Study Protocol

P3-C1-021

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

20/12/2024

Version 2.0

Contents

Study title	DARWIN EU® - Characterisation of exposure to acitretin and purpura and related conditions
Protocol version	V2.0
Date	20/12/2025
EU PAS number	EUPAS1000000429
Active substance	acitretin (D05BB02)
Medicinal product	
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
Country(ies) of study	Spain, Netherlands, Denmark, United Kingdom
Author(s)	W.Wang, E.H. Tan

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)

1 TITLE

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

2 RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Wanning Wang Eng Hooi (Cheryl) Tan	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*	**Names**	**Organisation**
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.

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 causal 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, Romania).

This study aims 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, will comprise the denominator population based on the respective treatment and indication groups.

Variables

Condition of interest

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

Exposure of interest is acitretin.

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

Co-variates for Objective 3

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

All co-morbidities and co-medications will be used for large-scale patient characterisation during cohort diagnostics, identified as concept/code and descendants. A separate list of pre-specified co-morbidities and co-medications of interest for acitretin new users will also be described.

Data source

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

Statistical analysis

Analytical methods:

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

Incidence rates (IRs) will be 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 will be estimated crude and age-sex standardised. Results will be reported for overall purpura and related conditions, and for thrombocytopenic purpura vs non-thrombocytopenic purpura.

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

4 AMENDMENTS AND UPDATES

None.

5 MILESTONES

Study milestones and deliverables	Planned dates
Draft Study Protocol	November 2024
Final Study Protocol	November 2024
Creation of Analytical code	December 2024- January 2025
Execution of Analytical Code on the data	January- February 2025
Draft Study Report	28 February 2025
Final Study Report	31 March 2025

6 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 causal 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 aims to characterise patients treated with acitretin, estimate the incidence rate of purpura and related conditions in patients with treatment indications for acitretin.

7 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 will be defined as having prescription of an 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 will start on the date of incident acitretin prescription and/or dispensation (index date). End of follow-up will be 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 will describe 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 will start 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 will be 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 rate of purpura and related conditions

8 RESEARCH METHODS

8.1 Study type and study design

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

New drug user cohort study will be conducted using routinely collected health data from 4 databases. **Table** 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

8.2 Study setting and data sources

This study will be 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) [Objective 1 to 3]
2. IPCI (Netherlands, Primary Care Database) [Objective 1 to 3]
3. DK-DHR (Denmark, National Registry) [Objective 1 to 3]
4. CPRD GOLD (United Kingdom [UK], Primary Care Database) [Objective 1 to 3]

Information on the data source(s) planned to be 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 (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Feasibility count of exposure (if relevant)	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 the feasibility request Contribute to geographical diversity of	Secondary Care and Hospital in-patient care	EHR, registries	5.8 million	12100 (Person count)	Non-thrombocytopenic purpura: 1500	21/5/2024

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Feasibility count of exposure (if relevant)	Feasibility count of outcome (Person counts)*	Data lock for the last update
		data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients contained						
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 anonymized 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 cradle to grave, 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 are 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.

8.3 Study period

For Objectives 1-3, the study period will be 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 would allow 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).

8.4 Follow-up

For Objectives 1-2, follow up will start with the first prescription (index date) of acitretin, and patients will be 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 will differ 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 will start 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 will stop 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 will not be 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 are included as denominators after the study start date at date of drug initiation as all are being observed in the database from a prior date. Person ID 2 and 4 enter the study after the study at drug initiation, when they have reached sufficient prior history of 365 days. Person ID 1, 2 and 4 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period would not contribute time as the treatment was not initiated, the second starts contributing time from drug initiation and exits at study end date.

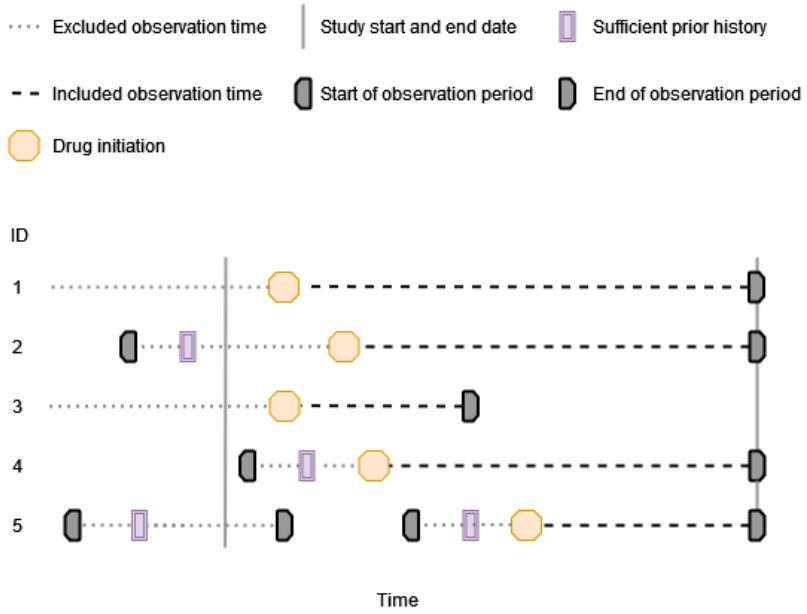


Figure 1. Incidence rate denominator visualisation for treatment groups of interest.

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 are included as denominators after the study start date at date of diagnosis of a condition of interest all are 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 have reached sufficient prior history of 365 days. Person ID 1, 2 and 4 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period would not contribute time as there was no diagnosis for the condition of interest, the second starts contributing time from date of diagnosis and exits at study end date.

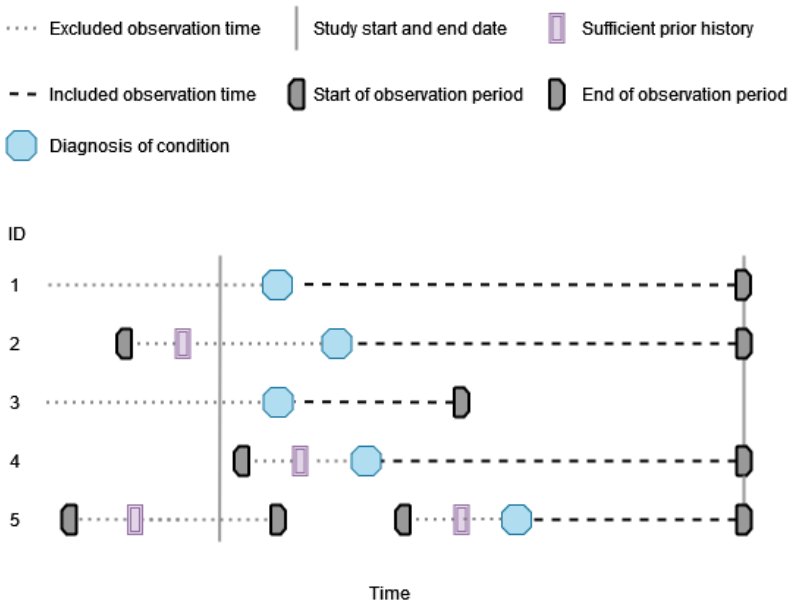


Figure 2. Incidence rate denominator visualisation for diagnosis of condition of interest.

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 can be any time before drug initiation. In this example, person ID 1, and 3 are 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 are being observed in the database from a prior date. Person ID 2 and 4 enter the study after the study, when they have reached sufficient prior history of 365 days and after date of diagnosis at date of drug initiation. Person ID 1, 2 and 4 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period would not contribute time as there was no diagnosis for the condition of interest, the second starts contributing time from drug initiation and exits at study end date.

Table 4 outlines the operation definitions for index dates.

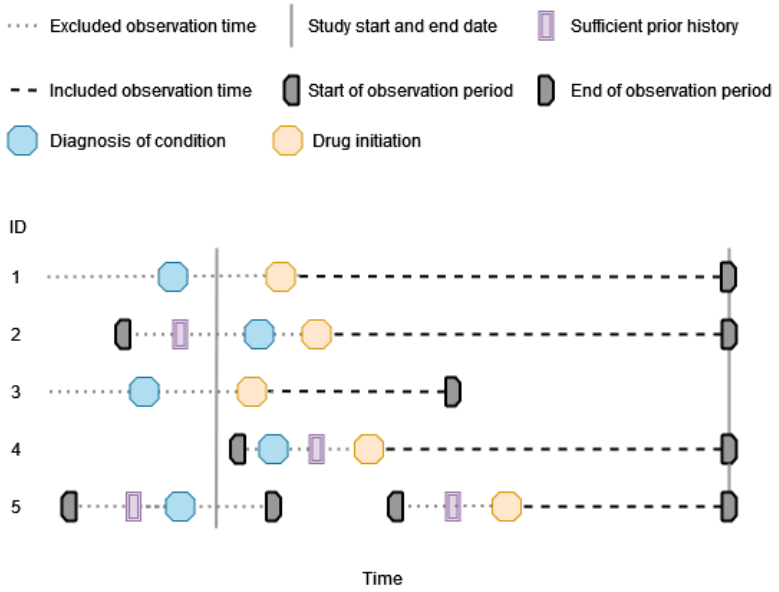


Figure 3 Incidence rate denominator visualisation for treatment-condition groups of interest.

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

8.5 Study population with inclusion 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 will be 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 will be 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 will be 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

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

8.6 Variables

8.6.1 Exposure/s

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

Acitretin exposure consists 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 will be estimated, where a maximum of 30 days between the end date of one prescription and the start date of the next prescription. Treatment discontinuation is defined as the prescription end date where there is no further prescription within the subsequent 30 days. The exposed risk window will therefore account for all periods when the patient is likely to be using the drug. The operational definition of exposure is described in Error! Reference source not found..

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

8.6.2 Outcome/s

The outcome for this study is first occurrence of purpura and related conditions. Outcomes will be 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 will be included in our analysis.

Purpura and related conditions will be 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)

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

Stratifications will only be conducted if sufficient sample size is achieved (each strata has a minimum cell count of 5).

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
- Preliminary list of risk factors for purpura and related conditions which may further be informed by large scale characterisation from cohort diagnostics (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)
- 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

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) which may further be informed by large scale characterisation from cohort diagnostics (1):
    - Other anti-psoriatic medications
        - methotrexate, cyclosporine or 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

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 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

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 will be 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	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,	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
	inflammatory bowel disease, malignant 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 or 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

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

8.7 Study size

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

8.8 Analysis

This section will describe 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 **Error! Not a valid bookmark self-reference.**.

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
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

8.8.1 Federated network analyses

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

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

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

8.8.2 Patient privacy protection

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

8.8.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use 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 will be 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 is retrieved from the drug exposure table in the CDM. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications. Two drug eras will be 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 will be considered as exposed by the first era as shown in **Figure 4.**

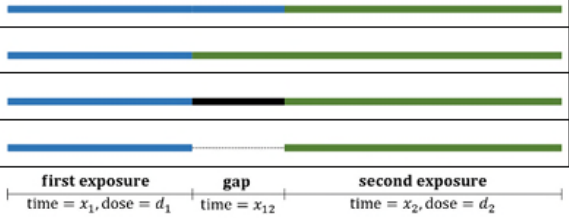
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		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 will be considered exposed by the first era (**Figure 5**). No time will be 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 will be considered exposed to both.

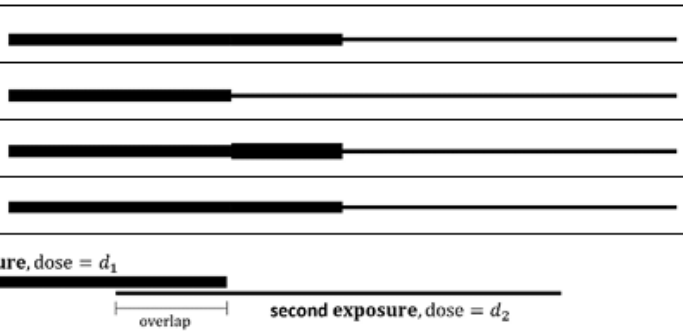
Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

Figure 5. Gap era overlap mode.

New user cohorts

New users will be 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 will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest any time prior to the current prescription. If the index date does not fulfil the exposure washout criteria the whole exposure is eliminated.

8.8.4 Methods to derive parameters of interest

Age

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

Indications

Indications of psoriasis, severe diseases of keratinization or other, will be 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 will be examined based on a pre-specified list. Covariates will be 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 will be 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 will be based on the European Standard Population using an average of male and female age-standardised rates.

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

Patient-level drug utilisation study

Patient level characterisation for drug utilisation will be summarized using the *DrugUtilisation* R package (11).

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 will be provided.

Indication

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

Treatment duration

Treatment duration will be calculated as the duration of the first continuous exposure episode, with less than a 30-day gap between prescriptions. Estimations of treatment duration will be summarized 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 will be provided. If a person has a record of more than one concomitant medication, that person will be included in both specific medication groups separately.

Population-level drug utilisation study

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

Incidence rates for purpura will be 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**) will be excluded. The study participants who enter the denominator population will then contribute time at risk up to a diagnosis of the condition of interest during the study period. Or if they do not have the condition, they will 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 contribute time at risk up to the point at which they have the outcome of interest. Patient ID 2 and 5 do not have a diagnosis of the outcome of interest and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 is excluded from the analysis as they had the outcome before the study start date.

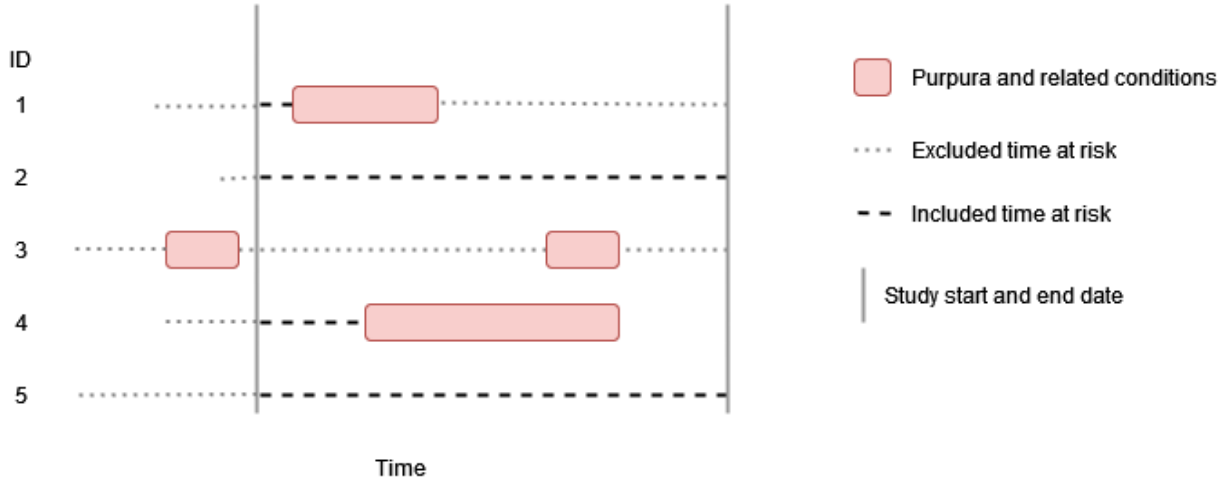


Figure 6. Incidence calculations.

8.8.6 Evidence synthesis

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

9 DATA MANAGEMENT

All databases have previously mapped their data to the OMOP common data model. This enables 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.

10 QUALITY CONTROL

Study specific quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level. A pharmacist will review the codes of the drug of interest. When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified

using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the necessary diagnostic tools will be 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 will include 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 will include 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 allows us to see how different is the cohort we identified from population of same age and sex).

11 LIMITATIONS OF THE RESEARCH METHODS

There are some limitations in the study design and data sources. First, purpura is a symptom that is indicative of an underlying disease, it is difficult to ascertain whether an increase in risk is associated with acitretin use or due to another cause. We included stratifications by indication to account for potential differences among populations. Second, our definition of purpura and related conditions is broad and includes conditions such as petechiae and ecchymosis. This increases our specificity but may be prone to

outcome misclassification. By reporting purpura, overall and grouped by thrombocytopenic vs non-thrombocytopenic purpura will allow for more sensitivity in our outcome definition. Third, since acitretin is a second line treatment for psoriasis it is more likely to be prescribed in a secondary care, specialist setting which may not be captured in all our databases. In addition, if the drug was first prescribed by a specialist and then later follow-up was done by a GP, the index date will be measured from the date of GP prescription, leading to misclassification of index date and length of follow up. Fourth, the study will be 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. Fifth, the actual reason for prescription of the drug is not recorded in any of the databases. We will assess indication via a proxy based on pre-defined conditions recorded on the date of therapy initiation. Therefore, recording of potential indication may be incomplete. Sixth, the intention to treat approach in estimating incidence rates in the treatment groups may lead to misclassification of exposure. Given the chronic condition of psoriasis where these treatments are indicated, we expect patients to remain on treatment. This approach allows 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. Lastly, the completeness of recordings of co-morbidities used for patient characterisation may vary across databases.

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be 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.

13 GOVERNANCE BOARD ASPECTS

All databases, except DK-DHR, require ethical approvals from their local Institutional Review Boards to perform this study. DK-DHR provided an umbrella approvement for DARWIN EU ®studies.

14 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Dissemination activities to be undertaken will include mainly, although not exclusively, the creation of a final report, scientific publications, and presentations at conferences.

15 OTHER ASPECTS

None.

16 REFERENCES

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17 ANNEXES

Appendix I: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Table 1. Preliminary list of treatment groups (ingredient level).

Treatment group	Concept ID	Concept Name
Acitretin	929638	Acitretin
Immunosuppressants	1305058	Methotrexate
	19010482	Cyclosporine
	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

Treatment group	Concept ID	Concept Name
	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
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
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
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

Table 3. Preliminary list of treatment indications

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

Appendix II: ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

EU PAS Register® number:
Study reference number (if applicable): P3-C1-021

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	5
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.3
	4.2.2 Age and sex	☒	☐	☐	8.6
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.6
	4.2.5 Duration of follow-up	☒	☐	☐	8.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.6, 8.4
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.6
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.8
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.8

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.6
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6

Section 9: Data sources	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.8
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.8
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.8

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	11
12.1.2 Information bias?	☒	☐	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	13
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: Wanning Wang

Date: 21/October/2024

Signature: WW

Appendix III: Additional Information

None.