DARWIN EU® Coordination Centre

Study Report

01/12/2023

Version 2.0

TABLE OF CONTENTS

DOCUMENT HISTORY

Version	Date	Description
V1.0	31/10/2023	**Final Version for EMA review**
V2.0	01/12/2023	**Final Version with feedback from EMA incorporated**

Study Title	DARWIN EU® - Treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus
Study Report Version identifier	V2.0
Dates Study Report updates	01/12/2023
EU PAS register number	EUPAS106436
Active substance	List of pharmacotherapeutic group(s)) and active substance(s) subject to the study Hydroxychloroquine Methotrexate Azathioprine Mycophenolate mofetil Cyclophosphamide Tacrolimus Cyclosporine Voclosporin Rituximab Belimumab Systemic glucocorticoids
Medicinal product	N/A
Research question and objectives	The overall objective of this study is to characterise paediatric and adult patients with systemic lupus erythematosus (SLE) diagnosed in the period 2013-2022. The specific objectives of this study are: 1. To describe demographic and clinical characteristics of paediatric patients with SLE at the time of diagnosis. 2. To describe demographic and clinical characteristics of adult patients with SLE at the time of diagnosis. 3. To describe the treatment patterns from diagnosis until end of

	follow up for paediatric patients newly diagnosed with SLE. 4. To describe the treatment patterns from diagnosis until end of follow up for adult patients newly diagnosed with SLE. 5. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in paediatric patients. 6. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in adult patients. All results will be reported by country/database, overall and stratified by age and sex when possible.
Country(-ies) of study	France, Germany, Spain, United Kingdom
Author	Eng Hooi (Cheryl) Tan (c.tan@darwin-eu.org); Daniel Prieto-Alhambra (d.prietoalhambra@darwin-eu.org)

1. DESCRIPTION OF STUDY TEAM

A table with the description of the Study team (by role, name and organisation). For off-the-shelf studies or routine repeated studies, it might be that a more lean composition of the study team is suggested (e.g. without need of Statistician, Clinical Domain Expert, etc)

Study team Role	Names	Organisation
Study Project Manager/Principal Investigator	Eng Hooi (Cheryl) Tan Daniel Prieto-Alhambra	University of Oxford University of Oxford/Erasmus MC
Epidemiologist	Eng Hooi (Cheryl) Tan Daniel Prieto-Alhambra	University of Oxford University of Oxford/Erasmus MC
Clinical Domain Expert	Daniel Prieto-Alhambra	University of Oxford/Erasmus MC
Data Analysts/statisticians	Martí Català Sabaté Mike Du	University of Oxford University of Oxford
Data Partner*	**Names**	**Organisation – Database**
Local Study Coordinator/Data Analyst	James Brash Hanne van Ballegooijen Núria Mercadé Talita Duarte-Salles Miguel-Angel Mayer Angela Leis Juan Manuel Ramirez Romain Griffier Antonella Delmestri Hezekiah Omulo Wai Yi (Teen) Man	IQVIA - DA Germany IQVIA - DA Germany IDIAPJGol - SIDIAP IDIAPJGol - SIDIAP PSMAR - IMASIS PSMAR - IMASIS PSMAR - IMASIS University of Bordeaux - CDWBordeaux University of Oxford – CPRD GOLD University of Oxford – CPRD GOLD University of Oxford – CPRD GOLD

*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

This study was conducted using routinely collected health data from 5 databases in 4 European countries. All databases were previously mapped to the OMOP CDM.

Data sources:

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
4. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France

5. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK)

Detailed information on the selected data sources and their ability to answer the study research questions are described in Table 1.

Table 1. Description of the selected Data Sources

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Latest observation period end date	Ability to answer study objectives
DE	IQVIA DA Germany	Covers primary care and outpatient specialist setting with information on SLE diagnoses and treatment.	Primary care and outpatient specialist care	EHR	8.5 million	01/04/2023	1 to 6
ES	SIDIAP	Covers primary care setting with a proportion with hospital linkage, data on SLE diagnoses.	Primary care with hospital linkage	EHR	5.8 million	30/06/2022	1 to 6
ES	IMASIS	Covers secondary care setting, database has information on SLE diagnosis and treatments in the in- and outpatient settings	Secondary care (in and outpatients)	EHR	0.6 million	13/05/2023	2, 4, 6
FR	CDWBordeaux	Covers secondary care setting, database has information on SLE diagnosis and in-hospital treatments	Secondary care (in and outpatients)	EHR	1.9 million	02/08/2023	1 to 6
UK	CPRD GOLD	Covers primary care setting, database has information on SLE diagnosis and treatments	Primary care	EHR	3.1 million	15/12/2022	1 to 6

DE = Germany, ES = Spain, FR = France, NL = The Netherlands, UK = United Kingdom, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS = Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CDWBordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD = Clinical Practice Research Datalink.

3. ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY REPORT)

Sections included in abstract are: title, rationale and background, research question and objectives, study design (see D1.3.8.1 Draft Catalogue of Data analytics), Setting, Subjects and study size (including drop-out), population, variables, results and discussion.

Title

DARWIN EU® - Treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus

Rationale and Background

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder of connective tissue characterized by autoantibodies that target nuclear antigens, remissions and flares, and a highly variable clinical presentation, disease course, and prognosis. The disease course is more severe in childhood-onset compared to adult-onset SLE, with higher prevalence of morbidities and lower survival rates.

Therefore, to review new drug applications in this disease area, it would be important for the European Medicines Agency (EMA) to understand the current clinical practice of treating SLE in paediatric population and differences with the treatment in adult population.

Research question and Objectives

The overall objective of this study is to characterise paediatric and adult patients with SLE diagnosed in the period 2013-2022, and to study the treatments they received in this same period.

The specific objectives of this study are:

1. To describe demographic and clinical characteristics of paediatric patients with SLE at the time of diagnosis.
2. To describe demographic and clinical characteristics of adult patients with SLE at the time of diagnosis.
3. To describe the treatment patterns from diagnosis until end of follow up for paediatric patients newly diagnosed with SLE.
4. To describe the treatment patterns from diagnosis until end of follow up for adult patients newly diagnosed with SLE.
5. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in paediatric patients.
6. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in adult patients.

All results were reported by country/database, overall and stratified by age and sex when possible.

Research Methods

Study design

A retrospective cohort study of all patients newly diagnosed with SLE was conducted. For the description of each treatment objective, a new drug user cohort was used to characterise patient-level SLE drug utilisation.

Population

The source population included all individuals eligible in the database between the patient selection period, which is 01/01/2013 and 180 days prior to the end of available data in each database. Eligibility criteria were applied for each study objective:

New diagnosis cohort

- First diagnosis of SLE in database during patient selection period

- At least 365 days of prior history available before date of first SLE diagnosis

In addition to the criteria above, the paediatric new diagnosis cohort (Cohort 1, Objectives 1 and 3) is aged < 18 years at date of first SLE diagnosis; the adult new diagnosis cohort (Cohort 2, Objectives 2 and 4) is aged ≥ 18 years at date of first SLE diagnosis.

New user cohort

- First diagnosis of SLE in database during patient selection period

- At least 365 days of prior history available before date of first SLE diagnosis

- Initiation of SLE treatment of interest after first diagnosis of SLE

- At least 365 days of washout period at treatment ingredient level prior to date of initiation of SLE treatment of interest

In addition to the criteria above, the paediatric new user cohort (Cohort 3, Objective 5) is aged < 18 years at date of first SLE diagnosis; the adult new user cohort (Cohort 4, Objective 6) is aged ≥ 18 years at date of first SLE diagnosis.

Variables

The main exposure of interest is the treatment of SLE: treatment/s initiated after new diagnosis of SLE. A pre-specified list of SLE treatments was generated (objectives 3, 4, 5, and 6).

All co-morbidities and co-medications were used for large-scale patient characterisation, identified as concept/code and descendants. A separate list of pre-specified co-morbidities and co-medications of interest for patients with SLE was described.

Data sources

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany – primary care and specialist data
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain – primary care data linked with hospital discharge.
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain – hospital data
4. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France – hospital data
5. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK) – primary care data

Sample size

No sample size has been calculated as this is a descriptive Disease Epidemiology Study where we are interested in the characteristics of all incident SLE patients. Prior to study initiation, feasibility counts were generated in the general population in each database.

Data analyses

Large-scale patient-level characterisation was conducted (objectives 1 and 2). Medical condition and medication use history was reported at any time and 365 days prior to index date, respectively.

The number and percentage of patients receiving each of a pre-specified list of SLE treatments and treatment combinations (objectives 3 and 4) was described. Additionally, sunburst plots and Sankey diagrams were used to describe treatment patterns and sequences over time (objectives 3 and 4).

For the new user cohort (objectives 5 and 6), the index date is the initiation of SLE treatment after SLE diagnosis. Treatment duration, initial dose/strength, cumulative dose, number of prescriptions were estimated for new users of each SLE treatments at the ingredient level.

For all continuous variables, median with interquartile range were reported. For all categorical analyses, number and percentages were reported. A minimum cell count of 5 will be used when reporting results, with any smaller counts reported as "<5". All analyses will be reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached). Additionally, to capture treatments availability and changes over time, sunburst plots, Sankey diagrams were further stratified by 5-year periods (2013-2017 and 2018-2022).

Results

We included 699 patients in CDWBordeaux, 1,555 in CPRD GOLD, 295 in IMASIS, 2,744 in IQVIA Germany DA, and 5,964 in SIDIAP for the new diagnosis cohort.

In the paediatric SLE cohort, 66% to 83% were female, with median age of 12 to 16 years. The most common comorbidities were asthma (6-15%), pneumonia (10-13%), anxiety (8-13%), and other autoimmune disease (3-16%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (35-38%) and systemic antibacterials (25-45%). In the adult SLE cohort, 80% to 88% were female, with median age of 49 to 54 years. The most common comorbidities were other autoimmune disease (9-35%), hypertension (15-27%), anxiety/depressive disorder (6-27%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (13-57%) and systemic antibacterials (8-53%).

Among the paediatric cohort, the most frequent treatments within the first year of diagnosis were hydroxychloroquine (9-62%), glucocorticoids (12-62%), and mycophenolate mofetil (5-46%) across all databases. Use of azathioprine (4%) and methotrexate (2%) was also observed in SIDIAP.

Among the adult cohort, the most frequent treatments within the first year of diagnosis were hydroxychloroquine (13-49%) and glucocorticoids (18-42%). The third most frequent treatment was mycophenolate mofetil (6%) in CDWBordeaux and methotrexate (4-7%) in all other databases.

Secondly, we included 406 patients in CDWBordeaux, 1,026 in CPRD GOLD, 209 in IMASIS, 999 in IQVIA Germany DA, and 3,047 in SIDIAP for the new user cohort.

In paediatric patients using hydroxychloroquine, median duration was 8 to 501 days, median initial daily dose ranged from 199 to 300 mg, median cumulative dose ranged from 20,000 to 116,600 mg. For prednisone/prednisolone, median duration was 13 to 246 days, median initial daily dose ranged from 10 to 60 mg, median cumulative dose ranged from 775 to 2,150 mg.

In adult patients using hydroxychloroquine, median duration was 4 to 485 days, median initial daily dose ranged from 13 to 400 mg, median cumulative dose ranged from 600 to 130,051 mg. For prednisone/prednisolone, median duration was 4 to 111 days, median initial daily dose ranged from 2 to 40 mg, median cumulative dose ranged from 20 to 1,038 mg.

Discussion

The characteristics of SLE patients in both paediatric and adult cohort were similar with respect to majority being female, and frequently used medications. Anxiety and other autoimmune disease were among the most frequent comorbidities in both groups. The most frequent treatments were hydroxychloroquine and

glucocorticoids in both groups, with a higher proportion of these treatments being used in paediatric patients, as adults were treated with a wider range of treatments such as methotrexate. SLE led to longer duration and higher doses of systemic glucocorticoid use in children vs adult patients, probably due to the lack of alternative options, like methotrexate.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
ADHD	Attention Deficit Hyperactivity Disorder
CDM	Common Data Model
CDWBordeaux	Clinical Data Warehouse of Bordeaux University Hospital
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DMARD	Disease-modifying antirheumatic drug
DOI	Declaration Of Interests
DRE	Digital Research Environment
DUS	Drug utilisation study
EHR	Electronic Health Records
EMA	European Medicines Agency
EULAR	European Alliance of Associations for Rheumatology
GERD	Gastro-esophageal reflux disease
GP	General Practitioner
IMASIS	Institut Municipal Assistència Sanitària Information System
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PSMar	Parc Salut Mar
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SLE	Systemic lupus erythematosus
SNOMED	Systematized Nomenclature of Medicine

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	01 Dec 2023	All	Update	Update following EMA's assessment

2	Date	Text	Text	Text
…	Date	Text	Text	Text

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINE (actual)
Draft Study Protocol	20 July 2023	20 July 2023
Final Study Protocol	18 August 2023	18 August 2023
Creation of Analytical code	August 2023	August 2023
Execution of Analytical Code on the data	September/October 2023	September/October 2023
Interim Study Report (if applicable)	Not applicable	Not applicable
Draft Study Report	31 October 2023	31 October 2023
Final Study Report	30 November 2023	01 December 2023
Draft Manuscript (if agreed on)	Not applicable	Not applicable
Final Manuscript (if agreed on)	Not applicable	Not applicable

7. RATIONALE AND BACKGROUND

Systemic SLE erythematosus (SLE) is a multisystem autoimmune disorder of connective tissue characterized by autoantibodies that target nuclear antigens, remissions and flares, and a highly variable clinical presentation, disease course, and prognosis. The disease course is more severe in childhood-onset compared to adult-onset SLE, with higher prevalence of morbidity and lower survival rates (1).

The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend hydroxychloroquine as first line treatment of adult SLE (2). Glucocorticoids provide rapid symptomatic relief, but long-term safety concerns limit their use. The guidelines also recommend the addition of a disease-modifying antirheumatic drug (DMARD) or immunosuppressant to control disease flares and facilitate glucocorticoid tapering (2). Examples of DMARDs often used are methotrexate, azathioprine, mycophenolate mofetil, or cyclophosphamide. Biological agents such as belimumab should be considered in extrarenal disease, while rituximab might be used off-label in patients with refractory or severe disease, as a result of negative clinical trial outcomes in terms of efficacy (2, 3). Calcineurin inhibitors are recommended as monotherapy or in combination with mycophenolate mofetil in patients at high risk of renal involvement (2). In contrast to adult SLE, there is limited good quality evidence on the treatment of

childhood SLE. A European-wide panel of 16 paediatric rheumatologists recommended routine treatment using hydroxychloroquine (4) with the addition of DMARDs if disease cannot be adequately controlled with hydroxychloroquine and corticosteroid tapering. Rituximab was used in a limited number of cases (4).

Therefore, to review new drug applications, it would be important for the European Medicines Agency (EMA) to understand the current clinical practice of treating SLE in paediatric population and differences with the treatment in adult population.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study is to characterise paediatric and adult patients with SLE diagnosed in the period 2013-2022.

The specific objectives of this study are:

1. To describe demographic and clinical characteristics of paediatric patients with SLE at the time of diagnosis.
2. To describe demographic and clinical characteristics of adult patients with SLE at the time of diagnosis.
3. To describe the treatment patterns from diagnosis until end of follow up for paediatric patients newly diagnosed with SLE.
4. To describe the treatment patterns from diagnosis until end of follow up for adult patients newly diagnosed with SLE.
5. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in paediatric patients.
6. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in adult patients.

All results were reported by country/database, overall and stratified by age and sex when possible.

Table 2: Primary and secondary research questions and objective

Objective:	1. To describe demographic and clinical characteristics of paediatric patients with SLE at the time of diagnosis. 2. To describe demographic and clinical characteristics of adult patients with SLE at the time of diagnosis. 3. To describe the treatment patterns from diagnosis until end of follow up for paediatric patients newly diagnosed with SLE. 4. To describe the treatment patterns from diagnosis until end of follow up for adult patients newly diagnosed with SLE. 5. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in paediatric patients. 6. To describe the use of treatment (including treatment duration, cumulative dose, number of repeated prescriptions for each medication) initiated after a diagnosis of SLE in adult patients.
Hypothesis:	N/A

Population ***(mention key inclusion-exclusion criteria):***	All individuals with a first diagnosis of SLE identified in the database between the patient selection period, which is 01/01/2013 and 180 days prior to the end of available data in each database. Additional eligibility criteria were applied for each study objective: **New diagnosis cohort** - First diagnosis of SLE in database during patient selection period - At least 365 days of prior history available before date of first SLE diagnosis In addition to the criteria above, the paediatric new diagnosis cohort (Cohort 1, Objectives 1 and 3) is aged < 18 years at date of first SLE diagnosis; the adult new diagnosis cohort (Cohort 2, Objectives 2 and 4) is aged ≥ 18 years at date of first SLE diagnosis. **New user cohort** - First diagnosis of SLE in database during patient selection period - At least 365 days of prior history available before date of first SLE diagnosis - Initiation of SLE treatment of interest after first diagnosis of SLE - At least 365 days of washout period at treatment ingredient level prior to date of initiation of SLE treatment of interest In addition to the criteria above, the paediatric new user cohort (Cohort 3, Objective 5) is aged < 18 years at date of first SLE diagnosis; the adult new user cohort (Cohort 4, Objective 6) is aged ≥ 18 years at date of first SLE diagnosis.
Exposure:	SLE treatments [hydroxychloroquine, systemic glucocorticoids, methotrexate, azathioprine, calcineurin inhibitors (tacrolimus, cyclosporine, voclosporin), mycophenolate, cyclophosphamide, rituximab, belimumab]
Comparator:	N/A
Outcome:	N/A
Time ***(when follow up begins and ends):***	For objectives 1 to 4, follow-up started from date of first SLE diagnosis until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death. For objectives 5 and 6, follow-up started from date of first SLE treatment after SLE diagnosis until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death.
Setting:	Inpatient and outpatient setting from 5 databases in 4 European countries.
Main measure of effect:	Proportions of patients on treatment types and sequences, patient-level drug utilisation.

9. RESEARCH METHODS

9.1 Study Type and Study Design

This was a **patient-level characterisation** and **drug utilisation study** (DUS) classified as "off-the-shelf" (C1) and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses. A retrospective cohort study of all incident SLE cases was conducted.

Table 3. Description of Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Patient-level characterisation and DUS	Cohort analysis New drug/s user cohort	Off-the-shelf (C1)

9.2 Study Setting and Data Sources

This study was conducted using routinely collected health data from 5 databases in 4 European countries. All databases were previously mapped to the OMOP CDM.

Data sources:

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
4. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
5. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK)

We selected 5 out of the 10 databases onboarded in DARWIN EU® in 2022. The selection of databases for this study was performed based on data reliability and relevance for the proposed research question, as well as sufficient coverage of the paediatric population. The selected databases fulfil the criteria required for a patient-level characterisation study allowing for large-scale characterisation, while covering different settings and regions of Europe.

Complete hospital-based SLE treatment data (needed for objectives 3, 4, 5, and 6) was available in all databases except CPRD (UK) and SIDIAP (Spain). A proportion of SIDIAP database had linkage to hospital data to allow for more accurate characterisation, but data on inpatient treatments is not available. In turn, any potential outpatient therapies were captured in these primary care datasets. In IMASIS, there were small numbers of paediatric patients with SLE, therefore the objectives associated with this population cannot be answered by this database.

Detailed information on the selected data sources and their ability to answer the study research questions are described in **Table 1** in Section 2. Data Sources.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings (5). Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to General, Orthopaedic Surgery, Otolaryngology, Dermatology, Obstetrics/Gynaecology, Neurology and Psychiatry, Paediatric, Urology, Cardiology, Gastroenterology, Pulmonary and Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies. The analysis was run on a version of the database that included GP and all specialties, i.e. a combined data set.

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

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams, consisting of GPs, nurses and non-clinical staff (6). The Catalan Health Institute manages 328 out of 370 such Primary Care Teams with a coverage of 5.8M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 15 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

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 (7). 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, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 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 anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures) (https://www.chu-bordeaux.fr/). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and

administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).

Clinical Practice Research Datalink GOLD, United Kingdom

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD (8) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 21 million patients, including 3.1 million currently registered patients (9). Access to CPRD GOLD data requires approval via the Research Data Governance Process.

9.3 Study Period

The study period was from 01/01/2013 to 180 days prior to last observation date in each of the data sources (see **Table 4** for more details).

Table 4. Study period for each database

Country	Name of Database	Study period start	Latest observation period end date	Study period end
DE	IQVIA DA Germany	01/01/2013	01/04/2023	01/10/2022
ES	SIDIAP		30/06/2022	30/12/2021
ES	IMASIS		13/05/2023	13/11/2022
FR	CDWBordeaux		02/08/2023	02/02/2023
UK	CPRD GOLD		15/12/2022	15/06/2022

DE = Germany, ES = Spain, FR = France, NL = The Netherlands, UK = United Kingdom, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS = Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CDWBordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD = Clinical Practice Research Datalink.

9.4 Follow-up

For objectives 1 to 4, follow-up started from date of first SLE diagnosis until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death.

For objectives 5 and 6, follow-up started from date of first SLE treatment after SLE diagnosis until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death.

9.5 Study Population with in and exclusion criteria

The study population included all individuals with a first diagnosis of SLE identified in the database during the patient selection period, which is between 01/01/2013 and 180 days prior to the end of latest observation date in each database. The index dates are defined in **Table 5**.

For this study, patients will be identified based on a record indicating a diagnosis of SLE. Conditions in the OMOP CDM use the Systematized Nomenclature of Medicine (SNOMED) as the standard vocabulary for diagnosis codes. A code list is provided in **Appendix 1 Table 1**

The following eligibility criteria will be applied for each study objective (see Inclusion criteria in **Table 6**):

Objectives 1 and 3

Cohort 1 – New diagnosis cohort (paediatric)

- Aged < 18 years

- First diagnosis of SLE in database during patient selection period

- At least 365 days of prior history available before date of first SLE diagnosis

Objectives 2 and 4

Cohort 2 – New diagnosis cohort (adult)

- Aged ≥ 18 years

- First diagnosis of SLE in database during patient selection period

- At least 365 days of prior history available before date of first SLE diagnosis

Objective 5

Cohort 3 – New user cohort (paediatric)

- Aged < 18 years

- First diagnosis of SLE in database during patient selection period

- At least 365 days of prior history available before date of first SLE diagnosis

- Initiation of SLE treatment of interest after first diagnosis of SLE

- At least 365 days of washout period at treatment ingredient level prior to date of initiation of SLE treatment of interest

Objective 6

Cohort 4 – New user cohort (adult)

- Aged ≥ 18 years

- First diagnosis of SLE in database during patient selection period

- At least 365 days of prior history available before date of first SLE diagnosis

- Initiation of SLE treatment of interest after first diagnosis of SLE

- At least 365 days of washout period at treatment ingredient level prior to date of initiation of SLE treatment of interest

Table 5: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description	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
New diagnosis cohort (objectives 1 to 4)	Date of first SLE diagnosis	Single entry	Incident	Any time prior to SLE diagnosis	IP, OP, OT	SNOMED	Any	SLE diagnosis	N/A	N/A
New user cohort (objectives 5 and 6)	Date of initiation of SLE treatment after first SLE diagnosis	Single entry	Incident	365 days prior to SLE treatment	IP, OP, OT	RxNorm	N/A	SLE treatment after first SLE diagnosis	N/A	N/A

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

Table 6. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Prior database history of 365 days (objectives 1 to 4)	Study participants were required to have 365 days of prior history observed before contributing observation time	After index date was determined	365 days	IP, OP, OT	N/A	N/A	All study participants with first SLE diagnosis	N/A	N/A
New user of SLE treatment (objectives 5 and 6)	Only participants with no use of SLE treatment at the ingredient level in the 365 days prior to initiation of SLE treatment (index date) were included	After index date was determined	365 days	IP, OP, OT	RxNorm	N/A	All study participants with first SLE diagnosis	N/A	N/A

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

9.6 Variables

9.6.1 Exposure/s

SLE treatments will include hydroxychloroquine, systemic glucocorticoids, methotrexate, azathioprine, calcineurin inhibitors (tacrolimus, cyclosporine, voclosporin), mycophenolate, cyclophosphamide, rituximab, belimumab. For the new diagnosis cohort, no washout period will be applied. Treatment patterns of SLE drugs of interest will be described after first diagnosis of SLE. For the new user cohort, washout period of 365 days at the ingredient level will be applied after first diagnosis of SLE, therefore it will not include patients who are prevalent users of treatment, if there are treatments initiated before diagnosis of SLE is recorded. Please see **Appendix 1 Table 2** for a list of codes to identify these treatments.

9.6.2 Outcome/s

Not applicable

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

Age at SLE diagnosis was calculated. The following age grouping was used: 0-4; 5-12; 13-17; 18-39; 40-49; 50-59; 60-69; 70 and over. The sex (male/ female) of study participants was also be reported.

All co-morbidities and co-medications recorded prior and at index date were used for large-scale patient characterisation, identified as concept/code and descendants (**Table 7**). Additionally, a list of pre-specified co-morbidities and co-medications relevant for patients with SLE was described. These include:

- Medical History: Anxiety, Asthma, other Autoimmune disease (Type 1 Diabetes Mellitus, Rheumatoid arthritis, Psoriasis, Psoriatic Arthritis, Multiple sclerosis, Addison's disease, Graves' disease, Sjogren's syndrome, Hashimoto thyroiditis, Myasthenia gravis, Vasculitis, Pernicious anemia, Celiac disease, Scleroderma, Sarcoidosis, Ulcerative colitis, Crohn's disease), Chronic Kidney Disease, Chronic Liver disease, Chronic obstructive pulmonary disease (COPD), Diabetes mellitus, Dementia, Depressive disorder, Gastro-esophageal reflux disease (GERD), Heart failure, Human Immunodeficiency Virus (HIV), Hypertension, Hypothyroidism, Inflammatory bowel disease, Malignant neoplastic disease, Myocardial infarction, Osteoporosis, Pneumonia, Psoriasis, Rheumatoid arthritis, Stroke, Venous thromboembolism
- Medication use: Agents acting on the renin-angiotensin system, Antibacterials for systemic use, Antidepressants, Antiepileptics, Antiinflammatory and antirheumatic products, Antineoplastic agents, Antithrombotic agents, Beta blocking agents, Calcium channel blockers, Diuretics, Drugs for acid related disorders, Drugs for obstructive airway diseases, Drugs used in diabetes, Immunosuppressants, Lipid modifying agents, Opioids, Psycholeptics, Psychostimulants

Table 7. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations:	Measurement characteristics /validation	Source for algorithm
Co-morbidities	Large-scale patient-level characterisation with regard to underlying comorbidities	Counts	At index date (ID); Before ID: 30 to 1 day, 365 to 31 days at any time and up to 366 days; After ID: 1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 365 days, 366+ days	OP, IP, OT	SNOMED	N/A	N/A	N/A	N/A
Concomitant medication	Large-scale patient-level characterisation with regard to use of concomitant drugs	Counts	At index date (ID); Before ID: 30 to 1 day, 365 to 31 days at any time and up to 366 days; After ID: 1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 365 days, 366+ days	OP, IP, OT	RxNorm	N/A	N/A	N/A	N/A

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

9.7 Study size

No sample size was calculated as this is a descriptive Disease Epidemiology Study with the objective of characterising all available incident SLE patients. Prior to the development of the study protocol, feasibility counts were generated for this study in the general population of the respective databases.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were
performed. After all the 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 against the OMOP-CDM 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 in the Digital Research Environment (DRE) and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

9.9.1 Main Summary Measures

For all continuous variables, median with interquartile range were reported. For all categorical analyses, number and percentages were reported.

9.9.2 Main Statistical Methods

This was a **patient-level characterisation** and **drug utilisation study** (DUS) classified as “off-the-shelf” (C1) and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses (**Table 8**).

Table 8. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Patient-level characterisation and DUS	Off-the-shelf (C1)	- Large-scale characterisation - Patient-level characteristics - Standard care description - Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
		dose/strength - Estimation of minimum, p25, median, p75, and maximum treatment duration

R-packages

We used R packages for the patient-level characterization of demographics and clinical characteristics; "DrugUtilisation" (https://github.com/darwin-eu/DrugUtilisation) for the patient-level drug utilisation analyses including patient-level characterisation and treatment duration, cumulative dose, number of repeated prescriptions for each medication; "TreatmentPatterns" (https://github.com/darwin-eu-dev/TreatmentPatterns) for the patient-level characterisation of treatments including combination and sequence of therapy. ion. The study package is available via https://github.com/darwin-eu-studies/P2-C1-006-SLE-Diagnostics/

Patient-level characterisation

Large-scale patient-level characterisation was conducted (objectives 1 and 2). Age and sex at time of SLE diagnosis was described for each of the generated study cohorts. The index date was the date of the first SLE diagnosis for each patient. Medical condition and medication use history was assessed for anytime – and up to 365 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. We reported medical condition and medication use for 1 to 30, 31 to 90, 91 to 180, 181 to 365 days, and 366 days to anytime post index date. These time windows were defined based on the options currently available in the standard analytical tools that were used in this project. For the main study report, medical conditions any time prior to index date and medication use 365 days prior to index date were presented. The other time windows is available in an interactive dashboard. Co-variates in a summary baseline characteristics table were pre-defined as described in section 9.6.3.

Patient-level drug utilisation

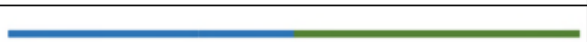
The number and percentage of patients receiving each of a pre-specified list of SLE treatments (see Appendix 1 Table 1) and treatment combinations (objectives 3 and 4) were described per calendar year. Additionally, sunburst plots and Sankey diagrams were used to describe treatment patterns and sequences over time (objectives 3 and 4). Sankey diagrams were censored at end of treatment or end of follow-up as described in section 9.4.

For the new user cohort (objectives 5 and 6), the index date is the initiation of each SLE treatment after SLE diagnosis. Treatment duration, initial dose/strength, cumulative dose, number of prescriptions were estimated for new users of SLE treatments at the ingredient level.

Drug exposure calculations

Drug eras were defined as follows: Exposure starts at date of the first prescription after the first SLE diagnosis. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM. Subsequent prescriptions for the same drug will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug exposures were merged into one continuous drug era if the distance in days between end of the first exposure and start of the second exposure is ≤ 30 days. The time between the two joined exposures was considered as exposed to the first era and the corresponding dose of the first era as shown in 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"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

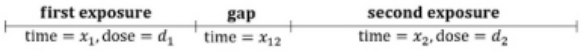


Figure 1. Gap era joint mode

If two exposures overlap, the overlap time will be considered exposed to the first exposure (Figure 2). No time will be added at the end of the combined drug era to account for the overlap.

If two exposures start at the same date, the overlapping period was considered exposed to both. We did not consider repetitive exposure. Complex dosing schedule for rituximab was not considered in constructing drug eras as this medication is off-label for SLE and rarely prescribed. Thus, only the first drug era was considered for rituximab.

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

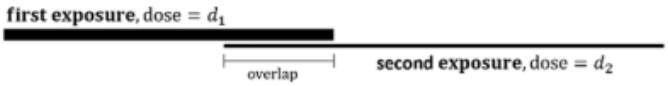


Figure 2. Gap era overlap mode

To construct treatment pathways, various parameters can be defined in the TreatmentPatterns package (Figure 3).

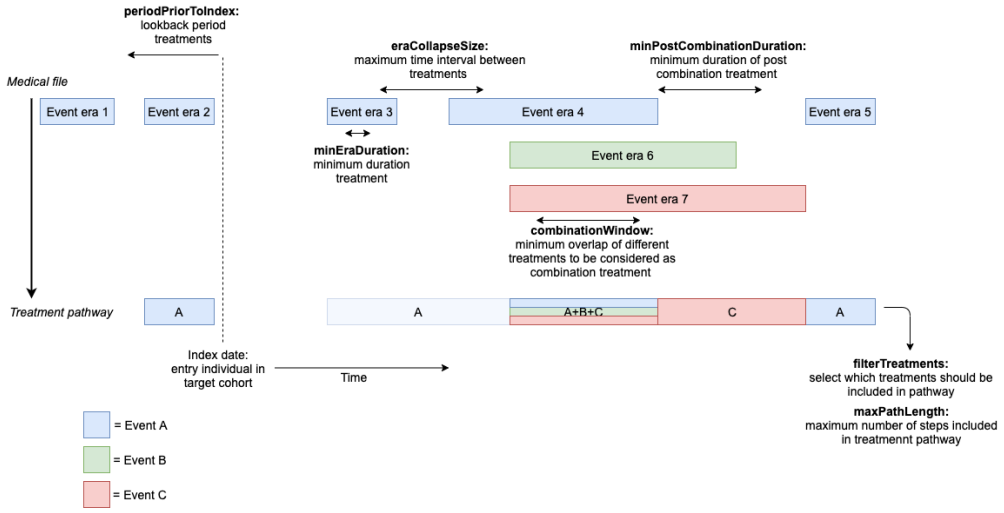


Figure 3. Parameters in TreatmentPatterns package

The following parameters were defined in this study. The target cohort refers to the specified study population, i.e. patients with first diagnosis of SLE whereas the event(s) refer to treatment(s) of interest. (10)

Individual pathway settings		
periodPriorToIndex	The period (number of days) prior to the index date of the target cohort from which treatments should be included	0
minEraDuration	Minimum time (days) an event era should last to be included in the analysis	0
eraCollapseSize	Maximum gap (days) within two eras of the same event cohort which would still allow the eras to be collapsed into one era	30
combinationWindow	Minimum time (days) that two event eras need to overlap to be considered a combination treatment	30
minPostCombinationDuration	Minimum time (days) that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	30
filterTreatments	Select which treatments should be included in pathway first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	First

maxPathLength	Maximum number of treatments included in pathway	5
Aggregate pathway settings		
minCellCount	Minimum number of persons with a specific treatment pathway for the pathway to be included in analysis	5
minCellMethod	Select to completely remove / sequentially adjust (by removing last step as often as necessary) treatment pathways below minCellCount	Adjust
groupCombinations	Select to group all non-fixed combinations in one category 'other' in the sunburst plot	TRUE/10
addNoPaths	Select to include untreated persons without treatment pathway in the sunburst plot	FALSE

A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5". All analyses will be reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached). Additionally, to capture treatments availability and changes over time, sunburst plots, Sankey diagrams were further stratified by study periods (2013-2017 and 2018-2022).

9.9.3 Missing Values

For the drug utilisation studies we assumed that the absence of prescription records meant that the person did not receive the respective drug. We reported the missingness of dose information for each treatment ingredient in each database, but no imputation was performed on the missing values.

9.9.4 Sensitivity Analysis

No sensitivity analysis was performed as the broad definition of SLE was not considered appropriate after review of cohort diagnostics.

10. DATA MANAGEMENT

Methods for data collection, retrieval, collection and preparation. Statistical software(s) to be used in the study should be specified.

Note: Standard text will be generated on Data Management which will fit all studies run by the DARWIN EU® CC.

11. QUALITY CONTROL

Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of the statistical programming performed to generate the results.

Note: This section will be automatically generated based on the DARWIN EU®Q/C processes, as detailed in a separate Deliverable 1.3.5.1.

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, it is expected that data partners will 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. Additionally, two more tools were used to control the quality of data during the onboarding. Achilles for database characterisation, running 293 analyses against the data. This output is not shared with the DARWIN-EU® CC as it reveals granular information of the data. It is expected that the data partners review the Achilles output internally. Secondly, CdmOnboarding generates a Word report with the most important database characteristics, providing insight in the readiness of the database to use for network studies. The output is shared with and inspected by the DARWIN-EU® CC.

Study specific quality control

When defining SLE, a systematic search of possible codes for inclusion was identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP CDM so as to find potentially relevant codes. The codes returned were reviewed by two clinical epidemiologists to consider their relevance. In addition, we ran cohort diagnostics 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 SLE in each of the databases, and informed decisions around whether multiple definitions are required.

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. A pharmacist reviewed the codes for the SLE treatments.

The study code was based on two R packages currently being developed to (1) characterise demographic and clinical characteristics, (2) characterise treatment patterns. These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R packages are publicly available via GitHub.

The study protocol was registered in the EUPAS Registry (EUPAS106436).

12. RESULTS

All results are available in a web application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS106436/

12.1 Participants

We included 11,257 patients with a first diagnosis of SLE: 699 were eligible in CDWBordeaux, 1,555 in CPRD GOLD, 295 in IMASIS, 2,744 in IQVIA Germany DA, and 5,964 in SIDIAP for the patient-level characterisation (**new diagnosis cohort**).

We included 5,687 patients who were started on SLE treatment after SLE diagnosis, without prior use at the treatment ingredient level in the past 365 days: There were 406 patients in CDWBordeaux, 1,026 in CPRD GOLD, 209 in IMASIS, 999 in IQVIA Germany DA, and 3,047 in SIDIAP (**new user cohort**). The cohorts attrition is presented in **Table 9**.

Table 9. Study cohort attrition

Reason	CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
First diagnosis of SLE	1487	7528	821	12497	11464
Limit cohort start date to study period	987	2030	390	7880	6315
At least 365 days of prior observation	699	1555	295	2744	5964
Limited to new user of SLE treatments	406	1026	209	999	3047

12.2 Descriptive Data

Paediatric cohort

In the new diagnosis cohort, there were a total of 378 paediatric patients (aged <18 years): 13 in CDWBordeaux, 42 in CPRD GOLD, none in IMASIS, 68 in IQVIA Germany DA, 255 in SIDIAP.

In the paediatric SLE cohort, 66 to 83% were female, with median age of 12 to 16 years. In general, there were few comorbidities recorded any time before SLE diagnosis in this group. The most common comorbidities were asthma (6-15%), pneumonia (10-13%), anxiety (8-13%), and other autoimmune disease (3-16%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (35-38%), systemic antibacterials (25-45%), and drugs for acid-related disorders (6-21%).

Adult cohort

There were a total of 10,879 adult patients: 686 CDW Bordeaux, 1,513 in CPRD GOLD, 295 in IMASIS, 2,676 in IQVIA Germany DA, 5,709 in SIDIAP.

In the adult SLE cohort, 80 to 88% were female, with median age of 49 to 54 years. The most common comorbidities were other autoimmune disease (9-35%), hypertension (15-27%), anxiety/depressive disorder (6-27%) across all databases. The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (13-57%), systemic antibacterials (8-53%), and drugs for acid-related disorders (11-51%).

The most relevant baseline characteristics for paediatric and adult SLE patients are summarised in **Table 10** and **Table 11.** The full list of baseline characteristics, and further stratification by age groups and sex, as well as large scale patient characteristics, stratified by age, sex, and time windows can be viewed in the Shiny web application.

Table 10. Baseline patient characteristics stratified by database (paediatric SLE)

Variable	CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
N	13	42	68	255
Female	10 (77%)	35 (83%)	52 (76%)	169 (66%)
Age median [min; q25 - q75; max]	16 [6; 14 - 16; 17]	15 [2; 12 - 16; 17]	14 [2; 10 - 16; 17]	12 [1; 8 - 15; 17]
Age group				
0 to 4	<5	<5	7 (10%)	23 (9%)
5 to 12	<5	9 (21%)	19 (28%)	111 (44%)
13 to 17	11 (85%)	30 (71%)	42 (62%)	121 (47%)
Comorbidities (any time prior)				
Anxiety	0 (0%)	<5	9 (13%)	21 (8%)
Asthma	0 (0%)	5 (12%)	10 (15%)	15 (6%)
Autoimmune disease	0 (0%)	<5	11 (16%)	8 (3%)
Pneumonia	0 (0%)	<5	7 (10%)	32 (13%)
Comedications (prior year)				
Antibacterials (systemic)	0 (0%)	19 (45%)	22 (32%)	64 (25%)
Anti-inflammatory/ antirheumatic products	<5 (NA%)	16 (38%)	24 (35%)	98 (38%)
Drugs for acid related disorder	<5 (NA%)	9 (21%)	6 (9%)	16 (6%)
Drugs for obstructive airway disorder	0 (0%)	5 (12%)	<5 (NA%)	28 (11%)

Table 11. Baseline patient characteristics stratified by database (adult SLE)

Variable	CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
N	686	1,513	295	2,676	5,709
Female	576 (84%)	1,331 (88%)	243 (82%)	2,218 (83%)	4,562 (80%)
Age median [min; q25 - q75; max]	49 [18; 36 - 61; 93]	49 [18; 38 - 61; 95]	54 [18; 44 - 67; 94]	54 [18; 43 - 65; 94]	50 [18; 39 - 64; 101]
Age group					
18 to 39	218 (32%)	443 (29%)	58 (20%)	554 (21%)	1,542 (27%)
40 to 49	128 (19%)	345 (23%)	49 (17%)	481 (18%)	1,247 (22%)
50 to 59	150 (22%)	305 (20%)	72 (24%)	676 (25%)	1,138 (20%)
60 to 69	102 (15%)	219 (14%)	53 (18%)	504 (19%)	796 (14%)
70 to 150	91 (13%)	201 (13%)	63 (21%)	461 (17%)	986 (17%)
Comorbidities (any time prior)					
Anxiety	42 (6%)	344 (23%)	27 (9%)	331 (12%)	1,557 (27%)
Asthma	22 (3%)	198 (13%)	7 (2%)	206 (8%)	309 (5%)
Other autoimmune disease	110 (16%)	320 (21%)	26 (9%)	936 (35%)	956 (17%)
Chronic kidney disease	31 (4%)	128 (8%)	14 (5%)	190 (7%)	399 (7%)
Chronic liver disease	7 (1%)	14 (1%)	9 (3%)	31 (1%)	92 (2%)
COPD	25 (4%)	47 (3%)	31 (11%)	190 (7%)	232 (4%)
Dementia	<5	<5	<5	25 (1%)	80 (1%)
Depressive disorder	44 (6%)	347 (23%)	32 (11%)	482 (18%)	858 (15%)
Diabetes	37 (5%)	70 (5%)	20 (7%)	240 (9%)	437 (8%)
Gastroesophageal reflux disease	22 (3%)	60 (4%)	<5	123 (5%)	335 (6%)
Heart failure	20 (3%)	17 (1%)	20 (7%)	125 (5%)	196 (3%)

Hypertension	106 (15%)	223 (15%)	59 (20%)	717 (27%)	1,359 (24%)
Hypothyroidism	33 (5%)	153 (10%)	12 (4%)	240 (9%)	692 (12%)
Inflammatory bowel disease	6 (1%)	21 (1%)	<5	53 (2%)	63 (1%)
Malignant neoplastic disease	32 (5%)	69 (5%)	30 (10%)	200 (7%)	475 (8%)
Myocardial infarction	5 (1%)	21 (1%)	<5	29 (1%)	83 (1%)
Osteoporosis	25 (4%)	67 (4%)	11 (4%)	238 (9%)	426 (7%)
Pneumonia	28 (4%)	53 (4%)	32 (11%)	133 (5%)	432 (8%)
Rheumatoid arthritis	26 (4%)	71 (5%)	8 (3%)	421 (16%)	184 (3%)
Stroke	14 (2%)	29 (2%)	5 (2%)	71 (3%)	158 (3%)
Venous thromboembolism	26 (4%)	93 (6%)	9 (3%)	150 (6%)	179 (3%)
Comedications (prior year)					
Agents acting on RAAS	22 (3%)	286 (19%)	21 (7%)	387 (14%)	1,201 (21%)
Antibacterials (systemic)	52 (8%)	798 (53%)	54 (18%)	399 (15%)	2,054 (36%)
Antidepressants	16 (2%)	534 (35%)	29 (10%)	170 (6%)	1,297 (23%)
Antiepileptics	22 (3%)	208 (14%)	28 (9%)	75 (3%)	677 (12%)
Anti-inflammatory/ antirheumatic products	87 (13%)	791 (52%)	116 (39%)	768 (29%)	3,230 (57%)
Antineoplastic agents	NA	104 (7%)	9 (3%)	104 (4%)	225 (4%)
Antithrombotics	55 (8%)	196 (13%)	41 (14%)	169 (6%)	612 (11%)
Beta blocking agents	18 (3%)	211 (14%)	12 (4%)	291 (11%)	510 (9%)
Calcium channel blockers	28 (4%)	215 (14%)	15 (5%)	152 (6%)	520 (9%)
Diuretics	24 (3%)	206 (14%)	25 (8%)	171 (6%)	624 (11%)
Drugs for acid related disorder	76 (11%)	768 (51%)	75 (25%)	486 (18%)	2,443 (43%)

Drugs for obstructive airway disorder	21 (3%)	425 (28%)	37 (13%)	167 (6%)	1,121 (20%)
Drugs used in diabetes	17 (2%)	68 (4%)	19 (6%)	93 (3%)	362 (6%)
Immunosuppressants	29 (4%)	172 (11%)	29 (10%)	230 (9%)	416 (7%)
Lipid modifying agents	23 (3%)	257 (17%)	12 (4%)	196 (7%)	1,011 (18%)
Opioids	45 (7%)	613 (41%)	37 (13%)	174 (7%)	1,049 (18%)
Psycholeptics*	58 (8%)	307 (20%)	57 (19%)	124 (5%)	1,952 (34%)

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, RAAS: Renin Aldosterone Angiotensin System

*Psycholeptics refer to the WHO-ATC N05 group, which includes antipsychotics, anxiolytics, hypnotics and sedatives

12.3 Outcome Data

Not applicable

12.4 Main Results

12.4.1 Treatment patterns of SLE patients (new diagnosis cohort)

Among the paediatric SLE cohort, the most commonly prescribed/dispensed treatments within the first 30 days after diagnosis were glucocorticoids (10-54%) and hydroxychloroquine (14-46%) (**Figure 4**) across CDWBordeaux, CPRD GOLD, and SIDIAP. There were too few treated patients in IQVIA Germany DA in this time window to be presented.

The most commonly used treatments within the first year of diagnosis were hydroxychloroquine (9-62%), glucocorticoids (12-62%), and mycophenolate mofetil (5-46%) across all databases (**Figure 5**) and use of rituximab (38%, n=5) was also observed in CDWBordeaux only.

Use of azathioprine (4%), tacrolimus (4%), and methotrexate (2%), were also observed albeit rare in SIDIAP.

Figure 4 New users of SLE treatment within 30 days of diagnosis, stratified by database (paediatric)

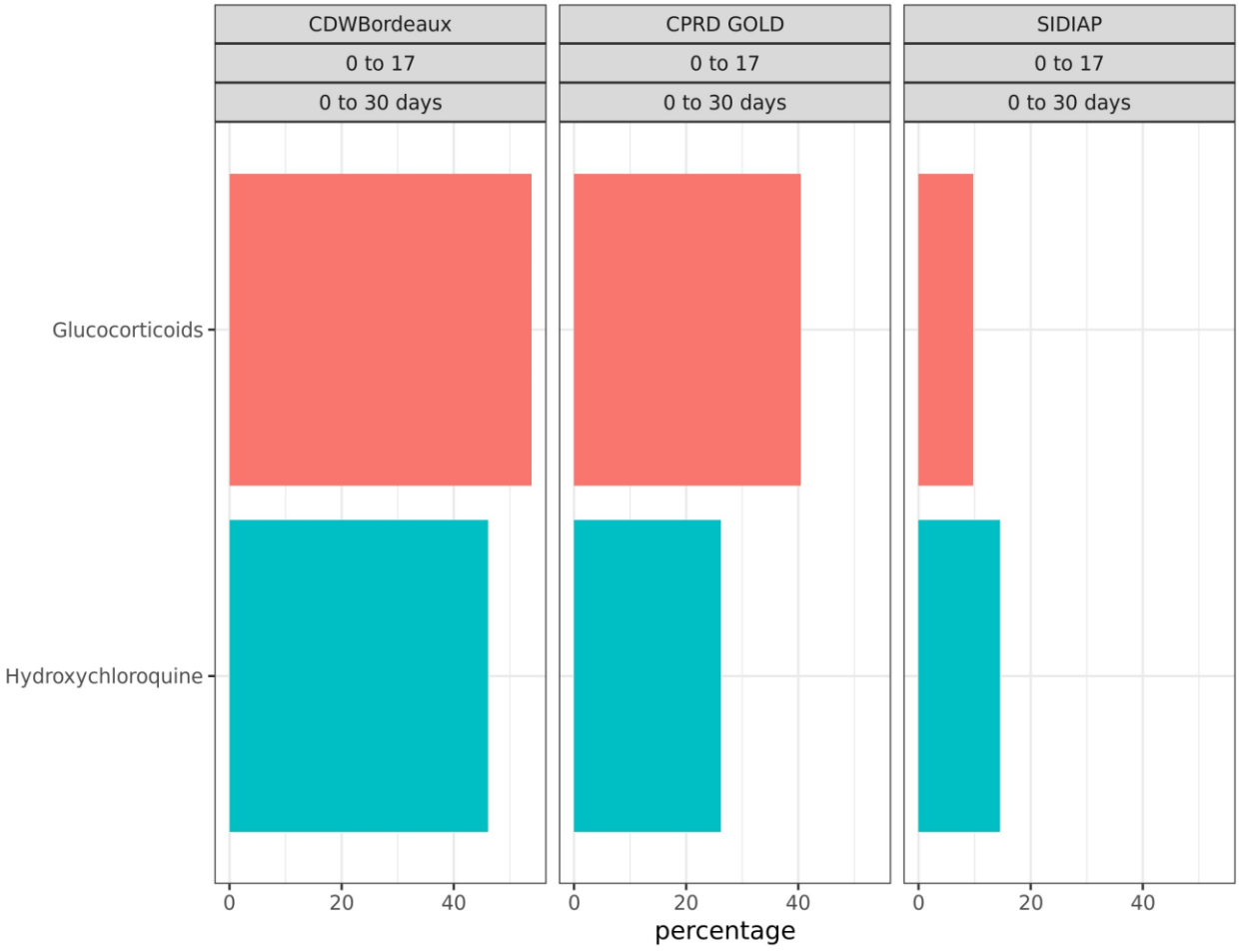
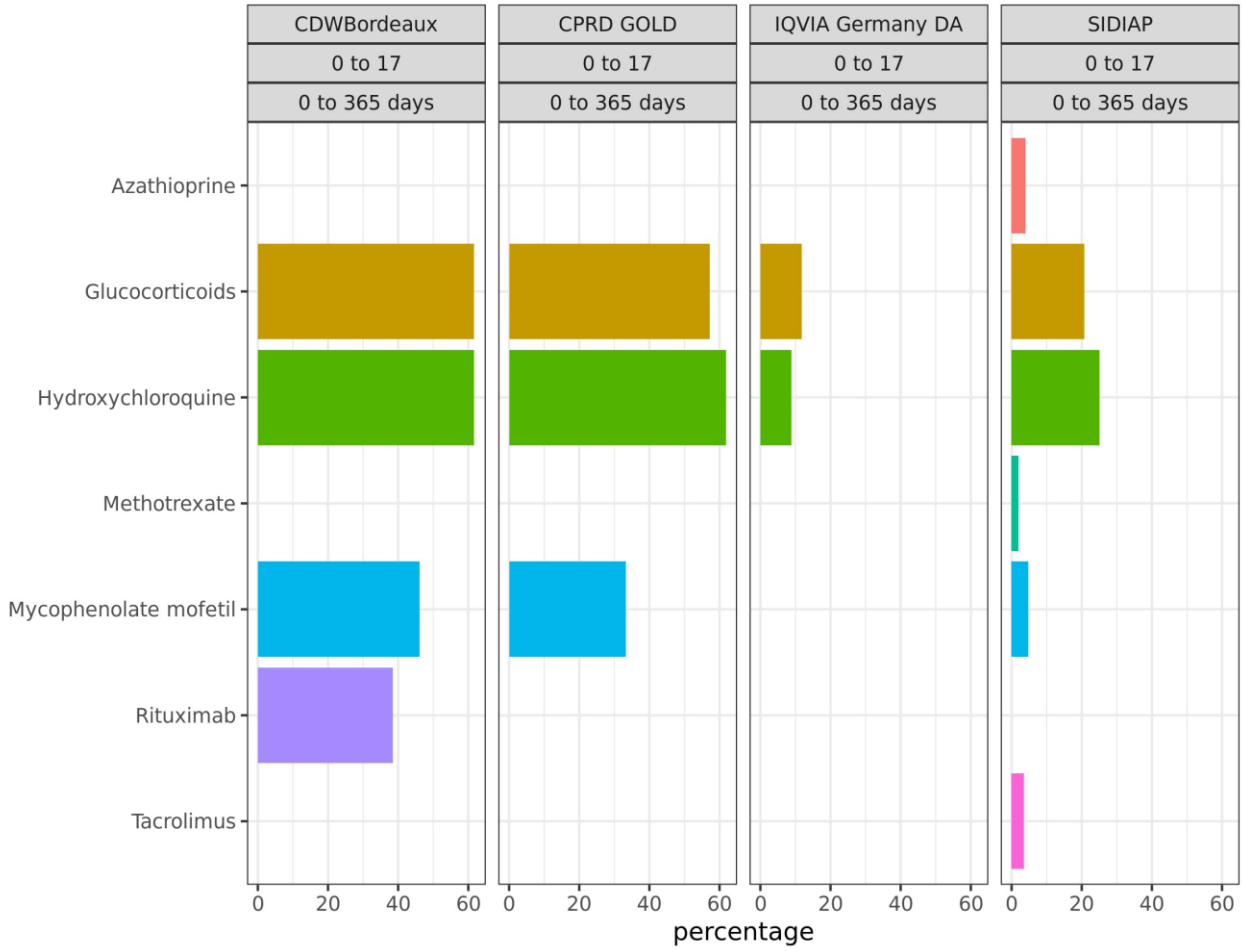


Figure 5 New users of SLE treatment within 365 days of diagnosis, stratified by database (paediatric)



In the adult cohort, the most commonly used treatments within the first 30 days of diagnosis are hydroxychloroquine (8-32%) and glucocorticoids (11-33%) (**Figure 6**). The most commonly used treatments within the first year of diagnosis are hydroxychloroquine (13-49%), glucocorticoids (18-42%). The third most frequently used treatment was mycophenolate mofetil (6%) in CDWBordeaux and methotrexate (4-7%) in all other databases (**Figure 7**). Use of rituximab was also observed in 2.0% of adult patients in CDWBordeaux hospital.

Figure 6 New users of SLE treatment within 30 days of diagnosis, stratified by database (adult)

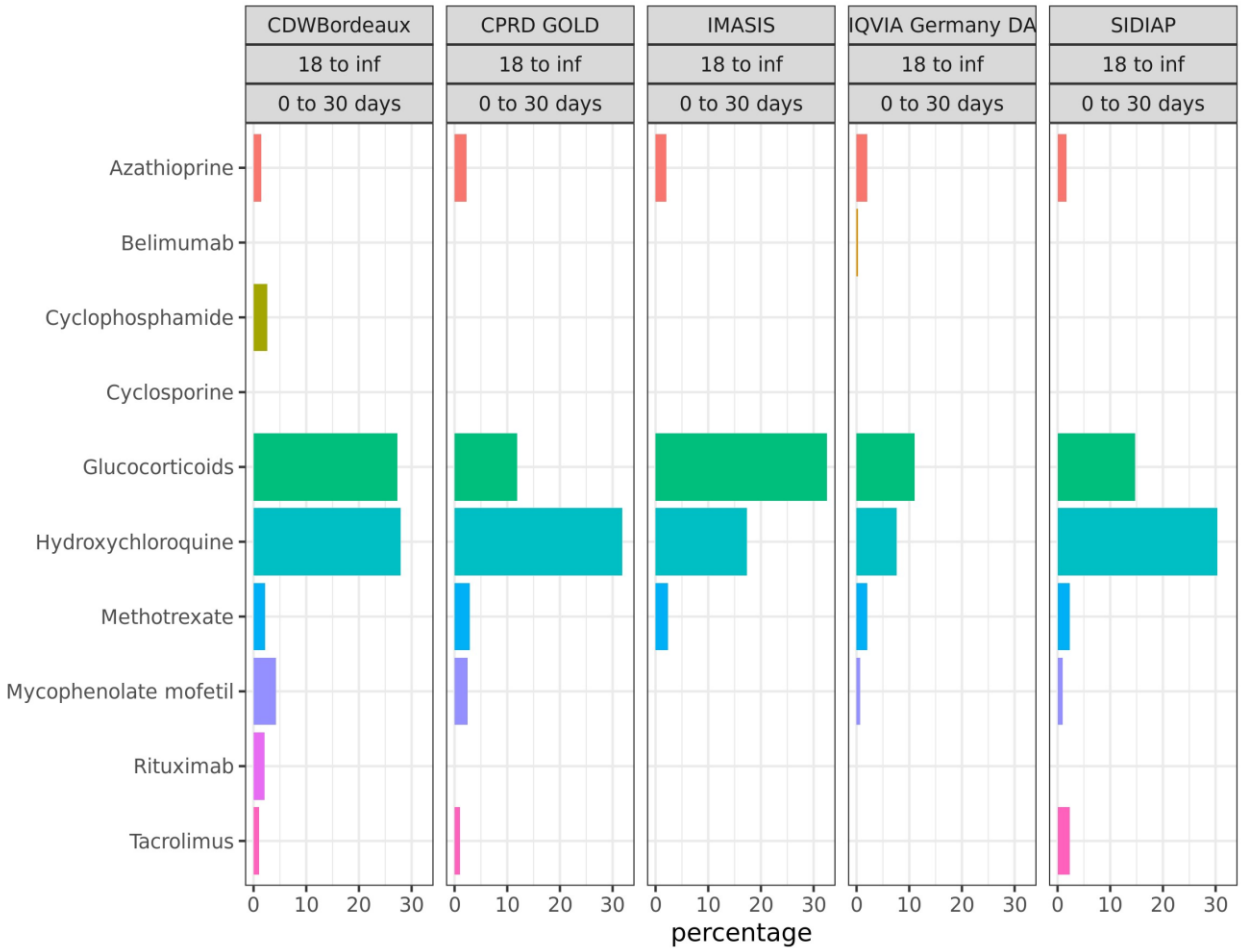
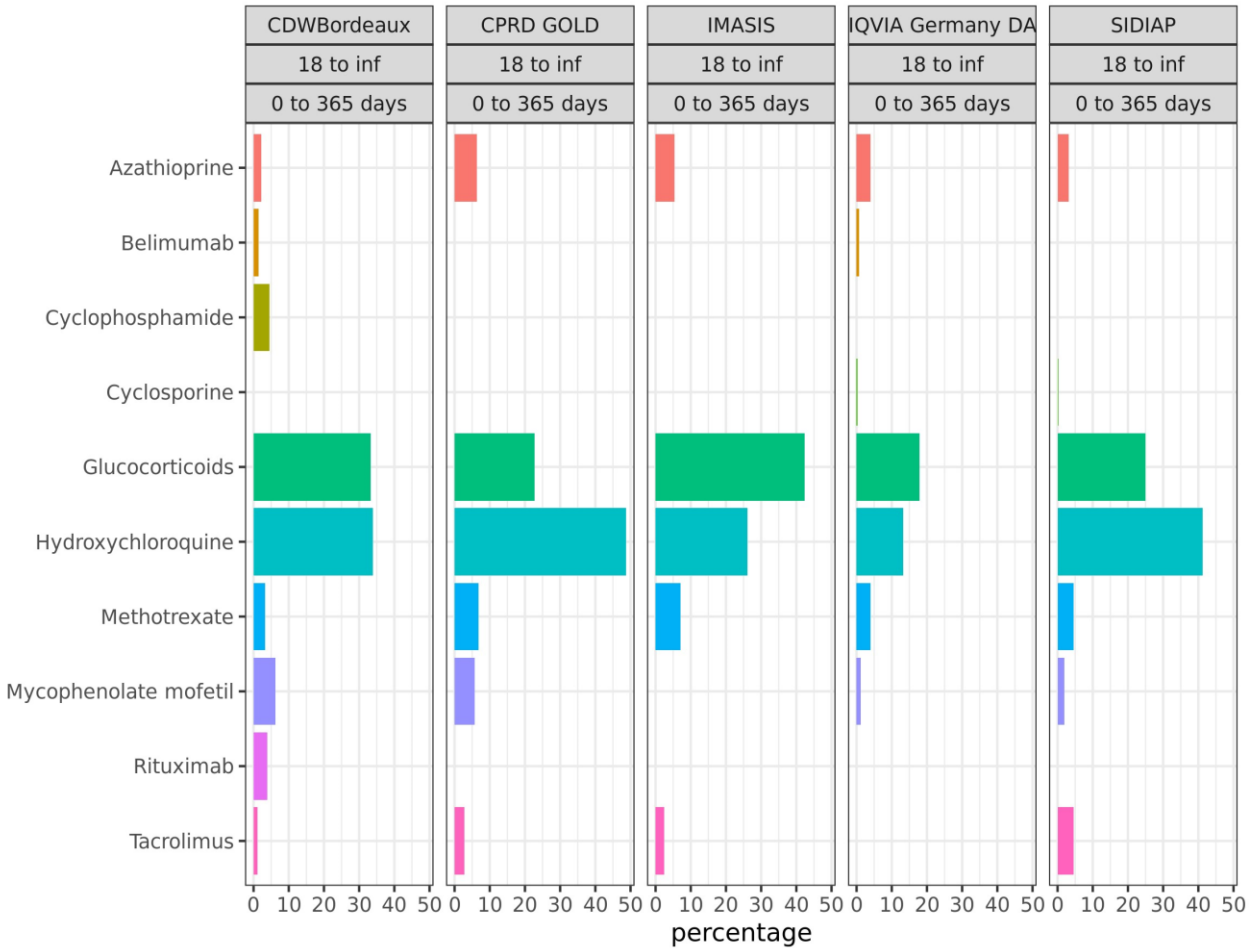


Figure 7 New users of SLE treatment within 365 days of diagnosis, stratified by database (adult)



The number and percentages of new users of each SLE treatment within 30 and 365 days after diagnosis of SLE is summarised in **Table 12** and **Table 13**, respectively. There was no major difference in treatment patterns when stratified by calendar periods. (see Shiny web application).

Table 12 New users of SLE treatment within 30 days of diagnosis, stratified by database and age

Age (years)	Treatment	CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
N		13	42	0	68	255
0 to 17	Azathioprine	<5	<5	NA	<5	<5
0 to 17	Glucocorticoids	7 (53.85%)	17 (40.48%)	NA	<5	25 (9.8%)
0 to 17	Hydroxychloroquine	6 (46.15%)	11 (26.19%)	NA	<5	37 (14.51%)
0 to 17	Methotrexate	<5	<5	NA	<5	<5
0 to 17	Mycophenolate mofetil	<5	<5	NA	<5	<5
0 to 17	Rituximab	<5	<5	NA	<5	<5
0 to 17	Tacrolimus	<5	<5	NA	<5	<5
N		686	1,513	295	2,676	5,709
18+	Azathioprine	10 (1.45%)	35 (2.31%)	6 (2.03%)	55 (2.06%)	96 (1.68%)
18+	Belimumab	<5	<5	<5	7 (0.26%)	<5
18+	Cyclophosphamide	18 (2.61%)	<5	<5	<5	<5
18+	Cyclosporine	<5	<5	<5	<5	5 (0.09%)
18+	Glucocorticoids	188 (27.29%)	180 (11.9%)	96 (32.54%)	294 (10.99%)	843 (14.77%)
18+	Hydroxychloroquine	192 (27.87%)	482 (31.86%)	51 (17.29%)	204 (7.62%)	1729 (30.29%)
18+	Methotrexate	15 (2.18%)	44 (2.91%)	7 (2.37%)	54 (2.02%)	131 (2.29%)
18+	Mycophenolate mofetil	29 (4.21%)	38 (2.51%)	<5	19 (0.71%)	57 (1%)
18+	Rituximab	14 (2.03%)	<5	<5	<5	<5
18+	Tacrolimus	7 (1.02%)	15 (0.99%)	<5	<5	133 (2.33%)

Table 13 New users of SLE treatment within 365 days of diagnosis, stratified by database and age

Age (years)	Treatment	CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
N		13	42	0	68	255
0 to 17	Azathioprine	<5	<5	NA	<5	10 (3.92%)
0 to 17	Glucocorticoids	8 (61.54%)	24 (57.14%)	NA	8 (11.76%)	53 (20.78%)
0 to 17	Hydroxychloroquine	8 (61.54%)	26 (61.9%)	NA	6 (8.82%)	64 (25.1%)
0 to 17	Methotrexate	<5	<5	NA	<5	5 (1.96%)
0 to 17	Mycophenolate mofetil	6 (46.15%)	14 (33.33%)	NA	<5	12 (4.71%)
0 to 17	Rituximab	5 (38.46%)	<5	NA	<5	<5
0 to 17	Tacrolimus	<5	<5	NA	<5	9 (3.53%)
N		686	1,513	295	2,676	5,709
18+	Azathioprine	15 (2.18%)	96 (6.35%)	16 (5.42%)	104 (3.89%)	184 (3.22%)
18+	Belimumab	10 (1.45%)	<5	<5	17 (0.64%)	<5
18+	Cyclophosphamide	31 (4.5%)	<5	<5	<5	<5
18+	Cyclosporine	<5	<5	<5	5 (0.19%)	9 (0.16%)
18+	Glucocorticoids	229 (33.24%)	345 (22.8%)	125 (42.37%)	479 (17.9%)	1426 (24.98%)
18+	Hydroxychloroquine	234 (33.96%)	737 (48.71%)	77 (26.1%)	355 (13.27%)	2349 (41.15%)
18+	Methotrexate	23 (3.34%)	104 (6.87%)	21 (7.12%)	104 (3.89%)	260 (4.55%)
18+	Methylprednisolone	89 (12.92%)	18 (1.19%)	39 (13.22%)	29 (1.08%)	171 (3%)
18+	Mycophenolate mofetil	43 (6.24%)	87 (5.75%)	<5	33 (1.23%)	111 (1.94%)
18+	Rituximab	27 (3.92%)	<5	<5	<5	<5
18+	Tacrolimus	8 (1.16%)	43 (2.84%)	7 (2.37%)	<5	259 (4.54%)

The sunburst plots are represented in the overall cohort (paediatric plus adult SLE) for each database in **Figures 8** to **10**, as small numbers in the paediatric cohort will cause the treatment pathways to be obscured. In CPRD GOLD and SIDIAP, hydroxychloroquine was most frequently used as first line treatment. Of these patients, in CPRD GOLD, the second line treatment was monotherapy/addition of glucocorticoids or methotrexate, monotherapy of mycophenolate mofetil. In SIDIAP, the second line treatment consisted of glucocorticoids, tacrolimus, and azathioprine. In IQVIA DA Germany, glucocorticoids was most frequently used as first line treatment. For these patients, the second line treatment consisted of azathioprine, hydroxychloroquine, and methotrexate.

When stratified by calendar period (2013-2017, 2018 and later), hydroxychloroquine was still the most frequent first line treatment in both periods in CPRD and SIDIAP, although there was a higher proportion of methotrexate use in CPRD as first line in the later period as compared to 2013-2017. In IQVIA DA Germany, the most frequent first line therapy changed from glucocorticoids (2013-2017) to hydroxychloroquine (2018 and later).

The Sankey diagrams showing the switches between SLE treatments are represented in the overall cohort for each database in **Figures 11** to **13**, as small numbers in the paediatric cohort will cause the treatment pathways to be obscured.

No plots were generated for CDWBordeaux and IMASIS as the TreatmentPatterns package does not allow for dispensations with the same start and end date, which were majority of the dispensations in these databases when reviewing the drug exposure diagnostics.

Figure 8 Sunburst plot of SLE treatment (CPRD GOLD)

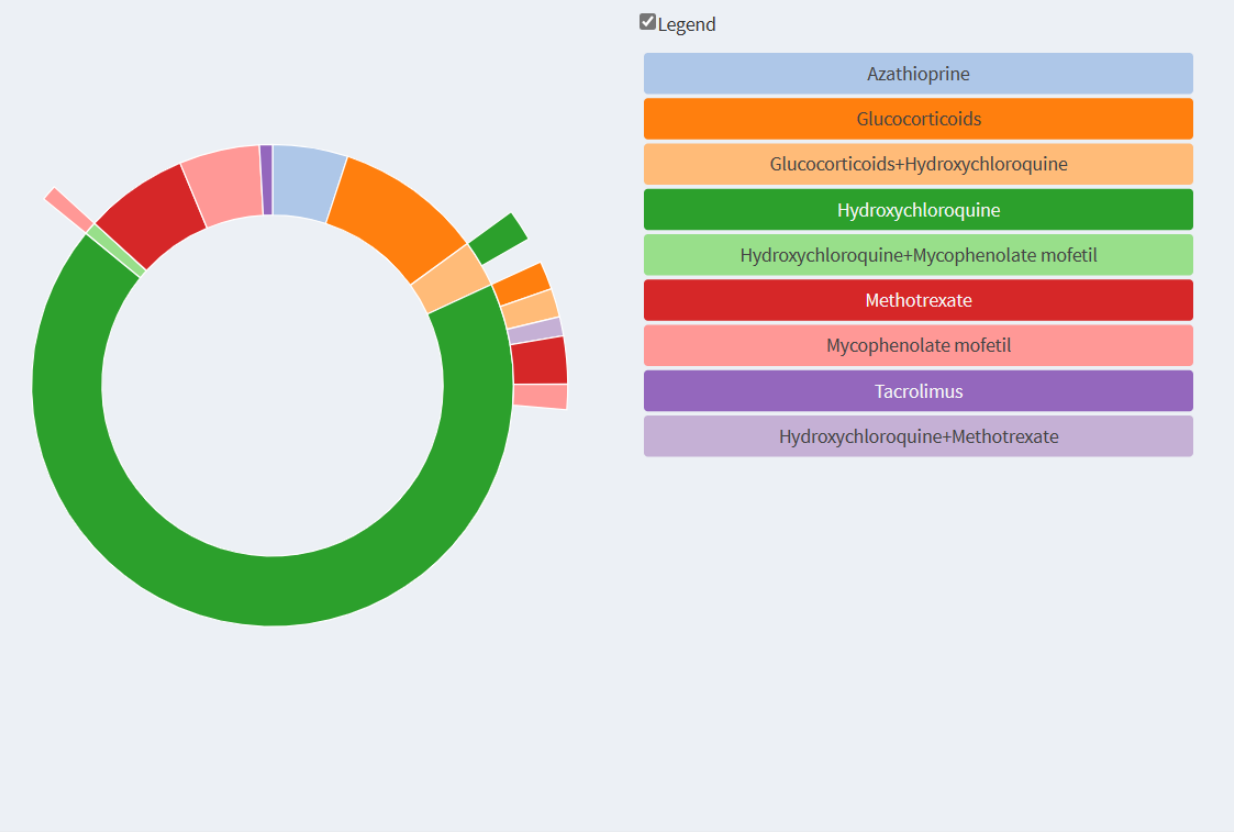


Figure 9 Sunburst plot of SLE treatment (IQVIA Germany DA)

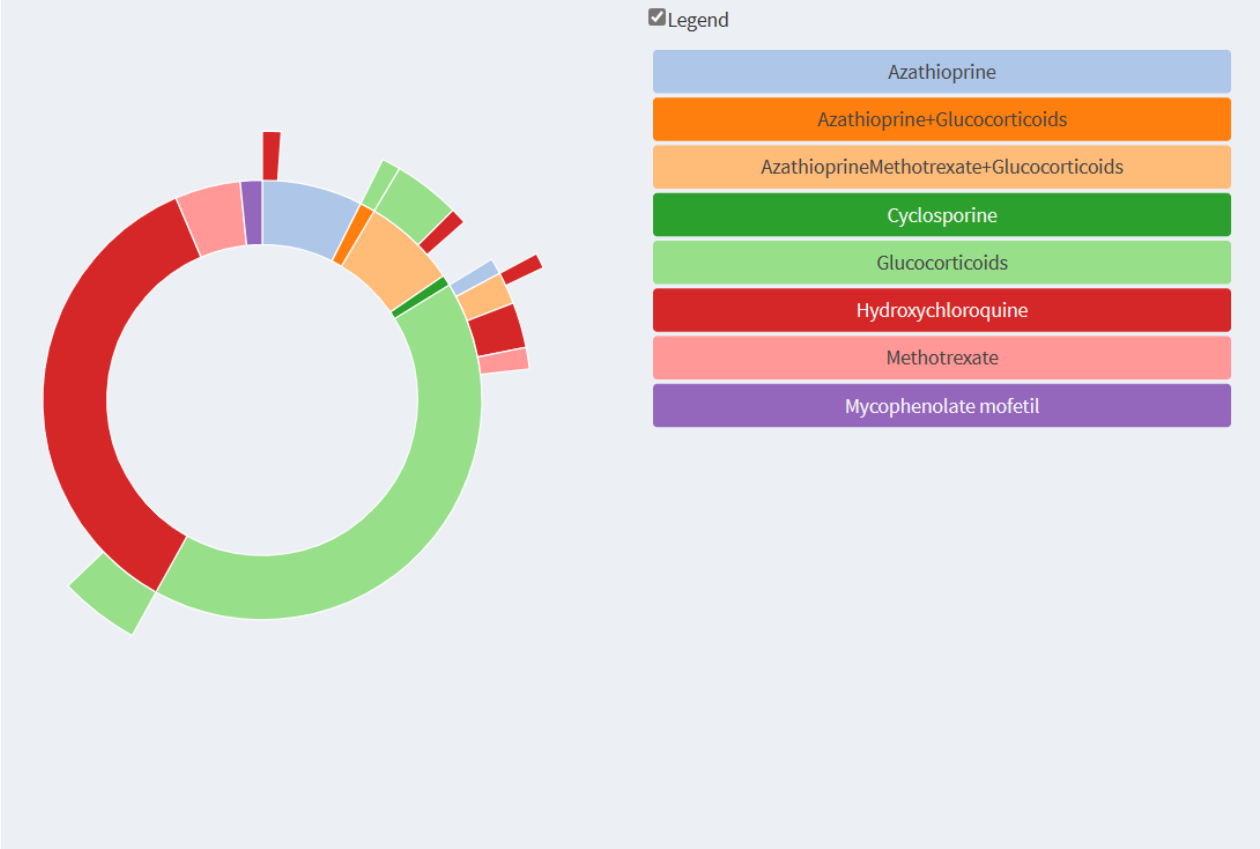


Figure 10 Sunburst plot of SLE treatment (SIDIAP)

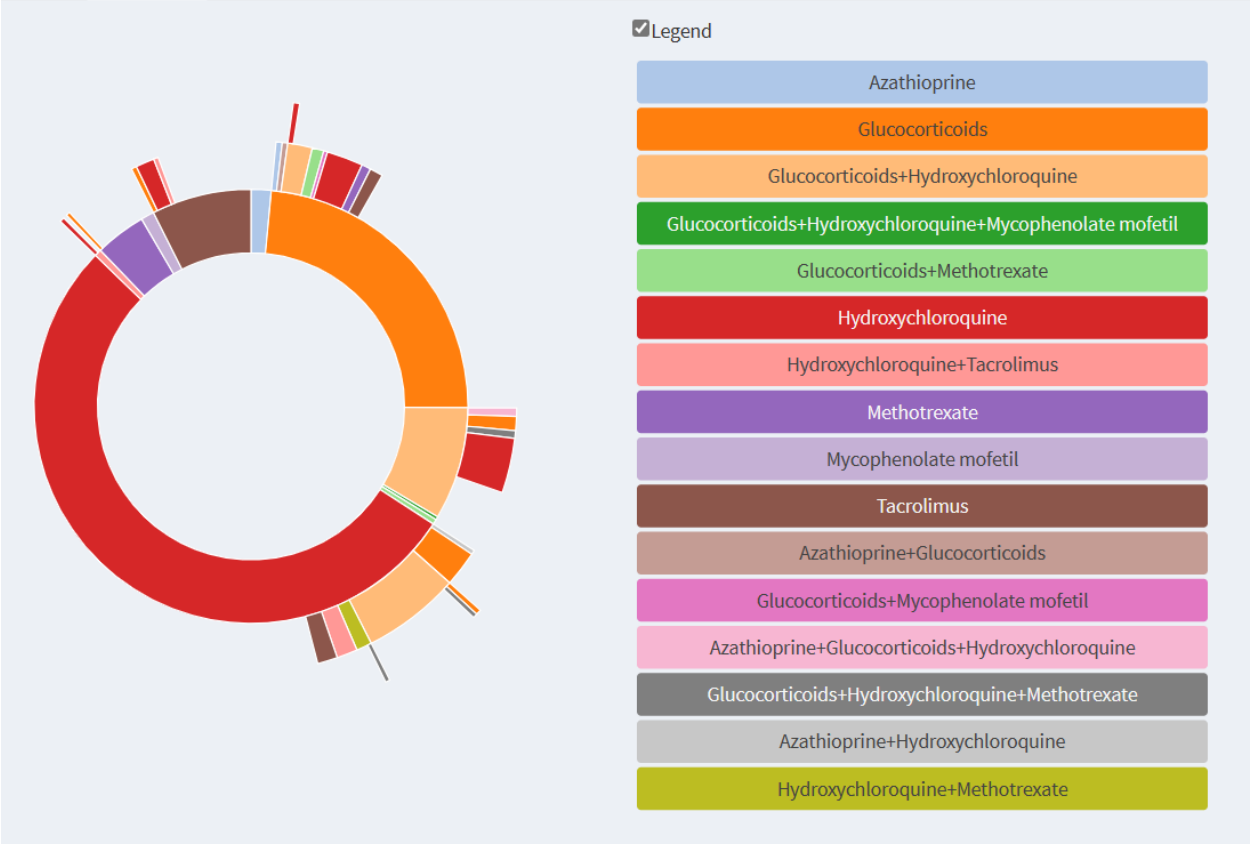


Figure 11 Sankey diagram of SLE treatment pathway (CPRD GOLD)

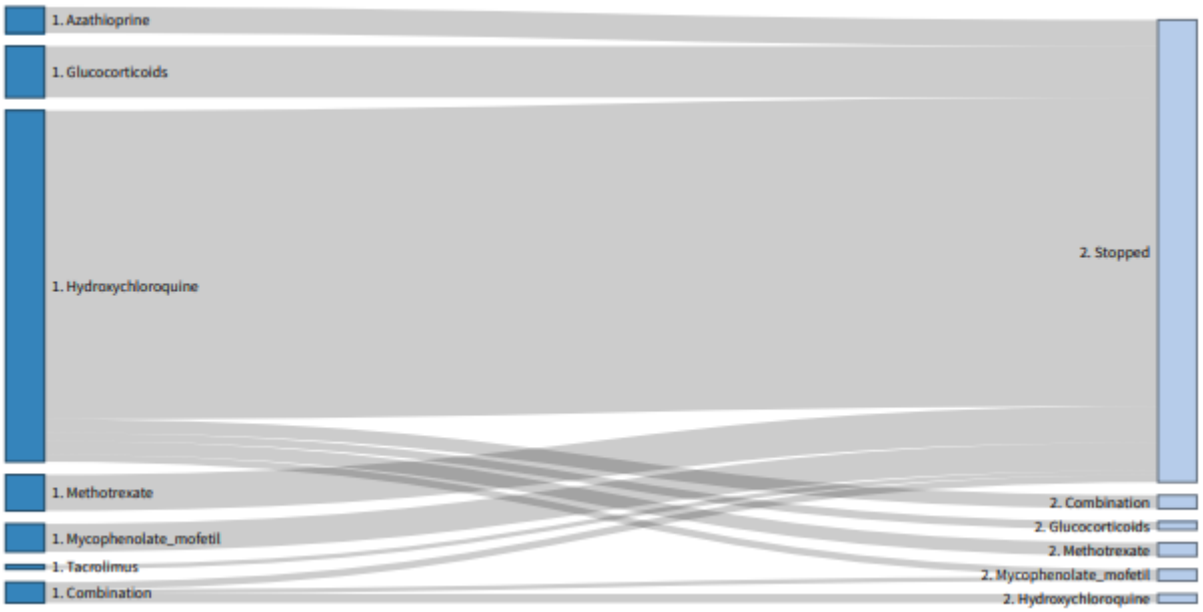


Figure 12 Sankey diagram of SLE treatment pathway (IQVIA Germany DA)

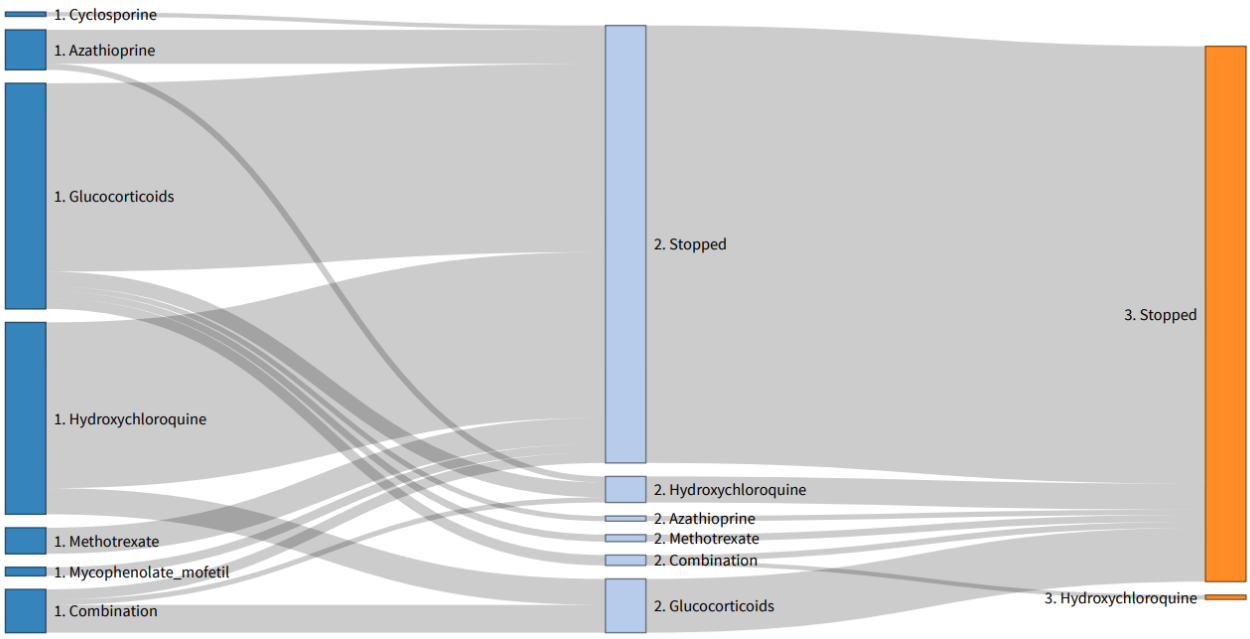
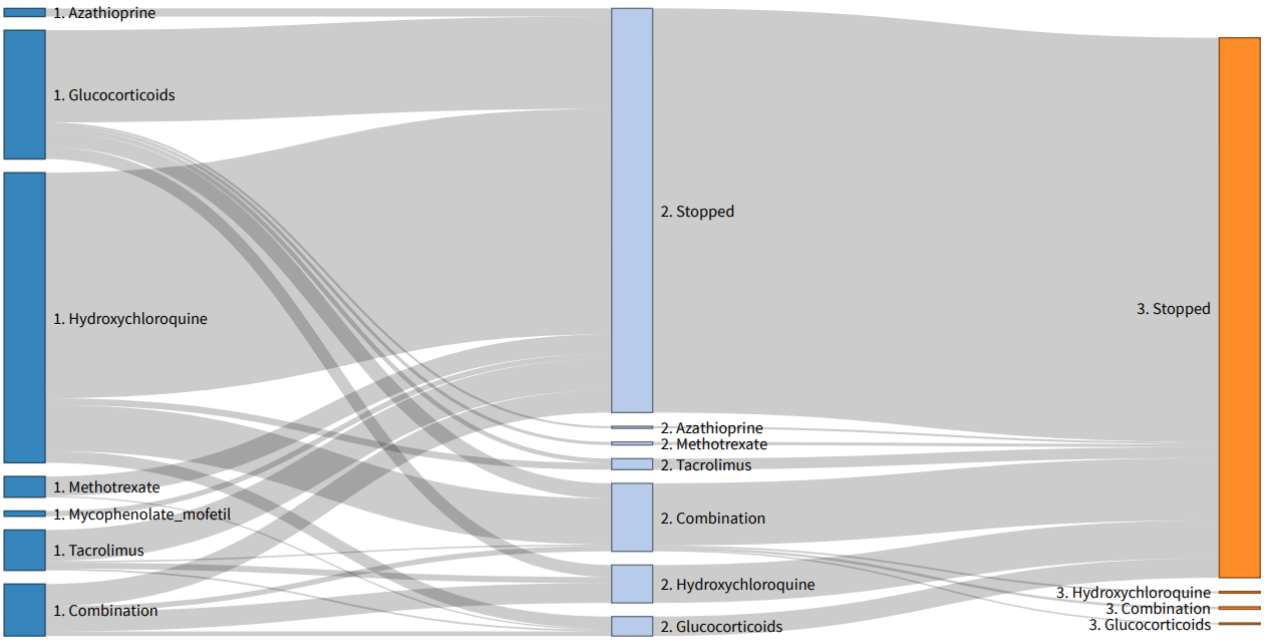


Figure 13 Sankey diagram of SLE treatment pathway (SIDIAP)



Note: Stopped refers to patient stopping treatment without initiation of another study medication within their observation period

Further stratification by age groups, sex, and calendar period can be visualised in the Shiny web application, however, small numbers of in the strata e.g. (male and paediatric patients) will cause the specific treatment combination or pathway to be obscured.

12.4.2 Drug utilisation analysis of SLE treatments (new user cohort)

The treatment duration, number of prescriptions, initial and cumulative dose in paediatric and adult patients are presented in **Table 14** and **Table 15**, respectively. Dose information was not available for CDWBordeaux.

In the paediatric new user cohort, the most frequently used SLE treatments are hydroxychloroquine, followed by prednisone/prednisolone, and mycophenolate mofetil. For hydroxychloroquine, median duration was between 50 to 501 days for primary care databases and 8 days for CDWBordeaux hospital, median initial daily dose ranged from 199 to 300 mg, median cumulative dose ranged from 20,000 to 116,600 mg, number of prescriptions in the first drug era was 1 to 10 across all databases. For prednisone/prednisolone, median duration was between 74 to 246 days for primary care databases and 13 days for CDWBordeaux hospital, median initial daily dose ranged from 10 to 60 mg, median cumulative dose ranged from 775 to 2,150 mg, number of prescriptions in the first drug era was 1 to 5 across all databases. For mycophenolate mofetil, median duration was 75 to 371 days for primary care databases and 4 days for CDWBordeaux hospital, median initial daily dose ranged from 893 to 1,974 mg, median cumulative dose ranged from 150,000 to 621,000 mg, number of prescriptions in the first drug era was 2 to 12 across all databases.

In the adult new user cohort, the most frequently used SLE treatments is hydroxychloroquine, followed by prednisone/prednisolone. For hydroxychloroquine, median duration was 39 to 485 days for primary care databases and 4 to 30 days for hospital databases, median initial daily dose ranged from 13 to 400 mg, median cumulative dose ranged from 600 to 130,051 mg, number of prescriptions in the first drug era was 1 to 6 across all databases. For prednisone/prednisolone, median duration was 7 to 111 days for primary care databases and 4 to 30 days for hospital databases, median initial daily dose ranged from 2 to 40 mg, median cumulative dose ranged from 20 to 1,038 mg, number of prescriptions in the first drug era was 1 to 4 across all databases. The results for the other SLE treatments in adult patients are summarised in **Table 14**. Only the most frequently used glucocorticoid (prednisone/prednisolone) and treatments where counts are available in at least 2 databases are presented in this report. The results for the other treatments are available in the Shiny web application.

Table 14 Drug utilisation of SLE treatments in paediatric cohort

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
0 to 17	Hydroxychloroquine	**Number of subjects**				
		count (n)	8	23	8	58
		Duration, days				
		Median (IQR)	8 [4 - 14]	110 [50 - 323]	50 [45 - 94]	501 [252 - 1,808]
		Number of prescriptions				
		Median (IQR)	10 [4 - 11]	4 [2 - 8]	1 [1 - 1]	3 [1 - 6]
		Initial daily dose, mg				
		Median (IQR)	NA	200 [200 - 200]	300 [200 - 400]	199 [197 - 199]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)
		Cumulative daily dose, mg				
		Median (IQR)	NA	24,000 [11,200 - 69,800]	20,000 [16,500 - 21,500]	116,600 [52,250 - 446,043]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)
0 to 17	Mycophenolate mofetil	**Number of subjects**				
		count (n)	7	16	5	14
		Duration, days				

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
		Median (IQR)	4 [2 - 15]	371 [114 - 796]	75 [44 - 80]	216 [104 - 344]
		Number of prescriptions				
		Median (IQR)	4 [2 - 15]	12 [6 - 27]	2 [1 - 2]	3 [1 - 5]
		Initial daily dose, mg				
		Median (IQR)	NA	893 [562 - 2,000]	1,974 [1,500 - 1,974]	992 [959 - 1,053]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg				
		Median (IQR)	NA	621,000 [212,500 - 1,627,750]	150,000 [75,000 - 150,000]	338,896 [133,312 - 767,522]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)
0 to 17	Prednisone/ Prednisolone*	**Number of subjects**				
		count (n)	6	21	8	47
		Duration, days				
		Median (IQR)	13 [1 - 25]	74 [17 - 157]	75 [42 - 102]	246 [48 - 616]
		Number of prescriptions				
		Median (IQR)	4 [1 - 8]	5 [2 - 10]	1 [1 - 2]	3 [1 - 4]
		Initial daily dose, mg				

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
		Median (IQR)	NA	60 [30 - 100]	20 [9 - 41]	10 [7 - 20]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg				
		Median (IQR)	NA	2,150 [1,000 - 3,660]	775 [438 - 1,250]	2,250 [430 - 7,100]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)

*Data presented for counts ≥5: prednisone in CDWBordeaux and SIDIAP; prednisolone in CPRD GOLD and IQVIA Germany DA

IQR: interquartile range

Table 15 Drug utilisation of SLE treatments in adult cohort

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
18+	Azathioprine	**Number of subjects**					
		count (n)	28	134	24	131	224
		Duration, days					
		Median (IQR)	3 [2 - 5]	92 [46 - 360]	30 [8 - 38]	100 [50 - 218]	284 [98 - 1,003]

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Number of prescriptions					
		Median (IQR)	4 [2 - 7]	4 [2 - 11]	2 [1 - 4]	2 [1 - 4]	2 [1 - 4]
		Initial daily dose, mg					
		Median (IQR)	NA	75 [50 - 125]	2 [2 - 50]	100 [75 - 100]	74 [49 - 99]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	8,400 [4,200 - 30,838]	100 [50 - 250]	10,000 [5,000 - 20,000]	23,387 [7,398 - 85,461]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18+	Belimumab	**Number of subjects**					
		count (n)	25		<5	32	
		Duration, days					
		Median (IQR)	16 [1 - 30]		NA [NA - NA]	102 [32 - 250]	
		Number of prescriptions					
		Median (IQR)	2 [1 - 4]		NA [NA - NA]	2 [1 - 4]	
		Initial daily dose, mg					
		Median (IQR)	NA		NA	25 [25 - 29]	
		Missing, n (%)	NA		NA	0 (0%)	

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Cumulative daily dose, mg					
		Median (IQR)	NA		NA	2,800 [800 - 7,200]	
		Missing, n (%)	NA		NA	0 (0%)	
18+	Cyclophosphamide	**Number of subjects**					
		count (n)	43	<5	5		
		Duration, days					
		Median (IQR)	72 [30 - 98]	NA [NA - NA]	1 [1 - 18]		
		Number of prescriptions					
		Median (IQR)	6 [3 - 6]	NA [NA - NA]	1 [1 - 3]		
		Initial daily dose, mg					
		Median (IQR)	NA	NA	NA		
		Missing, n (%)	NA	NA	NA		
		Cumulative daily dose, mg					
		Median (IQR)	NA	NA	NA		
		Missing, n (%)	NA	NA	NA		
18+	Cyclosporine	**Number of subjects**					
		count (n)	5	<5	<5	12	23

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Duration, days					
		Median (IQR)	20 [4 - 36]	NA [NA - NA]	NA [NA - NA]	62 [50 - 124]	146 [94 - 490]
		Number of prescriptions					
		Median (IQR)	20 [12 - 36]	NA [NA - NA]	NA [NA - NA]	2 [1 - 4]	2 [2 - 6]
		Initial daily dose, mg					
		Median (IQR)	NA	NA [NA - NA]	NA [NA - NA]	100 [50 - 169]	199 [99 - 275]
		Missing, n (%)	NA	NA (NA%)	NA (NA%)	0 (0%)	0 (0%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	NA [NA - NA]	NA [NA - NA]	5,100 [4,062 - 25,875]	27,250 [21,925 - 96,450]
		Missing, n (%)	NA	NA (NA%)	NA (NA%)	0 (0%)	0 (0%)
18+	Hydroxychloroquine	**Number of subjects**					
		count (n)	274	639	107	455	1,820
		Duration, days					
		Median (IQR)	4 [3 - 13]	143 [56 - 412]	30 [6 - 60]	59 [50 - 141]	485 [160 - 1,240]
		Number of prescriptions					
		Median (IQR)	6 [3 - 12]	4 [1 - 11]	3 [2 - 7]	1 [1 - 2]	2 [1 - 4]
		Initial daily dose, mg					

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Median (IQR)	NA	400 [200 - 400]	13 [7 - 200]	400 [200 - 400]	199 [197 - 381]
		Missing, n (%)	NA	<5 (NA%)	0 (0%)	0 (0%)	17 (1%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	47,600 [17,300 - 134,400]	600 [400 - 1,400]	20,000 [20,000 - 40,000]	130,051 [36,000 - 333,865]
		Missing, n (%)	NA	<5 (NA%)	0 (0%)	0 (0%)	<5 (NA%)
18+	Methotrexate	**Number of subjects**					
		count (n)	27	145	32	147	372
		Duration, days					
		Median (IQR)	1 [1 - 1]	141 [53 - 338]	76 [30 - 127]	70 [30 - 210]	364 [151 - 839]
		Number of prescriptions					
		Median (IQR)	1 [1 - 2]	6 [2 - 12]	3 [1 - 5]	1 [1 - 2]	3 [1 - 5]
		Initial daily dose, mg					
		Median (IQR)	NA	2 [1 - 2]	0 [0 - 2]	2 [1 - 4]	2 [1 - 4]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)	<5 (NA%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	300 [107 - 744]	32 [2 - 132]	180 [115 - 450]	1,078 [321 - 2,889]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)	0 (0%)

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
18+	Mycophenolate mofetil	**Number of subjects**					
		count (n)	64	125	<5	41	139
		Duration, days					
		Median (IQR)	4 [3 - 8]	139 [30 - 477]	NA [NA - NA]	63 [38 - 135]	454 [122 - 1,106]
		Number of prescriptions					
		Median (IQR)	6 [4 - 10]	4 [1 - 16]	NA [NA - NA]	1 [1 - 3]	3 [2 - 5]
		Initial daily dose, mg					
		Median (IQR)	NA	1,000 [625 - 1,500]	NA [NA - NA]	1,000 [1,000 - 1,974]	998 [970 - 1,978]
		Missing, n (%)	NA	0 (0%)	NA (NA%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	224,000 [42,000 - 837,000]	NA [NA - NA]	75,000 [25,000 - 175,000]	662,500 [159,721 - 1,761,187]
		Missing, n (%)	NA	0 (0%)	NA (NA%)	0 (0%)	<5 (NA%)
18+	Prednisone/ prednisolone*	**Number of subjects**					
		count (n)	242	505	115	556	1,419
		Duration, days					
		Median (IQR)	4 [2 - 13]	7 [5 - 43]	30 [5 - 39]	100 [40 - 139]	111 [31 - 481]

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Number of prescriptions					
		Median (IQR)	4 [2 - 8]	1 [1 - 3]	2 [1 - 5]	1 [1 - 2]	2 [1 - 3]
		Initial daily dose, mg					
		Median (IQR)	NA	40 [28 - 70]	2 [0 - 12]	8 [5 - 20]	9 [5 - 15]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	23 (2%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	400 [200 - 1,000]	20 [5 - 68]	500 [400 - 1,112]	1,038 [300 - 3,951]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	11 (1%)
18+	Rituximab	**Number of subjects**					
		count (n)	49	5	7	5	
		Duration, days					
		Median (IQR)	15 [9 - 16]	365 [365 - 477]	15 [13 - 25]	30 [30 - 33]	
		Number of prescriptions					
		Median (IQR)	4 [2 - 8]	1 [1 - 2]	2 [2 - 3]	1 [1 - 2]	
		Initial daily dose, mg					
		Median (IQR)	NA	0 [0 - 0]	1,000 [1,000 - 1,000]	33 [17 - 33]	
		Missing, n (%)	NA	0 (0%)	6 (86%)	0 (0%)	

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Cumulative daily dose, mg					
		Median (IQR)	NA	100 [100 - 200]	NA [NA - NA]	1,500 [1,000 - 2,000]	
		Missing, n (%)	NA	0 (0%)	7 (100%)	0 (0%)	
18+	Tacrolimus	**Number of subjects**					
		count (n)	18	78	16	13	455
		Duration, days					
		Median (IQR)	8 [4 - 14]	28 [15 - 30]	30 [30 - 53]	30 [30 - 50]	161 [61 - 443]
		Number of prescriptions					
		Median (IQR)	14 [4 - 20]	1 [1 - 1]	2 [1 - 2]	1 [1 - 1]	1 [1 - 3]
		Initial daily dose, mg					
		Median (IQR)	NA	2 [1 - 4]	6 [3 - 9]	2 [1 - 4]	4 [2 - 5]
		Missing, n (%)	NA	66 (85%)	13 (81%)	9 (69%)	368 (81%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	84 [44 - 182]	84 [43 - 161]	337 [237 - 406]	1,327 [278 - 4,711]
		Missing, n (%)	NA	66 (85%)	13 (81%)	9 (69%)	359 (79%)

*Data presented for the most frequent glucocorticoid: prednisone in CDWBordeaux, IMASIS and SIDIAP; prednisolone in CPRD GOLD and IQVIA Germany DA

IQR: interquartile range

12.5 Other Analysis

No sensitivity analysis was performed as the broad definition of SLE was not considered appropriate after review of cohort diagnostics.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

14. DISCUSSION

14.1 Key Results

Patient-level characterisation

We included a total of 11,257 patients: 699 in CDWBordeaux, 1,555 in CPRD GOLD, 295 in IMASIS, 2,744 in IQVIA Germany DA, and 5,964 in SIDIAP for the new diagnosis cohort.

In the paediatric and adult SLE cohort, median age at diagnosis was 12 to 16 years; 49 to 54 years, respectively. The characteristics of SLE patients in both paediatric and adult cohorts were similar with respect to majority being female (paediatric: 66 to 83%, adult: 80 to 88%) and common previously used medications being anti-inflammatory/anti-rheumatic products (paediatric: 35 to 38%, adult: 8 to 53%) and systemic antibacterials (paediatric: 25 to 45%, adult: 13 to 57%). Anxiety (paediatric: 8 to 13%, adult: 6 to 27%) and other autoimmune disease (paediatric: 3 to 16%, adult: 9 to 35%) were among the most frequent comorbidities in both groups.

Patient-level DUS

We included a total of 5,687 patients: 406 in CDWBordeaux, 1,026 in CPRD GOLD, 209 in IMASIS, 999 in IQVIA Germany DA, and 3,047 in SIDIAP for the new user cohort.

Among the paediatric cohort, the most frequent treatments within the first 30 days of diagnosis are glucocorticoids (10-54%) and hydroxychloroquine (14-46%) across all the databases. The most frequent treatments within the first year of diagnosis are hydroxychloroquine (9-62%), glucocorticoids (12-62%), and mycophenolate mofetil (5-46%) across all databases. Among patients aged 5-12 years, glucocorticoid use within the first year of diagnosis ranged from 10-89% compared to 35-64% in patients aged 13-17 years. A higher proportion of patients was being prescribed glucocorticoids as compared to hydroxychloroquine in the first 30 days in CDWBordeaux and CPRD GOLD, but percentage of hydroxychloroquine users was higher when followed up for up to one year. Hydroxychloroquine use was consistently higher than glucocorticoid use in SIDIAP.

Among the adult cohort, the most frequent treatments within the first 30 days of diagnosis were hydroxychloroquine (8-32%) and glucocorticoids (11-33%). The frequent treatments within the first year of diagnosis were hydroxychloroquine (13-49%), glucocorticoids (18-42%). The third most frequently used treatment was mycophenolate mofetil (6%) in CDWBordeaux and methotrexate (4-7%) in all other databases. In both time windows, hydroxychloroquine use was consistently higher than glucocorticoid use in CDWBordeaux, CPRD GOLD, and SIDIAP; and conversely in IMASIS and IQVIA Germany DA.

Among the adult cohort, the most frequent treatments within the first year of diagnosis are hydroxychloroquine (13-49%), glucocorticoids (18-42%). The third most frequent treatment was mycophenolate mofetil (6%) in CDWBordeaux and methotrexate (4-7%) in all other databases.

The drug utilisation varied between the databases, particularly with shorter treatment duration in CDWBordeaux and IMASIS, lower initial and cumulative dose in IMASIS, compared to CPRD GOLD, IQVIA Germany DA, and SIDIAP.

In paediatric patients using hydroxychloroquine, median duration was between 50 to 501 days for primary care databases and 8 days for CDWBordeaux hospital , median initial daily dose ranged from 199 to 300 mg, median cumulative dose ranged from 20,000 to 116,600 mg. For prednisone/prednisolone, median duration was median duration was between 74 to 246 days for primary care databases and 13 days for CDWBordeaux hospital, median initial daily dose ranged from 10 to 60 mg, median cumulative dose ranged from 775 to 2,150 mg.

In adult patients using hydroxychloroquine, median duration was 39 to 485 days for primary care databases and 4 to 30 days for hospital databases, median initial daily dose ranged from 13 to 400 mg, median cumulative dose ranged from 600 to 130,051 mg. For prednisone/prednisolone, median duration was 7 to 111 days for primary care databases and 4 to 30 days for hospital databases, median initial daily dose ranged from 2 to 40 mg, median cumulative dose ranged from 20 to 1,038 mg.

14.2 Limitations of the research methods

The study was informed by routinely collected health care data and so data quality issues, such as reliability and relevance must be considered. In particular, the identification of SLE patients and the recording of the co-morbidities may vary across databases and while relatively few false positives would be expected (i.e. those recorded with a condition who do not truly have the condition), false negatives (i.e. those with a condition that is not recorded) may be more likely especially for databases without patient-level linkage from primary care to secondary care data. There is scarce data on the validation of the SLE phenotype in administrative databases in Europe (11, 12). The SLE phenotype used in this study is defined using coding only and does not based upon other clinical data such as symptoms and autoantibody laboratory tests.

In addition, the recording of comorbid conditions and medication use defined for patient characterisation may vary across databases, at times because of selection bias. For example, we observed higher prevalence of rheumatoid arthritis in IQVIA DA Germany, as most of the SLE patients in that data source come from specialist rheumatology clinics rather than primary care data. In databases with information on SLE treatment, the recording of treatment use may be incomplete. This may affect differently primary care/outpatient and hospital records data. While the former are likely more complete for previous medication history, the latter is probably more complete for hospital-based treatments. We observed generally a lower prevalence of comedication in CDWBordeaux and IMASIS as compared to the other data sources, possibly because of lack of recording of outpatient treatment. To mitigate selection bias, we have

also specified a new user design for drug utilisation to exclude prevalent users. However, the definition of incident users is subject to the initial treatment being recorded in the data sources, which might not always be true in case of incomplete drug use data. CDWBordeaux and IMASIS cover hospital records and the treatment prescribed in hospital may not be the entire treatment of the patient. The medication dose may be underestimated if the medication code did not contain quantified concept which could be mapped to the CDM. In this case, the number of medication box would be considered in the calculation of dosages rather than the number of tablets. Finally, we did not differentiate between acute steroid treatments for the management of flares and long-term steroid exposure.

Small numbers of the paediatric cohort caused the treatment pathways to be obscured. For future studies, we will further specify rules for counts depending on possible treatment combinations for treatment patterns analysis in the standard catalogue to aid feasibility assessment.

14.3 Interpretation

The percentage of paediatric patients among the SLE new diagnosis cohort across the databases is lower than 5%, which is in line with the rarity of the disease, especially under the age of 5 years (13). The median age of the paediatric patients in our study covers the range where peak juvenile-onset SLE (JSLE) manifests, which is between 12 and 14 years old (14). The higher proportion of male patients in paediatric as compared to adult cohort in our study was also observed in the JSLE cohort in the UK (15). However, the majority of patients were female in both the paediatric and adult cohorts.

The most frequent first line treatments in both cohorts observed in our study appeared in line with the European treatment guidelines (2, 4), with hydroxychloroquine and glucocorticoids recommended for any disease severity, and methotrexate and mycophenolate as first line for moderate or severe disease. Rituximab was used rarely in both cohorts, only in one hospital database. However, we were unable to distinguish between mild, moderate, or severe SLE in our study. The duration of glucocorticoids in paediatric patients in our study was generally longer than adult patients. This is concerning as there is mounting evidence for steroid sparing in JSLE because of the increased risk of steroid-related adverse effects (16). While there are suggested doses of steroids including tapering in adult SLE treatment guidelines (2, 3), the appropriate use and dose of corticosteroids in JSLE has yet to be defined (4). The steroid doses used in some of the JSLE induction therapy was even higher than the adult treatment recommendations (16). It is well established in the literature that disease severity of SLE is higher in children than adults (1), combined with our observation in this study that steroid-sparing treatments such as methotrexate is rarely used in children, these could be reasons why steroid use is higher in children.

14.4 Generalisability

The study included paediatric and adult patients newly diagnosed with SLE from 5 different data sources across Europe. While we consider this representative of the source populations in the respective countries, we limited the new drug user cohort to patients initiated SLE treatments after SLE diagnosis, where we may have excluded patients if there was a lag in recording of diagnosis. However, this exclusion criterion was necessary as a proxy for indication of SLE in users of glucocorticoids.

14.5 Other information

None

15. CONCLUSION

The most frequent treatment for SLE was similar in paediatric and adult patients, being hydroxychloroquine and glucocorticoids, with a higher proportion of use in paediatric patients, with adults exposed to a wider range of treatment such as methotrexate. The duration and dose of SLE treatments varied between databases, particularly between primary care and hospital settings. Worryingly, children with SLE were exposed to longer and higher cumulative doses of systemic glucocorticoids compared to adults, suggesting the need for further guidance and for alternative therapeutic options in JSLE.

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17. ANNEXES

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

Appendix I: Definition of SLE Diagnosis and Treatments

Table 1: Code list for SLE.

CONCEPT_ID	CONCEPT_NAME
4295179	Acute systemic lupus erythematosus
36676444	Autosomal systemic lupus erythematosus
4346976	Bullous systemic lupus erythematosus
37110504	Chorea co-occurrent and due to systemic lupus erythematosus
4044056	Chorea in systemic lupus erythematosus
37110517	Demyelination of central nervous system co-occurrent and due to systemic lupus erythematosus
4269448	Dilated cardiomyopathy due to systemic lupus erythematosus
46273369	Endocarditis due to systemic lupus erythematosus
4296502	Fulminating systemic lupus erythematosus
37016279	Glomerular disease due to systemic lupus erythematosus
4055640	Lung disease with systemic lupus erythematosus
4299106	Lupus disease of the lung
4057084	Lupus hepatitis
4344399	Lupus panniculitis
4344495	Lupus vasculitis
4105023	Myopathy due to disseminated lupus erythematosus
46270384	Nephropathy co-occurrent and due to systemic lupus erythematosus
37399735	Nephrosis co-occurrent and due to systemic lupus erythematosus
37395585	Nephrotic syndrome co-occurrent and due to systemic lupus erythematosus
4101469	Pericarditis secondary to systemic lupus erythematosus
4105637	Polyneuropathy in disseminated lupus erythematosus
4319305	Rash of systemic lupus erythematosus
4145240	Renal tubulo-interstitial disorder in systemic lupus erythematosus
4217054	Retinal vasculitis due to systemic lupus erythematosus
37117740	Secondary autoimmune hemolytic anemia co-occurrent and due to systemic lupus erythematosus
4285717	SLE glomerulonephritis syndrome
4250483	SLE glomerulonephritis syndrome, WHO class I
4186940	SLE glomerulonephritis syndrome, WHO class II
4297164	SLE glomerulonephritis syndrome, WHO class III
4267801	SLE glomerulonephritis syndrome, WHO class IV
4178133	SLE glomerulonephritis syndrome, WHO class V
4002526	SLE glomerulonephritis syndrome, WHO class VI

257628	Systemic lupus erythematosus
4318863	Systemic lupus erythematosus encephalitis
4301051	Systemic lupus erythematosus of childhood
4344400	Systemic lupus erythematosus with multisystem involvement
4344158	Systemic lupus erythematosus with organ/system involvement
4149913	Systemic lupus erythematosus with pericarditis
44814064	Systemic lupus erythematosus/Sjogren's overlap syndrome
4300204	Systemic lupus erythematosus-associated antiphospholipid syndrome
4219859	Systemic lupus erythematosus-related syndrome

SLE Treatments

Table 2: Preliminary code list for SLE treatments.

Class	Treatment	WHO ATC code	Ingredient ConceptID
Antimalarial	Hydroxychloroquine	P01BA02	1777087
DMARD	Methotrexate	L01BA01 L04AX03	1305058
	Azathioprine	L04AX01	19014878
	Mycophenolate Mycophenolate mofetil	L04AA06	19068900 19003999
	Cyclophosphamide	L01AA01	1310317
Calcineurin inhibitors	Tacrolimus	L04AD02	950637
	Cyclosporine	L04AD01	19010482
	Voclosporin	L04AD03	739590
Biologic agents	Rituximab	L01FA01	1314273
	Belimumab	L04AA26	40236987
Glucocorticoids	Betamethasone	H02AB01	920458
	Dexamethasone	H02AB02	1518254
	Fluocortolone	H02AB03	19055344
	Methylprednisolone	H02AB04	1506270
	Paramethasone	H02AB05	19027186
	Prednisolone	H02AB06	1550557
	Prednisone	H02AB07	1551099
	Triamcinolone	H02AB08	903963
	Hydrocortisone	H02AB09	975125
	Cortisone	H02AB10	1507705
	Prednylidene	H02AB11	19011127
	Rimexolone	H02AB12	977421
	Deflazacort	H02AB13	19086888

	Cloprednol	H02AB14	19050907
	Meprednisone	H02AB15	19009116
	Cortivazol	H02AB17	19061907