or treatment-indication groups, overall, and stratified by thrombocytopenic purpura vs non-thrombocytopenic purpura

- Major treatment groups (acitretin; methotrexate; cyclosporine/azathioprine-containing immunosuppressants; TNF alpha inhibitors; interleukin inhibitors)
- Indication
    - Psoriasis
    - Severe disorders of keratinization: congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease.
- Treatment and indication combination groups of:
    - Acitretin-psoriasis
    - Acitretin-keratinization
    - Acitretin-unknown/other
    - Methotrexate-psoriasis
    - Azathioprine/cyclosporine immunosuppressants-psoriasis
    - TNF-alpha inhibitors-psoriasis
    - Interleukin inhibitors-psoriasis

The operational definition of the covariates is described in the **Table 8.**

Table 8. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics / validation	Source for algorithm
Age	Age groups of <40, 40- 59, 60-79, 80 and above years old	Categorical	At index date [0,0]	IP, OP	N/A	N/A	New drug user cohort	N/A	N/A
Sex	Male, female, other	Categorical	At index date [0,0]	IP, OP	N/A	N/A	New drug user cohort	N/A	N/A
Treatment indication	Psoriasis, severe forms of keratinization (congenital ichthyosis, pityriasis rubra pilaris, and Darier's disease), other For stratification, categories were Psoriasis vs other	Categorical Binary	Anytime before/on index date [-Inf, 0]	IP, OP	Snomed	N/A	New drug user cohort	N/A	N/A
Risk factors for purpura	Preliminary list: blood clotting disorders, nutrient deficiencies, connective tissue hereditary disorder, certain cancers and diseases of the bone marrow, infectious disease	Binary	Anytime before/on index date [-Inf, 0]	IP, OP	N/A	N/A	New drug user cohort	N/A	N/A
Other major diseases	Standard Table 1 (list of predefined conditions)- Anxiety, asthma, chronic kidney disease, chronic liver disease, COPD, dementia, GERD, heart failure, HIV, hypertension, hypothyroidism, inflammatory bowel disease, malignant	Binary	Anytime before/on index date [-Inf, 0]	IP, OP	Snomed	N/A	New drug user cohort	N/A	N/A

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics / validation	Source for algorithm
	neoplastic disease, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism								
Duration of use	Duration of use of first continuous treatment era	Median [IQR]	N/A	IP, OP	N/A	N/A	New drug user cohort	N/A	N/A
Concomitant medications	Predefined list	Binary	At index date, 90 days before and after index date [0,0], [-90, -1], [1,90]	IP, OP	RxNorm	N/A	New drug user cohort	N/A	N/A
Major treatment groups	Methotrexate; cyclosporine/azathioprine-containing immunosuppressants; acitretin; TNF alpha inhibitors; interleukin inhibitors	Binary	At index date, 90 days before and after index date [0,0], [-90, -1], [1,90]	IP, OP	RxNorm	N/A	Population-level descriptive epidemiology	N/A	N/A

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

9.7 Study size

No sample size had been calculated as this was a descriptive Disease Epidemiology Study where we were interested in the characteristics of all patients using acitretin or alternative treatments with incident purpura. The initial feasibility count is presented in **Table 3**.

9.8 Data transformation

9.8.1 Federated network analyses

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. Once all the tests were passed, the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed. A service desk was available during the study execution for support.

The study results of all data sources were checked after which they are made available to the team in the Digital Research Environment and the Dissemination Phase can start. All results were locked and timestamped for reproducibility and transparency.

9.8.2 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 were masked.

9.9 Statistical methods

9.9.1 Main statistical methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type. Description of type of analysis based on study type is provided in **Table 9**.

Table 9. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Patient Level Characterisation (Objective 1)	Off-the-shelf	- Frequency and % of age groups, sex, indication/s, risk factors for purpura and comorbidities any time before or on index date
Patient Level DUS (Objective 2)	Off-the-shelf	- Estimation of minimum, p25, median, p75, and maximum treatment duration - Frequency and % of concomitant medications 90 days before index date, at index date, and 90 days after index date

Study type	Study classification	Type of analysis
Population-level descriptive epidemiology (Objective 3)	Off-the-shelf	- Crude and age-sex standardised incidence rates for purpura and related conditions in patients in specific treatment groups and/or indications

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R package "DrugUtilization" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence" package for the population-level estimation of descriptive epidemiology.

Drug exposure calculations

Drug eras were defined as follows: Exposure starts at date of the first prescription, e.g. the index date the person entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications. Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras were considered as exposed by the first era as shown in **Figure 4.**

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 4: Gap era joint mode.

If two eras overlap, the overlap time was considered exposed by the first era (**Figure 5**). No time was added at the end of the combined drug era to account for the overlap. If two exposures start at the same date, the overlapping period was considered exposed to both.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

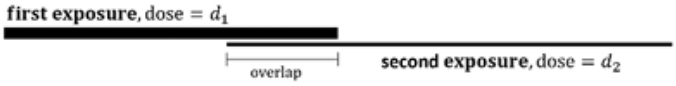

Figure 5. Gap era overlap mode.

New user cohorts

New users were selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility was required prior to that prescription. New users were required to not have been exposed to the drug of interest any time prior to the current prescription. If the index date did not fulfil the exposure washout criteria the whole exposure was eliminated.

9.9.3 Methods to derive parameters of interest

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups was used for stratification <40, 40- 59, 60-79, 80 and above years old.

Indications

Indications of psoriasis, severe diseases of keratinization or other, was determined at index date and any time prior in patient's history.

Characterisation of patient-level features

Patient-level characterisation of risk factors for purpura and comorbidities was examined based on a pre-specified list. Covariates were extracted for the any time prior to or on index date.

Incidence rates for purpura and related conditions

Crude and age-sex standardised incidence rates were estimated for the treatment groups (methotrexate, cyclosporine or azathioprine-containing immunosuppressants; acitretin; TNF alpha inhibitors; interleukin inhibitors), and indication groups of (psoriasis vs other), and a combination of indication and the treatment groups. Age-sex standardisation were based on the European Standard Population using an average of male and female age-standardised rates (4).

9.9.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Patient-level drug utilisation study

Patient level characterisation for drug utilisation was summarised using the *DrugUtilisation* R package (5).

New drug user patient-level characteristics on/before index date

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows was provided.

Indication

The number of persons (N, %) with a record of the respective indications on/before index date was provided. If a person has a record of more than one specific indication, that person was included in both specific indication groups separately.

Risk factors for purpura and related conditions

The number of persons (N, %) with a record of risk factors for purpura and related conditions on/before index date was provided. If a person has a record of more than one specific risk factor, that person was included in both specific risk factor groups separately.

Treatment duration

Treatment duration was calculated as the duration of the first continuous exposure episode, with less than a 30-day gap between prescriptions. Estimations of treatment duration was summarised providing the median [IQR] treatment duration.

Concomitant medications taken at index date

The number of persons (N, %) with a prescription of specific concomitant medications at the index date, 90 days before index, and 90 days after index date was provided. If a person has a record of more than one concomitant medication, that person was included in both specific medication groups separately.

Population-level drug utilisation study

Crude and age-sex standardised incidence rates was calculated in treatment groups, and/or indication groups for purpura related conditions overall, and thrombocytopenic vs non-thrombocytopenic purpura.

Age and sex specific rates were classified in the interpretation section using the WHO Council for International Organizations of Medical Sciences thresholds: very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1000), rare (<1/1000 to ≥1/10 000), and very rare (<1/10 000)(6). Incidence rates for purpura were calculated as the of number of new users per 100,000 person-years of the population at risk of getting exposed during the period from 2010 to 2023. Any study participants with the outcome of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described in **Section 8.4**) was excluded. The study participants who enter the denominator population would contribute time at risk up to a diagnosis of the condition of interest during the study period. Or if they did have the condition, they would contribute time at risk, as described above in **Section 8.4** (study end, end of observation period, or the last day of maximum age). An illustration of the calculation of incidence of purpura and related conditions is shown below in **Figure 6**. Patient ID 1 and 4 contributed time at risk up to the point at which they had the outcome of interest. Patient ID 2 and 5 did not have a diagnosis of the outcome of interest and so contributed time at risk but no incident outcomes. Meanwhile, patient ID 3 was excluded from the analysis as they had the outcome before the study start date.

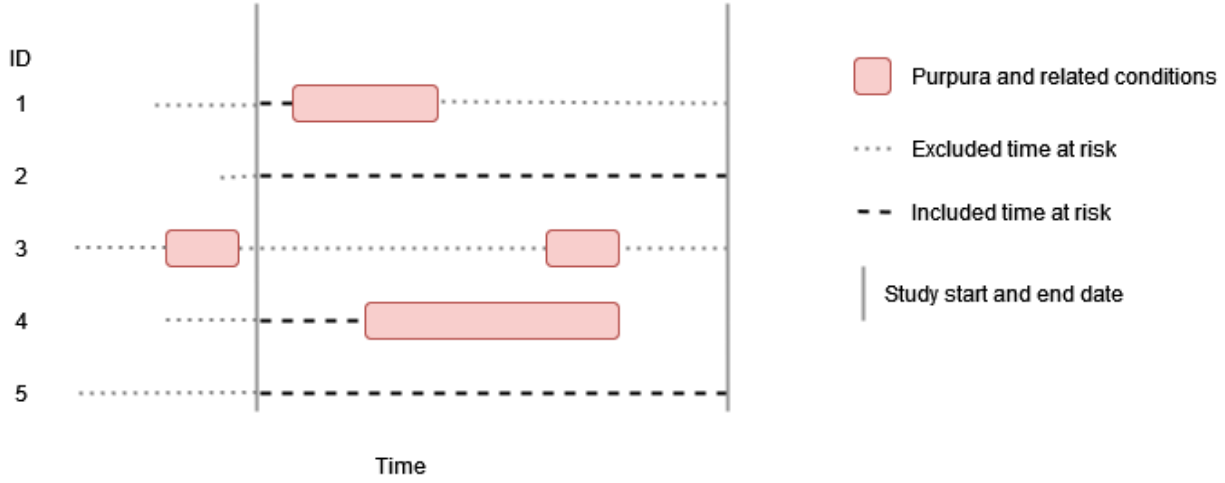

Figure 6. Incidence calculations.

9.9.5 Evidence synthesis

Patient characteristics, drug utilisation, and incidence rates of purpura will be reported separately for each database.

10. DATA MANAGEMENT

All databases have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI. http://book.ohdsi.org.

The analytic code for this study will be written in R and will use standardized analytics. Each data partner will execute the study code against their database containing patient-level data, and then return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

11. QUALITY CONTROL

Study specific quality control

When defining drug cohorts, non-systemic products was excluded from the list of included codes summarised on the ingredient level. A pharmacist reviewed the codes of the drug of interest. When defining cohorts for indications, a systematic search of possible codes for inclusion was identified using the CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this then queried the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the necessary diagnostic tools were run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error:

- The diagnostics to review drug codes included the overall counts in the population of interest, the routes, types, source concepts duration, days' supply, quantity, strength, daily dose, missingness and period covered.
- The diagnostics to review the conditions of interest included counts in the population of interest, attrition, cohort timing, specific code counts, counts of potential missing codes related to the condition of interest, distribution of index date, age and time; cohort overlap between different conditions of interest (including different flavours for the same condition), incidence and prevalence, and a large scale characterisation of the individuals with the condition of interest including a comparison with random sample from the general population matched by age and sex (the large scale characterisation allowed us to see how different was the cohort we identified from population of same age and sex).

12. RESULTS

All results for each individual drug and database are available in the shiny app at: https://data-dev.darwin-eu.org/connect/#/apps/1384169c-2c25-43bb-a9e1-d802bda221e7/runtime

The shiny app contains seven tabs:

- Summary information:
  - Background: brief description of the study
  - Summary: Summarises metadata for results
  - Snapshot: description of databases included in the study
- Cohort information:
  - Cohort count: number of patients in each of the cohorts
  - Cohort attrition: breakdown of cohort composition based on the inclusion criteria
  - Cohort characteristics: table describing characteristics of interest such as age, sex, length of follow up, indications and comorbidities.
- Drug Utilisation: summary of exposed time (duration of first continuous treatment episode) and number of exposures
- Alternative treatment: table of comedications at specific lengths of time
- Incidence:
  - Incidence values: crude incidence rates for strata of age group, sex and treatment/indication cohorts
  - Incidence attrition: breakdown of exclusion criteria for denominator of incidence rates
  - Incidence summary: summary of crude and age-sex standardised incidence rates

12.1 Participants

Complete flow-charts showing the attrition of the different cohorts in each of the study databases and their respective plots were included in the study shiny app under the "Cohort information - Cohort attrition" tab. The total number of acitretin new users in each database were as follows: 1,272 (CPRD GOLD); 7,167 (DK-DHR); 878 (IPCI); 8,991 (SIDIAP).

12.2 Descriptive data

12.2.1 Objective 1: Patient-level characteristics of new users

Characteristics of patients at the time of their first prescription of acitretin (i.e., incident users) are summarised in **Table 10**, and correspond to the "Cohort information - Cohort Characteristics" tab displayed in the shiny app.

Median age of new acitretin users was consistent across all four databases, and ranged between 56 [IQR: 46-66] (SIDIAP) and 60 [51-69] (IPCI). More males compared to females initiated acitretin, with the percentage of females ranging between 42% (CPRD GOLD) and 49% (IPCI). Psoriasis was the most common treatment indication, recorded in 68% of new acitretin users in CPRD GOLD, 23% in DK-DHR, 27% in IPCI, and 59% in SIDIAP. The most common comorbidity prespecified as known risk factor was infectious disease (69% in CPRD GOLD,21% in DK-DHR, 66% in IPCI, 76% in SIDIAP). Other risk factors including specific cancers and conditions of the bone marrow, nutrient deficiency, blood clotting disorders and connective tissue disorders saw lower frequencies. The most common recorded comorbidities were malignant neoplastic disease (12% in CPRD GOLD, 11% DK-DHR, 14% IPCI, 9.8% in SIDIAP), anxiety (16% CPRD GOLD, 5% DK-DHR, 18% IPCI, 23% SIDIAP), and hypertension (23% CPRD GOLD, 1% DK-DHR, 19% IPCI, 22% SIDIAP).

Table 10. Patient characteristics for new users of acitretin.

		CDM name			
Variable name	Variable level	CPRD GOLD	DK-DHR	IPCI	SIDIAP
Number subjects (N)	-	1,272	7,167	878	8,991
Age Median [Q25 - Q75]	-	58 [47 - 68]	57 [47 - 67]	60 [51 - 69]	56 [46 - 66]
Sex (N (%))	Female	540 (42.45%)	3,412 (47.61%)	430 (48.97%)	3,866 (43.00%)
	Male	732 (57.55%)	3,755 (52.39%)	448 (51.03%)	5,125 (57.00%)
Treatment indications (any time prior) N (%)	Psoriasis	860 (67.61%)	1,613 (22.51%)	236 (26.88%)	5,321 (59.18%)
	Severe diseases of keratinization	28 (2.20%)	75 (1.05%)	0 (0.00%)	65 (0.72%)
Risk factors for purpura and related conditions (diagnoses recorded any time prior) N (%)	Certain cancers and diseases of the bone marrow	25 (1.97%)	131 (1.83%)	8 (0.91%)	127 (1.41%)
	Infectious disease	877 (68.95%)	1,505 (21.00%)	583 (66.40%)	6,834 (76.01%)
	Nutrient deficiency	110 (8.65%)	158 (2.20%)	100 (11.39%)	1,316 (14.64%)
	Blood clotting disorders	-	40 (0.56%)	0 (0.00%)	29 (0.32%)
	Connective tissue hereditary disorder	0 (0.00%)	28 (0.39%)	0 (0.00%)	0 (0.00%)
Comorbidities (any time prior) N (%)	Dementia	12 (0.94%)	64 (0.89%)	5 (0.57%)	63 (0.70%)
	Renal impairment	155 (12.19%)	84 (1.17%)	52 (5.92%)	416 (4.63%)
	HIV	-	6 (0.08%)	0 (0.00%)	33 (0.37%)
	Malignant neoplastic disease	150 (11.79%)	821 (11.46%)	124 (14.12%)	882 (9.81%)
	Rheumatoid arthritis	13 (1.02%)	117 (1.63%)	12 (1.37%)	68 (0.76%)
	Stroke	23 (1.81%)	202 (2.82%)	10 (1.14%)	142 (1.58%)
	Chronic Kidney Disease	139 (10.93%)	69 (0.96%)	20 (2.28%)	384 (4.27%)
	Heart failure	26 (2.04%)	150 (2.09%)	19 (2.16%)	158 (1.76%)
	Pneumonia	30 (2.36%)	540 (7.53%)	46 (5.24%)	514 (5.72%)
	Asthma	113 (8.88%)	367 (5.12%)	59 (6.72%)	377 (4.19%)
	Osteoporosis	29 (2.28%)	269 (3.75%)	11 (1.25%)	361 (4.02%)
	Hypothyroidism	77 (6.05%)	144 (2.01%)	25 (2.85%)	691 (7.69%)
	Chronic Liver Disease	6 (0.47%)	76 (1.06%)	5 (0.57%)	141 (1.57%)
	Inflammatory bowel disease	17 (1.34%)	152 (2.12%)	7 (0.80%)	67 (0.75%)
	Anxiety	197 (15.49%)	385 (5.37%)	157 (17.88%)	2,101 (23.37%)

		CDM name			
Variable name	Variable level	CPRD GOLD	DK-DHR	IPCI	SIDIAP
	Gastroesophageal reflux disease	41 (3.22%)	119 (1.66%)	14 (1.59%)	496 (5.52%)
	Venous thromboembolism	50 (3.93%)	201 (2.80%)	15 (1.71%)	223 (2.48%)
	Chronic Obstructive Pulmonary Disease	87 (6.84%)	344 (4.80%)	47 (5.35%)	508 (5.65%)
	Myocardial infarction	37 (2.91%)	219 (3.06%)	18 (2.05%)	136 (1.51%)
	Hypertension	294 (23.11%)	43 (0.60%)	165 (18.79%)	1,988 (22.11%)

12.2.2 Objective 2: Patient-level acitretin utilisation for new users

Drug utilisation for the first drug era of acitretin use are summarised in **Table 11**, and correspond to the "Drug Utilisation" tab displayed in the shiny app.

Median number of prescriptions of acitretin ranged between 1 (CPRD GOLD) and 2 (DK-DHR, IPCI, SIDIAP). The duration of the first treatment era of acitretin use was 30 days (IQR: 28-60) in CPRD GOLD, 35 (35-98) in DK-DHR, 72 (30-157) in IPCI, and 159 (79 - 354) in SIDIAP.

Table 11. Drug exposure for first drug era of acitretin use.

		CDM Name			
Variable name	**Estimate name**	**CPRD GOLD**	**DK-DHR**	**IPCI**	**SIDIAP**
Number of prescriptions	Median (Q25 - Q75)	1 (1 - 2)	1 (1 - 2)	2 (1 - 4)	1 (1 - 2)
Days exposed (duration of first continuous treatment episode)	Median (Q25 - Q75)	30 (28 - 60)	35 (14 - 82)	72 (30 - 157)	159 (79 - 354)

Medications prescribed within 90 days before index date, at index date, and within 90 days after index date are summarised in **Table 12**, and correspond to the "Alternative treatment" tab displayed in the shiny app.

In CPRD GOLD the most common comedications taken up to 90 days before index date were systemic antibacterials (25%), antidepressants (24%) and anti-inflammatory/antirheumatic medications (17%). Overall, 46% of participants did not have a prescription of any of the pre-defined comedications during this time (untreated). These three drug classes were also the most common up to 90 days after the first prescription of acitretin (index date). These three drug classes were also the most common in DK-DHR, IPCI, and SIDIAP 90 days before index date (systemic antibacterials: 21%, 14%, 17%; antidepressants: 11%, 11%, 17%; anti-inflammatory agents: 18%, 20%, 31%, untreated: 50%, 51%, 41%; DK-DHR, IPCI and SIDIAP respectively). There were relatively lower frequencies of prescriptions for the other pre-defined medications of interest.

Table 12. Comedications taken 90 to 1 day before index date, at index date, and 1 day after to 90 days after index date.

		Co-medication		
Treatment	**Estimate name**	**Medication from 90 days before to 1 day before the index date**	**Medication on index date**	**Medication from 1 day after to 90 days after the index date**
CPRD GOLD				
Acitretin	N (%)	0 (0.0 %)	1,272 (100.0 %)	1,072 (84.3 %)
Systemic antibacterials	N (%)	322 (25.3 %)	68 (5.3 %)	304 (23.9 %)

Treatment	Estimate name	Co-medication		
		Medication from 90 days before to 1 day before the index date	Medication on index date	Medication from 1 day after to 90 days after the index date
Antidepressants	N (%)	303 (23.8 %)	254 (20.0 %)	307 (24.1 %)
Anti-inflammatory agents/ Antirheumatics	N (%)	214 (16.8 %)	117 (9.2 %)	226 (17.8 %)
Antineoplastic agents	N (%)	49 (3.9 %)	18 (1.4 %)	33 (2.6 %)
Antithrombotics	N (%)	95 (7.5 %)	84 (6.6 %)	108 (8.5 %)
Corticosteroids	N (%)	93 (7.3 %)	35 (2.8 %)	94 (7.4 %)
Cyclosporine/ azathioprine	N (%)	48 (3.8 %)	37 (2.9 %)	48 (3.8 %)
Systemic hormonal contraceptives	N (%)	19 (1.5 %)	18 (1.4 %)	19 (1.5 %)
Immunosuppressants	N (%)	88 (6.9 %)	49 (3.9 %)	85 (6.7 %)
Interleukin inhibitors	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Methotrexate	N (%)	37 (2.9 %)	12 (0.9 %)	23 (1.8 %)
TNF alpha blockers	N (%)	-	0 (0.0 %)	-
Untreated	N (%)	588 (46.2 %)	0 (0.0 %)	97 (7.6 %)
DK-DHR				
Acitretin	N (%)	0 (0.0 %)	7,167 (100.0 %)	7,167 (100.0 %)
Systemic antibacterials	N (%)	1,516 (21.2 %)	312 (4.4 %)	1,440 (20.1 %)
Antidepressants	N (%)	813 (11.3 %)	662 (9.2 %)	830 (11.6 %)
Anti-inflammatory agents/Antirheumatics	N (%)	1,294 (18.1 %)	657 (9.2 %)	1,257 (17.5 %)
Antineoplastic agents	N (%)	539 (7.5 %)	255 (3.6 %)	413 (5.8 %)
Antithrombotics	N (%)	490 (6.8 %)	401 (5.6 %)	509 (7.1 %)
Corticosteroids	N (%)	557 (7.8 %)	304 (4.2 %)	488 (6.8 %)
Cyclosporine/ azathioprine	N (%)	55 (0.8 %)	19 (0.3 %)	43 (0.6 %)
Systemic hormonal contraceptives	N (%)	157 (2.2 %)	121 (1.7 %)	154 (2.1 %)
Immunosuppressants	N (%)	603 (8.4 %)	277 (3.9 %)	439 (6.1 %)
Interleukin inhibitors	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Methotrexate	N (%)	524 (7.3 %)	251 (3.5 %)	387 (5.4 %)
TNF alpha blockers	N (%)	-	0 (0.0 %)	0 (0.0 %)
Untreated	N (%)	3,592 (50.1 %)	0 (0.0 %)	0 (0.0 %)
IPCI				
Acitretin	N (%)	0 (0.0 %)	878 (100.0 %)	872 (99.3 %)
Systemic antibacterials	N (%)	126 (14.4 %)	31 (3.5 %)	140 (15.9 %)
Antidepressants	N (%)	96 (10.9 %)	83 (9.5 %)	100 (11.4 %)
Anti- inflammatory agents/Antirheumatics	N (%)	171 (19.5 %)	76 (8.7 %)	167 (19.0 %)
Antineoplastic agents	N (%)	56 (6.4 %)	24 (2.7 %)	46 (5.2 %)
Antithrombotics	N (%)	72 (8.2 %)	58 (6.6 %)	83 (9.5 %)
Corticosteroids	N (%)	85 (9.7 %)	37 (4.2 %)	83 (9.5 %)
Cyclosporine/ azathioprine	N (%)	28 (3.2 %)	15 (1.7 %)	23 (2.6 %)
Systemic hormonal contraceptives	N (%)	15 (1.7 %)	12 (1.4 %)	16 (1.8 %)
Immunosuppressants	N (%)	76 (8.7 %)	44 (5.0 %)	74 (8.4 %)
Interleukin inhibitors	N (%)	-	-	-
Methotrexate	N (%)	22 (2.5 %)	8 (0.9 %)	20 (2.3 %)
TNF alpha blockers	N (%)	7 (0.8 %)	7 (0.8 %)	9 (1.0 %)
Untreated	N (%)	451 (51.4 %)	0 (0.0 %)	5 (0.6 %)
SIDIAP				
Acitretin	N (%)	0 (0.0 %)	8,991 (100.0 %)	8,988 (100.0 %)
Systemic antibacterials	N (%)	1,487 (16.5 %)	413 (4.6 %)	1,437 (16.0 %)

Treatment	Estimate name	Co-medication		
		Medication from 90 days before to 1 day before the index date	Medication on index date	Medication from 1 day after to 90 days after the index date
Antidepressants	N (%)	1,567 (17.4 %)	1,460 (16.2 %)	1,595 (17.7 %)
Anti- inflammatory agents/ Antirheumatics	N (%)	2,804 (31.2 %)	1,744 (19.4 %)	2,867 (31.9 %)
Antineoplastic agents	N (%)	450 (5.0 %)	181 (2.0 %)	344 (3.8 %)
Antithrombotics	N (%)	477 (5.3 %)	401 (4.5 %)	489 (5.4 %)
Corticosteroids	N (%)	1,106 (12.3 %)	676 (7.5 %)	1,070 (11.9 %)
Cyclosporine/ azathioprine	N (%)	184 (2.0 %)	105 (1.2 %)	176 (2.0 %)
Systemic hormonal contraceptives	N (%)	30 (0.3 %)	30 (0.3 %)	37 (0.4 %)
Immunosuppressants	N (%)	836 (9.3 %)	404 (4.5 %)	673 (7.5 %)
Interleukin inhibitors	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Methotrexate	N (%)	554 (6.2 %)	202 (2.2 %)	395 (4.4 %)
TNF alpha blockers	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Untreated	N (%)	4,086 (45.4 %)	0 (0.0 %)	0 (0.0 %)

12.2.3 Objective 3: Incidence rates of purpura and related conditions

Crude and age-sex standardised incidence rates (IRs) of purpura and related conditions for indication, treatment and indication-treatment groups are summarised in **Table 13.**

Across databases the outcome of purpura was relatively rare with many cohorts having zero outcomes.

CPRD GOLD

The treatment groups and corresponding treatment-indication groups of acitretin, interleukin inhibitors, and TNF alpha blockers had n<5 outcomes, precluding the estimation of IRs of overall purpura and related conditions.

For the indication of psoriasis, standardised IRs for overall purpura (and related conditions) was 189 cases per 100,000 person years [95% CI: 169-209]. For the outcome of non-thrombocytopenic purpura, standardised IRs were higher than thrombocytopenic purpura: 16 [10-23] vs 9 [4-14], respectively.

For cyclosporine/azathioprine treatment users, standardised IRs for purpura, non-thrombocytopenic purpura, thrombocytopenic purpura were as follows: 399 [287-511], 43 [4-82], 76 [28-123]. In the methotrexate treatment group, the standardised IR for purpura and related conditions was 295 [200-390], while the methotrexate with psoriasis group had a standardised IR of 206 [60, 353] for purpura. The additional outcome stratification of non-thrombocytopenic purpura and thrombocytopenic purpura led to n<5 events, precluding IR estimation.

DK-DHR

The treatment groups and corresponding treatment-indication groups of acitretin, cyclosporine/azathioprine, interleukin inhibitors and TNF alpha blockers did not have sufficient numbers of purpura events for IRs to be calculated.

For the indication of psoriasis, the standardised IR for purpura and related conditions was 71 per 100,000 person years [48-94], while for non-thrombocytopenic purpura it was 37 [22-53] compared to 9 [3-15] for thrombocytopenic purpura. For the methotrexate treatment group, standardised IRs for purpura overall, and non-thrombocytopenic purpura were 71 [0- 147] and 55 [0-131], respectively.

In IPCI, for all indication and treatment groups outcomes were less than 5 and IRs could not be calculated.

SIDIAP

No IRs could be generated for the indication cohorts and/or treatment groups of severe diseases of keratinization, acitretin, interleukin inhibitors, and TNF alpha blockers.

For the indication of psoriasis standardised IRs for purpura and related conditions, non-thrombocytopenic purpura and thrombocytopenic purpura were: 85 per 100,000 person years [56-114], 37 [26-47], 6 [3-10].

For the treatment group of cyclosporine/azathioprine standardised IRs for purpura and related conditions was 90 [51-129], standardised IRs for non-thrombocytopenic purpura and thrombocytopenic purpura were similar (32 [5-59] vs 22 [5-38], respectively). The treatment group of methotrexate standardised IRs for purpura was 108 [49-165] and for non-thrombocytopenic purpura was 51 [15-88], there was not enough outcomes to generate results for thrombocytopenic purpura. Moreover, for the population of methotrexate with psoriasis standardised IRs were 41 [9-75] for purpura and related conditions and 36 [6-65] for non-thrombocytopenic purpura.

Table 13. Crude and age-sex standardised incidence rates of purpura for indications, treatments, and treatment-indication groups.

	Purpura				Nonthrombocytopenic purpura				Thrombocytopenic purpura			
	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]
CPRD GOLD												
Psoriasis	391	194,985.80	200.53 [181.14 - 221.42]	188.97 [169.03 - 208.91]	31	197,951.74	15.66 [10.64 - 22.23]	16.35 [10.13 - 22.57]	15	198,102.33	7.57 [4.24 - 12.49]	9.00 [3.60 - 14.39]
Severe diseases of keratinization	6	2,421.24	247.81 [90.94 - 539.37]	225.84 [41.86 - 409.83]	0	2,471.29	0.00 [0.00 - 149.27]	0.00 [0.00 - 0.00]	0	2,476.51	0.00 [0.00 - 148.95]	0.00 [0.00 - 0.00]
Acitretin	<5	211.13	<5 [<5 - <5]	<5 [<5 - <5]	0	214.52	0.00 [0.00 - 1,719.56]	0.00 [0.00 - 0.00]	0	214.53	0.00 [0.00 - 1,719.54]	0.00 [0.00 - 0.00]
Acitretin with psoriasis	<5	137.25	<5 [<5 - <5]	<5 [<5 - <5]	0	139.89	0.00 [0.00 - 2,636.93]	0.00 [0.00 - 0.00]	0	139.89	0.00 [0.00 - 2,636.93]	0.00 [0.00 - 0.00]
Acitretin with keratinization	0	4.67	0.00 [0.00 - 79,024.24]	0.00 [0.00 - 0.00]	0	4.67	0.00 [0.00 - 79,024.24]	0.00 [0.00 - 0.00]	0	4.67	0.00 [0.00 - 79,024.24]	0.00 [0.00 - 0.00]
Acitretin other indications	0	69.69	0.00 [0.00 - 5,293.53]	0.00 [0.00 - 0.00]	0	70.44	0.00 [0.00 - 5,237.16]	0.00 [0.00 - 0.00]	0	70.44	0.00 [0.00 - 5,236.95]	0.00 [0.00 - 0.00]
Cyclosporine/azathioprine	52	11,761.40	442.12 [330.20 - 579.79]	399.44 [287.59 - 511.30]	5	12,013.18	41.62 [13.51 - 97.13]	42.92 [3.85 - 81.99]	10	12,020.87	83.19 [39.89 - 152.99]	75.70 [28.01 - 123.39]
Cyclosporine/ azathioprine with psoriasis	5	725.62	689.07 [223.74 - 1,608.05]	475.39 [42.62 - 908.16]	<5	757.27	n/a	n/a	<5	759.57	n/a	n/a
Interleukin inhibitors	0	0.45	0.00 [0.00 - 811,664.59]	0.00 [0.00 - 0.00]	0	0.47	0.00 [0.00 - 792,566.60]	0.00 [0.00 - 0.00]	0	0.47	0.00 [0.00 - 792,566.60]	0.00 [0.00 - 0.00]
Interleukin inhibitors with psoriasis	0	0.33	0.00 [0.00 - 1,104,396.08]	0.00 [0.00 - 0.00]	0	0.34	0.00 [0.00 - 1,086,583.24]	0.00 [0.00 - 0.00]	0	0.34	0.00 [0.00 - 1,086,583.24]	0.00 [0.00 - 0.00]

	Purpura				Nonthrombocytopenic purpura				Thrombocytopenic purpura			
	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]
Methotrexate	86	22,731.00	378.34 [302.62 - 467.24]	295.36 [200.31 - 390.41]	<5	23,242.94	n/a	n/a	0	23,236.87	0.00 [0.00 - 15.88]	0.00 [0.00 - 0.00]
Methotrexate with psoriasis	9	4,858.86	185.23 [84.70 - 351.62]	206.57 [59.71 - 353.42]	<5	4,949.55	n/a	n/a	0	4,948.04	0.00 [0.00 - 74.55]	0.00 [0.00 - 0.00]
Tnf alpha blockers	0	255.80	0.00 [0.00 - 1,442.11]	0.00 [0.00 - 0.00]	0	261.46	0.00 [0.00 - 1,410.85]	0.00 [0.00 - 0.00]	0	261.46	0.00 [0.00 - 1,410.87]	0.00 [0.00 - 0.00]
Tnf alpha blockers with psoriasis	0	58.03	0.00 [0.00 - 6,356.39]	0.00 [0.00 - 0.00]	0	59.64	0.00 [0.00 - 6,185.39]	0.00 [0.00 - 0.00]	0	59.64	0.00 [0.00 - 6,185.39]	0.00 [0.00 - 0.00]
DK-DHR												
Psoriasis	53	79,090.33	67.01 [50.20 - 87.65]	71.04 [47.73 - 94.35]	30	79,310.49	37.83 [25.52 - 54.00]	37.26 [21.79 - 52.74]	8	79,400.59	10.08 [4.35 - 19.85]	8.92 [2.62 - 15.22]
Severe diseases of keratinization	<5	2,310.96	n/a	n/a	<5	2,310.97	n/a	n/a	0	2,319.80	0.00 [0.00 - 159.02]	0.00 [0.00 - 0.00]
Acitretin	<5	1,500.42	n/a	n/a	0	1,503.39	0.00 [0.00 - 245.37]	0.00 [0.00 - 0.00]	<5	1,503.56	n/a	n/a
Acitretin with psoriasis	0	371.33	0.00 [0.00 - 993.43]	0.00 [0.00 - 0.00]	0	371.82	0.00 [0.00 - 992.12]	0.00 [0.00 - 0.00]	0	371.90	0.00 [0.00 - 991.90]	0.00 [0.00 - 0.00]
Acitretin with keratinization	0	20.21	0.00 [0.00 - 18,252.01]	0.00 [0.00 - 0.00]	0	20.21	0.00 [0.00 - 18,252.01]	0.00 [0.00 - 0.00]	0	20.21	0.00 [0.00 - 18,252.01]	0.00 [0.00 - 0.00]
Acitretin other indications	<5	1,109.88	n/a	n/a	0	1,112.36	0.00 [0.00 - 331.63]	0.00 [0.00 - 0.00]	<5	1,112.45	n/a	n/a
Cyclosporine/azathioprine	<5	5,294.88	n/a	n/a	<5	5,311.95	n/a	n/a	0	5,344.24	0.00 [0.00 - 69.03]	0.00 [0.00 - 0.00]

	Purpura				Nonthrombocytopenic purpura				Thrombocytopenic purpura			
	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]
Cyclosporine/ azathioprine with psoriasis	0	92.47	0.00 [0.00 - 3,989.47]	0.00 [0.00 - 0.00]	0	94.54	0.00 [0.00 - 3,902.01]	0.00 [0.00 - 0.00]	0	92.92	0.00 [0.00 - 3,970.07]	0.00 [0.00 - 0.00]
Interleukin inhibitors	0	3.03	0.00 [0.00 - 121,823.08]	0.00 [0.00 - 0.00]	0	3.03	0.00 [0.00 - 121,823.08]	0.00 [0.00 - 0.00]	0	3.59	0.00 [0.00 - 102,852.15]	0.00 [0.00 - 0.00]
Interleukin inhibitors with psoriasis	0	2.31	0.00 [0.00 - 160,019.38]	0.00 [0.00 - 0.00]	0	2.31	0.00 [0.00 - 160,019.38]	0.00 [0.00 - 0.00]	0	2.86	0.00 [0.00 - 128,811.02]	0.00 [0.00 - 0.00]
Methotrexate	15	28,115.56	53.35 [29.86 - 87.99]	70.55 [0.00 - 147.16]	8	28,167.66	28.40 [12.26 - 55.96]	55.00 [0.00 - 130.67]	<5	28,202.75	n/a	n/a
Methotrexate with psoriasis	<5	3,482.20	n/a	n/a	0	3,489.37	0.00 [0.00 - 105.72]	0.00 [0.00 - 0.00]	0	3,494.04	0.00 [0.00 - 105.58]	0.00 [0.00 - 0.00]
Tnf alpha blockers	0	160.46	0.00 [0.00 - 2,298.98]	0.00 [0.00 - 0.00]	0	160.46	0.00 [0.00 - 2,298.98]	0.00 [0.00 - 0.00]	0	160.46	0.00 [0.00 - 2,298.98]	0.00 [0.00 - 0.00]
Tnf alpha blockers with psoriasis	0	65.55	0.00 [0.00 - 5,627.38]	0.00 [0.00 - 0.00]	0	65.55	0.00 [0.00 - 5,627.38]	0.00 [0.00 - 0.00]	0	65.55	0.00 [0.00 - 5,627.38]	0.00 [0.00 - 0.00]
IPCI												
Psoriasis	<5	50,449.89	n/a	n/a	0	50,465.94	0.00 [0.00 - 7.31]	0.00 [0.00 - 0.00]	<5	50,449.89	n/a	n/a
Acitretin	0	263.29	0.00 [0.00 - 1,401.07]	0.00 [0.00 - 0.00]	0	263.37	0.00 [0.00 - 1,400.63]	0.00 [0.00 - 0.00]	0	263.29	0.00 [0.00 - 1,401.07]	0.00 [0.00 - 0.00]
Acitretin with psoriasis	0	71.38	0.00 [0.00 - 5,168.25]	0.00 [0.00 - 0.00]	0	71.46	0.00 [0.00 - 5,162.31]	0.00 [0.00 - 0.00]	0	71.38	0.00 [0.00 - 5,168.25]	0.00 [0.00 - 0.00]
Acitretin other indications	0	191.92	0.00 [0.00 - 1,922.14]	0.00 [0.00 - 0.00]	0	191.92	0.00 [0.00 - 1,922.14]	0.00 [0.00 - 0.00]	0	191.92	0.00 [0.00 - 1,922.14]	0.00 [0.00 - 0.00]
Cyclosporine/azathioprine	<5	2,072.89	n/a	n/a	0	2,082.40	0.00 [0.00 - 177.15]	0.00 [0.00 - 0.00]	<5	2,072.89	n/a	n/a

	Purpura				Nonthrombocytopenic purpura				Thrombocytopenic purpura			
	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]
Cyclosporine/ azathioprine with psoriasis	0	96.32	0.00 [0.00 - 3,829.91]	0.00 [0.00 - 0.00]	0	96.32	0.00 [0.00 - 3,829.91]	0.00 [0.00 - 0.00]	0	96.32	0.00 [0.00 - 3,829.91]	0.00 [0.00 - 0.00]
Interleukin inhibitors	0	213.15	0.00 [0.00 - 1,730.65]	0.00 [0.00 - 0.00]	0	213.15	0.00 [0.00 - 1,730.65]	0.00 [0.00 - 0.00]	0	213.15	0.00 [0.00 - 1,730.65]	0.00 [0.00 - 0.00]
Interleukin inhibitors with psoriasis	0	70.16	0.00 [0.00 - 5,257.59]	0.00 [0.00 - 0.00]	0	70.16	0.00 [0.00 - 5,257.59]	0.00 [0.00 - 0.00]	0	70.16	0.00 [0.00 - 5,257.59]	0.00 [0.00 - 0.00]
Methotrexate	<5	4,979.78	n/a	n/a	0	4,983.37	0.00 [0.00 - 74.02]	0.00 [0.00 - 0.00]	<5	4,979.78	n/a	n/a
Methotrexate with psoriasis	0	713.99	0.00 [0.00 - 516.66]	0.00 [0.00 - 0.00]	0	714.76	0.00 [0.00 - 516.10]	0.00 [0.00 - 0.00]	0	713.99	0.00 [0.00 - 516.66]	0.00 [0.00 - 0.00]
Tnf alpha blockers	0	1,646.83	0.00 [0.00 - 224.00]	0.00 [0.00 - 0.00]	0	1,646.96	0.00 [0.00 - 223.98]	0.00 [0.00 - 0.00]	0	1,646.83	0.00 [0.00 - 224.00]	0.00 [0.00 - 0.00]
Tnf alpha blockers with psoriasis	0	213.19	0.00 [0.00 - 1,730.34]	0.00 [0.00 - 0.00]	0	213.19	0.00 [0.00 - 1,730.34]	0.00 [0.00 - 0.00]	0	213.19	0.00 [0.00 - 1,730.34]	0.00 [0.00 - 0.00]
SIDIAP												
Psoriasis	138	227,631.36	60.62 [50.93 - 71.62]	84.77 [55.55 - 113.99]	72	228,050.91	31.57 [24.70 - 39.76]	36.67 [26.23 - 47.10]	15	228,283.69	6.57 [3.68 - 10.84]	6.25 [2.63 - 9.87]
Severe diseases of keratinization	<5	3,020.45	n/a	n/a	0	3,031.19	0.00 [0.00 - 121.70]	0.00 [0.00 - 0.00]	0	3,032.45	0.00 [0.00 - 121.65]	0.00 [0.00 - 0.00]
Acitretin	<5	5,647.06	n/a	n/a	<5	5,657.35	n/a	n/a	0	5,662.77	0.00 [0.00 - 65.14]	0.00 [0.00 - 0.00]
Acitretin with psoriasis	0	3,376.60	0.00 [0.00 - 109.25]	0.00 [0.00 - 0.00]	0	3,379.42	0.00 [0.00 - 109.16]	0.00 [0.00 - 0.00]	0	3,384.63	0.00 [0.00 - 108.99]	0.00 [0.00 - 0.00]
Acitretin with keratinization	0	51.18	0.00 [0.00 - 7,207.85]	0.00 [0.00 - 0.00]	0	51.18	0.00 [0.00 - 7,207.85]	0.00 [0.00 - 0.00]	0	51.18	0.00 [0.00 - 7,207.85]	0.00 [0.00 - 0.00]

	Purpura				Nonthrombocytopenic purpura				Thrombocytopenic purpura			
	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]	Outcomes (N)	Person-years	IR crude [95%CI]	IR standardised [95%CI]
Acitretin other indications	<5	2,224.37	n/a	n/a	<5	2,231.84	n/a	n/a	0	2,232.05	0.00 [0.00 - 165.27]	0.00 [0.00 - 0.00]
Cyclosporine/azathioprine	24	24,505.59	97.94 [62.75 - 145.72]	89.42 [50.51 - 128.32]	7	24,640.50	28.41 [11.42 - 58.53]	32.01 [4.86 - 59.17]	7	24,639.28	28.41 [11.42 - 58.54]	21.91 [5.43 - 38.39]
Cyclosporine/azathioprine with psoriasis	<5	1,607.04	n/a	n/a	0	1,609.78	0.00 [0.00 - 229.15]	0.00 [0.00 - 0.00]	<5	1,610.70	n/a	n/a
Methotrexate	37	51,908.97	71.28 [50.19 - 98.25]	107.22 [49.31 - 165.12]	22	52,033.12	42.28 [26.50 - 64.01]	51.40 [15.09 - 87.72]	<5	52,095.15	n/a	n/a
Methotrexate with psoriasis	7	11,310.93	61.89 [24.88 - 127.51]	41.44 [9.40 - 73.48]	6	11,331.14	52.95 [19.43 - 115.25]	35.52 [5.67 - 65.38]	0	11,336.44	0.00 [0.00 - 32.54]	0.00 [0.00 - 0.00]
Tnf alpha blockers	0	17.23	0.00 [0.00 - 21,413.91]	0.00 [0.00 - 0.00]	0	19.72	0.00 [0.00 - 18,708.18]	0.00 [0.00 - 0.00]	0	17.23	0.00 [0.00 - 21,413.91]	0.00 [0.00 - 0.00]
Tnf alpha blockers with psoriasis	0	<5	0.00 [0.00 - 76,992.18]	0.00 [0.00 - 0.00]	0	<5	0.00 [0.00 - 76,992.18]	0.00 [0.00 - 0.00]	0	<5	0.00 [0.00 - 76,992.18]	0.00 [0.00 - 0.00]

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14. DISCUSSION

14.1 Key results

Among our cohort study of new users of acitretin across four European databases, median age was similar at time of treatment initiation, ranging between 56 and 60 years of age, and there were consistently more males than females. The most common indication was psoriasis recorded for 68% in CPRD GOLD, 20% in IPCI, 66% in DK-DHR and 59% in SIDIAP). of new users of acitretin. The most common recorded risk factor for purpura and related conditions was infectious disease (69% in CPRD GOLD, 66% in IPCI, 21% in DK-DHR and 76% in SIDIAP), while the most common comorbidities were malignant neoplastic disease (12% in CPRD GOLD, 14% in IPCI, 11% in DK-DHR and 10% in SIDIAP), anxiety (15% in CPRD GOLD, 18% in IPCI, 5% in DK-DHR and 23% in SIDIAP) and hypertension (23% in CPRD GOLD, 19% in IPCI, 1% in DK-DHR and 22% in SIDIAP).

Regarding acitretin utilisation, the median number of prescriptions ranged between 1 (CPRD GOLD) and 2 (DK-DHR, IPCI and SIDIAP), and the median treatment duration (during the first/index treatment episode) was between 30 (CPRD GOLD) and 159 (SIDIAP) days long.

Common comedications taken 90 days or less before the first prescription of acitretin were systemic antibacterials, antidepressants and anti-inflammatory/anti-rheumatic drugs, consistently across the four databases. These same drugs were among the most commonly prescribed in the 90 days after acitretin initiation.

Due to low number of events of purpura and related conditions in IPCI, IRs were not able to be calculated for this database. Per the WHO Council for International Organizations of Medical Sciences (CIOMS) thresholds for categorizing events, purpura and related events ranged from “uncommon” (<1/100 to >1/1 000) to “very rare” (<1/10 000).Among the other three databases of SIDIAP, DK-DHR and CPRD GOLD, age-sex standardised IRs for purpura and related conditions in patients with psoriasis ranged from about 70 per 100,000 person-years in DK which is categorized as “rare” (<1/1000 to ≥ 1/10 000) to almost 190 in CPRD GOLD which is categorized as “uncommon”. Non-thrombocytopenic purpura showed consistently higher standardised rates than thrombocytopenic purpura. In CPRD GOLD, methotrexate users had the highest standardised rates for purpura and related conditions at 295 [200-390], compared to 107 [49-165] in SIDIAP. Per CIOM guidelines, both rates would be categorized as “uncommon”. Across all databases, new acitretin users had <5 outcomes, precluding the calculation of standardised rates of purpura and related conditions.

14.2 Limitations of the research methods

There were some limitations in the study design and data sources.

General limitations

First, purpura is a symptom that is indicative of an underlying disease causing it to be not well documented in electronic health records. To account for this, our definition of purpura and related conditions was broad and included conditions such as petechiae and ecchymosis. This increased our specificity but may be prone to outcome misclassification. Second, since acitretin is a second line treatment for psoriasis it is more likely to be prescribed in a secondary care, specialist setting. Only the DK-DHR included hospital and secondary care settings, thus records may not be as well captured in the other primary care databases. However, results between DK-DHR and other databases were relatively consistent, providing reassurance of the reliability of our results. In addition, if the drug was first prescribed by a specialist and then later follow-up was done by a GP, the index date was measured from the date of GP prescription, leading to misclassification of index date and length of follow up. Third, the study was informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription (or dispensation) does not mean that the patient actually took the drug. Fourth, the actual reason for prescription of the drug was not recorded in any of the databases. We assessed indication via a proxy based on pre-defined conditions recorded on the date of therapy initiation. Therefore, recording of potential indication was incomplete, and diagnoses of psoriasis recorded *after* acitretin prescription were not captured. Fifth, the intention to treat approach in estimating incidence rates in the treatment groups may have led to misclassification of exposure. Given the chronic condition of psoriasis where these treatments are indicated, we expected patients to remain on treatment. This approach allowed us to capture outcomes of interest after drug discontinuation and compare with incidence rates of the indication groups by applying the same follow up criteria.

Database specific limitations

The completeness of recordings of co-morbidities used for patient characterisation varied across databases. This was particularly evident in DK-DHR, for which due to differences in coding, frequency of comorbidities was lower than expected.

14.3 Interpretation

Our results showed that median age of new acitretin use was mid to late 50s with more males taking the medication. This is consistent with the expected population of acitretin users: due to the high teratogenicity, women of childbearing age are not recommended to take the drug (7). Per the box warning, acitretin must not be given to pregnant patients, patients who intend to become pregnant during therapy, or at least 3 years following treatment discontinuation(8). The most common indication of use of acitretin in our study was psoriasis, which is consistent with current international guidelines, where acitretin is indicated for moderate-to-severe plaque psoriasis in the UK, in the EU acitretin is not suggested as first choice monotherapy among conventional systemic treatment (9). Other indications for acitretin include keratinization disorder such as Darier disease, pityriasis rubra pilaris, and lamellar ichthyosis, which were relatively rare in our study (10). The most common risk factor for purpura and related conditions from our results was infectious disease, this may be due to the increased risk of infectious disease with psoriasis (11).

Our findings showed that the first continuous treatment episode/era of acitretin use consisted of 1 to 2 prescriptions, with patients taking the drug for between 30 to 159 days. This level of drug use corresponds with guidelines which suggests that for psoriasis treatment with acitretin, improvement is seen around weeks 4 to 6 and maximum benefit may take between 3 to 4 months (10).

The most common comedications taken in the 90 days before index date were systemic antibacterials, antidepressants and anti-inflammatory/anti-rheumatic drugs. Use of antidepressants is similar to trends of use in the general population (12). As acitretin is not recommended as monotherapy for psoriasis, the common use of other anti-inflammatory/anti-rheumatics is as expected (7). The high use of systemic antibacterials within 90 days prior to acitretin initiation may be due to an increased risk of infections among people with severe psoriasis (13), particularly when they are on immune suppressant therapies.

We examined age and sex standardised incidence rates for purpura and related conditions overall, and specifically for nonthrombocytopenic purpura and thrombocytopenic purpura. We used a broad definition for "Purpura and related conditions", which included conditions such as petechiae and ecchymosis. Patients with nonthrombocytopenic purpura have normal platelet levels whereas patients with thrombocytopenic purpura have lower than normal platelet levels (14). Many of our treatment and indication groups had low number of records precluding from the calculation of IRs. Per the WHO CIOMS thresholds for categorizing events, across the three databases of SIDIAP, DK-DHR and CPRD GOLD, purpura and related events ranged from "uncommon" (<1/100 to >1/1 000) to "very rare" (<1/10 000). Non-thrombocytopenic purpura showed consistently higher standardised rates than thrombocytopenic purpura. Among the psoriasis treatment group, overall purpura rates could be classified as "uncommon" in CPRD GOLD and "rare" in SIDIAP and DK-DHR. Non-thrombocytopenic purpura could be classified as "rare" (<1/1000 to ≥ 1/10 000) for all three databases and showed consistently higher standardised IRs than thrombocytopenic purpura which could be classified as "very rare" across the three databases. There is limited literature on IRs in purpura in different populations to corroborate our results. Previous research in the general population has showed that idiopathic thrombocytopenic purpura in the UK General Practice Research Database (a precursor to CPRD) between 1992 to 2005 crude incidence rates were 3.9 cases per 100,000 person years (15).

14.4 Generalisability

The study comprised individuals being prescribed acitretin or one of our additional treatments of interest or had a record of any relevant indication group in four databases from four different European countries in a primary care setting. While we consider the results representative for the study population in the respective regions, the results should not be generalised to other countries, databases or settings, but only reflect the situation in the specific region and setting covered by the respective database as documented by the differing patterns for some medicines.

15. CONCLUSION

Broadly, our study aimed to characterise acitretin use and purpura and related conditions across four routinely collected healthcare databases in the UK, Netherlands, Spain, and Denmark. New users of acitretin were generally in their mid-50s to 60s and with a higher proportion of males compared to females. Psoriasis was the most common indication, and the most common risk factor of acitretin new use was infectious disease.

Across the four databases, the median number of acitretin prescriptions ranged between 1 and 2, and treatment duration ranged from 30 to 159 days. Most frequent comedications were systemic antibacterials, antidepressants and anti-inflammatory/anti-rheumatic drugs.

Due to low number of events of purpura and related conditions overall in IPCI, IRs were not calculated for this database. Among the other three databases, age-sex standardised IRs for purpura and related conditions showed that events were uncommon (<1/100 to > 1/1000) to very rare (<1/10 000). Non-

thrombocytopenic purpura showed consistently higher standardised rates than thrombocytopenic purpura. The psoriasis treatment group had the highest number of events. In this treatment group, the outcome of overall purpura and related conditions were uncommon in CPRD GOLD and rare (<1/1000 to ≥ 1/10 000) in SIDIAP and DK-DHR. Moreover, the outcome of non-thrombocytopenic purpura among patients with psoriasis was rare for all three databases and thrombocytopenic purpura was very rare. Across all databases, the treatment group of acitretin did not have enough outcomes for IRs to be calculated.

Taken together, our results suggest that acitretin is most commonly used for psoriasis, and the outcome of purpura was rare in our populations of interest.

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17. ANNEXES

Appendix I: List Lists with concept definitions

Table 1. List of treatment groups (ingredient level).

Treatment group	Concept ID	Concept Name
Acitretin	929638	Acitretin
Methotrexate	1305058	Methotrexate
Cyclosporine/ Azathioprine	19010482	Cyclosporine
Cyclosporine/ Azathioprine	19014878	Azathioprine
TNF alpha inhibitors	937368	Infliximab
	1151789	Etanercept
	1119119	Adalimumab
	36853282	Afelimomab
	912263	Certolizumab pegol
	19041065	Golimumab
	36855655	Opinercept
Interleukin inhibitors	1593700	Guselkumab
	35200139	Tildrakizumab
	1511348	Risankizumab
	19036892	Daclizumab
	196102	Basiliximab
	1114375	Anakinra
	19023450	Rilonacept
	847083	Ustekinumab
	612865	Tocilizumab
	40161669	Canakinumab
	36854985	Briakinumab
	45892883	Secukinumab
	44818461	Siltuximab
	1592513	Brodalumab
	35603563	Ixekizumab
	1594587	Sarilumab
	36852812	Sirukumab
	37002573	Satralizumab
	36856524	Netakimab
	746895	Bimekizumab
	1525573	Spesolimab
	36860404	Olokizumab
	746977	Mirikizumab
	36860366	Levilimab

Table 2. Purpura and related conditions concept IDs and names for descendants of SNOMED terms associated with MedDRA Terms.

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
37117819	Acquired purpura fulminans	y	n	y
4204900	Acquired thrombotic thrombocytopenic purpura	y	y	n
4294427	Acute hemorrhagic edema of childhood	n	n	n
36716825	Acute purpuric eruption of skin	y	n	y
4027374	Alloimmune platelet transfusion refractoriness	n	n	n
4133984	Alloimmune thrombocytopenia	y	y	n
4172999	Autoimmune neonatal thrombocytopenia	y	y	n
4230266	Autoimmune thrombotic thrombocytopenic purpura	y	y	n
4100839	Benign primary hypergammaglobulinemic purpura	y	n	y
4051752	Calcaneal petechiae	y	n	y
4235591	Capillary fragility abnormality	n	n	n
318397	Chronic idiopathic thrombocytopenic purpura	y	y	n
4300126	Clothing purpura	y	n	y
437242	Congenital thrombocytopenic purpura	y	y	n
4299540	Contact purpura	y	n	y
4300128	Cryofibrinogenemic purpura	y	n	y
4096219	Cryoglobulinemic purpura	y	n	y
4148697	Cullen's sign	n	n	n
4263648	Dermite ocre of Favre	n	n	n
4258261	Drug induced thrombotic thrombocytopenic purpura	y	y	n
4000065	Drug-induced immune thrombocytopenia	y	y	n
4298842	Dysproteinemic purpura	y	n	y
4314452	Easy bruising	n	n	n
4241331	Ecchymoses in fetus OR newborn	y	n	y
4118793	Ecchymosis	y	n	y
4122009	Ecchymosis of buccal mucosa	y	n	y
4310314	Ecchymosis of eyelid	y	n	y
4123458	Ecchymosis of floor of mouth	y	n	y
4119329	Ecchymosis of gingivae	y	n	y
4123459	Ecchymosis of intraoral surface of lip	y	n	y
4117426	Ecchymosis of oral alveolar mucosa	y	n	y
4117425	Ecchymosis of oral cavity	y	n	y

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
4123460	Ecchymosis of oropharynx	y	n	y
4122007	Ecchymosis of palate	y	n	y
761067	Ecchymosis of periwound skin	y	n	y
608030	Ecchymosis of postauricular region	y	n	y
4122008	Ecchymosis of tongue	y	n	y
3655167	Ecchymosis present	y	n	y
4189651	Eczematid-like purpura of Doucas and Kapetanakis	y	n	y
4123077	Embolic purpura	y	n	y
436956	Evans syndrome	y	y	n
4012540	Factitious purpura	y	n	y
4033871	Familial pigmented purpuric eruption	y	n	y
4120100	Fulminant fat embolism syndrome	n	n	n
4168060	Gardner-Diamond syndrome	n	n	n
4271313	Grey Turner's sign	n	n	n
4128223	Henoch-SchÃƒÂ¶nlein nephritis	y	n	y
433749	Heparin-induced thrombocytopenia	y	y	n
4009307	Heparin-induced thrombocytopenia with thrombosis	y	y	n
4294426	Hyperglobulinemic purpura	y	n	y
4103532	Immune thrombocytopenia	y	y	n
4101602	Immunoglobulin A vasculitis	y	n	y
4216866	Infection-associated purpura	y	n	y
4032887	Itching purpura	y	n	y
4289307	Mechanical purpura	y	n	y
4121268	Metabolic purpura	y	n	y
4123461	Muscle ecchymosis	y	n	y
4345345	Neonatal alloimmune thrombocytopenia	y	y	n
4173004	Neonatal facial petechiae	y	n	y
4291461	Neonatal purpura fulminans (homozygous protein C deficiency)	y	n	y
4221109	Neonatal thrombocytopenia	y	y	n
4234257	Neonatal thrombocytopenia due to exchange transfusion	y	y	n
4264166	Neonatal thrombocytopenia due to idiopathic maternal thrombocytopenia	y	y	n
441259	Non-thrombocytopenic purpura	y	n	y
4032901	Paroxysmal hematoma of the finger	n	n	n

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
36717071	Perifollicular petechiae of skin	y	n	y
42872436	Perinatal cutaneous ecchymoses	y	n	y
42872437	Perinatal cutaneous petechiae	y	n	n
4071068	Perinatal purpura	y	n	y
603113	Periorbital ecchymosis	y	n	y
4155911	Petechiae	y	n	y
4264629	Petechiae in fetus OR newborn	y	n	y
4308009	Petechiae of skin	y	n	y
4067764	Pigmented purpuric lichenoid dermatitis of Gougerot and Blum	y	n	y
4140545	Post infectious thrombocytopenic purpura	y	y	n
4344255	Postinfective immunoglobulin A vasculitis	n	n	n
4247776	Posttransfusion purpura	y	n	y
4028065	Primary ITP (immune thrombocytopenia)	y	y	n
4121266	Primary non-thrombocytopenic purpura	y	n	y
4209297	Purpura annularis telangiectodes of Majocchi	y	n	y
4300127	Purpura due to increased intravascular pressure	y	n	y
4294425	Purpura due to prolonged vomiting and/or coughing	y	n	y
4028488	Purpura fulminans	y	n	y
37110572	Purpura of skin and or skin-associated mucous membrane co-occurrent and due to coagulation disorder	y	n	y
37110573	Purpura of skin caused by mechanical force	y	n	y
42539693	Purpura of skin co-occurrent and due to vascular fragility	y	n	y
4006156	Purpura pigmentosa chronica	y	n	y
4080556	Purpura simplex	y	n	y
4307580	Purpuric disorder	y	n	y
4154597	Purpuric rash	y	n	y
4133983	Secondary autoimmune thrombocytopenia	y	y	n
4033350	Secondary cutaneous vasculitis	n	n	n
4121267	Secondary non-thrombocytopenic purpura	y	n	y
4202511	Senile purpura	y	n	y
438252	Spontaneous ecchymosis	y	n	y
4263089	Stasis purpura	y	n	y
4301024	Stellate pseudoscar in senile purpura	y	n	y
4218081	Steroid purpura	y	n	y

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
4159646	Steroidal ecchymosis	y	n	y
4087648	Subconjunctival ecchymosis	y	n	y
4098148	Thrombocytopenia due to drugs	y	y	n
4119134	Thrombocytopenic purpura	y	y	n
4214947	Thrombocytopenic purpura associated with metabolic disorder	y	y	n
4299560	Thrombocytopenic purpura due to defective platelet production	y	y	n
4292531	Thrombocytopenic purpura due to platelet consumption	y	y	n
4301602	Thrombotic thrombocytopenic purpura	y	y	n
435076	Transient neonatal thrombocytopenia	y	y	n
4048930	Transient neonatal thrombocytopenia due to exchange transfusion	y	y	n
4049028	Transient neonatal thrombocytopenia due to idiopathic maternal thrombocytopenia	y	y	n
4048742	Transient neonatal thrombocytopenia due to isoimmunization	y	y	n
4094684	Traumatic petechiae	y	n	y
4159966	Upshaw-Schulman syndrome	y	n	y
608022	Vaccine-induced prothrombotic immune thrombocytopenia	y	y	n
4055720	Vascular hemostatic disease	n	n	n
4182711	Vasculitis of the skin	y	n	y
4100838	Waldenstrom's hypergammaglobulinemic purpura	y	n	y

y: included; n: not included

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
37117819	Acquired purpura fulminans	y	n	y
4204900	Acquired thrombotic thrombocytopenic purpura	y	y	n
4294427	Acute hemorrhagic edema of childhood	n	n	n

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
36716825	Acute purpuric eruption of skin	y	n	n
4027374	Alloimmune platelet transfusion refractoriness	n	n	n
4133984	Alloimmune thrombocytopenia	n	n	n
4172999	Autoimmune neonatal thrombocytopenia	n	n	n
4230266	Autoimmune thrombotic thrombocytopenic purpura	y	y	n
4100839	Benign primary hypergammaglobulinemic purpura	y	n	y
4051752	Calcaneal petechiae	y	n	n
4235591	Capillary fragility abnormality	n	n	n
318397	Chronic idiopathic thrombocytopenic purpura	y	y	n
4300126	Clothing purpura	y	n	y
4299540	Contact purpura	y	n	y
4300128	Cryofibrinogenemic purpura	y	n	y
4096219	Cryoglobulinemic purpura	y	n	y
4148697	Cullen's sign	n	n	n
4263648	Dermite ocre of Favre	n	n	n
4258261	Drug induced thrombotic thrombocytopenic purpura	y	y	n
4000065	Drug-induced immune thrombocytopenia	y	y	n
4298842	Dysproteinemic purpura	y	n	y
4314452	Easy bruising	n	n	n
4241331	Ecchymoses in fetus OR newborn	n	n	n
4118793	Ecchymosis	y	n	n
4122009	Ecchymosis of buccal mucosa	y	n	n
4310314	Ecchymosis of eyelid	y	n	n
4123458	Ecchymosis of floor of mouth	y	n	n
4119329	Ecchymosis of gingivae	y	n	n
4123459	Ecchymosis of intraoral surface of lip	y	n	n
4117426	Ecchymosis of oral alveolar mucosa	y	n	n
4117425	Ecchymosis of oral cavity	y	n	n
4123460	Ecchymosis of oropharynx	y	n	n
4122007	Ecchymosis of palate	y	n	n

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
761067	Ecchymosis of periwound skin	y	n	n
608030	Ecchymosis of postauricular region	y	n	n
4122008	Ecchymosis of tongue	y	n	n
3655167	Ecchymosis present	y	n	n
4189651	Eczematid-like purpura of Doucas and Kapetanakis	y	n	y
4123077	Embolic purpura	y	n	y
436956	Evans syndrome	y	y	n
4012540	Factitious purpura	n	n	n
4033871	Familial pigmented purpuric eruption	n	n	n
4120100	Fulminant fat embolism syndrome	n	n	n
4168060	Gardner-Diamond syndrome	n	n	n
4271313	Grey Turner's sign	n	n	n
4128223	Henoch-SchÃfÂ¶nlein nephritis	y	n	y
4294426	Hyperglobulinemic purpura	y	n	y
4103532	Immune thrombocytopenia	y	y	n
4101602	Immunoglobulin A vasculitis	y	n	y
4216866	Infection-associated purpura	n	n	n
4032887	Itching purpura	y	n	y
4289307	Mechanical purpura	y	n	y
4121268	Metabolic purpura	y	n	y
4123461	Muscle ecchymosis	y	n	n
4173004	Neonatal facial petechiae	n	n	n
4291461	Neonatal purpura fulminans (homozygous protein C deficiency)	n	n	n
4221109	Neonatal thrombocytopenia	n	n	n
4234257	Neonatal thrombocytopenia due to exchange transfusion	n	n	n
4264166	Neonatal thrombocytopenia due to idiopathic maternal thrombocytopenia	n	n	n
441259	Non-thrombocytopenic purpura	y	n	y
4032901	Paroxysmal hematoma of the finger	n	n	n
36717071	Perifollicular petechiae of skin	y	n	n

Concept id	Concept name	Overall purpura	Thrombo-cytopenic purpura	Non-thrombo-cytopenic purpura
42872436	Perinatal cutaneous ecchymoses	y	n	n
42872437	Perinatal cutaneous petechiae	y	n	n
4071068	Perinatal purpura	y	n	y
603113	Periorbital ecchymosis	y	n	n
4155911	Petechiae	y	n	n
4308009	Petechiae of skin	y	n	n
4067764	Pigmented purpuric lichenoid dermatitis of Gougerot and Blum	y	n	n
4140545	Post infectious thrombocytopenic purpura	n	n	n
4344255	Postinfective immunoglobulin A vasculitis	n	n	n
4121266	Primary non-thrombocytopenic purpura	y	n	y
4209297	Purpura annularis telangiectodes of Majocchi	y	n	y
4300127	Purpura due to increased intravascular pressure	y	n	y
4294425	Purpura due to prolonged vomiting and/or coughing	n	n	n
4028488	Purpura fulminans	y	n	y
37110572	Purpura of skin and or skin-associated mucous membrane co-occurrent and due to coagulation disorder	y	n	y
37110573	Purpura of skin caused by mechanical force	y	n	y
42539693	Purpura of skin co-occurrent and due to vascular fragility	y	n	y
4006156	Purpura pigmentosa chronica	n	n	n
4080556	Purpura simplex	y	n	y
4307580	Purpuric disorder	y	n	n
4154597	Purpuric rash	y	n	n
4133983	Secondary autoimmune thrombocytopenia	n	n	n
4033350	Secondary cutaneous vasculitis	n	n	n
4121267	Secondary non-thrombocytopenic purpura	y	n	y
4202511	Senile purpura	y	n	y
438252	Spontaneous ecchymosis	y	n	n
4263089	Stasis purpura	y	n	y
4301024	Stellate pseudoscar in senile purpura	y	n	y
4218081	Steroid purpura	y	n	y

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4087648	Subconjunctival ecchymosis	y	n	n
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4214947	Thrombocytopenic purpura associated with metabolic disorder	y	y	n
4299560	Thrombocytopenic purpura due to defective platelet production	y	y	n
4292531	Thrombocytopenic purpura due to platelet consumption	y	y	n
4301602	Thrombotic thrombocytopenic purpura	y	y	n
4094684	Traumatic petechiae	y	n	n
4159966	Upshaw-Schulman syndrome	n	n	n
608022	Vaccine-induced prothrombotic immune thrombocytopenia	n	n	n
4055720	Vascular hemostatic disease	n	n	n
4182711	Vasculitis of the skin	y	n	y
4100838	Waldenstrom's hypergammaglobulinemic purpura	y	n	y
4059014	Spontaneous bruising	y	n	n

Table 3. List of treatment indications.

	Concept ID	Concept Name
Psoriasis	140168	Psoriasis
Severe diseases of kertinization	134743	Congenital ichthyosis of skin
	136774	Pityriasis rubra pilaris
	4081065	Acquired keratosis follicularis (Darier's disease)