Study Protocol

P3-C1-001

Characterising the use of JAK inhibitors in Europe: a Drug Utilisation Study

29/01/2025

Version 3.0

Contents

Study title	DARWIN EU® - Characterising the use of JAK inhibitors in Europe: a Drug Utilisation Study
Protocol version	V3.0
Date	29/01/2025
EU PAS number	EUPAS1000000424
Active substance	JAKi (abrocitinib, baricitinib, filgotinib, tofacitinib, upadacitinib)
Medicinal product	N/A
Research question and objectives	This study aims to identify and characterise new JAKi users. The specific objectives are: 1. To estimate the incidence of new JAKi use, overall and for each individual JAKi ingredient. 2. To characterise new JAKi users and treatment for each individual JAKi, stratified by indication
Country(ies) of study	Finland, Germany, Netherlands, Norway, and Spain
Author(s)	Amy Lam, Daniel Prieto-Alhambra

LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilisation Study
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FinOMOP-HILMO	Finnish Care Register for Health Care
GP	General Practitioner
IPCI	Integrated Primary Care Information
JAKi	Janus kinase inhibitor/s
MACE	Major adverse cardiovascular event
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
ORAL	Oral Rheumatoid Arthritics Trial
TNF	Tumour Necrosis Factor
VID	Valencia Health System Integrated Dataset

1. TITLE

DARWIN EU® - Characterising the use of JAK inhibitors in Europe: a Drug Utilisation Study

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Amy Lam Daniel Prieto-Alhambra	University of Oxford Erasmus MC
Data Scientist	Xihang Chen Edward Burn	University of Oxford
Epidemiologist	Amy Lam Annika Jödicke	University of Oxford
Clinical Domain Expert	Daniel Prieto-Alhambra Alexa Escudero-Siosi	Erasmus MC University of Oxford
Data Partner*	**Names**	**Organisation**
FinOMOP-HILMO	Tiina Wahlfors Anna Hammais	Finnish Institute for Health and Welfare (THL)
IPCI	Katia Verhamme	Erasmus MC
IQVIA DA Germany	Dina Vojinovic Gargi Jadhav Isabella Kacmarczyl Akram Mendez	IQVIA
NLHR	Hedvig Marie Egeland Nordeng Nhung Trinh	University of Oslo
VID	Gabriel Sanfélix-Gimeno Celia Robles-Cabaniñas	FISABIO

*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

Characterising the use of JAK inhibitors in Europe: a Drug Utilisation Study

Rationale and background

JAKi therapy has been gaining popularity for the treatment of several autoimmune conditions, including rheumatoid arthritis, inflammatory bowel disease, and atopic dermatitis. The first JAKi, tofacitinib, was approved by the European Medicines Agency (EMA) for the management of rheumatoid arthritis in 2017. An FDA-requested study (the Oral Rheumatoid Arthritics Trial (ORAL) Surveillance trial) showed a higher risk of major adverse cardiovascular events (MACE), cancer and adjudicated opportunistic infection with tofacitinib compared to tumour necrosis factor (TNF) inhibitors in patients aged 50 years or older with at least one cardiovascular risk factor. Further research has been conducted on the safety profile of JAKi for other indications, including psoriatic arthritis, ulcerative colitis and atopic dermatitis. It was shown that risk of venous thrombotic events of JAKi users was similar to placebo users in patients with atopic dermatitis and ulcerative colitis. Incidence of adverse events, including herpes zoster infection and thrombotic events, remained similar with longer follow-up up to two years in psoriatic arthritis patients with JAKi. However, especially in these newer indications, the available evidence has been limited by short duration of follow-up and limited sample size.

The current study aims to identify the incidence of new JAKi use over time, and to characterise new users of JAKi in Europe to inform the feasibility of future safety studies.

Research question and objectives

This study aims to characterise the use of JAKi in Europe.

The specific objectives are:

1. To estimate the incidence of new JAKi use, overall and for each individual JAKi ingredient.
2. To characterise new JAKi users and treatment for each individual JAKi ingredient, over all indications and stratified by indication.

Methods

Study design

- Population level cohort study (objective 1)
- New user cohort study (objectives 2)

Population

The population level cohort study will include all subjects available in the selected databases from 1st January 2017 until the most recent data lock of their respective databases, with at least 365 days of data visibility.

The patient level cohort study will include all JAKi new users from the 1st January 2017 until the most recent data lock of their respective databases, with at least 365 days of data visibility.

Variables

Drugs of interest: JAKi: abrocitinib, filgotinib, baricitinib, upadacitinib, tofacitinib

Indications: atopic dermatitis, juvenile idiopathic arthritis, inflammatory bowel disease, alopecia areata, axial spondyloarthritis, psoriatic arthritis, rheumatoid arthritis, unknown indication

Patient characteristics: age, sex, time from first diagnosis of indication to JAKi therapy initiation

Treatment characteristics: duration of index treatment drug era

Stratification: ingredient (specific JAKi), and indication

Data source

1. FinOMOP-HILMO (Finland)
2. IPCI (The Netherlands)
3. IQVIA DA Germany (Germany)
4. NLHR (Norway)
5. VID (Spain)

Sample size

No sample size has been calculated for this study. Based on the preliminary feasibility assessment, expected number of subjects to be involved in each data source would be approximately between 600 and 7900.

Statistical analysis

Incidence of new JAKi use, overall and for each individual JAKi ingredient, will be calculated yearly as the number of new users per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year, with 95% Poisson exact confidence intervals. Patient characterisation on new JAKi users will be done based on age, sex and indication for each JAKi ingredient, over all indications and stratified by indication. Patient characterisation on time from first diagnosis of indication to first JAKi initiation, and treatment duration of the first drug era will be reported for each JAKi ingredient stratified by indication. Time from first diagnosis of indication to treatment initiation and treatment duration will be summarised, providing the minimum, p25, median, p75, and maximum duration.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates
Draft Study Protocol	29/11/2024
Final Study Protocol	December 2024
Creation of Analytical code	January-February 2025
Execution of Analytical Code on the data	January-February 2025
Draft Study Report	March 2025
Final Study Report	April 2025

6. RATIONALE AND BACKGROUND

JAKi therapy has been gaining popularity for the treatment of several autoimmune conditions, including rheumatoid arthritis, inflammatory bowel disease, and atopic dermatitis. The first JAKi, tofacitinib, was approved by the European Medicines Agency (EMA) for the management of rheumatoid arthritis in 2017.[1] An FDA-requested study (the Oral Rheumatoid Arthritics Trial (ORAL) Surveillance trial)[2] showed a higher risk of major adverse cardiovascular events (MACE), cancer and adjudicated opportunistic infection with tofacitinib compared to tumour necrosis factor (TNF) inhibitors in patients aged 50 years or older with at least one cardiovascular risk factor.[3] Further research has been conducted on the safety profile of JAKi for other indications, including psoriatic arthritis, ulcerative colitis and atopic dermatitis.[4-6] It was shown that risk of venous thrombotic events of JAK inhibitor users was similar to placebo users in patients with atopic dermatitis[6] and ulcerative colitis[5]. Incidence of adverse events, including herpes zoster infection and thrombotic events, remained similar with longer follow-up up to two years in psoriatic arthritis patients with JAK inhibitor.[4] A recent meta-analysis focusing on the JAKi use for immune-mediated skin conditions, including atopic dermatitis, alopecia areata and vitiligo, also showed no significant difference between JAKi and placebo or active comparators in the composite outcome of MACE and all-cause mortality, as well as risk of venous thrombotic events.[7] However, the available evidence, especially in other indications than RA, has been limited by short duration of follow-up and limited sample size and more research is needed to understand the safety profile in these populations. Since the new indications are relatively recently approved and the use of JAKi within those has not been that common, the sample size for these indications is an issue and hampers future research, therefore a study in a federated network such as DARWIN EU might be a solution.

The current study aims to identify the incidence of new JAKi use over time, and to characterise new users of JAKi in Europe to inform the feasibility of future safety studies.

7. RESEARCH QUESTION AND OBJECTIVES

Table 1. Primary and secondary research questions and objective.

A. Objective 1. Population-level drug utilisation

Objective 1:	To estimate the incidence of new JAKi use, overall and for each individual JAKi ingredient
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study includes all people available in the databases with at least 365 days of data visibility.
Exposure:	Not applicable
Comparator:	Not applicable
Outcome:	JAKi (abrocitinib, filgotinib, baricitinib, upadacitinib, tofacitinib)
Time *(when follow up begins and ends):*	From 1st January 2017 until the most recent data lock for each included database.
Setting:	Data will be collected from primary care and secondary care outpatient setting with the following databases: - FinOMOP-HILMO (primary care, secondary care outpatient) - IPCI (primary care) - IQVIA DA Germany (primary care) - NLHR (primary care, secondary care outpatient) - VID (primary care, secondary care outpatient)
Main measure of effect:	Annual incidence rates of JAKi use, for the entire class pooled together and for each JAKi ingredient

B. Objectives 2. Patient-level characterisation and drug utilisation studies

Objective 2:	To characterise new JAKi users and treatment, overall and stratified by ingredient and indication
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study includes all patients available in the databases initiating JAKi therapy, with at least 365 days of data visibility before therapy initiation
Exposure:	JAKi (abrocitinib, filgotinib, baricitinib, upadacitinib, tofacitinib)
Comparator:	Not available
Outcome:	Not available
Time *(when follow up begins and ends):*	For treatment characterisation: from each JAKi therapy initiation until the discontinuation of index drug
Setting:	Data will be collected from primary care and secondary care outpatient setting with the following databases: - FinOMOP-HILMO (primary care, secondary care outpatient)

	- IPCI (primary care) - IQVIA DA Germany (primary care) - NLHR (primary care, secondary care outpatient) - VID (primary care, secondary care outpatient)
Main measures of effect:	Patient characterisation: demographics and time from first diagnosis of indication to each JAKi therapy initiation Treatment characterisation: treatment duration in months

8. RESEARCH METHODS

8.1 Study type and study design

Cohort studies will be conducted using the data from the included databases. A population-level cohort analysis will be used for Objective 1. A new drug users cohort design will be used for Objectives 2 and 3.

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

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Patient Level DUS	New drug/s user cohort	Off the shelf

8.2 Study setting and data sources

This study will be conducted using 5 databases onboarded for DARWIN EU® network of data partners from 5 European countries. These databases have been selected based on geographic representativeness and availability of data on JAK inhibitors. The selected databases cover Finland, Germany, Norway, The Netherlands and Spain. The results generated from these databases will therefore cover regions of Northern, Central and Southern Europe.

Detailed information of the selected data sources is described in **Table 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[1]	Data lock for the last update
Finland	FinOMOP-HILMO	Databases include adequate number of records of JAK inhibitors for subsequent patient characterisation.	Primary care GP, primary care specialist, secondary care specialist, hospital inpatient care	EHR, registries	6.25M	2500	2024-04-16
The Netherlands	IPCI	Databases include adequate number of records of JAK inhibitors for subsequent patient characterisation.	Primary care GP	EHR	1.25M	700	2024-04-30
Germany	IQVIA DA Germany	Databases include adequate number of records of JAK inhibitors for subsequent patient characterisation.	Primary care GP, primary care specialist	EHR	4.35M	7900	2023-09-30
Norway	NLHR	Databases include adequate number of records of JAK inhibitors for subsequent patient characterisation.	Primary care GP, primary care specialist, secondary care specialist, hospital inpatient care	Registries	5.74M	2600	2024-06-30
Spain	VID [2]	Databases include adequate number of records of JAK inhibitors for subsequent patient characterisation.	Primary care GP, secondary care specialist, hospital inpatient care, nursing homes	EHR, registries	1.61M	600	2022-01-01

1. Feasibility count of exposure was identified as unique exposed individuals.
2. Only female individuals are included in this data source.

Information on data sources used is described below:

Finnish Care Register for Health Care [FinOMOP-HILMO] (Finland)

The THL HILMO database covers both public and private, primary and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care (fi:Hoitoilmoitusrekisteri, HILMO). It is a continuation of the former Hospital Discharge Register, which originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998 the register has covered both public outpatient and inpatient specialised care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, and positive COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM is currently produced from the above-mentioned, and limited to observation periods commencing after 1.1.2011. The National Population registry is also used as a source for the CDM database. The National Population registry data forms the basis for forming the patient population. This ensures up-to-date location (municipality of residence) of patients as well as complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

Integrated Primary Care Information [IPCI] (The Netherlands)

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 standardised 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 organisations 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).

IQVIA Disease Analyzer Germany [IQVIA DA Germany] (Germany)

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records. While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources. Routine updates are conducted at regular intervals.

IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies as previously demonstrated. The quality of data is assessed based on several criteria including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

Norwegian Linked Health Registry data [NLHR] (Norway)

Norway has a universal public health care system consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants. Many population-based health registries were established in the 1960s with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. We harmonised data from the following registries: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), Norway Control and Payment of Health Reimbursement (KUHR), the Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Immunisation Registry (SYSVAK), the National Death Registry, and the National Registry (NR). Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway. In brief: MBRN stores information about the pregnancy, the mother, father and child; NPR records diagnosis in secondary care (e.g., hospital); KUHR contains information about diagnosis and contact in primary care (e.g, GPs and outpatient specialists) – to be included in third release; NorPD recorded all medications dispensed outside of hospitals; MSIS collects test results of communicable diseases (e.g., Sars-Cov-2); SYSVAK recorded vaccinations.

Valencia Health System Integrated Dataset [VID] (Spain)

The Valencia Health System Integrated Dataset (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with about 5 million inhabitants and an annual birth cohort of 48 000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensing) and healthcare utilisation data from hospital care, emergency departments, specialised care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology (including COVID-19 test results registry) and others, and also public health databases from the population screening programmes. All the information in the VID databases can be linked at the individual level through a single personal identification code. The databases were initiated at different moments in time, but all in all the VID provides comprehensive individual-level data fed by all the databases from 2008 to date. The OMOP instance has been created using CONSIGN project data, where 1.96 million of females in fertile age are studied from start of 2018 to end of 2021.

8.3 Study period

The study period starts from 1st January 2017 until the most recent data lock for each included database (see **Table 3**).

8.4 Follow-up

For the population-level drug utilisation study (objective 1), eligible study participants will begin to contribute person time from the latest of the following: (1) study start date, (2) date at which the observation period starts (i.e. 1st January of each year), or (3) date with at least 365 days of data visibility. Respective study participants will stop contribute person time at the earliest date of the following: (1) date on which the observation period ends (i.e. 31st December of each year), (2) end of data availability, or (3) date of first JAKi exposure if applicable (outcome of the incidence analysis).

For patient-level characterisation (objectives 2), eligible study participants with at least 365 days of data visibility will be follow-up from the date of first JAKi exposure until the earliest of (1) end of index JAKi treatment exposure, (2) death, (3) loss to follow-up, or (4) end of data availability.

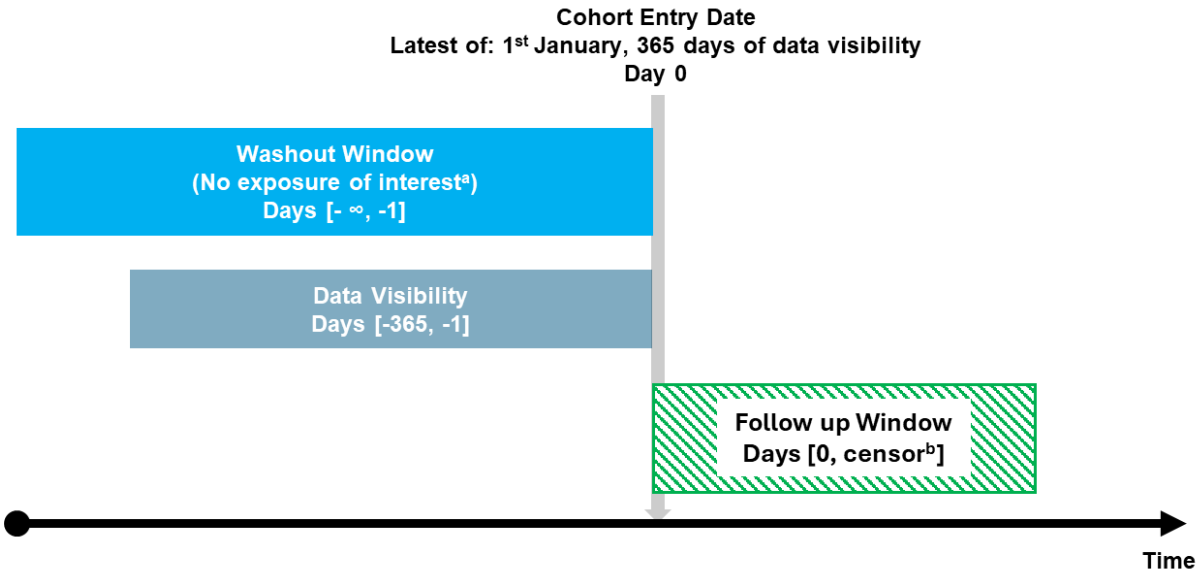

Figure 1. HARPER diagram for index date definition in population level DUS (Objective 1).

(a) Exposure of interest: any JAKi, individual JAKi ingredient
(b) Earliest of: 31st December of each year, loss of follow-up, end of data availability, initiation of exposure of interest

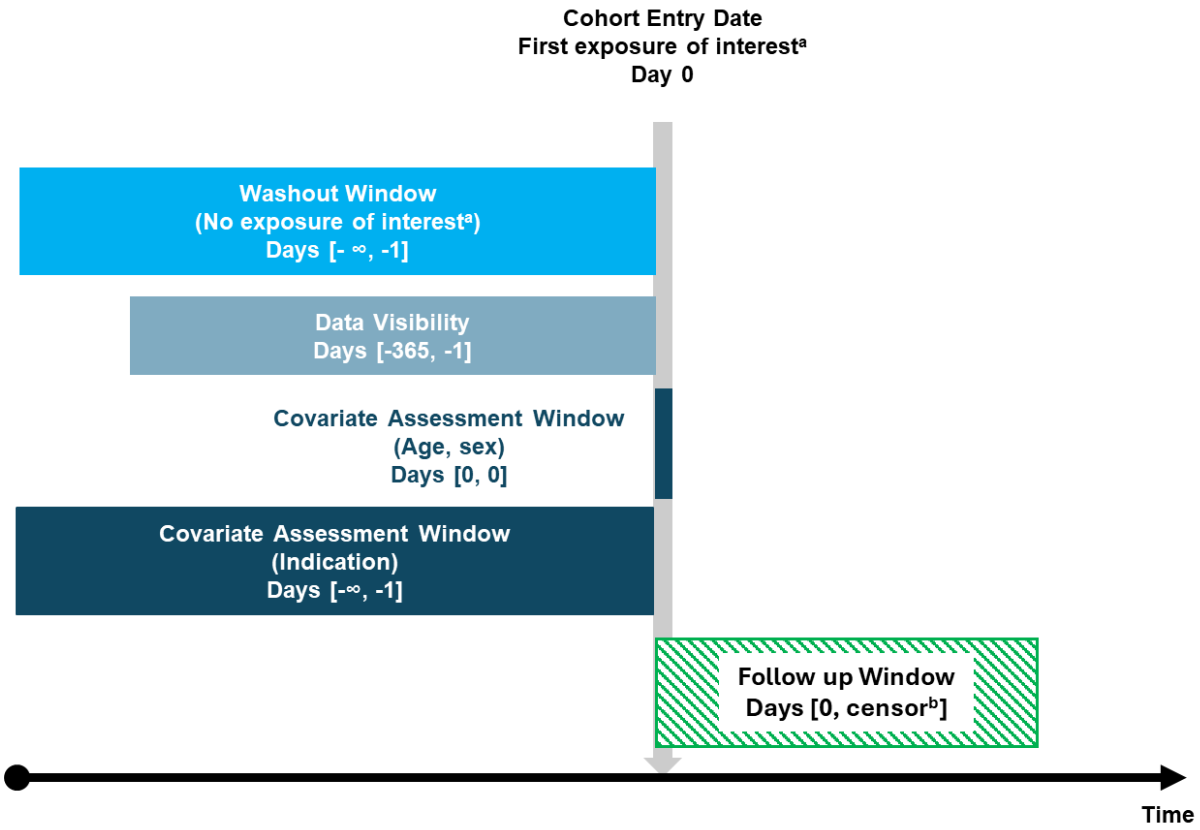

Figure 2. HARPER diagram for index date definition in patient level characterization (Objective 2).

(a) Exposure of interest: individual JAKi ingredient
(b) Earliest of: end of treatment with index exposure of interest, death, loss to follow-up, end of data availability

8.5 Study population with inclusion and exclusion criteria

For population level DUS (Objective 1)

All individuals available in the respective databases from 1st January 2017 until the end of data availability, with at least 365 days of data visibility, will be included in the population level DUS.

Different exclusion criteria will be applied corresponding to each outcome of the JAKi exposure incidence rate analysis (as defined in section 8.6.2). For incidence of first JAKi ever initiation, individuals with any JAKi exposure before index date will be excluded. For incidence of individual JAKi ingredient (abrocitinib/baricitinib/filgotinib/upadacitinib/tofacitinib) initiation, individuals with respective JAKi exposure before index date will be excluded.

For patient level characterization (Objectives 2)

All individuals available in the respective databases from 1st January 2017 until the end of data availability, that newly initiated JAKi and at least 365 days of data visibility, will be included in the patient level DUS. Individuals with specific JAKi exposure before the start of study period (i.e. 1st January 2017) will be excluded.

8.6 Variables

8.6.1 Exposure/s

In the population level DUS (Objective 1) no exposure variable will be defined. The incident use of JAKi will be the outcome in the analyses, as described in section 8.6.2 below.

Exposure of interest in the characterization of JAKi initiators (Objective 2) will be the initiation of treatment with the following JAKi, including abrocitinib, filgotinib, baricitinib, upadacitinib, and tofacitinib. Operational definition of exposure is described in **Table 4.**

Table 4. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Applied to study populations	Incident with respect to…	Measurement characteristics / validation	Source of algorithm
Individual JAKi ingredient	Preliminary code lists provided in Appendix I.	[-Inf, -1]	First ever exposure of each individual JAKi ingredient will be assessed during the study period of 2017-2024.	OP	RxNorm	For patient level characterization (objective 2)	Specific individual JAKi ingredient	N/A	N/A

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

8.6.2 Outcome/s

In the population level DUS (Objective 1), the incident use of JAKi will be the outcome in the analyses.

For the incidence of first JAKi ever initiation, the outcome will be defined as first prescription/dispensation of any JAKi. For incidence of individual JAKi ingredient (abrocitinib/ baricitinib/ filgotinib/ tofacitinib/ upadacitinib) initiation, the outcome will be defined as first prescription/dispensation of respective individual JAKi ingredient.

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

The following covariates will be reported as part of patient and treatment characterisation for each specific individual JAKi ingredient.

- Age at index date will be calculated. Age will be presented as a mean/median age as well as proportion of patient stratified within age groups (0-3, 4-12, 13-18, 19-40, 41-60, >60).
- Sex (male/female)
- Pre-specified indicated condition for JAKi, defined by condition recorded before index date (yes/no for each indication). Indications of JAKi will be defined by any records of the above-mentioned pre-specified conditions before the first exposure of specific individual JAKi ingredient. Multiple indications are allowed. Preliminary code lists for the pre-defined indications are provided in Appendix I.
    - Atopic dermatitis
    - Juvenile idiopathic arthritis
    - Inflammatory bowel disease
    - Alopecia areata
    - Axial spondyloarthritis
    - Psoriatic arthritis
    - Rheumatoid arthritis
    - Unknown indication (defined as none of the predefined indications were found)
- Time from first indication to first JAKi initiation, estimated separately for each pre-specified indication (more than one per patient is possible) and presented in months
- Duration of index JAKi treatment era (months)
- Prior use of other JAKi (yes/no)

In addition, a large-scale characterisation for identifying potentially missing diagnosis codes from pre-specified lists will be performed.

The following covariates will be used for the stratification in patient characterisation.

- Pre-defined indication

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in the **Table 5**.

Table 5. 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 at index date in years	Numeric, continuous	[0,0]	OP	N/A	N/A	individual JAKi ingredient	N/A	N/A
Sex	Biological sex as recorded	Binary, count	[0,0]	OP	N/A	N/A	individual JAKi ingredient	N/A	N/A
Indication	Diagnosis of pre-defined condition considered as possible indication for JAKi, including atopic dermatitis, juvenile idiopathic arthritis, inflammatory intestinal disease, alopecia areata, axial spondyloarthritis, psoriatic arthritis, rheumatoid arthritis and unknown indication	Binary, count	[-Inf, -1]	OP	SNO MED	N/A	individual JAKi ingredient	N/A	N/A
Time from first diagnosis of indication to JAKi initiation	Time from first possible indication for JAKi to first exposure of each individual JAKi ingredient	Numeric, continuous	[-Inf, 0]	OP	N/A	N/A	individual JAKi ingredient	N/A	N/A
Treatment duration	Duration of JAKi used	Numeric, continuous	[0, end of index drug era]	OP	N/A	N/A	individual JAKi ingredient	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 for this study. Based on the preliminary feasibility assessment, expected number of subjects to be involved in each data source would be approximately between 600 and 7900.

The feasibility count for each database is as follows: FinOMOP-HILMO (as of 2024-Nov): 2500; IPCI (as of 2024-Nov): 700; IQVIA-DA (as of 2024-Nov): 7900; NLHR (as of 2024-Jul): 2600; VID (as of 2024-Nov): 600

8.8 Analysis

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics will be performed on a subset of the data sources or on a simulated set of patients and quality control checks will be performed. Once all the tests are passed, the final package will be 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.

To prevent confidentiality issues, cell counts lower than 5 will be reported as “<5”.

Details on type of analysis is given in **Table 6**.

Table 6. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features - Frequency and % of indication/s - Estimation of minimum, p25, median, p75, and maximum treatment duration

8.8.1 Statistical model specification

The R package ‘IncidencePravalence’ (https://darwin-eu.github.io/IncidencePrevalence/) will be used to derive the incidence of JAKi use in the population level DUS, while R package ‘CohortCharacteristics’ (https://darwin-eu.github.io/CohortCharacteristics/) will be used for the patient characterisation and ‘DrugUtilisation’ (https://darwin-eu.github.io/DrugUtilisation/) for treatment characterisation in the patient level DUS.

8.8.2 Methods to derive parameters of interest

Incidence of new JAKi use

Incidence of new JAKi use (measured as prescription or dispensation), overall and for each individual JAKi ingredient, will be calculated annually as the number of individuals with a first JAKi prescription/dispensation per 100,000 per-years of the population at risk of getting exposed during the period for each calendar year. Those study participants who enter the denominator population will then contribute time at risk up to their first use during the study period or if they do not have a drug exposure, they will contribute time at risk up as described above in section 8.4 (Follow-up). Incidence rates will be given together with 95% Poisson exact confidence intervals. Illustration of the calculation of incidence use of the medicines of interest is shown below in **Figure 3**.

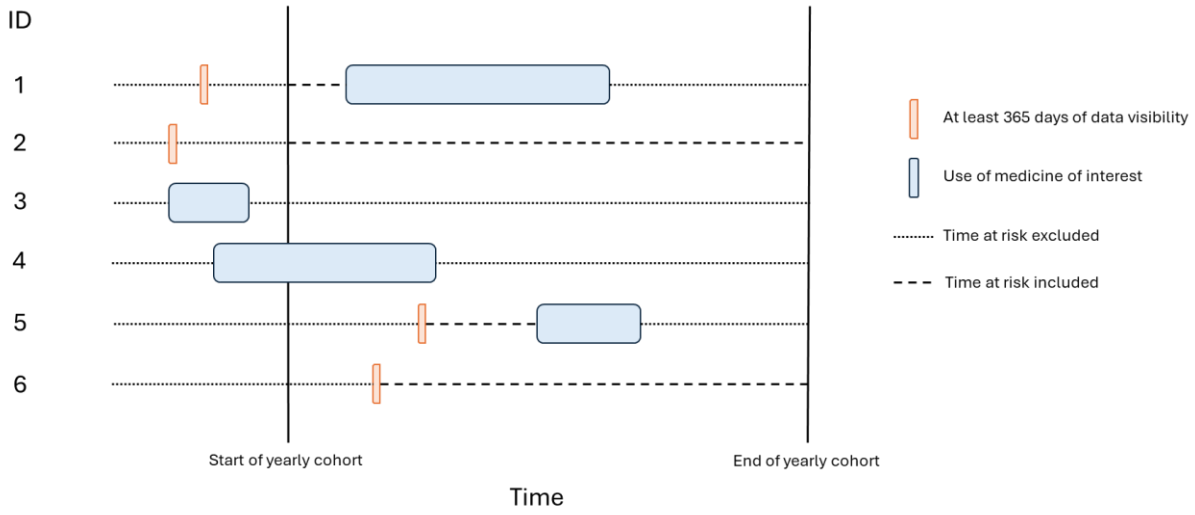

Figure 3. Illustration of the calculation of incidence on use of medicines of interest.

Example of incidence calculation is shown in **Figure 3**. Individuals (ID 1, 2) with sufficient data visibility will be included in the incidence calculation contributing to the time at risk (denominator). Individuals will be continued to contribute the time at risk until initiation of drug of interest (ID 1) or the end of follow-up for yearly cohort (ID 2). For individuals with exposure to JAKi before the start of the yearly cohort (ID 3) or with exposure at the start of the yearly cohort (ID 4), these subjects will not be included for the annual incidence calculation. Individuals will contribute time at risk only when they have with sufficient data visibility. Therefore, as illustrated by ID 5 and 6, individuals are only included and contribute to the denominator from the point with at least 365 days of data visibility.

For the incidence of each individual JAKi ingredient, only use of the specific individual JAKi ingredient will be considered. These subjects with previous exposure of other JAKi will be allowed to be included in the denominator during the calculation of population-level incidence. Each analysis on individual JAKi ingredient will be independent of other JAKi exposure. In another words, patients with exposure to different JAKi will be counted multiple times in different analyses.

Patient Characteristics

JAKi initiators will be characterized in terms of age, sex, and time from first diagnosis of prespecified indication to first JAKi exposure. Treatment characterisation will include indication and duration of treatment. Reporting on patient-level characterisation will be stratified by each individual JAKi ingredient and indication.

Duration of treatment

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 will be retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) if the distance in days between end of the first exposure and start of the second exposure is ≤ 90 days. For the included individuals, the duration of JAKi use will be calculated by sum of duration of first drug eras during the study period. Treatment duration will be summarised providing the minimum, p25, median, p75, and maximum duration.

8.9 Evidence synthesis

Results from analyses described in section 8.8 will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGEMENT

All databases will have been mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is 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.

This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set 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

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, data partners have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining specific drugs, conditions, and co-morbidities, a systematic search of possible codes for inclusion was previously 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 CDM to find potentially relevant codes. The codes returned will then be reviewed by two clinical epidemiologists to consider their relevance. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) or a similar tool will be run to

assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This will allow for a consideration of the validity of the study cohort of patients with the selected conditions, drugs, and co-morbidities in each of the databases and inform decisions around whether multiple definitions are required.

11. LIMITATIONS OF THE RESEARCH METHODS

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. In addition, assumptions around the duration of drug use will be unavoidable.

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. In addition, the completeness of recordings of co-morbidities used for patient characterisation may variate across databases.

In IQVIA DA Germany, the observation period of the patients in these databases is calculated based on the last visit, observation or interaction of the patient with the health care system. This methodology impacts the individuals considered "at risk" for the different medicines of interest of the study (i.e., the individuals included in the denominator populations) during the latest months of available data from the latest data lock, where healthy and/or non-frequent users of the health care system will not be considered active. Consequently, the denominators that will be used to calculate the incident use of drugs in the population may present an artefactual decrease whilst the incident users will remain. The presence of these artefacts will be considered when interpreting the results.

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 data sources require approval from their respective IRB boards, except IQVIA DA Germany, which will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A PDF report, including an executive summary and the following specified tables and/or figures, will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

Counts for annual incident use of first ever JAKi use, for the entire class pooled together and for each JAKi ingredient, will be present in table format. Annual incidence rates of first ever JAKi use, for the entire class pooled together and for each JAKi ingredient, will be described in plot. For incidence of individual JAKi ingredient (abrocitinib/ baricitinib/ filgotinib/ upadacitinib/ tofacitinib) initiation, with individuals with respective JAKi exposure before index date being excluded, counts will be present in table while incidence rates being given in plot.

Patient level characterisation will be given by each individual JAKi on age, sex and indication. Characteristics of each JAKi initiators will be given for each prespecified indication on age, time from first identified indication diagnosis to JAKi initiation, treatment duration of the first drug era, and percentage of previous use of other JAKi.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the PDF report. The full set of underlying aggregated data used in the dashboard will also be made available if requested. The large-scale characterisation for identifying potentially missing diagnosis codes will only be included in the interactive dashboard.

15. OTHER ASPECTS

None.

16. REFERENCES

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17. ANNEXES

Appendix I: List of concept definitions

Table s1. Preliminary code list for JAKi

Ingredient concept ID	Drug of interest	ATC code
1758974	Abrocitinib	D11AH08
1510627	Baricitinib	L04AF02
35891916	Filgotinib	L04AF04
1361580	Upadacitinib	L04AF03
42904205	Tofacitinib	L04AF01

Table s2. Preliminary code list for pre-specified indication

Indication	Concept ID	Name	Domain
Inflammatory bowel disease	46269838	Abscess of intestine co-occurrent and due to chronic ulcerative pancolitis	Condition
Inflammatory bowel disease	46269848	Abscess of intestine co-occurrent and due to chronic ulcerative rectosigmoiditis	Condition
Inflammatory bowel disease	46269888	Abscess of intestine co-occurrent and due to Crohn's disease	Condition
Inflammatory bowel disease	46274073	Abscess of intestine co-occurrent and due to Crohn's disease of large intestine	Condition
Inflammatory bowel disease	46269878	Abscess of intestine co-occurrent and due to Crohn's disease of small and large intestine	Condition
Inflammatory bowel disease	46269883	Abscess of intestine co-occurrent and due to Crohn's disease of small intestine	Condition
Inflammatory bowel disease	46269951	Abscess of intestine co-occurrent and due to ulcerative colitis	Condition
Inflammatory bowel disease	602594	Acute left-sided ulcerative colitis	Condition
Inflammatory bowel disease	4029372	Acute ulcerative colitis	Condition
Inflammatory bowel disease	602593	Acute ulcerative pancolitis	Condition
Inflammatory bowel disease	602607	Acute ulcerative rectosigmoiditis	Condition
Inflammatory bowel disease	36716986	Arthritis co-occurrent and due to Crohn's disease	Condition
Inflammatory bowel disease	40481367	Chronic left-sided ulcerative colitis	Condition
Inflammatory bowel disease	40479837	Chronic ulcerative colitis	Condition
Inflammatory bowel disease	194077	Chronic ulcerative enterocolitis	Condition
Inflammatory bowel disease	787979	Chronic ulcerative ileocolitis	Condition
Inflammatory bowel disease	40482241	Chronic ulcerative pancolitis	Condition

Inflammatory bowel disease	77317	Chronic ulcerative rectosigmoiditis	Condition
Inflammatory bowel disease	46269889	Complication due to Crohn's disease	Condition
Inflammatory bowel disease	46269874	Complication due to Crohn's disease of large intestine	Condition
Inflammatory bowel disease	46269879	Complication due to Crohn's disease of small and large intestines	Condition
Inflammatory bowel disease	46269884	Complication due to Crohn's disease of small intestine	Condition
Inflammatory bowel disease	36715915	Crohn disease of anal canal	Condition
Inflammatory bowel disease	37116446	Crohn disease of appendix	Condition
Inflammatory bowel disease	42537666	Crohn disease of upper gastrointestinal tract	Condition
Inflammatory bowel disease	201606	Crohn's disease	Condition
Inflammatory bowel disease	4142544	Crohn's disease in remission	Condition
Inflammatory bowel disease	4177488	Crohn's disease of colon	Condition
Inflammatory bowel disease	4210469	Crohn's disease of duodenum	Condition
Inflammatory bowel disease	4340114	Crohn's disease of esophagus	Condition
Inflammatory bowel disease	36716695	Crohn's disease of gastrointestinal anastomosis	Condition
Inflammatory bowel disease	4122617	Crohn's disease of gingivae	Condition
Inflammatory bowel disease	4244235	Crohn's disease of ileum	Condition
Inflammatory bowel disease	4246693	Crohn's disease of intestine	Condition
Inflammatory bowel disease	4239382	Crohn's disease of jejunum	Condition
Inflammatory bowel disease	194684	Crohn's disease of large bowel	Condition
Inflammatory bowel disease	40558884	Crohn's disease of oral soft tissues	Condition
Inflammatory bowel disease	4323289	Crohn's disease of pyloric antrum	Condition
Inflammatory bowel disease	4266370	Crohn's disease of pylorus	Condition
Inflammatory bowel disease	4242392	Crohn's disease of rectum	Condition
Inflammatory bowel disease	195575	Crohn's disease of small AND large intestines	Condition
Inflammatory bowel disease	195585	Crohn's disease of small intestine	Condition
Inflammatory bowel disease	36686095	Crohn's disease of small intestine with stenosis	Condition
Inflammatory bowel disease	4342643	Crohn's disease of stomach	Condition
Inflammatory bowel disease	40550020	Crohn's disease of terminal ileum	Condition
Inflammatory bowel disease	4131542	Crohn's stricture of colon	Condition
Inflammatory bowel disease	4086978	Eosinophilic ulcerative colitis	Condition

Inflammatory bowel disease	1340297	Exacerbation of Crohn's disease	Condition
Inflammatory bowel disease	42129991	Exacerbation of Crohn's disease of large intestine	Condition
Inflammatory bowel disease	42129992	Exacerbation of Crohn's disease of small intestine	Condition
Inflammatory bowel disease	4187900	Exacerbation of ulcerative colitis	Condition
Inflammatory bowel disease	1340490	Exacerbation of ulcerative colitis	Condition
Inflammatory bowel disease	1340491	Exacerbation of ulcerative proctocolitis	Condition
Inflammatory bowel disease	46269880	Fistula of intestine due to Crohn's disease of small and large intestine	Condition
Inflammatory bowel disease	46269875	Fistula of large intestine due to Crohn's disease	Condition
Inflammatory bowel disease	46269885	Fistula of small intestine due to Crohn's disease	Condition
Inflammatory bowel disease	4264850	Gastrointestinal Crohn's disease	Condition
Inflammatory bowel disease	46269999	History of Crohns disease	Observation
Inflammatory bowel disease	46269890	Intestinal obstruction due to Crohn's disease	Condition
Inflammatory bowel disease	46269876	Intestinal obstruction due to Crohn's disease of large intestine	Condition
Inflammatory bowel disease	46269881	Intestinal obstruction due to Crohn's disease of small and large intestine	Condition
Inflammatory bowel disease	46269886	Intestinal obstruction due to Crohn's disease of small intestine	Condition
Inflammatory bowel disease	4259504	Iritis with ulcerative colitis	Condition
Inflammatory bowel disease	40482865	Left sided ulcerative colitis	Condition
Inflammatory bowel disease	4301738	Mild chronic ulcerative colitis	Condition
Inflammatory bowel disease	4302002	Moderate chronic ulcerative colitis	Condition
Inflammatory bowel disease	3184226	Pancolonic ulcerative colitis	Condition
Inflammatory bowel disease	46269891	Rectal hemorrhage due to Crohn's disease	Condition
Inflammatory bowel disease	46269877	Rectal hemorrhage due to Crohn's disease of large intestine	Condition
Inflammatory bowel disease	46269882	Rectal hemorrhage due to Crohn's disease of small and large intestines	Condition
Inflammatory bowel disease	46269887	Rectal hemorrhage due to Crohn's disease of small intestine	Condition
Inflammatory bowel disease	4031048	Severe chronic ulcerative colitis	Condition
Inflammatory bowel disease	81893	Ulcerative colitis	Condition
Inflammatory bowel disease	44783784	Ulcerative colitis in remission	Condition
Inflammatory bowel disease	4342656	Ulcerative enterocolitis	Condition
Inflammatory bowel disease	4025853	Ulcerative ileocolitis	Condition
Inflammatory bowel disease	40479839	Ulcerative pancolitis	Condition

Inflammatory bowel disease	4166480	Ulcerative proctocolitis	Condition
Psoriatic arthritis	4025831	Arthritis mutilans	Condition
Psoriatic arthritis	1340448	Exacerbation of psoriatic arthritis	Condition
Psoriatic arthritis	4132495	Iritis in psoriatic arthritis	Condition
Psoriatic arthritis	4079734	Juvenile psoriatic arthritis with psoriasis	Condition
Psoriatic arthritis	1340520	Progression of psoriatic arthritis	Condition
Psoriatic arthritis	81931	Psoriasis with arthropathy	Condition
Psoriatic arthritis	40319772	Psoriatic arthritis	Condition
Psoriatic arthritis	46274123	Psoriatic arthritis mutilans	Condition
Psoriatic arthritis	4083682	Psoriatic arthritis with distal interphalangeal joint involvement	Condition
Psoriatic arthritis	4064048	Psoriatic arthritis with spine involvement	Condition
Psoriatic arthritis	4035742	Psoriatic dactylitis	Condition
Rheumatoid arthritis	46273442	Deformity of hand due to rheumatoid arthritis	condition
Rheumatoid arthritis	44811155	Rheumatoid arthritis monitoring telephone invitation	observation
Rheumatoid arthritis	44811154	Rheumatoid arthritis monitoring verbal invitation	observation
Rheumatoid arthritis	44811153	Rheumatoid arthritis monitoring invitation third letter	observation
Rheumatoid arthritis	44811152	Rheumatoid arthritis monitoring invitation second letter	observation
Rheumatoid arthritis	44811151	Rheumatoid arthritis monitoring invitation first letter	observation
Rheumatoid arthritis	44811073	Rheumatoid arthritis monitoring invitation	observation
Rheumatoid arthritis	44808003	Rheumatoid arthritis annual review	observation
Rheumatoid arthritis	44790163	Delivery of rehabilitation for rheumatoid arthritis	observation
Rheumatoid arthritis	42689682	Rheumatoid arthritis monitoring SMS (short message service) text message third invitation	observation
Rheumatoid arthritis	42689681	Rheumatoid arthritis monitoring SMS (short message service) text message second invitation	observation
Rheumatoid arthritis	42689680	Rheumatoid arthritis monitoring SMS (short message service) text message first invitation	observation
Rheumatoid arthritis	42689679	Rheumatoid arthritis monitoring invitation by SMS (short message service) text messaging	observation
Rheumatoid arthritis	42539550	Erosion of joint surface co-occurrent and due to rheumatoid arthritis	condition
Rheumatoid arthritis	42536657	Rheumatoid arthritis without erosion	condition
Rheumatoid arthritis	42534841	Deformity of left foot co-occurrent and due to rheumatoid arthritis	condition
Rheumatoid arthritis	42534840	Deformity of right foot co-occurrent and due to rheumatoid arthritis	condition
Rheumatoid arthritis	42534839	Deformity of left hand co-occurrent and due to rheumatoid arthritis	condition

Rheumatoid arthritis	42534838	Deformity of right hand co-occurrent and due to rheumatoid arthritis	condition
Rheumatoid arthritis	42534837	Rheumatoid arthritis of right hip	condition
Rheumatoid arthritis	42534836	Rheumatoid arthritis of right hand	condition
Rheumatoid arthritis	42534835	Rheumatoid arthritis of left hip	condition
Rheumatoid arthritis	42534834	Rheumatoid arthritis of left hand	condition
Rheumatoid arthritis	40484633	Disease activity score in rheumatoid arthritis using C-reactive protein	observation
Rheumatoid arthritis	40482696	Rheumatoid arthritis disease activity score using C-reactive protein	observation
Rheumatoid arthritis	37395590	Rheumatoid lung disease with rheumatoid arthritis	condition
Rheumatoid arthritis	37309724	Bilateral deformity of hands due to rheumatoid arthritis	condition
Rheumatoid arthritis	37309723	Bilateral deformity of wrists due to rheumatoid arthritis	condition
Rheumatoid arthritis	37309722	Bilateral deformity of feet due to rheumatoid arthritis	condition
Rheumatoid arthritis	37209329	Seropositive rheumatoid arthritis of bilateral hands	condition
Rheumatoid arthritis	37209328	Seronegative rheumatoid arthritis of bilateral hands	condition
Rheumatoid arthritis	37209323	Bilateral rheumatoid arthritis of hands	condition
Rheumatoid arthritis	37209322	Bilateral rheumatoid arthritis of knees	condition
Rheumatoid arthritis	37209321	Bilateral rheumatoid arthritis of feet	condition
Rheumatoid arthritis	37207810	Seronegative rheumatoid arthritis of right hand	condition
Rheumatoid arthritis	37207809	Seronegative rheumatoid arthritis of multiple sites	condition
Rheumatoid arthritis	37207808	Seronegative rheumatoid arthritis of left hand	condition
Rheumatoid arthritis	37207807	Seropositive rheumatoid arthritis of right knee	condition
Rheumatoid arthritis	37207806	Seropositive rheumatoid arthritis of right hip	condition
Rheumatoid arthritis	37207805	Seropositive rheumatoid arthritis of left knee	condition
Rheumatoid arthritis	37207804	Seropositive rheumatoid arthritis of left hip	condition
Rheumatoid arthritis	37108714	Seropositive rheumatoid arthritis of multiple joints	condition
Rheumatoid arthritis	37108591	Rheumatoid arthritis of right knee	condition
Rheumatoid arthritis	37108590	Rheumatoid arthritis of left knee	condition
Rheumatoid arthritis	36687006	Rheumatoid arthritis of bilateral wrists	condition
Rheumatoid arthritis	36687005	Rheumatoid arthritis of bilateral ankles	condition
Rheumatoid arthritis	36687003	Rheumatoid arthritis of bilateral hips	condition
Rheumatoid arthritis	36687002	Rheumatoid arthritis of bilateral elbows	condition

Rheumatoid arthritis	36687001	Rheumatoid arthritis of left temporomandibular joint	condition
Rheumatoid arthritis	36687000	Rheumatoid arthritis of right temporomandibular joint	condition
Rheumatoid arthritis	36686999	Rheumatoid arthritis of bilateral temporomandibular joints	condition
Rheumatoid arthritis	36685024	Rheumatoid arthritis of right wrist	condition
Rheumatoid arthritis	36685023	Rheumatoid arthritis of right foot	condition
Rheumatoid arthritis	36685022	Rheumatoid arthritis of right elbow	condition
Rheumatoid arthritis	36685021	Rheumatoid arthritis of right ankle	condition
Rheumatoid arthritis	36685020	Rheumatoid arthritis of left wrist	condition
Rheumatoid arthritis	36685019	Rheumatoid arthritis of left foot	condition
Rheumatoid arthritis	36685018	Rheumatoid arthritis of left elbow	condition
Rheumatoid arthritis	36685017	Rheumatoid arthritis of left ankle	condition
Rheumatoid arthritis	36684998	Rheumatoid factor positive rheumatoid arthritis of the shoulder	condition
Rheumatoid arthritis	36684997	Rheumatoid factor positive rheumatoid arthritis	condition
Rheumatoid arthritis	36683391	Rheumatoid arthritis of joint of spine	condition
Rheumatoid arthritis	36304514	Rheumatoid arthritis disease activity level [CDAI]	observation
Rheumatoid arthritis	35609010	Rheumatoid arthritis of right shoulder	condition
Rheumatoid arthritis	35609009	Rheumatoid arthritis of left shoulder	condition
Rheumatoid arthritis	43344806	Deformity of foot due to rheumatoid arthritis	condition
Rheumatoid arthritis	43306635	Deformity of wrist due to rheumatoid arthritis	condition
Rheumatoid arthritis	43113391	Uveitis-rheumatoid arthritis syndrome	condition
Rheumatoid arthritis	42976650	Cutaneous atrophy due to rheumatoid arthritis	condition
Rheumatoid arthritis	42964152	Pericarditis secondary to rheumatoid arthritis	condition
Rheumatoid arthritis	42710003	Rheumatoid vasculitis	condition
Rheumatoid arthritis	42432205	Subacute rheumatic arthritis	condition
Rheumatoid arthritis	42165531	Acute rheumatic arthritis	condition
Rheumatoid arthritis	41795536	Rheumatoid arthritis of temporomandibular joint	condition
Rheumatoid arthritis	41795528	Rheumatic arthritis of temporomandibular joint	condition
Rheumatoid arthritis	41795378	Rheumatoid arthritis of foot	condition
Rheumatoid arthritis	41474418	Seropositive erosive rheumatoid arthritis	condition
Rheumatoid arthritis	41174687	Rheumatoid arthritis - ankle and/or foot	condition

Rheumatoid arthritis	4117686	Rheumatoid arthritis of multiple joints	condition
Rheumatoid arthritis	4116446	Rheumatoid arthritis of subtalar joint	condition
Rheumatoid arthritis	4116445	Rheumatoid arthritis of ankle	condition
Rheumatoid arthritis	4116444	Rheumatoid arthritis of sacroiliac joint	condition
Rheumatoid arthritis	4116443	Rheumatoid arthritis of proximal interphalangeal joint of finger	condition
Rheumatoid arthritis	4116442	Rheumatoid arthritis of metacarpophalangeal joint	condition
Rheumatoid arthritis	4116441	Rheumatoid arthritis of wrist	condition
Rheumatoid arthritis	4116440	Rheumatoid arthritis of elbow	condition
Rheumatoid arthritis	4116439	Rheumatoid arthritis of cervical spine	condition
Rheumatoid arthritis	4116153	Rheumatoid arthritis of lesser metatarsophalangeal joint	condition
Rheumatoid arthritis	4116152	Rheumatoid arthritis of talonavicular joint	condition
Rheumatoid arthritis	4116151	Rheumatoid arthritis of knee	condition
Rheumatoid arthritis	4116150	Rheumatoid arthritis of hip	condition
Rheumatoid arthritis	4116149	Rheumatoid arthritis of acromioclavicular joint	condition
Rheumatoid arthritis	4116148	Rheumatoid arthritis of sternoclavicular joint	condition
Rheumatoid arthritis	4115161	Rheumatoid arthritis - hand joint	condition
Rheumatoid arthritis	4115051	Rheumatoid arthritis of tibiofibular joint	condition
Rheumatoid arthritis	4115050	Rheumatoid arthritis of distal radioulnar joint	condition
Rheumatoid arthritis	4114444	Flare of rheumatoid arthritis	condition
Rheumatoid arthritis	4114442	Rheumatoid arthritis of interphalangeal joint of toe	condition
Rheumatoid arthritis	4114441	Rheumatoid arthritis of first metatarsophalangeal joint	condition
Rheumatoid arthritis	4114440	Rheumatoid arthritis of distal interphalangeal joint of finger	condition
Rheumatoid arthritis	4114439	Rheumatoid arthritis of shoulder	condition
Rheumatoid arthritis	4107913	Myopathy due to rheumatoid arthritis	condition
Rheumatoid arthritis	4102493	Polyneuropathy in rheumatoid arthritis	condition
Rheumatoid arthritis	4083556	Seronegative rheumatoid arthritis	condition
Rheumatoid arthritis	4078299	Rheumatoid arthritis monitoring	observation
Rheumatoid arthritis	4060405	Dilated cardiomyopathy secondary to rheumatoid arthritis	condition
Rheumatoid arthritis	4035611	Seropositive rheumatoid arthritis	condition
Rheumatoid arthritis	4035427	Rheumatoid arthritis with multisystem involvement	condition

Rheumatoid arthritis	2108722	Patient not receiving first-time biologic disease modifying anti-rheumatic drug therapy for rheumatoid arthritis (RA)	observation
Rheumatoid arthritis	2108721	Patient receiving first-time biologic disease modifying anti-rheumatic drug therapy for rheumatoid arthritis (RA)	observation
Rheumatoid arthritis	2108720	Patient receiving >/=10 mg daily prednisone (or equivalent) for longer than 6 months, and improvement or no change in disease activity (RA)	observation
Rheumatoid arthritis	2108719	Patient receiving <10 mg daily prednisone (or equivalent), or RA activity is worsening, or glucocorticoid use is for less than 6 months (RA)	observation
Rheumatoid arthritis	2107572	Disease prognosis for rheumatoid arthritis assessed, good prognosis documented (RA)	observation
Rheumatoid arthritis	2107561	Disease prognosis for rheumatoid arthritis assessed, poor prognosis documented (RA)	observation
Rheumatoid arthritis	2107560	Rheumatoid arthritis (RA) disease activity, high (RA)	observation
Rheumatoid arthritis	2107559	Rheumatoid arthritis (RA) disease activity, moderate (RA)	observation
Rheumatoid arthritis	2107558	Rheumatoid arthritis (RA) disease activity, low (RA)	observation
Rheumatoid arthritis	1176038	Rheumatoid arthritis disease severity level [RAPID3]	observation
Rheumatoid arthritis	256197	Rheumatoid lung disease	condition
Rheumatoid arthritis	81097	Felty's syndrome	condition
Rheumatoid arthritis	80809	Rheumatoid arthritis	condition
Rheumatoid arthritis	40481048	Disease activity score in rheumatoid arthritis	measurement
Rheumatoid arthritis	40481959	Disease activity score in rheumatoid arthritis using C-reactive protein	measurement
Rheumatoid arthritis	40482839	Disease activity score 28 joint in rheumatoid arthritis	measurement
Rheumatoid arthritis	4028118	Diffuse interstitial rheumatoid disease of lung	Condition
Rheumatoid arthritis	3654567	Spindling of fingers of bilateral hands due to rheumatoid arthritis	Condition
Alopecia areata	4300910	Circumscribed alopecia areata of scalp	Condition
Alopecia areata	4300911	Circumscribed alopecia areata of eyelashes/eyebrows	Condition
Alopecia areata	4300912	Circumscribed alopecia areata of beard area	Condition
Alopecia areata	4300913	Circumscribed alopecia areata of limbs	Condition
Alopecia areata	4300914	Circumscribed alopecia areata of trunk	Condition
Alopecia areata	4263194	Diffuse alopecia areata	Condition
Alopecia areata	141933	Alopecia areata	Condition
Alopecia areata	4300094	Concentric alopecia areata	Condition
Alopecia areata	4312756	Alopecia universalis	Condition
Alopecia areata	4239312	Ophiasis	Condition
Alopecia areata	4056343	Alopecia totalis	Condition
Alopecia areata	36715349	Alopecia, psychomotor epilepsy, periodontal pyorrhea, intellectual disability syndrome	Condition

Alopecia areata	3720 3833	Alopecia antibody deficiency	Condition
Atopic dermatitis	1340 257	Exacerbation of atopic dermatitis	Condition
Atopic dermatitis	4066 382	Atopic neurodermatitis	Condition
Atopic dermatitis	4031 012	Atopic dermatitis of bilateral hands	Condition
Atopic dermatitis	4031 630	Inverse pattern atopic dermatitis	Condition
Atopic dermatitis	4031 631	Discoid atopic dermatitis	Condition
Atopic dermatitis	4080 927	Erythrodermic atopic dermatitis	Condition
Atopic dermatitis	4080 928	Follicular atopic dermatitis	Condition
Atopic dermatitis	4080 929	Pruriginous atopic dermatitis	Condition
Atopic dermatitis	4033 671	Photosensitive atopic dermatitis	Condition
Atopic dermatitis	4031 013	Photoaggravated atopic dermatitis	Condition
Atopic dermatitis	1338 34	Atopic dermatitis	Condition
Atopic dermatitis	4206 125	Chronic lichenified atopic dermatitis	Condition
Atopic dermatitis	4290 734	Flexural atopic dermatitis	Condition
Atopic dermatitis	4290 735	Discoid pattern atopic hand dermatitis	Condition
Atopic dermatitis	4298 597	Generalized atopic dermatitis	Condition
Atopic dermatitis	4290 736	Prurigo pattern atopic dermatitis	Condition
Atopic dermatitis	4290 737	Atopic dermatitis aggravated by type 1 immune reaction	Condition
Atopic dermatitis	4290 738	Xerosis due to atopic dermatitis	Condition
Atopic dermatitis	4296 190	Atopic dermatitis of scalp	Condition
Atopic dermatitis	4298 598	Atopic dermatitis of face	Condition
Atopic dermatitis	4290 740	Atopic dermatitis of eyelid	Condition
Atopic dermatitis	4296 191	Cheilitis due to atopic dermatitis	Condition
Atopic dermatitis	4298 599	Infantile atopic dermatitis	Condition
Atopic dermatitis	4296 192	Childhood atopic dermatitis	Condition
Atopic dermatitis	4296 193	Adult atopic dermatitis	Condition
Atopic dermatitis	4297 362	Adult atopic dermatitis persistent from childhood	Condition
Atopic dermatitis	4298 600	Adult atopic dermatitis recurrent in adult life	Condition
Atopic dermatitis	4298 601	Adult atopic dermatitis commencing in adult life	Condition
Atopic dermatitis	4297 478	Impetiginized atopic dermatitis	Condition

Atopic dermatitis	4223641	Acute atopic dermatitis of hand	Condition
Atopic dermatitis	4223478	Chronic atopic dermatitis of hand	Condition
Atopic dermatitis	40482226	Atopic dermatitis due to animal dander	Condition
Atopic dermatitis	4221831	Acute-on-chronic vesicular eczema of hands and feet	Condition
Atopic dermatitis	4291279	Constitutional predisposition as co-factor in eczema	Condition
Atopic dermatitis	4033770	Constitutional fingertip eczema	Condition
Atopic dermatitis	37110589	Exacerbation of constitutional dermatitis due to occupation	Condition
Atopic dermatitis	4223498	Chronic vesicular eczema of hands and feet	Condition
Atopic dermatitis	4223477	Vesicular hand eczema	Condition
Atopic dermatitis	4080931	Constitutional discoid hand eczema	Condition
Atopic dermatitis	4066727	Besnier's prurigo	Condition
Atopic dermatitis	4031634	Constitutional eczema of foot	Condition
Atopic dermatitis	4309200	Allergic inhalant dermatitis	Condition
Atopic dermatitis	4031017	Chronic podopompholyx	Condition
Atopic dermatitis	37203896	Acute vesicular eczema of foot	Condition
Atopic dermatitis	4297495	Chronic constitutional eczema	Condition
Atopic dermatitis	4031016	Constitutional eczema of hand	Condition
Atopic dermatitis	4033769	Apron pattern of vesicular eczema of hands	Condition
Atopic dermatitis	4221832	Acute-on-chronic vesicular eczema of hands	Condition
Atopic dermatitis	4033672	Constitutional eczema of hands and feet	Condition
Atopic dermatitis	4221829	Acute vesicular eczema of hand	Condition
Atopic dermatitis	4297494	Acute constitutional eczema	Condition
Atopic dermatitis	4290745	Chronic relapsing vesiculosquamous hand eczema	Condition
Atopic dermatitis	3654806	Eczema coxsackium	Condition
Atopic dermatitis	4067178	Podopompholyx	Condition
Atopic dermatitis	4223639	Chronic vesicular eczema of hands	Condition
Axial spondyloarthritis	607398	Axial spondyloarthritis with peripheral joint involvement	Condition
Axial spondyloarthritis	37017494	Non-radiographic axial spondyloarthritis	Condition

Axial spondyloarthritis	36716891	Axial spondyloarthritis	Condition
Axial spondyloarthritis	437082	Ankylosing spondylitis	Condition
Axial spondyloarthritis	1340249	Exacerbation of ankylosing spondylitis	Condition
Axial spondyloarthritis	4035741	Ankylosing spondylitis with multisystem involvement	Condition
Axial spondyloarthritis	37203959	Ankylosing spondylitis co-occurrent with anterior uveitis	Condition
Axial spondyloarthritis	4079735	Juvenile spondyloarthropathy	Condition
Axial spondyloarthritis	4035614	Ankylosing spondylitis with organ / system involvement	Condition
Axial spondyloarthritis	4083681	Juvenile ankylosing spondylitis	Condition
Juvenile idiopathic arthritis	1340385	Exacerbation of juvenile idiopathic arthritis	Condition
Juvenile idiopathic arthritis	608034	Persistent onset antinuclear antibody negative juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608035	Persistent onset antinuclear antibody positive juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608075	Extended onset antinuclear antibody positive juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608076	Extended onset antinuclear antibody negative juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608092	Uveitis due to persistent onset antinuclear antibody negative juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608093	Uveitis due to persistent onset antinuclear antibody positive juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608094	Uveitis due to extended onset antinuclear antibody negative juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	608095	Uveitis due to extended onset antinuclear antibody positive juvenile idiopathic oligoarthritis	Condition
Juvenile idiopathic arthritis	42535150	Acute polyarticular juvenile idiopathic arthritis	Condition
Juvenile idiopathic arthritis	42535177	Polyarticular juvenile idiopathic arthritis	Condition
Juvenile idiopathic arthritis	762178	Juvenile idiopathic arthritis of left hand	Condition

Juvenile idiopathic arthritis	762180	Juvenile idiopathic arthritis of right hand	Condition
Juvenile idiopathic arthritis	4259507	Juvenile idiopathic arthritis	Condition
Juvenile idiopathic arthritis	4132811	Juvenile idiopathic arthritis, oligoarthritis	Condition
Juvenile idiopathic arthritis	4132812	Juvenile idiopathic arthritis, persistent oligoarthritis	Condition
Juvenile idiopathic arthritis	4261027	Juvenile idiopathic arthritis, extended oligoarthritis	Condition
Juvenile idiopathic arthritis	4253902	Juvenile idiopathic arthritis, enthesitis related arthritis	Condition
Juvenile idiopathic arthritis	4257972	Juvenile idiopathic arthritis, undifferentiated arthritis	Condition
Juvenile idiopathic arthritis	4211939	Anterior uveitis due to juvenile idiopathic arthritis	Condition
Juvenile idiopathic arthritis	37207517	Juvenile idiopathic arthritis, persistent monoarthritis	Condition
Juvenile idiopathic arthritis	4116447	Systemic onset juvenile chronic arthritis	Condition
Juvenile idiopathic arthritis	4132810	Juvenile seronegative polyarthritis	Condition
Juvenile idiopathic arthritis	4132809	Juvenile seropositive polyarthritis	Condition
Juvenile idiopathic arthritis	4079734	Juvenile psoriatic arthritis with psoriasis	Condition
Juvenile idiopathic arthritis	608043	Rheumatoid factor negative and anti-citrullinated protein antibody negative juvenile polyarthritis	Condition
Juvenile idiopathic arthritis	4079733	Juvenile psoriatic arthritis	Condition
Juvenile idiopathic arthritis	608042	Rheumatoid factor positive and anti-citrullinated protein antibody negative juvenile polyarthritis	Condition
Juvenile idiopathic arthritis	608044	Rheumatoid factor negative and anti-citrullinated protein antibody positive juvenile polyarthritis	Condition
Juvenile idiopathic arthritis	4035612	Early onset polyarticular juvenile chronic arthritis	Condition
Juvenile idiopathic arthritis	608041	Rheumatoid factor positive and anti-citrullinated protein antibody positive juvenile polyarthritis	Condition
Juvenile idiopathic arthritis	4083680	Juvenile psoriatic arthritis without psoriasis	Condition

Appendix II: ENCePP checklist for study protocols

Study title:

Characterising the use of JAK inhibitors in Europe: a Drug Utilisation Study

EU PAS Register® number: N/A

Study reference number (if applicable): P3-C1-001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	X			8.5
1.1.2 End of data collection[3]	X			8.5
1.1.3 Progress report(s)			X	
1.1.4 Interim report(s)			X	
1.1.5 Registration in the EU PAS Register®			X	
1.1.6 Final report of study results.	X			5

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)	X			6, 7
2.1.2 The objective(s) of the study?	X			7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			7
2.1.4 Which hypothesis(-es) is (are) to be tested?			X	

2.1.5 If applicable, that there is no *a priori* hypothesis?			X	

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)	X			8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X			8.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X			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))			X	
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)			X	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	X			8.2, 8.5
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	X			8.5
4.2.2 Age and sex	X			8.6.3
4.2.3 Country of origin	X			8.2
4.2.4 Disease/indication	X			8.6.3

4.2.5 Duration of follow-up	X			8.8.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X			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)	X			8.6.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)			X	
5.3 Is exposure categorised according to time windows?			X	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	X			8.8.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			X	
5.6 Is (are) (an) appropriate comparator(s) identified?			X	

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?	X			8.6.2
6.2 Does the protocol describe how the outcomes are defined and measured?			X	

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)			X	
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)			X	

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)			X	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)			X	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)			X	

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)	X			8.6.3

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)	X			8.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)			X	
9.1.3 Covariates and other characteristics?	X			8.6.3
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)	X			8.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)			X	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X			8.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X			8.6.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))			X	
9.3.3 Covariates and other characteristics?	X			8.8.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)			X	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**

10.1 Are the statistical methods and the reason for their choice described?	X			8.8
10.2 Is study size and/or statistical precision estimated?			X	
10.3 Are descriptive analyses included?	X			8.8
10.4 Are stratified analyses included?	X			8.8
10.5 Does the plan describe methods for analytic control of confounding?			X	
10.6 Does the plan describe methods for analytic control of outcome misclassification?			X	
10.7 Does the plan describe methods for handling missing data?			X	
10.8 Are relevant sensitivity analyses described?			X	

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)	X			9
11.2 Are methods of quality assurance described?	X			10
11.3 Is there a system in place for independent review of study results?			X	

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? 12.1.2 Information bias? 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).			X X	 11
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)	X			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?	X			13
13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?	X			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?	X			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)?	X			14
15.2 Are plans described for disseminating study results externally, including publication?	X			14

Comments:

Name of the main author of the protocol: Amy Lam

Date: 29/11/2024

Signature: A. Lam