Study Report

P3-C1-014

DARWIN EU® – Azathioprine - user characteristics

24/01/2024

Version 3.0

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DARWIN EU	**P3-C1-014 Study report**	
	Author(s): G.J. van Leeuwen, K. Verhamme	**Version:** V3.0
		Dissemination level: Public

Study title	DARWIN EU® - Azathioprine - user characteristics
Study report version	V3.0
Date	24/01/2024
EU PAS number	EUPAS1000000322
Active substance	Azathioprine Therapeutic Drug class: L04AX
Medicinal product	Azathioprine
Research question and objectives	The aim of this study was to characterise individuals treated with Azathioprine. The specific study objectives were: 1. Characterisation of patients newly treated with Azathioprine by sex and age at first prescription, overall and per indication 2. Characterisation of patients newly treated with Azathioprine by indication: a. Organ transplantation b. Severe rheumatoid arthritis or chronic polyarthritis c. Inflammatory bowel diseases d. Autoimmune hepatitis e. Systemic lupus erythematosus f. Dermatomyositis g. Polyarteritis nodosa h. Pemphigus vulgaris and bullous pemphigoid i. Behcet's disease j. Refractory autoimmune haemolytic anaemia k. Refractory idiopathic thrombocytopenic purpura l. Polymyositis m. Pyoderma gangrenosum n. Multiple sclerosis o. Myasthenia gravis p. None of the above/missing 3. Large-scale characterisation overall and per indication of drugs and conditions within one year prior to the index date (-365 to -1 day to the index date) and on the index date were assessed. 4. Characterisation of patients newly treated with Azathioprine in terms of treatment duration, overall and for each indication
Country(-ies) of study	This study included 5 databases, representing 4 countries in Europe: • Germany: IQVIA DA Germany • United Kingdom: CPRD GOLD • Netherlands: IPCI • Spain: IMASIS and SIDIAP
Author(s)	Guido van Leeuwen (g.vanleeuwen@darwin-eu.org) Katia Verhamme (k.verhamme@darwin-eu.org)

TITLE

DARWIN EU® - Azathioprine – user characteristics

1. DESCRIPTION OF STUDY TEAM

Study team role(s)	Name(s)	Organisation(s)
Study Manager/Principal Investigator	Guido van Leeuwen Katia Verhamme	Erasmus MC
Data Scientist	Ross Williams Maarten van Kessel Cesar Barbosa Ger Inberg Adam Black	Erasmus MC
Epidemiologist/Clinical Domain Expert	Guido van Leeuwen Katia Verhamme	Erasmus MC
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
CRPD GOLD	Antonella Delmestri	University of Oxford
IPCI	Katia Verhamme	Erasmus MC
IQVIA DA Germany	James Brash Isabella Kaczmarczyk Dina Vojinovic	IQVIA
IMASIS	Miguel-Angel Mayer Maria Angeles Leis Machin Juan Manuel Ramirez Anguita	Consorci Mar Parc de Salut Barcelona (PSMar)
SIDIAP	Talita Duarte-Salles Anna Palomar Agustina Giuliodori Picco	IDIAPJGol

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

2. DATA SOURCES

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source
United Kingdom	CPRD GOLD	Primary care	EHR	17m	01/01/2000 to 31/12/2023
Netherlands	IPCI	Primary Care	EHR	1.39m	01/01/2006 to 31/12/2023
Spain	SIDIAP	Primary care	EHR	5.8m	01/01/2006 to 31/12/2023
Germany	IQVIA DA Germany	Primary care and outpatient secondary care	EHR	43m	01/01/2000 to 31/12/2023
Spain	IMASIS	Inpatient hospital care and secondary outpatient care	EHR	1.1m	01/01/2000 to 31/12/2023

CPRD=Clinical Practice Research Datalink, DA=Disease Analyzer, IMASIS=Institut Municipal Assistència Sanitària Information System, IPCI=Integrated Primary Care Information, m=million, PSMAR=Consorci Mar Parc de Salut Barcelona, SIDIAP=The Information System for Research in Primary Care.

3. ABSTRACT

Title

DARWIN EU® – Azathioprine – user characteristics

Rationale and background

Azathioprine is a purine analogue and prodrug of mercaptopurine that is used as an immunosuppressive medication alone or in combination with other immunosuppressive therapy to prevent rejection following organ transplantation and to treat certain autoimmune diseases, where it is considered a steroid-sparing agent. The Pharmacovigilance Risk Assessment Committee (PRAC) recently discussed a signal procedure regarding the association between treatment with azathioprine and non-cirrhotic portal hypertension/porto-sinusoidal vascular disease (PSVD).

Through this study we aimed to characterize patients newly treated with azathioprine, to contextualise the signal assessment.

Research question and objectives

This is a study in incident users of azathioprine aiming to characterise new users of azathioprine with respect to indications for treatment, age at treatment initiation, and sex, and to summarise the treatment durations with azathioprine for all indications combined, and for each individual treatment indication.

Study specific objectives were as following:

1. Characterisation of patients newly treated with Azathioprine by sex and age at first prescription, overall and per indication
2. Identify potential indications for azathioprine, and the percentage of azathioprine-treated patients for each pre-defined approved indication:
    a. Organ transplantation
    b. Severe rheumatoid arthritis or chronic polyarthritis
    c. Inflammatory bowel diseases
    d. Autoimmune hepatitis
    e. Systemic lupus erythematosus
    f. Dermatomyositis
    g. Polyarteritis nodosa
    h. Pemphigus vulgaris and bullous pemphigoid
    i. Behcet's disease
    j. Refractory autoimmune haemolytic anaemia
    k. Refractory idiopathic thrombocytopenic purpura
    l. Polymyositis
    m. Pyoderma gangrenosum
    n. Multiple sclerosis
    o. Myasthenia gravis
    p. None of the above/missing
3. Large-scale characterisation overall and per indication of drugs and conditions within one year prior to the index date (-365 to -1 day to the index date) and on the index date were assessed.
4. Estimate and summarise duration of treatment with azathioprine, overall, and stratified per indication.

Study design

Patient-level drug utilisation study

Setting

Study period

01/01/2000 – 31/12/2023

Data source

1. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom
2. Integrated Primary Care Information (IPCI), Netherlands
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
5. The Information System for Research in Primary Care (SIDIAP), Spain

Subjects and study size

The person counts for patients newly treated with Azathioprine and at least 1 year of prior database history were 692 for IMASIS, 3,020 for IPCI, 11,932 for IQVIA DA Germany, 19,341 for SIDIAP and 31,857 for CPRD GOLD.

Population

The study population consists of individuals newly treated with Azathioprine with at least 1 year of prior database history in the years 01/01/2000 to 31/12/2023

Variables

Exposure of interest

Azathioprine use

Outcomes of interest

- Characteristics (sex and age)
- Indication
    - Organ transplantation
    - Severe rheumatoid arthritis or chronic polyarthritis
    - Inflammatory bowel diseases
    - Autoimmune hepatitis
    - Systemic lupus erythematosus
    - Dermatomyositis
    - Polyarteritis nodosa
    - Pemphigus vulgaris and bullous pemphigoid
    - Behcet's disease
    - Refractory autoimmune haemolytic anaemia
    - Refractory idiopathic thrombocytopenic purpura
    - Polymyositis
    - Pyoderma gangrenosum
    - Multiple sclerosis
    - Myasthenia gravis
    - None of the above/missing
- Large-scale characterisation: drugs and comorbidities within one year prior to the index date (-365 to -1 day to the index date) and on the index date
- Treatment duration, overall and by indication

Results

The number of incident azathioprine users per database were 692 for IMASIS, 3,020 for IPCI, 11,932 for IQVIA DA Germany, 19,341 for SIDIAP, and 31,857 for CPRD GOLD. Generally, the proportion of females was higher than males, approximately 55% vs. 45%, except for the indication myasthenia gravis where the proportion of males was higher than females (roughly 60% vs. 40%). The median age of incident azathioprine users ranged between 48 (IPCI and SIDIAP) -53 (IQVIA DA Germany) years and most of the individuals were in the age group of 18 to 44 years, followed by the age group 45 to 64 years. The median age was the highest in individuals with myasthenia gravis, ranging between 66 (IPCI) -74 years (IMASIS). Most incident azathioprine users in this study did not have one of the indications in the 3 months before or 1 month after the index date (55.6 (IMASIS) -71.4% (IPCI)). IBD was by far the most prevalent indication with rates ranging between 20.7 (SIDIAP) -24.9% (IQVIA DA Germany), followed by autoimmune hepatitis (2.03 (CPRD) - 8.67% (IMASIS)). Moreover, the median age in individuals with IBD was much lower than the whole population and varying between 33 (IPCI) – 43 years (IMASIS).

Overall, median treatment duration ranged between 90-1019 days, where treatment duration was the shortest in IMASIS and the longest in SIDIAP. Between the different indications there were no clear differences in median treatment duration or proportion of individuals per treatment duration group. Many individuals only had a short treatment duration since they had a treatment duration of less than 1 year (30.4 (SIDIAP) - 87.9% (IMASIS) or a treatment duration of 1 to 2 years (9.0 (IMASIS) -16.2% (IPCI)). Prednisone/prednisolone was the most often prescribed drug in the year before index date with rates of 32.8 (IQVIA DA Germany) - 66.4% (CPRD) and mesalamine was also prescribed in all databases (11.4 (IMASIS and IQVIA DA Germany) - 27.7% (CPRD)). Conditions related to abdominal pain and IBD were present in the year before index date, most notably Crohn's disease (3.7 (IQVIA DA Germany) - 9.7% (IPCI) not recorded among the most frequent conditions in IMASIS) and ulcerative colitis (3.9 (IQVIA DA Germany) - 8.4% (IPCI) not recorded among the most frequent conditions in CPRD or IMASIS).

Discussion

In this study the number of incident azathioprine ranged between 692 to 31,857 patients. Azathioprine users were slightly more often female than male, with a median age ranging between 48-53 years. Median treatment duration ranged between 90 to 1,019 days and most patients had a treatment duration of less than 1 year. IBD was most often the indication for azathioprine use, followed by autoimmune hepatitis. In the azathioprine users without an indication prednisone/prednisolone was the most prescribed drug in the year before treatment initiation. Lastly conditions related to abdominal pain and IBD, specifically Crohn's disease and ulcerative colitis, were also often present in the year before treatment initiation in azathioprine users without an indication.

4. LIST OF ABBREVIATIONS

Acronyms/term	Description
CDM	Common Data Model
CC	Coordinating centre
CPRD	Clinical Practice Research Datalink
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DRE	Digital Research Environment
DQD	Data Quality Dashboard
DUS	Drug Utilisation Study
EHR	Electronic Health Records
ED	Emergency department
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
MA	Marketing Authorisation
MS	Multiple Sclerosis
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
PRAC	Pharmacovigilance Risk Assessment Committee
PSMAR	Consorci Mar Parc de Salut Barcelona
SD	Standard deviation
SIDIAP	The Information System for Research in Primary Care
SLE	Systemic Lupus Erythematosus
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	23/08/2024	23/08/2024
Final Study Protocol	25/09/2024	25/09/2024
Creation of Analytical code	August/September 2024	27/09/2024
Execution of Analytical Code on the data	27/09/2024	02/10/2024
Draft Study Report	15/10/2024	15/10/2024
Final Study Report	15/11/2024	19/11/2024

7. RATIONALE AND BACKGROUND

Azathioprine is a purine analogue and prodrug of mercaptopurine that is used as an immunosuppressive medication alone or in combination with other immunosuppressive therapy to prevent rejection following organ transplantation and to treat certain autoimmune diseases, where it is considered a steroid-sparing agent. Examples of autoimmune diseases that could be treated with azathioprine are rheumatoid arthritis, inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), polymyositis, dermatomyositis, multiple sclerosis (MS) and myasthenia gravis.(1-7)

Azathioprine is associated with minor usually transient and asymptomatic elevations of aminotransferase levels and with rare instances of acute cholestatic liver injury and with long-term use, portal hypertension may occur.(8, 9)

A signal regarding a potential association between azathioprine and non-cirrhotic portal hypertension/portosinusoidal vascular disease (PSVD) was raised in June 2024, and PRAC concluded that the potential association should be further evaluated in a signal procedure (Minutes of the PRAC meeting on 8-11 July 2024). PSVD is a rare disorder characterised by signs of portal hypertension in the absence of an identifiable aetiology, such as cirrhosis. A liver biopsy is mandatory for the diagnosis of PSVD.(10) Specific histologic signs include obliterative portal venopathy, nodular regenerative hyperplasia and incomplete septal fibrosis.(10) In the product information of azathiophrine containing products,some signs and symptoms related to PVSD are already listed. These include thrombocytopenia, liver function test abnormalities and histological findings (sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia).(11)

This study is intended to support the signal evaluation by providing information about the use of azathioprine, including the most frequent indications, the age- and sex distribution at initiation of treatment, and the treatment duration for all indications combined, and for each indication separately.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study was to characterise individuals treated with Azathioprine.

The specific study objectives were:

1. Characterise azathioprine initiators by sex and age at first prescription, overall and per indication

2. Identify potential indications for azathioprine, and the percentage of azathioprine-treated patients for each pre-defined approved indication:

a) Organ transplantation
b) Severe rheumatoid arthritis or chronic polyarthritis
c) Inflammatory bowel disease
d) Systemic lupus erythematosus
e) Dermatomyositis
f) Polyarteritis nodosa
g) Pemphigus vulgaris and bullous pemphigoid
h) Behçet's disease
i) Refractory autoimmune haemolytic anaemia
j) Refractory idiopathic thrombocytopenic purpura
k) Polymyositis
l) Pyoderma gangrenosum
m) Multiple sclerosis
n) Myasthenia gravis
o) None of the above/missing

3. Large-scale characterisation overall and per indication of drugs and conditions within one year prior to the index date (-365 to -1 day to the index date) and on the index date were assessed.

4. Estimate and summarise duration of treatment with azathioprine, overall, and stratified per indication

Description of the proposed objectives are described in (**Table 1**).

Table 1. Primary research questions and objective.

Objective 1,2,3 and 4:	To characterise individuals newly treated with Azathioprine by age and sex. In addition, new users of Azathioprine were characterised in terms of indication and treatment of use. Characterisation was done in terms of demographics, indication, treatment duration and prior drug use and comorbidities
Hypothesis:	N/A
Population *(mention key inclusion-exclusion criteria):*	All patients present in the databases with at least 365 days of prior history and newly treated with Azathioprine
Exposure:	Exposure to Azathioprine
Comparator:	N/A
Outcome:	N/A

Time *(when follow up begins and ends):*	Study period was from 1st January 2000 to 31st December 2023. Within this study period, we identified individuals newly treated with azathioprine. To generate information on duration of use, follow-up was from the first date of azathioprine during the study period until 1) censuring or loss to follow-up, 2) end of data availability, or 3) the end date of exposure (whichever occurs first).
Setting:	Primary care data (CPRD GOLD, IPCI, IQVIA DA Germany and SIDIAP) and outpatient secondary care (IQVIA DA Germany)
Main measure of effect:	Counts

9. RESEARCH METHODS

9.1 Study type and study design

The proposed design for this study is a patient-level DUS study as "off-the-shelf", as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses.

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

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

9.2 Study setting and data sources

This study used routinely collected health data from 5 databases in the DARWIN EU® network of data partners from 4 European countries. All databases were previously mapped to the OMOP CDM.

Data sources:

- Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom
- Integrated Primary Care Information (IPCI), Netherlands
- IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
- Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
- The Information System for Research in Primary Care (SIDIAP), Spain

These databases fulfil the criteria required for patient-level drug utilisation, and characterisation allowing for large-scale characterisation while covering different regions of Europe. The selection of databases was based on the availability of data on the selected drugs of interest, the conditions of interest, and other variables needed to perform the described analyses. As information needed to be provided in a timeline manner, data partners not requiring IRB approval or DPs with fast IRB review time (for instance because of

basket protocol approval) have been selected. Detailed information on the selected data sources is described in **Table 3**.

When it comes to assessing the reliability of data sources, the data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the Achilles tool, which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources. In terms of relevance, more general-purpose diagnostic tools, CohortDiagnostics and DrugExposureDiagnostics, were developed. The CohortDiagnostics package provides additional insights into cohort characteristics, record counts and index event misclassification. The *DrugExposureDiagnostics* package assesses ingredient specific diagnostics for drug exposure records.

Furthermore, data is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time covered by each released database, as this can vary across different domains. To facilitate this, the C*DMOnboarding* (and *Achilles*) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows us to get insights when data collection started, when new sources of data were added and when until when data was included.

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 (Azathioprine)*	Data lock for the last update
United Kingdom	CPRD GOLD	Adequate number of patients exposed to Azathioprine, availability of medical history for cohort characterisation. Able to perform study and produce results before mid-October deadline.	Primary care	EHR	17m	199,700	01/01/2024
Netherlands	IPCI	Adequate number of patients exposed to Azathioprine, availability of medical history for cohort characterisation. Able to perform study and produce results before mid-October deadline.	Primary Care	EHR	1.39m	15,700	30/04/2024
Spain	SIDIAP	Adequate number of patients exposed to Azathioprine, availability of medical history for cohort characterisation.	Primary care	EHR	5.8m	29,200	30/06/2023
Germany	IQVIA DA Germany	Adequate number of patients exposed to Azathioprine, availability of medical history for cohort characterisation. Able to perform study and produce results before mid-October deadline.	Primary care and outpatient secondary care	EHR	43m	80,400	30/09/2023
Spain	IMASIS	Adequate number of patients exposed to Azathioprine, availability of medical history for cohort characterisation. Able to perform study and produce results before mid-October deadline.	Inpatient hospital care and secondary outpatient care	EHR	1.1m	2,100	10/02/2024

CPRD=Clinical Practice Research Datalink, DA=Disease Analyzer, IMASIS=Institut Municipal Assistència Sanitària Information System, IPCI=Integrated Primary Care Information, m=million, PSMAR=Consorci Mar Parc de Salut Barcelona, SIDIAP=The Information System for Research in Primary Care.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.(12) The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.(12) GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far.(13-15)

The Integrated Primary Care Information (IPCI), the Netherlands

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data extracted from computer-based patient records of a selected group of general practitioners (GPs) across the Netherlands.(16) IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex. Although the geographical spread is limited, GP practices are located in urban and non-urban areas.

Patient-level data includes demographic information, patient's complaints and symptoms, diagnoses, laboratory test results, lifestyle factors and correspondence with secondary care, such as referral and discharge letters. For complaints, symptoms and diagnoses, Dutch GPs use International Classification of Primary Care (ICPC-1) coding, an international standard developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee.

IPCI data quality has been previously documented and IPCI has proved valuable for epidemiological studies.(17-21) In terms of quality control, extensive quality control steps are performed prior to each data release. These include comparison of patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and prescriptions, proportion of patients with blood pressure measurement, etc.(16) Based on this information, two quality scores have been created. Practices with low scores have been excluded.

Information System for Research in Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a dynamic database of pseudo-anonymized electronic health records of the primary care patient population in Catalonia, Spain.(22) It contains data of approximately 80% of the Catalan population registered in over 280 primary care practices throughout Catalonia since 2005.

The database contains data recorded in primary care centres on a daily basis. Additionally, it integrates data from external sources including biomarkers data from laboratories and records of drug prescription and dispensation. The dataset covers demographics, all-cause mortality, disease diagnoses classified under the International Classification of Diseases 10th revision (ICD-10), prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent–child linkage and various clinical parameters. Additional data from other data sources such as hospital discharges, mental health centres or specific disease registries can be obtained through diverse linkages. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. The database is updated every 6 months.

SIDIAP data quality has been previously documented and SIDIAP has proved valuable for epidemiological studies.(23-31) In terms of data integrity and reliability, SIDIAP has been subject to rigorous evaluation. Quality checks have been implemented including central identification of duplicate patient ID and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values) and consistency using visualisation tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

IQVIA Disease Analyser (DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialized 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.(32, 33) 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.(32, 33) 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.(33) While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore information on mortality is incomplete. Routine updates are conducted at regular intervals. The quality of data is assessed based on several criteria including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions). IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies as previously demonstrated.(26, 33, 34)

The Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, that are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information from around 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is

the anonymised relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

9.3 Study period

The study period was from 01/01/2000 to 31/12/2023 (when the study end date was not reached in a data source, the study end for that source was the last date of available data) (see **Table 3** for more details).

9.4 Follow-up

Study participants were followed up from the date of first exposure to Azathioprine (index date) until date of:

1) censuring or loss to follow-up,

2) end of data availability, or

3) the end date of exposure (whichever occurs first).

The operational definition of index date is specified in **Table 4.**

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	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Individuals initiating treatment with Azathioprine (objective 1,2, 3 and 4)	Date of first treatment with Azathioprine during study period	Single entry	Incident	Any time prior to study entry date	OP	RxNorm	N/A	Exposure	N/A	N/A

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

9.5 Study population with in and exclusion criteria

The study population included all individuals observed in one of the participating data sources during the study period (1st January 2000 to 31st December 2023) and having at least 1 year of database history.

Patients were excluded if the start date in the database fell within 365 days prior to the index date, as sufficient data availability is required.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5** and **Table 6**, respectively.

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:
Prior database history	Study participants were required to have 365 days of prior history observed before the index date	Prior	[-365,-1]	OP	N/A	N/A	All individuals within selected databases
Observation period in the database during the period	All individuals present in the 2000-2023 (or the latest date available)	after	N/A	OP	N/A	N/A	All individuals within selected databases
User of Azathioprine (exposure)	Prescription record of azathioprine	after	Study period	OP	RxNorm	N/A	All individuals within selected databases

[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)

Table 6. Operational definitions of exclusion 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
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

9.6 Variables

Concept/code lists used for the identification of exposure/s and/or outcomes are included as Supplementary Documents in **Appendix I**.

9.6.1 Exposure/s

Azathioprine exposure consisted of a prescription record of azathioprine (for systemic use thus oral or parenteral use). The operational definition of exposure is described by means of **Table 7**.

Table 7. 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
Azathioprine	Preliminary code lists provided in Appendix I	[-inf,-1], for incident use only	Anytime post start of the study date	OP	RxNorm	N/A	All eligible individuals in the database	Azathioprine use	N/A	N/A
Azathioprine + indication of use	Preliminary code lists provided in Appendix I	n/a = not applicable	Indication of use in -90/+30 days of index date	OP	SNOMED codes to assess indication of use	Yes (indication of use)	All incident users of azathioprine	Azathioprine use	N/A	N/A

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

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

9.6.2 Outcome/s

The operational definition of the outcomes is presented in the **Table 8**.

Table 8. 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
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

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

Covariates for the patient-level characterisation

To characterise the new initiators of Azathioprine, the covariates included:

- age at the index date (first prescription of Azathioprine) presented as a mean/median age as well as proportion of patient stratified within age groups (<18, 18-44, 45-64, 65-79, and >=80), overall and per indication.
- sex (male/ female), overall and per indication.
- Conditions considered indications for Azathioprine use, were assessed within –90/+30 days of the index date. These indications were identified based on the presence of disease codes.
  The code list for each condition of interest is available in **Appendix I** - Indications:
    - Organ transplantation
    - Severe rheumatoid arthritis or chronic polyarthritis
    - Inflammatory bowel diseases
    - Autoimmune hepatitis
    - Systemic lupus erythematosus
    - Dermatomyositis
    - Polyarteritis nodosa
    - Pemphigus vulgaris and bullous pemphigoid
    - Behcet's disease
    - Refractory autoimmune haemolytic anaemia
    - Refractory idiopathic thrombocytopenic purpura
    - Polymyositis
    - Pyoderma gangrenosum
    - Multiple sclerosis
    - Myasthenia gravis
    - None of the above/missing

- Large-scale characterisation: overall and per indication of use within one year prior to the index date (-365 to -1 day to the index date) and at the index date were assessed.
  Large scale characterisation consisted of use of drugs (at RxNorm code level) and conditions (by standard SNOMED code) While all conditions and medications above 1% were made available within the Shiny App, only the 10 most frequent conditions and drugs were described within the report. Drugs were reported by ingredient and not by strength or formulation.
- Treatment duration overall and per indication, was assessed from the index date until date of: 1) censuring or loss to follow-up, 2) end of data availability, or 3) the end date of exposure (whichever occurs first).
  Furthermore, to provide more context, also the proportion (%) of patients with a duration that fell within a prespecified treatment duration group was calculated and provided, both for the overall treatment duration as per indication.
  The prespecified treatment duration groups were: <12 months, 12-24 months, 2-3 years, 3-4 years, 4-5 years, 5-10 years and ≥10 years.

The operational definition of the covariates is described in the **Table 9**.

Table 9. 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
Demographics	Age at index date and sex	Numeric, continuous, binary	All history	OP	N/A	N/A	Incident azathioprine users	N/A	N/A
Indications	Prespecified indications of interest -90/+30 days of the index date	Count, binary	[-90, +30]	OP	SNOMED	N/A	Incident azathioprine users	N/A	N/A
Medication use, comorbidities	All history prior to the index date (large-scale characterisation)	Count, binary	[-365,-1] and [0,0]	OP	SNOMED, RxNorm	N/A	Incident Azathioprine users	N/A	N/A
Treatment duration	Duration of treatment with Azathioprine for the: - new users of azathioprine use - New users of azathioprine per indication	Numeric, continuous	[0, end of exposure]	OP	N/A	N/A	Incident azathioprine users	N/A	N/A

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

9.7 Study size

No sample size has been calculated as this is a descriptive Drug Utilisation Study where we are interested in the characteristics of all incident cases of new users of Azathioprine in each database. Based on a preliminary feasibility assessment, the expected person counts for Azathioprine were 900 for IMASIS, 6,000 for IPCI, 23,700 for IQVIA DA Germany, 24,500 for SIDIAP and 52,100 for CPRD GOLD.

The study period was from 2000-2023 but it should be noted that not all DPs do have observations period starting from 2000 on. For IPCI and SIDIAP, observation period starts from 2006.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on the data sources and quality control checks were performed. After all tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics in R studio and reviewed and approved the – by default – aggregated results.

The study results of all data sources were checked after which they were made available to the team and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical methods

The type of analysis performed in this study is described in **Table 10**.

Table 10. Description of study types and types of analysis.

Study type	Study classification	Type of analysis
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features - Frequency and % of indication/s - Large-scale characterisation of drug use and comorbidities - Estimation of minimum, p25, median, p75, and maximum treatment duration

9.9.1 Main summary measures

Results were presented by counts, proportions, median and IQR.

9.9.2 Main statistical methods

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as a proxy for the actual birthday. Age was presented as both a median age as well as proportions of patients within the following age groups which were used for stratification: <18, 18-44, 45-64, 65-79, and >=80.

Sex

Results were presented stratified by sex (men/women).

Drug exposure calculation

Drug eras were defined as follows: Exposure started at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed as shown in the first three rows of **Figure 1.**

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"	first exposure (time $= x_1$, dose $= d_1$) gap (time $= x_{12}$) second exposure (time $= x_2$, dose $= d_2$)	NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 1. Gap-era joint mode.

For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure, and calculated as the duration of the first treatment era of the azathioprine during the study period. Treatment duration was summarized providing the minimum, p25, median, p75, and maximum treatment duration.

R-packages

The R package "DrugUtilization" package was used to calculate the duration of interest and the *PatientProfiles* and *CohortDiagnostics* R packages were used to describe the characteristics of individuals initiating treatment with Azathioprine.

Characterisation of patients newly treated with Azathioprine

The R package "PatientsProfiles" was used for the patient-level characterisation of demographics and predefined clinical characteristics, as well as large-scale characterisation. The co-variates to be presented in a summary baseline characteristics table have been described in section 8.6.3.

Characterisation of treatment with azathioprine in a cohort of new users

The "DrugUtilisation" package was used to characterise the use of Azathioprine.

The number and % of patients receiving Azathioprine for a prespecified list of indications including duration of treatment as well as the proportion (%) of patients with a duration that fell within prespecified treatment duration groups (<12 months, 12-24 months, 2-3 years, 3-4 years, 4-5 years, 5-10 years and ≥10 years).

9.9.3 Missing values

For drug utilisation studies we assumed that the absence of a prescription record means that the person did not receive the respective drug and for indications, we assumed that the missingness of a record of the respective condition means that the condition was not the indication for the drug prescription.

9.9.4 Sensitivity analysis

None.

10. DATA MANAGEMENT

Data management

All databases are 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.

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses ran, which generated non-identifiable aggregate summary results.

The output files are stored in the DARWIN Digital Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. 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) and/or Darwin EU® Atlas. This allows the user to define a search strategy and, using this then query the vocabulary tables of the OMOP CDM to find potentially relevant codes. The codes returned were reviewed by two clinical epidemiologists to consider their relevance.

In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) ran to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed 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.

12. RESULTS

All results are available in a web application ("Shiny app") at: https://data-dev.darwin-eu.org/P3-C1-014-Azathioprine

12.1 Participants

Details on attrition and the numbers of individuals contributing to each study objective by database are described in **Table 11**. During the study period, the number of individuals initiating incident azathioprine was 66,842 and this number ranged between 692 (1.0%) (IMASIS) and 31,857 (47.7%) (CPRD) when stratifying by database.

Table 11. Study attrition of individuals included in each cohort per database

	CPRD (UK)	IMASIS (SP)	IPCI (NI)	IQVIA DA Germany	SIDIAP (SP)
Database population	17,521,504	1,084,151	2,870,221	43,553,860	8,553,325
Population in the database between 01/01/2000 and 31/12/2023.	16,313,661	942,959	2,870,221	43,145,366	8,553,325
Newly treated Azathioprine users between 01/01/2000 and 31/12/2023. With 365 days of prior observation	31,857	692	3,020	11,932	19,341

12.2 Descriptive data and main results

12.2.1 Characterisation

Table 12 describes the characteristics of incident azathioprine users in terms of sex, age and age-groups across all databases. In all the databases, the proportion of females (range 53.9 (IMASIS) – 58.0% (CPRD)) was slightly higher than males (range 42.1 (IMASIS) - 46.1% (CPRD)). The median age ranged between 48 (IPCI and SIDIAP) -53 years (IQVIA DA Germany) and most of the individuals in all databases were in the age group of 18 to 44 (30.4 (IQVIA DA Germany) - 39.2% (SIDIAP)), followed by the age group 45 to 64 (30.2 (IPCI) – 36.0% (IQVIA DA Germany)).

Table 12. Demographics of incident azathioprine users.

Variable name	Variable level		CPRD (UK) N=31,857	IMASIS (SP) N=692	IPCI (NL) N=3,020	IQVIA DA Germany N=11,932	SIDIAP (SP) N=19,341
Sex	Female	N (%)	17,181 (53.93)	401 (57.95)	1,667 (55.20)	6,856 (57.46)	10,722 (55.44)
	Male	N (%)	14,676 (46.07)	291 (42.05)	1,353 (44.80)	5,070 (42.49)	8,619 (44.56)
	None	N (%)	n/a	n/a	n/a	6 (0.05)	n/a
Age	n/a	Median [Q25-Q75]	50 [33-65]	52 [37-66]	48 [29-63]	53 [37-67]	48 [34-63]
	n/a	Mean (SD)	48.59 (19.84)	51.71 (18.84)	46.54 (19.90)	51.45 (19.47)	48.03 (18.94)
	n/a	Range	1-104	7-93	3-96	2-96	1-101
Age group	0 to 17	N (%)	2,067 (6.49)	20 (2.89)	217 (7.19)	606 (5.08)	1,023 (5.29)
	18 to 44	N (%)	11,300 (35.47)	243 (35.12)	1,162 (38.48)	3,632 (30.44)	7,583 (39.21)
	45 to 64	N (%)	10,426 (32.73)	242 (34.97)	972 (32.19)	4,291 (35.96)	6,428 (33.24)
	65 to 79	N (%)	6,656 (20.89)	130 (18.79)	569 (18.84)	2,622 (21.97)	3,440 (17.79)
	≥ 80	N (%)	1,408 (4.42)	57 (8.24)	100 (3.31)	781 (6.55)	867 (4.48)

n/a = not applicable

Table 13 describes the distribution of indications in the period of 3 months before and 1 month after index date in incident azathioprine users across all databases. In all databases most individuals had none of the prespecified indications, ranging between 55.6% (IMASIS) - 71.4% (IPCI). Amongst the predefined indications, IBD was the most prevalent indication with prevalences ranging between 20.7% (SIDIAP) - 24.9% (IQVIA DA Germany). Autoimmune hepatitis was the next most prevalent with rates ranging between 2.0% (CPRD) - 8.7% (IMASIS) (no individuals with auto-immune hepatitis in IPCI). Other

more prevalent indications were myasthenia gravis and SLE, with rates ranging from 1.2% (CPRD) -3.9% (IQVIA DA Germany) and 0.5% (IPCI) - 5.1% (IMASIS) respectively. In IPCI multiple indications were not present at all or had a count of <5.

Table 13. Distribution of indications in incident azathioprine users.

Indication*		CPRD (UK) N=31,857	IMASIS (SP) N=692	IPCI (NL) N=3,020	IQVIA DA Germany N=11,932	SIDIAP (SP) N=19,341
Autoimmune hepatitis	N (%)	647 (2.03)	60 (8.67)	0 (0.0)	314 (2.63)	786 (4.06)
Behçet's disease	N (%)	84 (0.26)	7 (1.01)	0 (0.0)	32 (0.27)	87 (0.45)
Dermatomyositis	N (%)	67 (0.21)	<5	0 (0.0)	60 (0.50)	122 (0.63)
Hemolytic anemia	N (%)	71 (0.22)	<5	<5	25 (0.21)	78 (0.40)
Idiopathic thrombocytopenic purpura	N (%)	61 (0.19)	8 (1.16)	<5	22 (0.18)	43 (0.22)
Inflammatory bowel disease	N (%)	6,840 (21.47)	151 (21.82)	738 (24.44)	2,974 (24.92)	4,012 (20.74)
Multiple sclerosis	N (%)	47 (0.15)	<5	<5	196 (1.64)	38 (0.20)
Myasthenia gravis	N (%)	365 (1.15)	25 (3.61)	48 (1.59)	470 (3.94)	367 (1.90)
Organ transplantation	N (%)	33 (0.10)	<5	0 (0.0)	0 (0.0)	47 (0.24)
Pemphigus vulgaris and bullous pemphigoid	N (%)	176 (0.55)	9 (1.30)	0 (0.0)	268 (2.25)	112 (0.58)
Polyarteritis nodosa	N (%)	22 (0.07)	6 (0.87)	0 (0.0)	33 (0.28)	56 (0.29)
Polymyositis	N (%)	79 (0.25)	<5	0 (0.0)	57 (0.48)	40 (0.21)
Pyoderma gangrenosum	N (%)	28 (0.09)	<5	0 (0.0)	42 (0.35)	17 (0.09)

Indication*		CPRD (UK) N=31,857	IMASIS (SP) N=692	IPCI (NL) N=3,020	IQVIA DA Germany N=11,932	SIDIAP (SP) N=19,341
Rheumatoid arthritis and chronic polyarthritis	N (%)	452 (1.42)	13 (1.88)	52 (1.72)	468 (3.92)	118 (0.61)
Systemic lupus erythematosus	N (%)	286 (0.90)	35 (5.06)	16 (0.53)	310 (2.60)	272 (1.41)
None of the above/missing	N (%)	22,171 (69.60)	385 (55.64)	2,155 (71.36)	6,861 (57.50)	13,325 (68.90)

*Percentages do not add up to 100%, since patients could be in multiple indication groups.

Table 14 describes the demographics of incident azathioprine users per indication in terms of sex, age and age-groups across all databases. Generally, across all indications the proportion of females was higher than males, which was similar as the proportion in all incident azathioprine users (**Table 12**). There were some exceptions however, namely inflammatory bowel disease where the proportion was almost 50/50 and myasthenia gravis where the proportion of males was clearly higher than females, approximately 60% vs. 40%. The median age was the highest in individuals with myasthenia gravis, ranging between 66 (IPCI) - 74 years (IMASIS), and individuals with pemphigus vulgaris and bullous pemphigoid, ranging between 49 (IMASIS) - 77 years (IQVIA DA Germany). In individuals with IBD, median age was much lower and ranged between 33 (IPCI) - 43 years (IMASIS) and approximately 50% were in the age group of 18 to 44 years. In the other more prevalent indications such as autoimmune hepatitis and SLE, median age ranged between 55 (IQVIA DA Germany) - 66 years (IMASIS) and 40 (IPCI) - 45 years (SIDIAP) respectively. Most individuals with autoimmune hepatitis were in the age group 45 to 64 years and in individuals with SLE in the age group 18 to 44 years.

Table 14. Demographics of incident azathioprine users per indication.

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
Autoimmune hepatitis	Total subjects	Number of subjects	N	647	60	0	314	786
	Sex	Female	N (%)	507 (78.36)	44 (73.33)	0 (0.0)	230 (73.25)	551 (70.10)
		Male	N (%)	140 (21.64)	16 (26.67)	0 (0.0)	84 (26.75)	235 (29.90)
	Age	Years	Median [Q25-Q75]	57 [43-67]	66 [55-75]	n/a	55 [38-68]	55 [43-66]
			Mean (SD)	53.64 (18.05)	63.58 (15.62)	n/a	51.31 (21.59)	53.00 (18.39)
			Range	7-87	17-93	n/a	2-89	1-90
	Age group	0 to 17	N (%)	40 (6.18)	<5	0 (0.0)	41 (13.06)	52 (6.62)
		18 to 44	N (%)	128 (19.78)	8 (13.33)	0 (0.0)	55 (17.52)	162 (20.61)
		45 to 64	N (%)	285 (44.05)	19 (31.67)	0 (0.0)	120 (38.22)	346 (44.02)
		65 to 79	N (%)	171 (26.43)	23 (38.33)	0 (0.0)	75 (23.89)	198 (25.19)
		≥ 80	N (%)	23 (3.55)	9 (15.00)	0 (0.0)	23 (7.32)	28 (3.56)
Behçet's disease	Total subjects	Number of subjects	N	84	7	0	32	87
	Sex	Female	N (%)	55 (65.48)	<5	0 (0.0)	21 (65.62)	52 (59.77)
		Male	N (%)	29 (34.52)	<5	0 (0.0)	11 (34.38)	35 (40.23)
	Age	Years	Median [Q25-Q75]	38 [29-46]	50 [40-53]	n/a	36 [28-47]	35 [28-45]
			Mean (SD)	37.76 (11.09)	44.86 (14.74)	n/a	38.28 (16.53)	38.29 (15.01)
			Range	14-62	19-60	n/a	8-82	8-79
	Age group	0 to 17	N (%)	<5	0 (0.0)	0 (0.0)	<5	5 (5.75)
		18 to 44	N (%)	59 (70.24)	<5	0 (0.0)	19 (59.38)	60 (68.97)
		45 to 64	N (%)	23 (27.38)	5 (71.43)	0 (0.0)	9 (28.12)	15 (17.24)
		65 to 79	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	7 (8.05)
		≥ 80	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.0)
Dermatomyositis	Total subjects	Number of subjects	N	67	<5	0	60	122

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
	Sex	Female	N (%)	50 (74.63)	<5	0 (0.0)	40 (66.67)	84 (68.85)
		Male	N (%)	17 (25.37)	<5	0 (0.0)	20 (33.33)	38 (31.15)
	Age	Years	Median [Q25-Q75]	54 [41-66]	<5	n/a	56 {43-65]	55 [47-70]
			Mean (SD)	52.67 (17.90)	<5	n/a	53.45 (17.17)	56.41 (16.37)
			Range	8-87	<5	n/a	10-81	17-88
	Age group	0 to 17	N (%)	<5	<5	0 (0.0)	<5	<5
		18 to 44	N (%)	19 (28.36)	<5	0 (0.0)	14 (23.33)	26 (21.31)
		45 to 64	N (%)	26 (38.81)	<5	0 (0.0)	26 (43.33)	55 (45.08)
		65 to 79	N (%)	16 (23.88)	<5	0 (0.0)	16 (26.67)	29 (23.77)
		≥ 80	N (%)	<5	<5	0 (0.0)	<5	11 (9.02)
Hemolytic anemia	Total subjects	Number of subjects	N	71	<5	<5	25	78
	Sex	Female	N (%)	39 (54.93)	<5	<5	9 (36.00)	50 (64.10)
		Male	N (%)	32 (45.07)	<5	<5	15 (60.00)	28 (35.90)
		None	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.0)
	Age	Years	Median [Q25-Q75]	68 [61-76]	n/a	n/a	63 [48-75]	60 [43-75]
			Mean (SD)	67.25 (12.72)	n/a	n/a	58.72 (19.19)	57.05 (21.42)
			Range	30-87	n/a	n/a	20-85	3-90
	Age group	0 to 17	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.41)
		18 to 44	N (%)	<5	<5	<5	6 (24.00)	16 (20.51)
		45 to 64	N (%)	24 (33.80)	0 (0.0)	0 (0.0)	7 (28.00)	25 (32.05)
		65 to 79	N (%)	32 (45.07)	0 (0.0)	0 (0.0)	8 (32.00)	23 (29.49)
		≥ 80	N (%)	11 (15.49)	0 (0.0)	0 (0.0)	<5	9 (11.54)
Idiopathic thrombocytopenic purpura	Total subjects	Number of subjects	N	61	8	<5	22	43
	Sex	Female	N (%)	32 (52.46)	6 (75.00)	<5	13 (59.09)	32 (74.42)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		Male	N (%)	29 (47.54)	<5	<5	9 (40.91)	11 (25.58)
	Age	Years	Median [Q25-Q75]	66 [44-77]	57 [52-61]	n/a	69 [45-73]	59 [46-72]
			Mean (SD)	60.46 (20.23)	58.12 (13.89)	n/a	58.91 (21.47)	57.09 (19.47)
			Range	22-92	37-85	n/a	10-83	12-86
	Age group	0 to 17	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5
		18 to 44	N (%)	16 (26.23)	<5	<5	5 (22.73)	8 (18.60)
		45 to 64	N (%)	13 (21.31)	5 (62.50)	0 (0.0)	<5	14 (32.56)
		65 to 79	N (%)	21 (34.43)	<5	0 (0.0)	10 (45.45)	14 (32.56)
		≥ 80	N (%)	11 (18.03)	<5	0 (0.0)	<5	5 (11.63)
Inflammatory bowel disease	Total subjects	Number of subjects	N	6,840	151	738	2,974	4,012
	Sex	Female	N (%)	3,388 (49.53)	74 (49.01)	392 (53.12)	1,460 (49.09)	1,868 (46.56)
		Male	N (%)	3,452 (50.47)	77 (50.99)	346 (46.88)	1,513 (50.87)	2,144 (53.44)
		None	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.0)
	Age	Years	Median [Q25-Q75]	36 [23-52]	43 [29-57]	33 [21-52]	39 [25-53]	37 [25-49]
			Mean (SD)	38.30 (18.30)	43.07 (18.25)	37.47 (18.60)	39.65 (17.95)	37.83 (16.93)
			Range	1-94	7-92	3-84	2-91	1-89
	Age group	0 to 17	N (%)	918 (13.42)	13 (8.61)	105 (14.23)	377 (12.68)	485 (12.09)
		18 to 44	N (%)	3,486 (50.96)	68 (45.03)	375 (50.81)	1,408 (47.34)	2,192 (54.64)
		45 to 64	N (%)	1,755 (25.66)	54 (35.76)	182 (24.66)	900 (30.26)	1,039 (25.90)
		65 to 79	N (%)	592 (8.65)	13 (8.61)	71 (9.62)	256 (8.61)	261 (6.51)
		≥ 80	N (%)	89 (1.30)	<5	5 (0.68)	33 (1.11)	35 (0.87)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
Multiple sclerosis	Total subjects	Number of subjects	N	47	<5	<5	196	38
	Sex	Female	N (%)	32 (68.09)	<5	<5	143 (72.96)	31 (81.58)
		Male	N (%)	15 (31.91)	<5	<5	53 (27.04)	7 (18.42)
	Age	Years	Median [Q25-Q75]	47 [38-52]	n/a	n/a	48 [39-59]	48 [38-58]
			Mean (SD)	46.74 (10.76)	n/a	n/a	49.40 (13.57)	47.47 (14.26)
			Range	24-70	n/a	n/a	17-83	17-72
	Age group	0 to 17	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5
		18 to 44	N (%)	22 (46.81)	<5	<5	72 (36.73)	16 (42.11)
		45 to 64	N (%)	22 (46.81)	<5	0 (0.0)	92 (46.94)	14 (36.84)
		65 to 79	N (%)	<5	0 (0.0)	<5	28 (14.29)	7 (18.42)
		≥ 80	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.00)
Myasthenia gravis	Total subjects	Number of subjects	N	365	25	48	470	367
	Sex	Female	N (%)	138 (37.81)	10 (40.00)	21 (43.75)	197 (41.91)	165 (44.96)
		Male	N (%)	227 (62.19)	15 (60.00)	27 (56.25)	273 (58.09)	202 (55.04)
	Age	Years	Median [Q25-Q75]	68 [59-76]	74 [68-81]	66 [47-74]	70 [59-78]	72 [58-79]
			Mean (SD)	65.10 (15.46)	71.68 (13.71)	59.73 (18.69)	66.05 (16.38)	66.71 (16.48)
			Range	12-90	38-92	19-88	11-94	10-90
	Age group	0 to 17	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5
		18 to 44	N (%)	31 (8.49)	<5	12 (25.00)	49 (10.43)	43 (11.72)
		45 to 64	N (%)	110 (30.14)	<5	11 (22.92)	124 (26.38)	81 (22.07)
		65 to 79	N (%)	169 (46.30)	12 (48.00)	21 (43.75)	195 (41.49)	161 (43.87)
		≥ 80	N (%)	51 (13.97)	8 (32.00)	<5	99 (21.06)	80 (21.80)
Organ transplantation	Total subjects	Number of subjects	N	33	<5	0	0	47
	Sex	Female	N (%)	12 (36.36)	<5	0 (0.0)	n/a	18 (38.30)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		Male	N (%)	21 (63.64)	<5	0 (0.0)	n/a	29 (61.70)
	Age	Years	Median [Q25-Q75]	55 [37-61]	n/a	n/a	n/a	58 [45-68]
			Mean (SD)	49.61 (16.04)	n/a	n/a	n/a	52.32 (20.96)
			Range	6-74	n/a	n/a	n/a	2-81
	Age group	0 to 17	N (%)	<5	0 (0.00)	0 (0.0)	n/a	5 (10.64)
		18 to 44	N (%)	9 (27.27)	<5	0 (0.0)	n/a	6 (12.77)
		45 to 64	N (%)	19 (57.58)	0 (0.0)	0 (0.0)	n/a	20 (42.55)
		65 to 79	N (%)	<5	<5	0 (0.0)	n/a	15 (31.91)
		≥ 80	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	n/a	<5
Pemphigus vulgaris and bullous pemphigoid	Total subjects	Number of subjects	N	176	9	0	268	112
	Sex	Female	N (%)	84 (47.73)	<5	0 (0.0)	147 (54.85)	55 (49.11)
		Male	N (%)	92 (52.27)	7 (77.78)	0 (0.0)	121 (45.15)	57 (50.89)
	Age	Years	Median [Q25-Q75]	73 [60-83]	49 [40-69]	n/a	77 [68-83]	62 [46-79]
			Mean (SD)	70.14 (16.18)	56.44 (19.59)	n/a	73.53 (13.51)	60.71 (19.56)
			Range	24-97	36-86	n/a	21-96	13-93
	Age group	0 to 17	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)	<5
		18 to 44	N (%)	16 (9.09)	<5	0 (0.0)	12 (4.48)	24 (21.43)
		45 to 64	N (%)	37 (21.02)	<5	0 (0.0)	43 (16.04)	38 (33.93)
		65 to 79	N (%)	60 (34.09)	<5	0 (0.0)	108 (40.30)	26 (23.21)
		≥ 80	N (%)	63 (35.80)	<5	0 (0.0)	105 (39.18)	23 (20.54)
Polyarteritis nodosa	Total subjects	Number of subjects	N	22	6	0	33 (0.28)	56
	Sex	Female	N (%)	13 (59.09)	<5	0 (0.0)	19 (57.58)	30 (53.57)
		Male	N (%)	9 (40.91)	<5	0 (0.0)	14 (42.42)	26 (46.43)
	Age	Years	Median [Q25-Q75]	62 [45-72]	72 [57-79]	n/a	66 [54-7]	65 [52-71]

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
			Mean (SD)	56.50 (17.96)	64.83 (21.89)	n/a	59.67 (17.77)	60.29 (15.17)
			Range	13-74	27-86	n/a	12-82	15-85
	Age group	0 to 17	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5
		18 to 44	N (%)	5 (22.73)	<5	0 (0.0)	5 (15.15)	8 (14.29)
		45 to 64	N (%)	6 (27.27)	<5	0 (0.0)	9 (27.27)	18 (32.14)
		65 to 79	N (%)	10 (45.45)	<5	0 (0.0)	14 (42.42)	27 (48.21)
		≥ 80	N (%)	0 (0.0)	<5	0 (0.0)	<5	<5
Polymyositis	Total subjects	Number of subjects	N	79	<5	0	57	40
	Sex	Female	N (%)	52 (65.82)	0 (0.0)	0 (0.0)	38 (66.67)	36 (90.00)
		Male	N (%)	27 (34.18)	<5	0 (0.0)	19 (33.33)	<5
	Age	Years	Median [Q25-Q75]	56 [46-64]	n/a	n/a	59 [54-70]	66 [50-75]
			Mean (SD)	54.28 (13.90)	n/a	n/a	60.93 (12.39)	63.40 (14.17)
			Range	19-83	n/a	n/a	31-83	40-87
	Age group	0 to 17	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		18 to 44	N (%)	18 (22.78)	0 (0.0)	0 (0.0)	5 (8.77)	5 (12.50)
		45 to 64	N (%)	43 (54.43)	0 (0.0)	0 (0.0)	29 (50.88)	14 (35.00)
		65 to 79	N (%)	17 (21.52)	0 (0.0)	0 (0.0)	19 (33.33)	14 (35.00)
		≥ 80	N (%)	<5	<5	0 (0.0)	<5	7 (17.50)
Pyoderma gangrenosum	Total subjects	Number of subjects	N	28	<5	0	42	17
	Sex	Female	N (%)	22 (78.57)	<5	0 (0.0)	27 (64.29)	13 (76.47)
		Male	N (%)	6 (21.43)	0 (0.0)	0 (0.0)	15 (35.71)	<5
	Age	Years	Median [Q25-Q75]	59 [35-69]	n/a	n/a	59 [49-68]	52 [45-65]
			Mean (SD)	52.29 (23.07)	n/a	n/a	57.95 (17.57)	54.71 (17.01)
			Range	9-92	n/a	n/a	18-96	19-84

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
	Age group	0 to 17	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		18 to 44	N (%)	6 (21.43%)	0 (0.0)	0 (0.0)	8 (19.05%)	<5
		45 to 64	N (%)	9 (32.14)	<5	0 (0.0)	20 (47.62)	8 (47.06)
		65 to 79	N (%)	9 (32.14%)	0 (0.00)	0 (0.0)	9 (21.43%)	<5
		≥ 80	N (%)	<5	0 (0.00)	0 (0.0)	5 (11.90%)	<5
Rheumatoid arthritis and chronic polyarthritis	Total subjects	Number of subjects	N	452	13	52	468	118
	Sex	Female	N (%)	300 (66.37)	9 (69.23)	36 (69.23)	365 (77.99)	80 (67.80)
		Male	N (%)	152 (33.63)	<5	16 (30.77)	103 (22.01)	38 (32.20)
	Age	Years	Median [Q25-Q75]	64 [55-72]	62 [60-71]	56 [37-68]	60 [49-71]	64 [52-74]
			Mean (SD)	62.93 (13.05)	65.62 (12.07)	53.40 (20.05)	59.24 (15.60)	62.17 (15.27)
			Range	21-94	49-85	14-85	8-87	18-88
	Age group	0 to 17	N (%)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)
		18 to 44	N (%)	45 (9.96)	0 (0.0)	13 (25.00)	77 (16.45)	15 (12.71)
		45 to 64	N (%)	189 (41.81)	7 (53.85)	17 (32.69)	192 (41.03)	45 (38.14)
		65 to 79	N (%)	187 (41.37)	<5	15 (28.85)	162 (34.62)	48 (40.68)
		≥ 80	N (%)	31 (6.86)	<5	<5	34 (7.26)	10 (8.47)
Systemic lupus erythematosus	Total subjects	Number of subjects	N	286	35	16	310	272
	Sex	Female	N (%)	247 (86.36)	32 (91.43)	11 (68.75)	260 (83.87)	240 (88.24)
		Male	N (%)	39 (13.64)	<5	5 (31.25)	50 (16.13)	32 (11.76)
	Age	Years	Median [Q25-Q75]	44 [32-56]	46 [36-63]	40 [26-50]	51 [40-61]	45 [33-58]
			Mean (SD)	45.24 (16.81)	48.60 (17.12)	40.81 (19.37)	50.30 (16.84)	45.75 (17.41)
			Range	6-82	18-86	13-79	8-85	11-89
	Age group	0 to 17	N (%)	12 (4.20)	0 (0.0)	<5	11 (3.55)	
		18 to 44	N (%)	131 (45.80)	16 (45.71)	9 (56.25)	96 (30.97)	
		45 to 64	N (%)	98 (34.27)	11 (31.43)	<5	136 (43.87)	

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		65 to 79	N (%)	41 (14.34)	6 (17.14)	<5	57 (18.39)	
		≥ 80	N (%)	<5	<5	0 (0.0)	10 (3.23)	
None of the above/missing	Total subjects	Number of subjects	N	22,171	385	2,155	6,861	13,325
	Sex	Female	N (%)	12,045 (54.33)	226 (58.70)	1,200 (55.68)	4,032 (58.77)	7,544 (56.62)
		Male	N (%)	10,126 (45.67)	159 (41.30)	955 (44.32)	2,825 (41.17)	5,781 (43.38)
		None	N (%)	n/a	n/a	n/a	<5	n/a
	Age	Years	Median [Q25-Q75]	53 [36-67]	51 [38-64]	51 [34-65]	56 [41-68]	50 [36-64]
			Mean (SD)	50.86 (19.40)	51.37 (17.69)	49.20 (19.36)	54.14 (18.17)	49.92 (18.34)
			Range	1-104	13- 91	6-96	3-94	2-101
	Age group	0 to 17	N (%)	1,059 (4.78)	6 (1.56)	108 (5.01)	172 (2.51)	470 (3.53)
		18 to 44	N (%)	7,180 (32.38)	141 (36.62)	748 (34.71)	1,860 (27.11)	4,922 (36.94)
		45 to 64	N (%)	7,544 (34.03)	145 (37.66)	755 (35.03)	2,651 (38.64)	4,675 (35.08)
		65 to 79	N (%)	5,266 (23.75)	68 (17.66)	457 (21.21)	1,713 (24.97)	2,610 (19.59)
		≥ 80	N (%)	1,122 (5.06)	25 (6.49)	87 (4.04)	465 (6.78)	648 (4.86)

n/a = not applicable

12.2.2 Large-scale characterisation

Large-scale characterisations of incident azathioprine users without one of the prespecified indications in the year prior to the index date are presented below for both the 10 most prevalent drugs and conditions and correspond to drug and disease codes being recorded both within the year prior to index date (-365,-1) and on the index date.

The results within one year prior to the index date are described in **Table 15** for drugs and **Table 16** for conditions.

In the year before index date, the most often prescribed drug was prednisone/prednisolone across all databases with rates of 32.8% (IQVIA DA Germany) - 66.4% (CPRD Gold). With proportions of 11.4% (IMASIS)-27.7% (CPRD Gold) mesalamine was also frequently prescribed in the year before index date across all databases. Other medications that often were present, but not in all databases, were acetaminophen (31.4% (IMASIS) - 36.8% (CPRD) not IPCI), and omeprazole (18.4 (IMASIS) -41.0% (SIDIAP) not IQVIA DA Germany).

With regard to underlying conditions, conditions regarding blood pressure were frequently reported in all databases in the year before index date: namely blood pressure finding in CPRD (59.89%) and essential hypertension in the other databases (7.5 (IPCI) - 12.8% (IQVIA DA Germany)). In all databases various conditions concerning abdominal pain and IBD were present in the year before index date, most notably Crohn's disease (3.7 (IQVIA DA Germany) - 9.7% (IPCI) not IMASIS) and ulcerative colitis (3.9 (IQVIA DA Germany) - 8.4% (IPCI) not CPRD or IMASIS).

Large-scale characterisation of incident azathioprine users without one of the prespecified indications on the index date (0,0) are shown in the **Appendix II: Table S3** and **Table S4.** On index date the most prescribed drugs were azathioprine (100% in all databases) followed by prednisone/prednisolone with rates of 29.6% (IMASIS) - 45.2% (SIDIAP). With proportions of 10.9% (IQVIA DA Germany) - 19.4% (CPRD GOLD) mesalamine was also still frequently prescribed on index date, but not in IMASIS. Regarding conditions on the index date only IQVIA DA Germany provided 10 conditions, while other databases did not provide any conditions or very low counts or counts <5. In IQVIA DA Germany notably there were multiple conditions related to the airways and/or lungs namely interstitial lung disease (2.0%), fibrosis of lung (1.5%), sarcoidosis (1.1%) and Sjögren's syndrome (0.8%).

Large-scale characterisation overall and by indication are available in the Shiny app: https://data-dev.darwin-eu.org/P3-C1-014-Azathioprine

Table 15. Large-scale characterisation of incident azathioprine users without a prespecified indication in terms of drugs in the year prior to index date [-365, -1].

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
Drug	**N=22,171 (100.0%)**	**Drug**	**N=385 (100.0 %)**	**Drug**	**N=2,155 (100.0 %)**	**Drug**	**N=6,861 (100.0 %)**	**Drug**	**N=13,325 (100.0%)**
Prednisolone	14,715 (66.37)	Prednisone	135 (35.06)	Prednisolone	1,055 (48.96)	Prednisolone	2,248 (32.76)	Prednisone	5,672 (42.57)
Acetaminophen	8,153 (36.77)	Acetaminophen	121 (31.43)	Sodium chloride	661 (30.67)	Pantoprazole	1,380 (20.11)	Omeprazole	5,464 (41.01)
Omeprazole	6,550 (29.54)	Calcium carbonate	93 (24.16)	Potassium chloride	660 (30.63)	Cholecalciferol	1,155 (16.83)	Acetaminophen	4,883 (36.65)
Mesalamine	6,149 (27.73)	Sodium chloride	74 (19.22)	Polyethylene glycol 3350	578 (26.82)	Dipyrone	802 (11.69)	Calcium carbonate	3,454 (25.92)
Amoxicillin	6,125 (27.63)	Omeprazole	71 (18.44)	Omeprazole	517 (23.99)	Mesalamine	782 (11.40)	Cholecalciferol	2,882 (21.63)
Cholecalciferol	6,099 (27.51)	Cholecalciferol	69 (17.92)	Mesalamine	494 (22.92)	Budesonide	633 (9.23)	Mesalamine	2,732 (20.50)
Calcium carbonate	5,935 (26.77)	Potassium chloride	51 (13.25)	Budesonide	478 (22.18)	Calcium	603 (8.79)	Amoxicillin	2,321 (17.42)

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
Codeine	5,549 (25.03)	Mesalamine	44 (11.43)	Sodium bicarbonate	466 (21.62)	Levothyroxine	602 (8.77)	Budesonide	2,161 (16.22)
Hydrocortisone	4,210 (18.99)	Dipyrone	43 (11.17)	Pantoprazole	463 (21.48)	Ibuprofen	577 (8.41)	Ibuprofen	2,121 (15.92)
Albuterol	4,143 (18.69)	Methylprednisolone	41 (10.65)	Sodium sulfate	419 (19.44)	Ramipril	564 (8.22)	Dipyrone	1,866 (14.00)

Table 16. Large-scale characterisation of incident azathioprine users without a prespecified indication in terms of conditions in the year prior to index date [-365, -1].

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
Condition	N=22,171 (100.0%)	Condition	N=385 (100.0%)	Condition	N=2,155 (100.0%)	Condition	N=6,861 (100.0%)	Condition	N=13,325 (100.0%)
Blood pressure finding	13,278 (59.89)	Essential hypertension	32 (8.31)	Crohn's disease	208 (9.65)	Essential hypertension	877 (12.78)	Essential hypertension	1,153 (8.65)
Cough	2,409 (10.87)	Hyperlipidemia	19 (4.94)	Ulcerative colitis	181 (8.40)	Illness	568 (8.28)	Crohn's disease	955 (7.17)

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
Finding of pulse rate	2,375 (10.71)	Disorder of intestine	18 (4.68)	Essential hypertension	162 (7.52)	Inflammatory disorder of digestive tract	399 (5.82)	Common cold	739 (5.55)
Crohn's disease	1,702 (7.68)	Type 2 diabetes mellitus without complication	15 (3.90)	Cough	148 (6.87)	Acute upper respiratory infection	366 (5.33)	Ulcerative colitis	721 (5.41)
Allergic reaction to drug	1,575 (7.10)	Osteoporosis	15 (3.90)	Localized abdominal pain	140 (6.50)	Nerve root disorder	356 (5.19)	Nicotine dependence	611 (4.59)
Exercise grading	1,484 (6.69)	Abdominal pain	13 (3.38)	Urinary tract infectious disease	134 (6.22)	Type 2 diabetes mellitus without complication	282 (4.11)	Urinary tract infectious disease	605 (4.54)
Abdominal pain	1,477 (6.66)	Diaphragmatic hernia	12 (3.12)	Diarrheal disorder	134 (6.22)	Acute bronchitis	273 (3.98)	Hyperlipidemia	580 (4.35)
Dyspnea	1,410 (6.36)	Nicotine dependence	12 (3.12)	Type 2 diabetes mellitus	125 (5.80)	Ulcerative colitis	270 (3.94)	Abdominal pain	557 (4.18)

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
Cervical smear-negative	1,380 (6.22)	Urinary tract infectious disease	12 (3.12)	Generalized abdominal pain	112 (5.20)	Crohn's disease	253 (3.69)	Type 2 diabetes mellitus without complication	545 (4.09)
Eruption	1,349 (6.08)	Chronic kidney disease	11 (2.86)	Finding of region of thorax	109 (5.06)	Depressive disorder	248 (3.61)	Traumatic or non-traumatic injury	537 (4.03)

12.2.3 Treatment duration

Table 17 describes treatment duration overall and per indication of newly treated azathioprine users. Overall, median duration was the longest in SIDIAP, with a median of 1,019 days (IQR 238-2,484 days), followed by CPRD Gold, with a median of 354 days (IQR 76-1,237 days), and was the shortest in IMASIS, with a median of 90 days (IQR 30-212 days).

Across all databases, for the different duration categories, a higher proportion of individuals (30.4 (SIDIAP) - 87.9% (IMASIS)) had less than 1 year of treatment duration, followed by the group of individuals with a duration between 1 to 2 years (9.0 (IMASIS) - 16.2% (IPCI)). A noteworthy exception was the SIDIAP database where after the <1 year group, the 5 to 10 and ≥10 years groups were most prominent, with 20.9% and 13.4% of individuals respectively. In CPRD GOLD the 5-10 year group only had a slightly lower number of individuals (12.25%) than the 1 to 2 year groups (13.06%).

Between the different indications in general there were no clear differences in median treatment duration or proportion of individuals per treatment duration group. Nevertheless, in CPRD GOLD, patients with autoimmune hepatitis or myasthenia gravis seemed to lean towards a higher proportion with a treatment duration of 5 years or longer (34.0% and 30.14% respectively). The differences between SIDIAP and the other databases in relation to treatment duration groups was consistent among all indications. For the most prevalent indication namely IBD, the median treatment duration ranged between 59 (IMASIS) - 1,294 days (SIDIAP). For the other more prevalent indications autoimmune hepatitis, myasthenia gravis and SLE, the median treatment duration was 86 (IMASIS) - 978 days (CPRD), 14 (IMASIS) - 939 days (CPRD) and 26 (IMASIS) - 710 days (SIDIAP) respectively.

Table 17. Treatment duration overall and per indication of newly treated azathioprine users.

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
Overall	Total subjects	Number of subjects	N	31,857	692	3,020	11,932	19,341
	Treatment duration	Number of days	Min	1	1	1	1	1
			Q25	76	30	72	51	238
			Median	354	90	207	175	1,019
			Q75	1,237	212	646	658	2,484
			Max	8,461	4,516	4,712	7,017	6,024
	Treatment duration groups	<1 year	N (%)	16,093 (50.52)	608 (87.86)	1,868 (61.85)	7,700 (64.53)	5,881 (30.41)
		1 to 2 years	N (%)	4,159 (13.06)	62 (8.96)	488 (16.16)	1,490 (12.49)	2,396 (12.39)
		2 to 3 years	N (%)	2,759 (8.66)	14 (2.02)	231 (7.65)	850 (7.12)	1,741 (9.00)
		3 to 4 years	N (%)	1,996 (6.27)	5 (0.72)	154 (5.10)	551 (4.62)	1,432 (7.40)
		4 to 5 years	N (%)	1,546 (4.85)	<5	99 (3.28)	377 (3.16)	1,254 (6.48)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		5 to 10 years	N (%)	3,903 (12.25)	<5	173 (5.73)	807 (6.76)	4,050 (20.94)
		≥10 years	N (%)	1,401 (4.40)	<5 (<5)	7 (0.23)	157 (1.32)	2,587 (13.38)
Autoimmune hepatitis	Total subjects	Number of subjects	N	647	60	0	314	786
	Treatment duration	Number of days	Min	2	1	n/a	14	3
			Q25	177	30	n/a	100	198
			Median	978	86	n/a	293	876
			Q75	2,388	159	n/a	1,144	2,002
			Max	7,415	454	n/a	5,467	4,902
	Treatment duration groups	<1 year	N (%)	211 (32.61)	57 (95.00)	0 (0.0)	167 (53.18)	251 (31.93)
		1 to 2 years	N (%)	74 (11.44)	<5	0 (0.0)	52 (16.56)	107 (13.61)
		2 to 3 years	N (%)	55 (8.50)	0 (0.0)	0 (0.0)	14 (4.46)	68 (8.65)
		3 to 4 years	N (%)	53 (8.19)	0 (0.0)	0 (0.0)	21 (6.69)	59 (7.51)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		4 to 5 years	N (%)	34 (5.26)	0 (0.0)	0 (0.0)	14 (4.46)	72 (9.16)
		5 to 10 years	N (%)	140 (21.64)	0 (0.0)	0 (0.0)	36 (11.46)	187 (23.79)
		≥10 years	N (%)	80 (12.36)	0 (0.0)	0 (0.0)	10 (3.18)	42 (5.34)
Behçet's disease	Total subjects	Number of subjects	N	84	7	0	32	87
	Treatment duration	Number of days	Min	1	2	n/a	17	2
			Q25	83	16	n/a	50	330
			Median	291	60	n/a	172	931
			Q75	643	169	n/a	1,017	2,041
			Max	4,890	469	n/a	3,461	5,278
	Treatment duration groups	<1 year	N (%)	50 (59.52)	6 (85.71)	n/a	20 (62.50)	23 (26.44)
		1 to 2 years	N (%)	17 (20.24)	<5	0 (0.0)	<5	16 (18.39)
		2 to 3 years	N (%)	6 (7.14)	0 (0.0)	0 (0.0)	<5	7 (8.05)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	7 (8.05)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	7 (8.05)
		5 to 10 years	N (%)	5 (5.95)	0 (0.0)	0 (0.0)	5 (15.62)	20 (22.99)
		≥10 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	7 (8.05)
Dermatomyositis	Total subjects	Number of subjects	N	67	<5	0	60	122
	Treatment duration	Number of days	Min	14	n/a	n/a	50	9
			Q25	59	n/a	n/a	50	181
			Median	381	n/a	n/a	166	664
			Q75	1,372	n/a	n/a	750	1,714
			Max	6,771	n/a	n/a	3,265	4,706
	Treatment duration groups	<1 year	N (%)	33 (49.25)	<5	0 (0.0)	38 (63.33)	42 (34.43)
		1 to 2 years	N (%)	9 (13.43)	<5	0 (0.0)	6 (10.00)	23 (18.85)
		2 to 3 years	N (%)	7 (10.45)	0 (0.0)	0 (0.0)	9 (15.00)	10 (8.20)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	10 (8.20)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	9 (7.38)
		5 to 10 years	N (%)	8 (11.94)	0 (0.0)	0 (0.0)	<5	24 (19.67)
		≥10 years	N (%)	6 (8.96)	0 (0.0)	0 (0.0)	0 (0.0)	<5
Hemolytic anemia	Total subjects	Number of subjects	N	71	<5	<5	25	78
	Treatment duration	Number of days	Min	1	n/a	n/a	25	8
			Q25	56	n/a	n/a	71	88
			Median	201	n/a	n/a	105	378
			Q75	650	n/a	n/a	310	1,308
			Max	2,392	n/a	n/a	5,223	4,507
	Treatment duration groups	<1 year	N (%)	44 (61.97)	<5	0 (0.0)	19 (76.00)	36 (46.15)
		1 to 2 years	N (%)	11 (15.49)	0 (0.0)	<5	<5	14 (17.95)
		2 to 3 years	N (%)	6 (8.45)	0 (0.0)	0 (0.0)	<5	6 (7.69)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	5 (6.41)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5
		5 to 10 years	N (%)	5 (7.04)	0 (0.0)	0 (0.0)	0 (0.0)	9 (11.54)
		≥10 years	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5
Idiopathic thrombocytopenic purpura	Total subjects	Number of subjects	N	61	8	<5	22	43
	Treatment duration	Number of days	Min	2	1	n/a	25	5
			Q25	55	5	n/a	100	63
			Median	133	56	n/a	242	208
			Q75	503	59	n/a	631	1,044
			Max	3,934	61	n/a	2,334	4,574
	Treatment duration groups	<1 year	N (%)	45 (73.77)	8 (100.0)	0 (0.0)	13 (59.09)	28 (65.12)
		1 to 2 years	N (%)	<5	0 (0.0)	<5	<5	<5
		2 to 3 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	<5
		3 to 4 years	N (%)	5 (8.20)	0 (0.0)	0 (0.0)	<5	<5

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5
		5 to 10 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5
		≥10 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	<5
Inflammatory bowel disease	Total subjects	Number of subjects	N	6,840	151	738	2,974	4,012
	Treatment duration	Number of days	Min	1	1	1	13	2
			Q25	84	8	60	68	289
			Median	451	59	190	194	1,294
			Q75	1,408	158	624	681	2,833
			Max	8,003	1,400	4,712	7,017	6,024
	Treatment duration groups	<1 year	N (%)	3,176 (46.43)	138 (91.39)	465 (63.01)	1,868 (62.81)	1,121 (27.94)
		1 to 2 years	N (%)	877 (12.82)	8 (5.30)	125 (16.94)	401 (13.48)	444 (11.07)
		2 to 3 years	N (%)	635 (9.28)	<5	48 (6.50)	216 (7.26)	291 (7.25)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		3 to 4 years	N (%)	497 (7.27)	<5	39 (5.28)	135 (4.54)	261 (6.51)
		4 to 5 years	N (%)	401 (5.86)	0 (0.0)	22 (2.98)	90 (3.03)	269 (6.70)
		5 to 10 years	N (%)	948 (13.86)	0 (0.0)	38 (5.15)	217 (7.30)	991 (24.70)
		≥10 years	N (%)	306 (4.47)	0 (0.0)	<5	47 (1.58)	635 (15.83)
Multiple sclerosis	Total subjects	Number of subjects	N	47	<5	<5	196	38
	Treatment duration	Number of days	Min	7	n/a	n/a	6	2
			Q25	72	n/a	n/a	83	184
			Median	196	n/a	n/a	196	592
			Q75	1,496	n/a	n/a	631	1,641
			Max	4,369	n/a	n/a	5,903	4,820
	Treatment duration groups	<1 year	N (%)	27 (57.45)	<5	<5	123 (62.76)	13 (34.21)
		1 to 2 years	N (%)	<5	0 (0.0)	0 (0.0)	31 (15.82)	8 (21.05)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		2 to 3 years	N (%)	<5	0 (0.0)	0 (0.0)	14 (7.14)	<5
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	9 (4.59)	0 (0.0)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	5 (2.55)	6 (15.79)
		5 to 10 years	N (%)	9 (19.15)	0 (0.0)	0 (0.0)	8 (4.08)	5 (13.16)
		≥10 years	N (%)	<5	0 (0.0)	0 (0.0)	6 (3.06)	<5
Myasthenia gravis	Total subjects	Number of subjects	N	365	25	48	470	367
	Treatment duration	Number of days	Min	2	1	2	10	2
			Q25	161	5	119	99	180
			Median	939	14	423	222	716
			Q75	2,343	49	806	897	1,836
			Max	7,742	417	3,300	5,992	5,972
	Treatment duration groups	<1 year	N (%)	122 (33.42)	24 (96.00)	22 (45.83)	273 (58.09)	137 (37.33)
		1 to 2 years	N (%)	43 (11.78)	<5	10 (20.83)	57 (12.13)	48 (13.08)
		2 to 3 years	N (%)	35 (9.59)	0 (0.0)	7 (14.58)	43 (9.15)	35 (9.54)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		3 to 4 years	N (%)	26 (7.12)	0 (0.0)	<5	20 (4.26)	31 (8.45)
		4 to 5 years	N (%)	29 (7.95)	0 (0.0)	<5	21 (4.47)	24 (6.54)
		5 to 10 years	N (%)	75 (20.55)	0 (0.0)	6 (12.50)	47 (10.00)	65 (17.71)
		≥10 years	N (%)	35 (9.59)	0 (0.0)	0 (0.0)	9 (1.91)	27 (7.36)
Organ transplantation	Total subjects	Number of subjects	N	33	<5	0	0	47
	Treatment duration	Number of days	Min	28	n/a	n/a	n/a	8
			Q25	56	n/a	n/a	n/a	120
			Median	208	n/a	n/a	n/a	476
			Q75	1,075	n/a	n/a	n/a	1,898
			Max	6,718	n/a	n/a	n/a	4,749
	Treatment duration groups	<1 year	N (%)	20 (60.61)	0 (0.0)	0 (0.0)	0 (0.0)	20 (42.55)
		1 to 2 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	10 (21.28)
		2 to 3 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	<5

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		3 to 4 years	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	<5
		5 to 10 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	8 (17.02)
		≥10 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	<5
Pemphigus vulgaris and bullous pemphigoid	Total subjects	Number of subjects	N	176	9	0	268	112
	Treatment duration	Number of days	Min	1	2	n/a	12	12
			Q25	57	5	n/a	50	84
			Median	186	94	n/a	102	409
			Q75	675	341	n/a	345	822
			Max	5,045	636	n/a	3,296	5,531
	Treatment duration groups	<1 year	N (%)	105 (59.66)	7 (77.78)	0 (0.0)	206 (76.87)	54 (48.21)
		1 to 2 years	N (%)	32 (18.18)	<5	0 (0.0)	25 (9.33)	27 (24.11)
		2 to 3 years	N (%)	14 (7.95)	0 (0.0)	0 (0.0)	14 (5.22)	6 (5.36)
		3 to 4 years	N (%)	10 (5.68)	0 (0.0)	0 (0.0)	9 (3.36)	<5

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	7 (2.61)	5 (4.46)
		5 to 10 years	N (%)	10 (5.68)	0 (0.0)	0 (0.0)	7 (2.61)	14 (12.50)
		≥10 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	<5
Polyarteritis nodosa	Total subjects	Number of subjects	N	22	6	0	33 (0.28)	56
	Treatment duration	Number of days	Min	28	53	n/a	40	3
			Q25	78	76	n/a	92	130
			Median	220	126	n/a	246	632
			Q75	1,476	214	n/a	1,048	1,928
			Max	3,151	576	n/a	5,075	5,307
	Treatment duration groups	<1 year	N (%)	13 (59.09)	5 (83.33)	0 (0.0)	20 (60.61)	23 (41.07)
		1 to 2 years	N (%)	0 (0.0)	<5	0 (0.0)	<5	8 (14.29)
		2 to 3 years	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.0)
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.93)
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		5 to 10 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	12 (21.43)
		≥10 years	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	6 (10.71)
Polymyositis	Total subjects	Number of subjects	N	79	<5	0	57	40
	Treatment duration	Number of days	Min	15	n/a	n/a	17	14
			Q25	78	n/a	n/a	50	94
			Median	320	n/a	n/a	100	316
			Q75	1,171	n/a	n/a	463	1,898
			Max	6,946	n/a	n/a	2,430	3,978
	Treatment duration groups	<1 year	N (%)	40 (50.63)	<5	0 (0.0)	40 (70.18)	21 (52.50)
		1 to 2 years	N (%)	12 (15.19)	0 (0.0)	0 (0.0)	7 (12.28)	5 (12.50)
		2 to 3 years	N (%)	5 (6.33)	0 (0.0)	0 (0.0)	5 (8.77)	<5
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	<5
		4 to 5 years	N (%)	<5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		5 to 10 years	N (%)	11 (13.92)	0 (0.0)	0 (0.0)	<5	9 (22.50)
		≥10 years	N (%)	5 (6.33)	0 (0.0)	0 (0.0)	0 (0.0)	<5 (<5)
Pyoderma gangrenosum	Total subjects	Number of subjects	N	28	<5	0	42	17
	Treatment duration	Number of days	Min	3	n/a	n/a	25	29
			Q25	89	n/a	n/a	50	240
			Median	180	n/a	n/a	258	1,710
			Q75	714	n/a	n/a	868	2,387
			Max	3,137	n/a	n/a	3,887	4,411
	Treatment duration groups	<1 year	N (%)	17 (60.71)	<5	0 (0.0)	25 (59.52)	5 (29.41)
		1 to 2 years	N (%)	<5	0 (0.0)	0 (0.0)	5 (11.90)	<5
		2 to 3 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	0 (0.0)
		3 to 4 years	N (%)	<5	0 (0.0)	0 (0.0)	<5	0 (0.0)
		4 to 5 years	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5
		5 to 10 years	N (%)	<5	0 (0.0)	0 (0.0)	6 (14.29)	7 (41.18)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		≥10 years	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5
Rheumatoid arthritis and chronic polyarthritis	Total subjects	Number of subjects	N	452	13	52	468	118
	Treatment duration	Number of days	Min	14	1	1	17	2
			Q25	56	5	37	50	128
			Median	131	15	122	100	507
			Q75	719	67	339	355	1,822
			Max	8,126	944	3,611	6,884	4,991
	Treatment duration groups	<1 year	N (%)	290 (64.16)	12 (92.31)	43 (82.69)	352 (75.21)	50 (42.37)
		1 to 2 years	N (%)	51 (11.28)	0 (0.0)	6 (11.54)	45 (9.62)	15 (12.71)
		2 to 3 years	N (%)	22 (4.87)	<5	<5	22 (4.70)	9 (7.63)
		3 to 4 years	N (%)	21 (4.65)	0 (0.0)	n/a	12 (2.56)	7 (5.93)
		4 to 5 years	N (%)	17 (3.76)	0 (0.0)	<5	11 (2.35)	7 (5.93)
		5 to 10 years	N (%)	37 (8.19)	0 (0.0)	<5	22 (4.70)	24 (20.34)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		≥10 years	N (%)	14 (3.10)	0 (0.0)	0 (0.0)	<5	6 (5.08)
Systemic lupus erythematosus	Total subjects	Number of subjects	N	286	35	16	310	272
	Treatment duration	Number of days	Min	28	1	1	17	4
			Q25	92	4	26	93	172
			Median	350	26	102	224	710
			Q75	1,141	150	297	894	1,542
			Max	8,112	485	1,619	3,880	5,217
	Treatment duration groups	<1 year	N (%)	145 (50.70)	33 (94.29)	13 (81.25)	197 (63.55)	102 (37.50)
		1 to 2 years	N (%)	37 (12.94)	<5	<5	24 (7.74)	35 (12.87)
		2 to 3 years	N (%)	30 (10.49)	0 (0.0)	<5	26 (8.39)	36 (13.24)
		3 to 4 years	N (%)	15 (5.24)	0 (0.0)	0 (0.0)	12 (3.87)	26 (9.56)
		4 to 5 years	N (%)	11 (3.85)	0 (0.0)	<5	18 (5.81)	18 (6.62)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		5 to 10 years	N (%)	37 (12.94)	0 (0.0)	0 (0.0)	28 (9.03)	38 (13.97)
		≥10 years	N (%)	11 (3.85)	0 (0.0)	0 (0.0)	5 (1.61)	17 (6.25)
None of the above/missing	Total subjects	Number of subjects	N	22,171	385	2,155	6,861	13,325
	Treatment duration	Number of days	Min	1	1	1	1	1
			Q25	70	38	80	50	244
			Median	321	120	210	170	1,003
			Q75	1,150	271	663	640	2,487
			Max	8,461	4,516	4,538	6,045	6,022
	Treatment duration groups	<1 year	N (%)	11,596 (52.30)	326 (84.68)	1,322 (61.35)	4,474 (65.21)	4,023 (30.19)
		1 to 2 years	N (%)	2,936 (13.24)	43 (11.17)	342 (15.87)	843 (12.29)	1,659 (12.45)
		2 to 3 years	N (%)	1,899 (8.57)	10 (2.60)	173 (8.03)	492 (7.17)	1,273 (9.55)
		3 to 4 years	N (%)	1,328 (5.99)	<5	112 (5.20)	327 (4.77)	1,019 (7.65)

Indication	Variable name	Variable level		CPRD (UK)	IMASIS (SP)	IPCI (NL)	IQVIA DA Germany	SIDIAP (SP)
		4 to 5 years	N (%)	1,003 (4.52)	<5	72 (3.34)	208 (3.03)	840 (6.30)
		5 to 10 years	N (%)	2,516 (11.35)	<5	128 (5.94)	442 (6.44)	2,668 (20.02)
		≥10 years	N (%)	893 (4.03)	<5	6 (0.28)	75 (1.09)	1,843 (13.83)

n/a = not applicable

12.3 Outcome data

None.

12.4 Other analysis

None.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

14. DISCUSSION

14.1 Key results

The number of incident azathioprine users per database were 692 for IMASIS, 3,020 for IPCI, 11,932 for IQVIA DA Germany, 19,341 for SIDIAP, and 31,857 for CPRD GOLD. Generally, the proportion of females was higher than males, approximately 55% vs. 45%, except for the indication myasthenia gravis where the proportion of males was higher than females (roughly 60% vs. 40%). The median age of incident azathioprine users ranged between 48-53 years and most of the individuals were in the age group of 18 to 44 years, followed by the age group 45 to 64 years. The median age was the highest in individuals with myasthenia gravis, ranging between 66-74 years.

Most incident azathioprine users in this study did not have one of the indications in the 3 months before or 1 month after the index date (55.64-71.36%). IBD was by far the most prevalent indication with rates ranging between 20.7-24.9%, followed by autoimmune hepatitis (2.0-8.7%).

Moreover, the median age in individuals with IBD was much lower than the whole population and varying between 33-43 years compared to 48-53 years.

Overall, the median treatment duration ranged between 90-1019 days in the different databases, where treatment duration was the shortest in IMASIS and the longest in SIDIAP. Between the different indications there were no clear differences in median treatment duration or proportion of individuals per treatment duration group although a treatment duration of 5 years or longer tended to be comparatively frequent in patients with autoimmune hepatitis and myasthenia gravis in CPRD. Among the different duration categories, a high proportion of individuals only had a relatively short treatment duration since they had a treatment duration of less than 1 year (30.4-87.9%) or a treatment duration of 1 to 2 years (9.0-16.2%). However, in SIDIAP and CPRD there was a comparatively high proportion of patients that had a duration of 5 years or longer (34.3% for SIDIAP and 16.6% for CPRD).

Regarding the large-scale characterisation of incident azathioprine users without one of the prespecified indications in the year prior to the index date, prednisone/prednisolone was the most often prescribed drug in the year before index date with rates of 32.8 (IQVIA DA Germany) - 66.4% (CPRD) and mesalamine was also prescribed in all databases (11.4 (IMASIS) - 27.7% (CPRD)). Conditions related to abdominal pain

and IBD were present in the year before index date, most notably Crohn's disease (3.7 (IQVIA DA Germany) - 9.7% (IPCI)) and ulcerative colitis (3.9 (IQVIA DA Germany) - 8.4% (IPCI)).

14.2 Limitations of the research methods

As this is an observational study, there is the potential of misclassification of the exposure of interest. Indeed, with regard to azathioprine use, the recording of the prescription of the drug (e.g. concept id at clinical drug level or at ingredient level), and the prescriptions themselves may vary across databases. In addition, a recording of a prescription or dispensation does not actually mean that the patient took the drug. Moreover, we are restricted by the fact that we can only derive information from the time a patient has in the database, it is possible that we do not capture full information on continued treatment with azathioprine if a patient leaves the database. This could especially play a role in IMASIS (a secondary care database) if a patient gets referred back to primary care and therefore the registrations in the database stop while azathioprine use could continue.

Assumptions around the duration of drug use are unavoidable and might lead to overestimating treatment duration (considering a 30-day drug gap era). The possible overestimation seems limited since it seems unlikely that a patient taking azathioprine, which is a drug that needs to be taken daily, would abstain from taking the medication for more than 30 days. On the other hand, in this current study the follow-up time of the patient in the database is not considered. Therefore, to provide more context to the median treatment duration also the proportion of patients that fall within prespecified treatment duration groups is provided.

For this study, the indication of use is important and predefined indications of use have been identified. Not all indications of interest might be present within the database (i.e. in DP with less granular source coding such as IPCI). For that reason, based on preliminary counts, broader indications were used for some of the indications, for example "hemolytic anemia" instead of "Refractory autoimmune haemolytic anaemia". Nevertheless, in the future it might be interesting to use even more broader definitions of the indication of use (e.g. look for "inflammatory disease of liver" and not necessarily "autoimmune hepatitis"). Even though that broad searches might impose a potential of misclassification, the risk of misclassification is probably minimal since we search in a relatively small window, 3 months before and 1 month after, around the index date (first prescription of azathioprine during study period Also, the large-scale characterisation (looking for top 10 drug and disease codes) might provide insight into the indication of use on top of the indications which have been predefined.). Nonetheless, 51-71% of the patients did still did not have any of the predefined indications for azathioprine. From the results of the large-scale characterisation however, we could not identify disease codes which were not yet part of the predefined cohort definitions for the indications of use. In the individuals without an indication, we did however find a diagnosis of IBD (predominantly Crohn's disease and ulcerative colitis) in the year before index date. This seems to indicate that the diagnosis was not made in the 3 months prior to the date of prescribing of azathioprine but in the period of 3-12 months before index dat. Moreover, in primary care databases such as IPCI, it could be that the specialist first diagnoses and prescribes azathioprine and the follow-up visits and repeat prescriptions are done by the GP and that those are not linked to the diagnosis of IBD.

Moreover, small cell counts may affect the analysis for some subgroup strata. If the numbers are too low (e.g. <5), counts are not disclosed for governance reasons. In general, IPCI and IMASIS had the lowest counts because of the smaller size of the database and therefore also lower counts of incident azathioprine users.

Lastly, the study period is from 2000 until 2023 however not all DPs have that long observation time. For IPCI and SIDIAP, observation period starts from 2006.

14.3 Interpretation

In this study IBD was the most prevalent indication amongst incident azathioprine users with rates ranging between 20.7 (SIDIAP) - 24.9% (IQVIA DA Germany). To our knowledge, there currently is no other research that looks in the characterisation of incident azathioprine users and the indications of use. Therefore, it is not possible to evaluate and compare these rates with other studies and results. This makes it not possible to at this moment place the usage rates and indication in this study in a broader context.

In general, the proportion of azathioprine users that had a disease code for any of the indications aside from IBD were relatively low across all databases. This might be the result of the fact that most of the indications for the use of azathioprine are diagnosed and treated in secondary care as opposed to primary care. This is illustrated for autoimmune hepatitis, the second most common indication in this study. The highest rate for autoimmune hepatitis was 8.7% in IMASIS (covering inpatient hospital care and secondary outpatient care), while in the other databases rates ranged between 2.0 (CPRD) - 4.1% (SIDIAP). Similarly, the rate for SLE, another condition likely treated in secondary care, is also higher in IMASIS than the other databases namely 5.1% vs. 0.5-2.6%. In general, the percentage of individuals without an indication was very high, with the lowest percentage in IMASIS already being 55.6%.

Although the indication of use was missing, when exploring the results of the large-scale characterisation, we observed that conditions related to abdominal pain and IBD were quite often reported in the year prior to index date. Specifically, Crohn's disease (3.7-9.7% in CPRD, IPCI, IQVIA DA Germany SIDIAP) and ulcerative colitis (3.9-8.4% in IPCI, IQVIA DA Germany and SIDIAP) were frequently reported. Since the window for the indication in this study is set at 3 months and 1 month around the index date this would mean that these conditions must occur more than 4 months before the index date. On the other hand, it seems unlikely that a patient with IBD that is going to be treated with azathioprine does not have a contact with a physician in the 4 months before treatment is initiated, or that IBD is diagnosed and treatment with azathioprine is initiated in secondary care before the patients are referred back to primary care. Another explanation could be that the indication of the azathioprine use is registered with the first treatment course. In IBD this for example often would be corticosteroids (i.e. prednisone/prednisolone), which are the most frequently prescribed drug in all databases in the year prior to index date. This could also explain the aforementioned presence of Crohn's disease or ulcerative colitis in the large-scale characterisation of patients without an indication.

Moreover, it should also be mentioned that there are other possible indications for azathioprine use outside the ones that were predefined within the study protocol such as eczema/atopic dermatitis.(35, 36) The large-scale characterisation of conditions on the index date in IQVIA DA Germany also provided possible conditions such as namely interstitial lung disease, fibrosis of lung, sarcoidosis and Sjögren's syndrome. For all these conditions azathioprine has previously been suggested as a possible treatment, however at this moment there is no conclusive evidence for the efficacy of azathioprine.(37-40).

Lastly, in general the overall median treatment duration for all databases, except SIDIAP, was less than 365 days and most people were in the <1 year treatment duration groups. This is somewhat unexpected because azathioprine often is taken long-term for the various indication and therefore longer treatment durations were maybe anticipated more. However, we did not take the follow-up time of the included patients into account, which could have influence on the treatment duration and possibly lead to underestimation. For example, if a person that takes azathioprine for multiple years but only contributes 6 months of database time would be wrongly classified in the <1 year treatment duration group.

14.4 Generalisability

The generalisability of the study results seems relatively good since this study uses data from 5 different databases from 4 countries around Europe. The databases include both primary care and (outpatient) secondary care data, which is the intended population of azathioprine users. However, most of the databases consist of primary care data so (outpatient) secondary care might still be slightly under-represented.

14.5 Other information

None.

15. CONCLUSION

In this study the number of incident azathioprine ranged between 692 to 31,857 patients in the different databases. Azathioprine users were slightly more often female than male, with a median age ranging between 48-53 years. Median treatment duration ranged between 90 to 1,019 days and most patients had a treatment duration of less than 1 year. IBD was most often the indication for azathioprine use, followed by autoimmune hepatitis. In the azathioprine users without an indication prednisone/prednisolone was the most prescribed drug in the year before treatment initiation. Lastly conditions related to abdominal pain and IBD, specifically Crohn's disease and ulcerative colitis, were also often present in the year before treatment initiation in azathioprine users without an indication.

16. REFERENCES

1. Abu-Shakra M, Shoenfeld Y. Azathioprine therapy for patients with systemic lupus erythematosus. Lupus. 2001;10(3):152-3.
2. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. Arthritis Rheum. 1981;24(1):45-8.
3. Casetta I, Iuliano G, Filippini G. Azathioprine for multiple sclerosis. Cochrane Database of Systematic Reviews. 2007(4).
4. de Boer NKH, Peyrin-Biroulet L, Jharap B, Sanderson JD, Meijer B, Atreya I, et al. Thiopurines in Inflammatory Bowel Disease: New Findings and Perspectives. J Crohns Colitis. 2018;12(5):610-20.
5. Gordon PA, Winer JB, Hoogendijk JE, Choy EH. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. Cochrane Database of Systematic Reviews. 2012(8).
6. Palace J, Newsom-Davis J, Lecky B, Group MGS. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Neurology. 1998;50(6):1778-83.
7. Woodland J, De Saintonge DC, Evans S, Sharman V, Currey H. Azathioprine in rheumatoid arthritis: double-blind study of full versus half doses versus placebo. Annals of the Rheumatic Diseases. 1981;40(4):355-9.
8. Björnsson ES, Gu J, Kleiner DE, Chalasani N, Hayashi PH, Hoofnagle JH. Azathioprine and 6-Mercaptopurine-induced Liver Injury: Clinical Features and Outcomes. J Clin Gastroenterol. 2017;51(1):63-9.
9. Koller T, Galambosova M, Filakovska S, Kubincova M, Hlavaty T, Toth J, et al. Drug-induced liver injury in inflammatory bowel disease: 1-year prospective observational study. World J Gastroenterol. 2017;23(22):4102-11.

10. De Gottardi A, Rautou PE, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol Hepatol. 2019;4(5):399-411.
11. EMA. Jayempi (Azathioprine) product information [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/jayempi.
12. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.
13. Carey IM, Nirmalananthan N, Harris T, DeWilde S, Chaudhry UAR, Limb E, et al. Prevalence of co-morbidity and history of recent infection in patients with neuromuscular disease: A cross-sectional analysis of United Kingdom primary care data. PLoS One. 2023;18(3):e0282513.
14. Fahmi A, Wong D, Walker L, Buchan I, Pirmohamed M, Sharma A, et al. Combinations of medicines in patients with polypharmacy aged 65-100 in primary care: Large variability in risks of adverse drug related and emergency hospital admissions. PLoS One. 2023;18(2):e0281466.
15. Wigglesworth S, Neligan A, Dickson JM, Pullen A, Yelland E, Anjuman T, et al. The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data. Seizure. 2023;105:37-42.
16. de Ridder MAJ, de Wilde M, de Ben C, Leyba AR, Mosseveld BMT, Verhamme KMC, et al. Data Resource Profile: The Integrated Primary Care Information (IPCI) database, The Netherlands. Int J Epidemiol. 2022;51(6):e314-e23.
17. Ali MS, Berencsi K, Marinier K, Deltour N, Perez-Guthann S, Pedersen L, et al. Comparative cardiovascular safety of strontium ranelate and bisphosphonates: a multi-database study in 5 EU countries by the EU-ADR Alliance. Osteoporos Int. 2020;31(12):2425-38.
18. Baan EJ, van den Akker ELT, Engelkes M, de Rijke YB, de Jongste JC, Sturkenboom M, et al. Hair cortisol and inhaled corticosteroid use in asthmatic children. Pediatr Pulmonol. 2020;55(2):316-21.
19. Berencsi K, Sami A, Ali MS, Marinier K, Deltour N, Perez-Gutthann S, et al. Impact of risk minimisation measures on the use of strontium ranelate in Europe: a multi-national cohort study in 5 EU countries by the EU-ADR Alliance. Osteoporos Int. 2020;31(4):721-55.
20. Engelkes M, Baan EJ, de Ridder MAJ, Svensson E, Prieto-Alhambra D, Lapi F, et al. Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study. Pediatr Allergy Immunol. 2020;31(5):496-505.
21. James G, Collin E, Lawrance M, Mueller A, Podhorna J, Zaremba-Pechmann L, et al. Treatment pathway analysis of newly diagnosed dementia patients in four electronic health record databases in Europe. Soc Psychiatry Psychiatr Epidemiol. 2021;56(3):409-16.
22. Recalde M, Rodríguez C, Burn E, Far M, García D, Carrere-Molina J, et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol. 2022;51(6):e324-e36.
23. Braeye T, Emborg HD, Llorente-García A, Huerta C, Martín-Merino E, Duarte-Salles T, et al. Age-specific vaccination coverage estimates for influenza, human papillomavirus and measles containing vaccines from seven population-based healthcare databases from four EU countries - The ADVANCE project. Vaccine. 2020;38(16):3243-54.
24. Burn E, Tebé C, Fernandez-Bertolin S, Aragon M, Recalde M, Roel E, et al. The natural history of symptomatic COVID-19 during the first wave in Catalonia. Nat Commun. 2021;12(1):777.
25. Lane JC, Butler KL, Poveda-Marina JL, Martinez-Laguna D, Reyes C, de Bont J, et al. Preschool Obesity Is Associated With an Increased Risk of Childhood Fracture: A Longitudinal Cohort Study of 466,997 Children and Up to 11 Years of Follow-up in Catalonia, Spain. J Bone Miner Res. 2020;35(6):1022-30.
26. Ly NF, Flach C, Lysen TS, Markov E, van Ballegooijen H, Rijnbeek P, et al. Impact of European Union Label Changes for Fluoroquinolone-Containing Medicinal Products for Systemic and Inhalation Use: Post-Referral Prescribing Trends. Drug Saf. 2023;46(4):405-16.

27. Monteagudo M, Nuñez A, Solntseva I, Dhalwani N, Booth A, Barrecheguren M, et al. Treatment Pathways Before and After Triple Therapy in COPD: A Population-based Study in Primary Care in Spain. Arch Bronconeumol (Engl Ed). 2021;57(3):205-13.
28. Ortega Y, Aragonès E, Piñol JL, Basora J, Araujo A, Cabré JJ. Impact of depression and/or anxiety on the presentation of cardiovascular events in a cohort with metabolic syndrome. StreX project: Five years of follow-up. Prim Care Diabetes. 2018;12(2):163-71.
29. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. Bmj. 2018;362:k3359.
30. Recalde M, Davila-Batista V, Díaz Y, Leitzmann M, Romieu I, Freisling H, et al. Body mass index and waist circumference in relation to the risk of 26 types of cancer: a prospective cohort study of 3.5 million adults in Spain. BMC Med. 2021;19(1):10.
31. Troncoso-Mariño A, López-Jiménez T, Roso-Llorach A, Villén N, Amado-Guirado E, Guisado-Clavero M, et al. Medication-related problems in older people in Catalonia: A real-world data study. Pharmacoepidemiol Drug Saf. 2021;30(2):220-8.
32. Rathmann W, Bongaerts B, Carius HJ, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database . Int J Clin Pharmacol Ther. 2018;56(10):459-66.
33. Zappacosta S, Cascarano A, Konrad M, Tanislav C, Kostev K. Association between COVID-19 and subsequent vascular events in primary care patients in Germany. Public Health. 2022;213:107-13.
34. Tanislav C, Rosenbauer J, Zingel R, Kostev K. No increased incidence of venous thrombosis or pulmonary embolism after SARS-CoV-2 vaccination in Germany. Public Health. 2022;207:14-8.
35. Bracho-Borro M, Franco-Ruiz PA, Magaña M. The use of azathioprine in atopic dermatitis: A review. Dermatol Ther. 2022;35(9):e15665.
36. Buckley DA, Baldwin P, Rogers S. The use of azathioprine in severe adult atopic eczema. Journal of the European Academy of Dermatology and Venereology. 1998;11(2):137-40.
37. Francesco L, Iain S, Laura F, Wendy A, Leticia K-D, Christopher JR, et al. Mycophenolate and azathioprine efficacy in interstitial lung disease: a systematic review and meta-analysis. BMJ Open Respiratory Research. 2024;11(1):e002163.
38. Muller-Quernheim J, Kienast K, Held M, Pfeifer S, Costabel U. Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen. European Respiratory Journal.14(5):1117-22.
39. Oldham JM, Lee C, Valenzi E, Witt LJ, Adegunsoye A, Hsu S, et al. Azathioprine response in patients with fibrotic connective tissue disease-associated interstitial lung disease. Respir Med. 2016;121:117-22.
40. van der Heijden EHM, Kruize AA, Radstake TRDJ, van Roon JAG. Optimizing conventional DMARD therapy for Sjögren's syndrome. Autoimmunity Reviews. 2018;17(5):480-92.

17. ANNEXES

Appendix I:

Table S1. Code list for drug of interest.

Concept set name	IDs (including descendants)
Azathioprine	19014878

Table S2. Code list for indication definitions.

Concept set name	Included concepts	IDs (including descendants)
Organ transplantation	Transplantation Transplant follow-up Disorder related to transplantation	4300185 4081759 4179244
Severe rheumatoid arthritis or chronic polyarthritis	Rheumatoid arthritis Chronic polyarthritis	80809 3168431
Inflammatory bowel diseases	Inflammatory bowel disease Ulcerative colitis Crohn's disease	4074815 81893 201606
Autoimmune hepatitis	Autoimmune hepatitis	200762
Systemic lupus erythematosus	Systemic lupus erythematosus Cutaneous lupus erythematosus	257628 4324123
Dermatomyositis	Dermatomyositis	80182
Polyarteritis nodosa	Polyarteritis nodosa	320749
Pemphigus vulgaris and bullous pemphigoid	Pemphigus Bullous pemphigoid	135338 4298692
Behcet's disease	Behcet's syndrome	436642
Refractory autoimmune haemolytic anaemia	Hemolytic anemia	435503
Refractory idiopathic thrombocytopenic purpura	Immune thrombocytopenia Thrombocytopenic purpura	4103532 4119134
Polymyositis	Polymyositis	80800
Pyoderma gangrenosum	Pyoderma gangrenosum	133283
Multiple sclerosis	Multiple sclerosis	374919
Myasthenia gravis	Myasthenia gravis	76685

Appendix II: Additional tables and figures

Table S3. Large-scale characterisation of individuals without a prespecified indication initiating treatment with azathioprine in terms of drugs on index date [0, 0].

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (UK)	
Drug	N=22,171 (100.0 %)	Drug	N=385 (100.0 %)	Drug	N=2,155 (100.0 %)	Drug	N=6,861 (100.0 %)	Drug	N=13,325 (100.0 %)
Azathioprine	22,171 (100.0)	Azathioprine	385 (100.0)	Azathioprine	2,155 (100.0)	Azathioprine	6,861 (100.0)	Azathioprine	13,325 (100.0)
Prednisolone	9,628 (43.43)	Prednisone	114 (29.61)	Prednisolone	895 (41.53)	Prednisolone	2,155 (31.41)	Prednisone	6,030 (45.25)
Omeprazole	4,560 (20.57)	Calcium carbonate	61 (15.84)	Mesalamine	381 (17.68)	Pantoprazole	1,199 (17.48)	Omeprazole	5,093 (38.22)
Cholecalciferol	4,446 (20.05)	Acetaminophen	50 (12.99)	Pantoprazole	371 (17.22)	Cholecalciferol	1,044 (15.22)	Calcium carbonate	3,742 (28.08)
Mesalamine	4,304 (19.41)	Cholecalciferol	45 (11.69)	Omeprazole	334 (15.50)	Mesalamine	749 (10.92)	Cholecalciferol	3,047 (22.87)

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (UK)	
Calcium carbonate	4,194 (18.92)	Omeprazole	44 (11.43)	Budesonide	303 (14.06)	Levothyroxine	595 (8.67)	Acetaminophen	2,548 (19.12)
Acetaminophen	3,396 (15.32)	Pantoprazole	31 (8.05)	Alendronate	261 (12.11)	Calcium	488 (7.11)	Mesalamine	2,500 (18.76)
Alendronate	3,007 (13.56)	Sodium chloride	26 (6.75)	Metoprolol	185 (8.58)	Ramipril	487 (7.10)	Budesonide	1,469 (11.02)
Lansoprazole	2,502 (11.29)	Budesonide	23 (5.97)	Sodium chloride	181 (8.40)	Bisoprolol	375 (5.47)	Hydrochlorothiazide	1,036 (7.77)
Aspirin	2,392 (10.80)	Methylprednisolone	19 (4.94)	Potassium chloride	181 (8.40)	Hydrochlorothiazide	369 (5.38)	Enalapril	1,013 (7.60)

Table S4. Large-scale characterisation of individuals without a prespecified indication initiating treatment with azathioprine in terms of conditions on index date [0, 0].

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
Condition	**N=22,171 (100.0%)**	**Condition**	**N=385 (100.0%)**	**Condition**	**N=2,155 (100.0%)**	**Condition**	**N=6,861 (100.0%)**	**Condition**	**N=13,325 (100.0%)**
Blood pressure finding	743 (3.35)	Atherosclerosis of artery of lower limb	<5	Renal impairment	13 (0.60)	Essential hypertension	234 (3.41)	n/a	n/a
n/a	n/a	Urinary tract infectious disease	<5	Type 2 diabetes mellitus	12 (0.56)	Illness	143 (2.08)	n/a	n/a
n/a	n/a	Chronic hepatitis C	<5	Disorder of musculoskeletal system	12 (0.56)	Interstitial lung disease	139 (2.03)	n/a	n/a
n/a	n/a	n/a	n/a	Essential hypertension	11 (0.51)	Fibrosis of lung	104 (1.52)	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	Disorder of connective tissue	86 (1.25)	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	Sarcoidosis	73 (1.06)	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	Inflammatory disorder of	63 (0.92)	n/a	n/a

CPRD (UK)		IMASIS (SP)		IPCI (NL)		IQVIA DA Germany		SIDIAP (SP)	
						digestive tract			
n/a	n/a	n/a	n/a	n/a	n/a	Osteoporosis	57 (0.83)	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	Arteritis	54 (0.79)	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	Sjögren's syndrome	53 (0.77)	n/a	n/a

n/a = not applicable

Appendix III: Other Additional Information

None.