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Active substance	Anifrolumab
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Date	28 April 2023

A Non-Interventional Multi-Country Post-Authorisation Safety Study (PASS) to Assess the Incidence of Serious Infections & Malignancies in Systemic Lupus Erythematosus (SLE) Patients Exposed to Anifrolumab

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	AstraZeneca AB, Södertälje, SE-151 85, Sweden
MAH contact person	[redacted] [redacted] AstraZeneca [redacted]

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1 PASS Information

Title	A Non-Interventional Multi-Country Post-Authorisation Safety Study (PASS) to Assess the Incidence of Serious Infections & Malignancies in Systemic Lupus Erythematosus (SLE) Patients Exposed to Anifrolumab
Protocol version identifier	V3.0
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Active substance	Anifrolumab (L04AA51)
Medicinal product	Saphnelo™
Product reference	EMEA/H/C/004975
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Marketing authorisation holder	AstraZeneca AB, 151 85, Södertälje, Sweden
Joint PASS	No
Research question and objectives	This is an observational study, in which the main research question is to evaluate the risk of malignancies and serious infections among moderate/severe SLE patients who receive anifrolumab compared with a comparable population of moderate/severe SLE patients on standard of care (SOC) who do not initiate anifrolumab. **Primary objectives** <u>The following objectives pertain to the malignancy outcomes</u> 1) To estimate the incidence of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab and in comparable

	moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). 2) To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). <u>The following objectives pertain to the serious infection outcomes:</u> 3) To estimate the incidence of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). 4) To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). **Secondary objectives** <u>The following objective pertain to the malignancy and serious infection outcome cohorts</u>: 5) To describe the demographic and clinical characteristics of patients in each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab versus exposed to SLE SOC). <u>The following objectives pertain to the malignancy outcomes:</u>

	6) To estimate the incidence of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). 7) To compare hazard rates of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). <u>The following objectives pertain to the serious infection outcomes:</u> 8) To estimate the incidence of serious infection components - infections leading to hospitalisation, infections requiring treatment with intravenous antimicrobials, and infections related to death – in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). 9) To estimate the incidence of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). 10) To compare hazard rates of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate

	anifrolumab (exposed to SLE SOC), where feasible (i.e., if sample size is sufficient). **Exploratory objectives** <u>The following objectives pertain to the serious infection outcomes:</u> 11) To estimate the incidence of recurrent infections leading to hospitalisation, in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). 12) To compare the hazard rates of recurrent infections leading to hospitalisation in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible.
Countries of study	Denmark, France, Germany, Spain

Authors	[redacted] [redacted] IQVIA [redacted] [redacted] [redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted]

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3 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AIDS	Acquired immune deficiency syndrome
ATC	Anatomical therapeutic chemical
BMI	Body Mass Index
CDR	Cause of Death Register
CI	Confidence intervals
CPR	Central Person Register
CPRD	Clinical practice research datalink
DCIR	*Données de consommation interrégimes* (National health insurance reimbursement database)
DDD	Defined daily dose
ENCePP	European Network of Centres of Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union electronic Register of Post-Authorisation Studies
EULAR	European League Against Rheumatism
EMA	European Medicines Agency
GM	German Modification
GP	General practitioners
GPP	Good pharmacoepidemiology practices
GVP	Good pharmacovigilance practices
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratios
HRU	Healthcare resource utilisation
ICD	International classification of diseases
ICD-O	International classification of diseases for oncology
IFN	Interferon
IR	Incidence rates
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IM	Intramuscular
IV	Intravenous
LLoQ	Lowest level of quantification
LTD	Long-term chronic disease
M	Malignancy

Abbreviation or special term	Explanation
MAH	Marketing authorisation holder
NA	Not applicable
NPR	National Patient Register
NSAID	Non-steroidal anti-inflammatory drugs
OPS	*Operationen und Prozedurenschlüssel* (Operation and procedure classification system)
PASS	Post-authorisation safety study
PMSI	*Programme de médicalisation des systèmes d'information* (Hospital discharge summaries database system)
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity score
RCT	Randomized Controlled Trial
RMPS	Register of Medicinal Product Statistics (*Lægemiddelstatistikregisteret*)
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SHI	Statutory health insurance
SI	Serious infection
SIDIAP	*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària* (System for the development of primary care research database)
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SMR	*Sygehusmedicinregisteret* (Danish National Hospital Medication Register)
SNIIRAM	*Système national d'information interrégimes de l'Assurance maladie* (French National Health Insurance database)
SNDS	*Système National des Données de Santé* (National Health Data System)
SOC	Standard of care
UK	United Kingdom
US	United States
WHO	World Health Organization

4 RESPONSIBLE PARTIES

Responsible parties	**Contact details**
Principal investigator	Mickael Arnaud, PhD Associate Director Epidemiologist IQVIA mickael.arnaud@iqvia.com
Marketing authorisation holder	[redacted] AstraZeneca [redacted]

5 ABSTRACT

Title A Non-Interventional Multi-Country Post-Authorisation Safety Study (PASS) to Assess the Incidence of Serious Infections & Malignancies in Systemic Lupus Erythematosus (SLE) Patients Exposed to Anifrolumab

Rationale and background

SLE is a chronic, multisystemic, autoimmune, systemic rheumatic disease of clinical and biologic heterogeneity. Given the individual variability in SLE manifestations, there is no single treatment paradigm. A tailored, multidisciplinary strategy is required which needs to be adjusted to patients' individual clinical manifestations. Anifrolumab, a human monoclonal antibody that binds to subunit 1 of the type 1 interferon receptor (IFNAR1), was developed based on the evidence supporting the role of type 1 interferon pathway in SLE. Anifrolumab was approved via a centralised procedure in the European Union (EU) on 14 February 2022. It is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody SLE, despite standard therapy (EMEA/H/C/004975/0000). As part of the original marketing authorisation application to the European Medicines Agency, AstraZeneca included a proposal to conduct a non-interventional multi-country post-authorisation safety study to characterise the risk of malignancies and serious infections among real-world users of anifrolumab.

Research question and objectives

The main research question is to evaluate the risk of malignancies and serious infections among moderate/severe SLE patients who receive anifrolumab compared with a comparable population of moderate/severe SLE patients on standard of care (SOC) who do not initiate anifrolumab.

Primary objectives

<u>The following objectives pertain to the malignancy outcomes:</u>

1) To estimate the incidence of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).
2) To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

<u>The following objectives pertain to the serious infection outcomes:</u>

3) To estimate the incidence of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

4) To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

Secondary objectives

The following objective pertain to the malignancy and serious infection outcome cohorts:

5) To describe the demographic and clinical characteristics of patients in each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab vs. exposed to SLE SOC).

The following objectives pertain to the malignancy outcomes:

6) To estimate the incidence of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

7) To compare hazard rates of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

The following objectives pertain to the serious infection outcomes:

8) To estimate the incidence of serious infection components - infections leading to hospitalisation, infections requiring treatment with intravenous antimicrobials, or infections related to death – in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

9) To estimate the incidence of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

10) To compare hazard rates of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible (i.e., if sample size allows).

Exploratory objectives

The following objectives pertain to the serious infection outcomes:

11) To estimate the incidence of recurrent infections leading to hospitalisation, in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

12) To compare the hazard rates of recurrent infections leading to hospitalisation in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible.

Study design

This long-term safety study is a cohort study based on secondary use of data from Denmark, France, Germany, and Spain. The study will start after anifrolumab market launch dates in each of these countries. For malignancies, the study period will end on the 31st of May 2029 and for serious infections it will end on the 31st of May 2025.

This study is based on a prevalent new-user design, i.e., adult patients with a SLE diagnosis, previous exposure to SLE SOC (indicated for moderate to severe SLE), uncontrolled SLE and initiating anifrolumab (exposed to anifrolumab) will be compared with a comparable group of patients who do not initiate anifrolumab (exposed to SLE SOC). Time-based exposure sets will be created to identify comparative study cohorts. Exposure sets will be defined within a time interval (+/- 45 days, [wider time intervals may be considered if matches cannot be obtained using this time window]) of anifrolumab initiation where all comparator members within each set match the anifrolumab exposed patient according to time since first SLE SOC prescription. Additionally, to increase comparability, comparators will be selected taking into account SLE disease activity (uncontrolled SLE despite SOC), disease severity and matched on propensity scores (PS).

Two cohorts will be constructed for the outcomes of interest (a malignancies cohort – for evaluating new malignancies as a composite outcome and for malignancies' sub-types; and a serious infections cohort – for evaluating serious infections outcomes), considering outcome-specific inclusion and exclusion criteria. In the main analysis, on-treatment definition of exposure will be considered: patients will be considered at risk while exposed to the first anifrolumab treatment (or the SOC treatment for the exposed to SLE SOC group). For the analysis of malignancy outcomes, follow-up will start after a 12-months latency period after the index date and an additional 12-months period at risk (off-drug) will be considered to capture outcomes that might occur after drug cessation.

Exposure variables

Patients exposed to anifrolumab will be defined by the initiation of anifrolumab (anatomical therapeutic chemical code L04AA51).

SLE SOC patients will be defined by the use of drugs indicated for moderate to severe SLE (in addition to antimalarials and/or low dose corticosteroids): medium to high dose corticosteroids, immunosuppressants (synthetic or biologics [except anifrolumab]), plasmapheresis or intravenous immunoglobulins.

Outcome variables

Primary outcomes

Malignancies will be defined as the first coded diagnosis for haematological malignancies and solid tumours available in the data sources.

Serious infection will be defined as an infection leading to hospitalisation, use of intravenous antimicrobials or an infection-related death, operationalised as:

- Infections leading to hospitalisation: a) infection diagnosis as part of a hospitalisation episode or b) infection diagnosis in primary or secondary care settings up to 7 days before hospitalisation.
- Prescription/administration of intravenous antimicrobials.
- Infection-related death: recorded diagnosis of infection in primary or secondary care settings with record of death within the subsequent month.

Secondary outcomes

Specific types of malignancies: haematologic, solid and skin malignancies.

Serious infection components: infection leading to hospitalisation, infection requiring treatment with IV antimicrobials and infection-related death.

Serious infection types grouped as opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately).

Exploratory outcomes

All episodes of infections leading to hospitalisation.

Other variables

The following variables will be used to describe the cohorts' characteristics and to control for confounding: demographics, lifestyle characteristics, SLE disease history (including measures of disease severity and activity), medical history and comorbidities, healthcare resource utilisation and other risk factors specific for malignancies and/or serious infections.

Data sources

This study will use secondary data from multiple countries. The final list of data sources is based on a feasibility assessment conducted between June 2022 and January 2023.

All data elements for this study will be collected from information routinely recorded in the regional and national data sources of:

- Denmark (Danish National Registries)

- France (National Health Data System)

- Germany (Statutory Health Insurance Claims)

- Spain (Information System for the Development of Primary Care Research)

Study size

Study size estimations were carried out for the primary outcomes (serious infections and malignancies) at the meta-analysis level varying four parameters – hazard ratio, standard deviation (SD) of hazard ratio, background estimate of the primary outcome, and matching ratios of exposed:non-exposed patients. Simulations were run to calculate expected power to detect a pre-specified hazard ratio (HR) given an overall sample size; and to get exact sample size estimates to achieve 80% power to detect the pre-specified HR. Three specifications of HR threshold were considered, 1.5, 1.8, and 2.0, along with two pre-specified SD (0.1 and 0.2) of HR to get an effect-distribution in lognormal space within which the true HR lies. The background estimate of incidence of serious infections was varied from 9.6 to 39.8 per 1000 person-years, while the background estimate of incidence of malignancies incidence was varied from 5.26 to 6.31 per 1000 person-years. Matching ratios of exposed to non-exposed patients were specified as 1:1 and 1:3. Achieved power was computed for sample sizes ranging from a total of 500 anifrolumab exposed patients across all study countries to 5000 anifrolumab exposed across all study countries.

Approximately **1,312** anifrolumab exposed patients across all study countries would be necessary to achieve 80% power to detect a true HR of 1.5 (geometric mean of 0.405 in lognormal space) from an effect distribution with 0.2 SD (geometric coefficient of variation of 0.132 in lognormal space) for serious infections outcome. This assumes a matching ratio of 1:3, and background IRs of serious infection of 39.8 per 1000 person years.

Approximately **3,195** anifrolumab exposed patients across all study countries would be necessary to achieve 80% power to detect a true HR of 1.5 (geometric mean of 0.405 in lognormal space) from an effect distribution with 0.2 SD (geometric coefficient of variation of 0.132 in lognormal space) for malignancy outcome. This assumes a matching ratio of 1:3, and background IRs of malignancies of 6.31 per 1000 person years.

Statistical analyses

The data analysis for all the study objectives will be performed separately for each data source and using appropriate study sub-cohorts. In this study, PS adjustment will be performed separately in each data source to control for confounding using a prevalent new user design. First, time-based exposure sets will be defined based on duration of SLE SOC use: for each exposed patient, the time-based exposure set will include all unexposed patients with a similar duration of SLE SOC use as the exposed when they become exposed to anifrolumab. A single time-conditional propensity score model will be fit using all the exposure sets. This model will then be used to compute a time-conditional propensity score for all patients (exposed and unexposed) in each time-based exposure set. Each exposed patient will then be matched with up to three unexposed patients from his time-based exposure set by selecting those patients with the closest time-conditional propensity score. Covariate balance after matching will be assessed by calculating the absolute standardised differences for each variable between the study sub-cohorts.

Descriptive analysis will be performed in the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab. Baseline characteristics will be presented before and after PS matching. For baseline characteristics collected as continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1^{st}) and upper (3^{rd}) quartiles, as well as 5^{th} and 95^{th} percentiles will be presented. For categorical variables, the numbers, and percentages of observations for each of the categories and numbers and percentages of missing values will be presented in descriptive analysis. Incidence rates and cumulative incidence, with associated 95% confidence intervals (CIs) will be presented for all relevant study objectives.

For the comparison of the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab within the study cohorts, HRs, with associated 95% CIs will be estimated for each relevant outcome. Unbalanced variables after matching will be used as covariates in the outcome models.

For the primary objectives, meta-analysis will be conducted to combine results from individual data sources. The meta-analysis for the primary objectives will be performed using results from all study countries for which comparative analysis was successfully performed. Prior to conducting the meta-analyses, heterogeneity across the study countries will be assessed. Country-level logHRs and their standard errors will be entered in a random-effect inverse-variance model. Data source-specific results and the overall combined estimate will be presented in forest plots including effect size and 95% CI for each study country included in the analysis.

Milestones

Planned study milestone dates are dependent on protocol endorsement date. Therefore, any deviation from the protocol approval date will trigger changes in all subsequent dates. Study progress will be reported in the periodic safety update reports. One joint interim report will be provided for both serious infection and malignancies outcomes, and the last interim report for malignancies only will be provided. Final study reports will be provided separately for serious infections and malignancies. Tentative study milestones are listed below:

PRAC approval	31 August 2023
Registration in the EU PAS register	30 November 2023
Start of data collection	31 May 2025
Interim report 1 (serious infections & malignancies)	31 May 2027
Final report of study results (serious infections)	30 November 2028
Interim report 2 (malignancies)	31 May 2030
End of data collection	30 November 2031
Final report of study results (malignancies)	30 November 2032

6 AMENDMENTS AND UPDATES

None (original protocol).

7 MILESTONES

Study milestones are summarised in Table 1.

Data collection (this refers to first data extraction) is expected to start on 31 May 2025. This start date considers the duration of time required to process all required ethics and data access applications in the countries of interest. This time may vary between approximately 7 and 18 months.

Study progress will be reported in the Periodic Safety Update Reports and will contain patient counts for the available data sources and any relevant amendments required for database applications. A preliminary assessment of the assumptions of anifrolumab uptake will be conducted to address the need of mitigation plans such as the inclusion of additional data sources or extension of the study time period.

One joint interim report (Interim report 1 SI & M) will be submitted for the *serious infections* and *malignancy* outcomes on 31 May 2027. Another interim report (Interim report 2 M) will be submitted exclusively for the *malignancy* outcome on 31 May 2030. Interim report 1 will contain descriptive analyses relevant to primary and secondary objectives, only for those data sources for which relevant data are available for reporting. The assumptions of anifrolumab uptake will be re-assessed to evaluate the feasibility of the final study report milestones. If the assumptions do not hold, mitigation steps will be explored.

The second interim report is related to *malignancy outcomes* and will be submitted 36 months after the first interim report. It will contain descriptive analyses relevant to primary and secondary objectives, only for those data sources for which relevant data are available for the reporting.

The final study reports are planned[1] for 30 November 2028 for *serious infections outcomes* and for 30 November 2032 for *malignancy outcomes*, provided that required sample sizes are reached at that time. It is estimated that the required sample size of 1,312 anifrolumab users for the serious infections outcomes, and 3,195 anifrolumab users for the malignancies outcome (see Section 10.5.2) will be attained, under the assumption that anifrolumab uptake will increase during the study period from less than 1% to ~16% at the end of the study enrolment (see Section 10.5.1 and Table 27 for further details on the estimated number of annual anifrolumab users in each data source). However, these assumptions of anifrolumab uptake will be assessed at the progress report and the first interim report to confirm the milestones for the final study reports. The final study reports will include all descriptive, comparative, exploratory, sensitivity analyses and meta-analysis for all the data sources for the outcomes of interest.

[1] Assuming protocol approval by PRAC on 31st August 2023.

Table 1 Study milestones

Milestone	Planned date[a]
PRAC approval	31 August 2023[b]
Registration in the EU PAS register	30 November 2023
Start of data collection[c]	31 May 2025
Interim report 1 (SI & M)	31 May 2027
Final report of study results (SI)	30 November 2028
Interim report 2 (M)	31 May 2030
End of data collection[d]	30 November 2031
Final report of study results (M)	30 November 2032

[a]Schedule is dependent on the date of protocol approval by PRAC. Any deviations from this tentative date may lead to an amendment of all subsequent dates.
[b]This is a tentative date and will be revised to reflect actual date of approval if needed.
[c]Date at which data extraction starts.
[d]Date at which the analytical dataset is completely available.
Abbreviations: EU PAS - European Union electronic Register of Post-Authorisation Studies; PRAC - Pharmacovigilance Risk Assessment Committee SI - Serious Infections Outcomes; M – Malignancies Outcomes

8 RATIONALE AND BACKGROUND

8.1 Disease burden of SLE

Systemic Lupus Erythematosus (SLE) is a chronic, multisystemic, autoimmune rheumatic disorder with a disease course characterised by periods of exacerbations and reduced activity or less commonly remission [71]. The multisystem disease is characterised by the production of autoantibodies and the occurrence of tissue damage resulting from inflammation and deposition of immune complexes as well as SLE-specific treatments [73]. There is significant heterogeneity in the clinical and biological manifestations with variable involvement of multiple organ systems including the skin, joints, kidneys, neurological and haematological systems. The fluctuating time course and diverse manifestations of SLE can lead to delays in diagnosis [73].

Epidemiological studies on SLE show marked gender, age, racial, temporal, and regional variations. Women are disproportionally more affected than men, with estimated female: male ratios ranging from 8:1 to 15:1 and peak incidence occurring between the ages of 15 and 45 years [71, 73]. Disease burden is estimated to be 2 to 3 times higher in people of African and Asian descent compared to people of Caucasian descent [70].

Globally, the incidence of SLE ranges from 0.3 to 23.7 cases per 100,000 person-years [71]. In the European Union (EU) and the United States of America (USA), incidence of SLE is estimated to range from 3.3 to 5.0, and 1.8 to 23.7 per 100,000 person-years [71] respectively. Prevalence estimates of SLE are 6.5 to 178.0 per 100,000 persons globally, 40.0 to 143.7 per 100,000 persons in the USA and 25.4 to 91.0 per 100,000 persons in Europe [71]. The prevalence of SLE has been increasing in recent years in the USA and in the United Kingdom (UK) [74, 96].

SLE is a complex, heterogenous disease with unknown aetiology. Identified risk factors include inherent genetic susceptibility, environmental triggers (sunlight/ultraviolet light, infection, smoking, alcohol), and immune system dysregulation [17, 21, 24, 61, 62].

8.2 Current treatment paradigm

Given the individual variability in SLE manifestations, there is no single treatment paradigm. A tailored, multidisciplinary strategy is required which needs to be adjusted to patients' individual clinical manifestations. The 2019 update of the European League Against Rheumatism (EULAR) recommendations for the management of SLE advises that treatment goals include long-term survival, prevention of organ damage, and optimisation of health-related quality of life [33].

For mild disease, first line treatments include antimalarials (e.g., hydroxychloroquine) and oral glucocorticoids (e.g., prednisone). Treatment options for moderate to severe disease and refractory disease (in addition to antimalarials and glucocorticoids) include conventional synthetic immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide), calcineurin inhibitors, and more recently biologics such as anifrolumab and

belimumab. Rituximab (and it is biosimilars) are considered in severe, organ-threatening refractory cases [33].

Excluding the biologics, current therapy options are non-specific and inhibit broad inflammatory pathways that are not always relevant to SLE pathogenesis, leading to significant toxicity and organ damage [57]. Long-term use of hydroxychloroquine can cause retinopathy and poor adherence to treatment remains an issue with this drug [33]. Glucocorticoids are powerful immunosuppressant and anti-inflammatory agents that remain a mainstay of treatment for mild to severe disease [4]. Although glucocorticoids provide benefits in SLE, over time, organ damage from glucocorticoid use increases. Chronic glucocorticoid use is a contributing factor in long-term morbidity and early cardiovascular mortality [1, 68, 77] and the risk of irreversible organ damage increases with glucocorticoid dose [69, 90]. The use of non-specific conventional immunosuppressants is associated with an increased risk of infection, malignancy, and cardiovascular disease [8, 40, 41, 82]. Furthermore, these conventional immunosuppressants are not effective in all patients for all manifestations of SLE.

In the EU, belimumab and anifrolumab are the only medicines approved for SLE in the last 60 years since hydroxychloroquine was approved for use in discoid lupus and SLE. Belimumab, a neutralising anti-B-lymphocyte stimulatory monoclonal antibody, was approved by the European Medicines Agency in 2011, for the treatment of adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti- double stranded deoxyribonucleic acid and low complement) despite standard therapy. It targets one pathway, while patients are likely to have different underlying immunopathological pathways driving their SLE disease manifestations [26]. As such, it is not effective in all patients [7]. Anifrolumab, a human monoclonal antibody that binds to subunit 1 of the type 1 interferon receptor (IFNAR1) which was developed based on the evidence supporting the role of type 1 interferon pathway in SLE [37], was approved in the EU, via a centralised procedure, in 2022 as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy. This was based on clinical trial evidence from TULIP 1, TULIP 2 and Phase 2 MUSE which showed that monthly administration of anifrolumab led to a higher percentage of patients with a response, assessed with the British Isles Lupus Assessment Group–based Composite Lupus Assessment, compared to patients receiving placebo [38, 65].

8.3 Serious infections and knowledge gaps

SLE patients have an intrinsically dysfunctional immune system which is exacerbated by disease activity that leaves them vulnerable to infection compared to the general population. Furthermore, treatment with immunosuppressive agents, even in the absence of other impairments of host defences, increases susceptibility to infection. This makes infections a major cause of morbidity and mortality among SLE patients.

Type 1 Interferons (IFN) are a fundamental innate defence system against viral infections. Large quantities of IFNs are produced during viral infections, resulting in the inhibition of viral

replication. As anifrolumab binds to IFNAR1, blocks dimerisation of IFNAR2 and reduces the number of available IFNAR1 receptors, there may be a potential risk of increased susceptibility to infections during treatment on anifrolumab.

In placebo controlled clinical trials, patients exposed to anifrolumab showed higher frequency of infections when compared with placebo, particularly upper respiratory tract infections (34.4% vs. 23.2%), bronchitis (10.7% vs. 5.2%), herpes zoster (6.1% vs. 1.3%) and respiratory tract infection (overall) (3.3% vs. 1.5%) [29]. The majority of the infections in patients exposed to anifrolumab were mild or moderate in intensity. In addition, patients exposed to anifrolumab showed lower frequency of non-opportunistic serious infections when compared with placebo (4.8% vs. 5.6%) [92]. In phase III long term safety data, the most common non-opportunistic serious infection was pneumonia in both the anifrolumab and the placebo group. Pneumonia was also the commonest cause of fatal infections [28].

8.4 Malignancies and knowledge gaps

Published studies have identified an increased frequency of some malignancies among patients with SLE, particularly for non-Hodgkin's lymphoma, leukaemia, and cancer of the vulva, lung, thyroid, and liver [13]. Although there is a decreased risk of other select types of cancer in patients with SLE, the overall cancer risk in SLE is slightly greater as compared with the general population [13]. Possible pathways linking SLE and malignancies include inherent immune system abnormalities, SLE medication exposures, interactions between medication and viral exposure, co-existing conditions (such as Sjögren's syndrome) and presence of "traditional" risk factors for malignancy (such as smoking, obesity and reproductive history) [10, 52, 59, 103].

Treatments that induce immune suppression may impair immune surveillance and thereby increase the risk for initiation or growth acceleration of malignancies. Furthermore, Type 1 IFNs may play a role in tumour surveillance. Therefore, while blocking type 1 IFN might be beneficial in controlling autoimmune diseases, the same pathway of suppression could potentially increase the risk of malignancies.

The impact of treatment with anifrolumab on the potential risk of malignancies is not known. In the placebo-controlled clinical trials, at any dose, malignant neoplasms (including non-melanoma skin cancers) were reported in 1.3% patients receiving anifrolumab, compared to 0.6% patients receiving placebo [92]. Malignancies excluding non-melanoma skin cancers were observed in 0.7% and 0.6% of patients receiving anifrolumab and placebo, respectively. In patients receiving anifrolumab, breast and squamous cell carcinoma were observed in more than one patient [92].

8.5 Regulatory commitment

As part of the original marketing authorisation application to the EMA, AstraZeneca included a proposal to conduct a non-interventional multi-country post-authorisation safety study to characterise the important potential risks of serious infections and malignancies among real-world users of anifrolumab.

8.6 Study rationale and main aims

Considering the knowledge gaps and regulatory commitments, the main aims of this post-authorisation safety study are to assess the risk of serious infections and malignancies in a population of patients receiving treatment with anifrolumab compared to a comparable population of SLE patients who receive standard therapy.

9 RESEARCH QUESTION AND OBJECTIVES

This is an observational study, in which the main research question is to evaluate the risk of malignancies and serious infections among moderate/severe SLE patients who receive anifrolumab compared with a comparable population of moderate/severe SLE patients on standard of care (SOC) who do not initiate anifrolumab.

To address this research question two study cohorts will be defined - one for the evaluation of malignancy outcomes and the other for the evaluation of serious infection outcomes. Further details of each study cohort definition are provided in Section 10.2.2.

The specific research objectives (primary, secondary, and exploratory) to answer the research question are detailed below. Within each objective section i.e., primary, secondary, and exploratory, objectives related to the malignancy outcomes are specified first, followed by serious infection-related objectives.

9.1 Objectives

The following objectives pertain to the malignancy outcomes:

1) To estimate the incidence of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).
2) To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

The following objectives pertain to the serious infection outcomes:

3) To estimate the incidence of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).
4) To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

Secondary objectives

The following objective pertains to the malignancy and serious infection outcome cohorts:

5) To describe the demographic and clinical characteristics of patients in each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab vs. exposed to SLE SOC).

The following objectives pertain to the malignancy outcomes:

6) To estimate the incidence of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

7) To compare hazard rates of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

The following objectives pertain to the serious infection outcomes:

8) To estimate the incidence of serious infection components (i.e., infections leading to hospitalisation, infections requiring treatment with intravenous antimicrobials, and infections related to death) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

9) To estimate the incidence of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

10) To compare hazard rates of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible (i.e., if sample size allows).

Exploratory objectives

The following objectives pertain to the serious infection outcomes:

11) To estimate the incidence of recurrent infections leading to hospitalisation, in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

12) To compare the hazard rates of recurrent infections leading to hospitalisation in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible.

10 RESEARCH METHODS

10.1 Study design

This is a protocol for conducting a multi-country, long-term safety study based on secondary use of data from Denmark, France, Germany, and Spain, allowing the inclusion of large number of patients and enhancing representativeness across the European setting. Section 10.4 provides details on the selected data sources. The study will start after anifrolumab market launch dates in the countries included in this study. Of the included studies, the first anifrolumab launch date was in Q1-2022, Table 3). The study period will end on the 31st of May 2029 for malignancies and 31st of May 2025 for serious infections. Country-specific dates of study start are detailed in Section 10.2.1.

The study is a non-interventional cohort study to evaluate the risk of malignancies and serious infections in patients who receive anifrolumab in addition to SLE SOC compared to a similar population who are on SLE SOC alone. It will consider a prevalent new-user design [88], i.e., those initiating anifrolumab (hereafter designated as exposed to anifrolumab) will be compared with a comparable group of patients who are not exposed to anifrolumab (hereafter designated as exposed to SLE SOC). The design allows for the evaluation of the effect of anifrolumab when a) there is no direct contemporaneous active comparator and b) most patients that initiate anifrolumab are likely to have been exposed to SLE SOC indicated for moderate to severe SLE in the past. According to the indication, it is expected that the number of patients initiating anifrolumab with no concomitant SLE SOC indicated for moderate to severe SLE (i.e., anifrolumab in monotherapy) will be small, as patients will be exposed to anifrolumab as an add-on therapy (polytherapy).

Exposure risk sets creation

The main challenge of the prevalent new-user design is the identification of the adequate and comparable comparators. In this study, the duration of previous exposure to SLE SOC is important in assessing disease course (and consequent risk of malignancy and serious infections). To minimise the *prevalent user bias* (Section 10.9), time-based exposure sets will be created. This approach aims at identifying a group of SLE SOC (indicated for moderate/severe SLE) comparator patients for each patient who initiated anifrolumab, taking into account the underlying person-time of observation and length of exposure to SLE SOC. The time-based exposure sets are defined within a time interval (+/- 45 days, wider time intervals may be considered if matches cannot be obtained using this time window)[2] of anifrolumab initiation where all comparator members within each set match the anifrolumab exposed patient according to time since first SLE SOC prescription (Figure 1; Section 10.7.1). This approach also means that participants in the comparator group (exposed to SLE SOC) who subsequently become exposed to anifrolumab during their follow up

[2] The identification of SLE SOC prescriptions given at the same time as the point at which patients start anifrolumab may not be possible. The time interval is defined to capture SLE SOC prescribed for longer periods with the assumption of limited changes in the disease severity and activity during the same period.

will be censored as comparators at the time of anifrolumab initiation. Participants may contribute to the exposed group at the time they become exposed (with their own risk set of eligible patients constructed). Additionally, to promote comparability with anifrolumab patients, comparators will be selected taking into account SLE disease activity (uncontrolled SLE despite SOC) and disease severity (moderate and severe SLE). Patients will be further matched on a time dependent propensity score (PS) estimated at study entry with characteristics related with the probability of being exposed to anifrolumab (Section 10.7.1).

Two cohorts will be constructed for each of the outcomes of interest: new malignancies (composite and separately by malignancies sub-types) and serious infections for serious infections outcomes), considering outcome-specific inclusion and exclusion criteria (Figure 2 and Figure 3). This approach maximises sample size and overcomes cessation of follow-up due to occurrence of multiple events. Patients may be included in multiple cohorts.

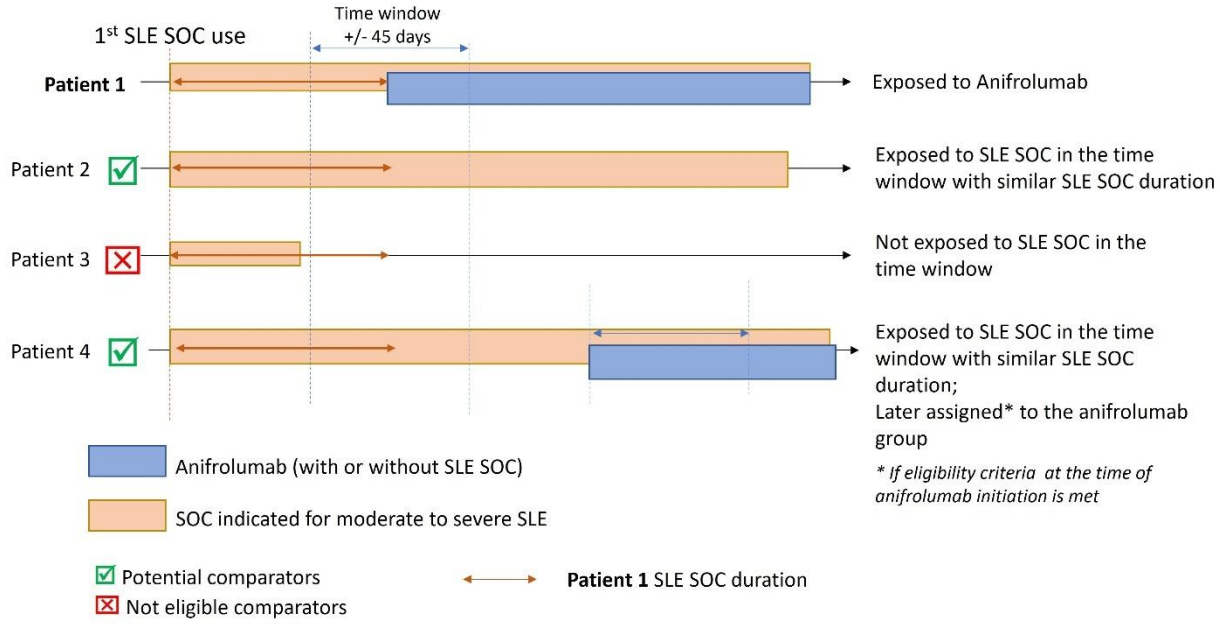

Figure 1 Time-based exposure sets for the potential eligible comparators

Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

Note: The figure presents time since the first SLE SOC (not calendar time). Patient 1 represents one patient that initiated anifrolumab; patients 2 and 4 are potential comparators for patient 1, considering SLE SOC around anifrolumab initiation for patient 1 and the same duration of SLE SOC until anifrolumab initiation.

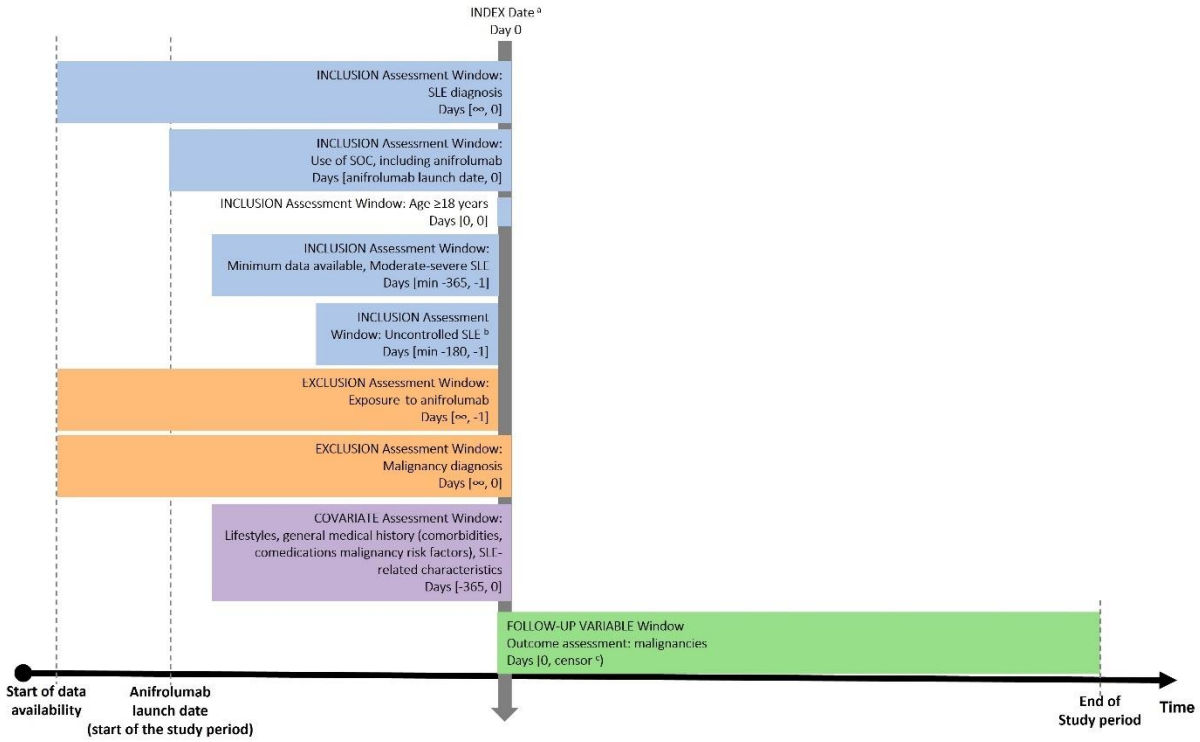

Figure 2 Overview of study design for malignancies

[a] Date of the first anifrolumab prescription (and corresponding date for SLE SOC patients).
[b] Uncontrolled SLE: ≥1 flare.
[c]Censoring criteria will be the earliest of: malignancy diagnosis; end of treatment episode; loss to follow-up (disenrollment/de-registering); death; end of study period.
Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

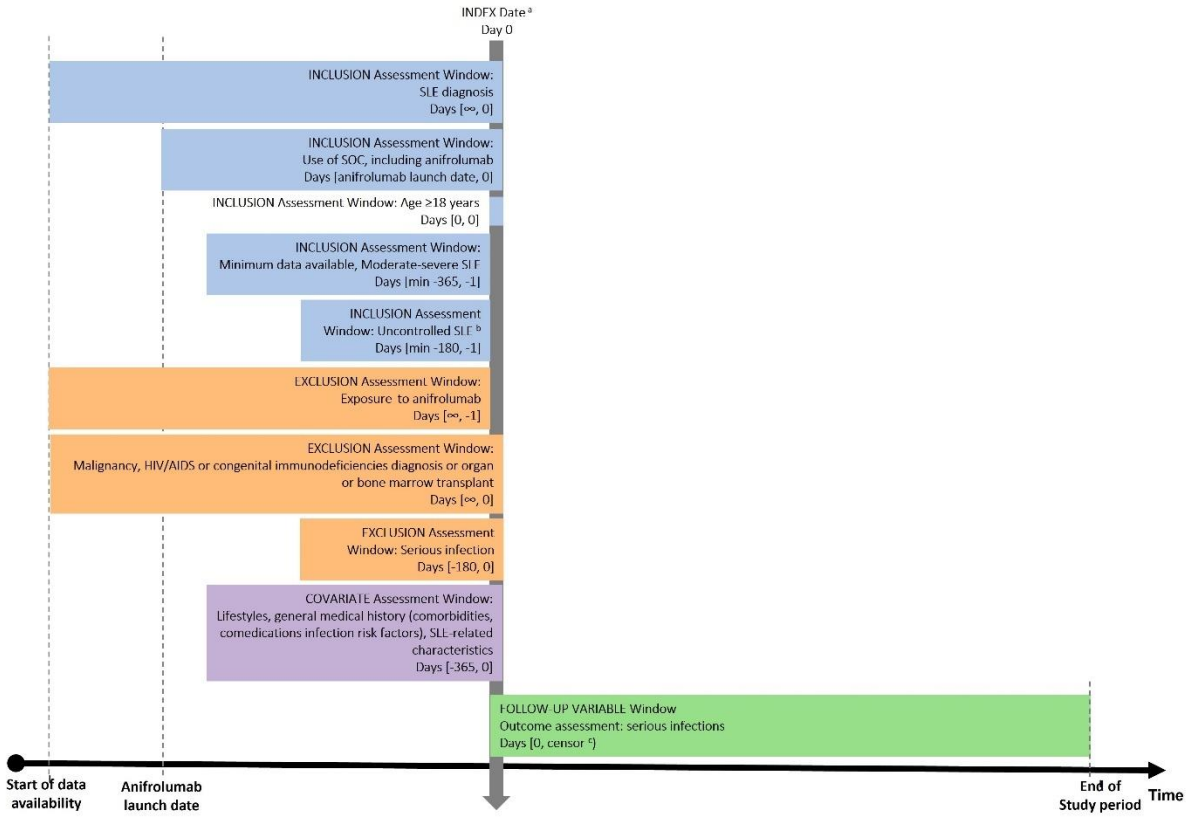

Figure 3 Overview of study design for serious infections

[a] Date of the first anifrolumab prescription (and corresponding date for SLE SOC patients).
[b] Uncontrolled SLE: ≥1 flare.
[c]Censoring criteria will be the earliest of: serious infection diagnosis; end of treatment episode; loss to follow-up (disenrollment/de-registering); death; end of study period. For the analysis of recurrent infections (exploratory objectives 11 and 12), serious infection diagnosis will not be considered as censoring variable.
Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

The summary of study design for each objective is presented in Table 2.

Table 2 Summary of study design for each objective

Obj	Description	Population[a]	Follow-up	Outcome	Analysis			Analysis stratification
					D	C	MA	
Primary objectives								
1	Estimate the incidence of new **malignancies** (composite)	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - Matching on: SOC duration, PS	12 months after index date[b] until: - End of treatment episode plus 12 months off-drug period - Occurrence of the first malignancy - Other censoring criteria[c]	First malignancy coded diagnosis	X			Treatment group (exposed and unexposed to anifrolumab)
2	Compare the incidence of new **malignancies** (composite) by treatment group	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - Matching on: SOC duration, PS	12 months after index date [b] until: - End of treatment episode plus 12 months off-drug period - Occurrence of the first malignancy - Other censoring criteria[c]	First malignancy coded diagnosis		X	X	NA
3	Estimate the incidence of **serious infections** (composite)	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS	Index date until: - End of treatment episode - Occurrence of the first serious infection - Other censoring criteria[c]	First serious infection: coded diagnosis in a hospitalisation episode; coded diagnosis (other settings) with subsequent hospitalisation; use of IV AM; death after a coded diagnosis of infection	X			Treatment group (exposed and unexposed to anifrolumab)
4	Compare the incidence of **serious infections** (composite) by treatment group	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant	Index date until: - End of treatment episode - Occurrence of the first serious infection - Other censoring criteria[c]	First serious infection: coded diagnosis in a hospitalisation episode; coded diagnosis (other settings) with subsequent hospitalisation; use of IV AM; death after a coded diagnosis of infection		X	X	NA

Obj	Description	Population[a]	Follow-up	Outcome	Analysis			Analysis stratification
					D	C	MA	
		- No prior serious infection (6 months) - Matching on: SOC duration, PS						
Secondary objectives								
5a	Describe **malignancy** cohort in terms of demographic and clinical characteristics	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - Matching on: SOC duration, PS	NA: At baseline (index date)	- Demographics - SLE disease history - Prior SOC use (drug class) - Comorbidities - Comedication - HRU - Malignancy risk factors	X			Treatment group (exposed and unexposed to anifrolumab)
5b	Describe **serious infection** cohort in terms of demographic and clinical characteristics	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS	NA: At baseline (index date)	- Demographics - SLE disease history - Prior SOC use (drug class) - Comorbidities - Comedication - HRU - Serious Infection risk factors	X			Treatment group (exposed and unexposed to anifrolumab)
6	Estimate the incidence of new **malignancies** sub-types	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - Matching on: SOC duration, PS	12 months after index date[b] until: - End of treatment episode plus 12 months off-drug period - Occurrence of the first malignancy - Other censoring criteria[c]	First malignancy sub-type (separately): - Haematological malignancies - Solid malignancies - Skin malignancies	X			Treatment group (exposed and unexposed to anifrolumab)
7	Compare the incidence of new **malignancies** sub-types by treatment group	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - Matching on: SOC duration, PS	12 months after index date [b] until: - End of treatment episode plus 12 months off-drug period - Occurrence of the first malignancy - Other censoring criteria[c]	First malignancy sub-type (separately): - Haematological malignancies - Solid malignancies - Skin malignancies		X		NA

Obj	Description	Population[a]	Follow-up	Outcome	Analysis			Analysis stratification
					D	C	MA	
8	Describe the frequency of each component of **serious infection** definition	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS	NA: At the first serious infection	First serious infection component (separately): - Infection leading to hospitalisation - Use of IV antimicrobials - Infection-related death	X			Treatment group (exposed and unexposed to anifrolumab)
9	Estimate the incidence of **opportunistic serious infections, other serious infections, pneumonia (overall, fatal and non-fatal)** (separately)	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS	Index date until: - End of treatment episode - Occurrence of the first serious infection - Other censoring criteria[c]	First serious infection sub-type (separately): - Opportunistic serious infection - Other serious infections - Pneumonia (overall) - Fatal pneumonia - Non-fatal pneumonia	X			Treatment group (exposed and unexposed to anifrolumab)
10	Compare the incidence of opportunistic serious infections, other serious infections, pneumonia (overall, fatal and non-fatal) (separately) by treatment group	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS	Index date until: - End of treatment episode - Occurrence of the first serious infection - Other censoring criteria[c]	First serious infection sub-type (separately): - Opportunistic serious infection - Other serious infections - Pneumonia (overall) - Fatal pneumonia - Non-fatal pneumonia		X		NA
Exploratory objectives								
11	Describe the incidence of recurrent infections leading to hospitalisation	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab	Index date until: - End of treatment episode - Other censoring criteria[c]	- All infections leading to hospitalisation	X			Treatment group (exposed and unexposed to anifrolumab)

Obj	Description	Population[a]	Follow-up	Outcome	Analysis			Analysis stratification
					D	C	MA	
		- No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS						
12	Compare the incidence of recurrent infections leading to hospitalisation	- Adult patients - Moderate to severe SLE - Uncontrolled SLE - Exposure to SOC or anifrolumab - No prior malignancy diagnosis - No prior HIV/AIDS or congenital immunodeficiency diagnosis - No prior transplant - No prior serious infection (6 months) - Matching on: SOC duration, PS	Index date until: - End of treatment episode - Other censoring criteria[c]	- All infections leading to hospitalisation		X		NA

Abbreviations: AIDS, acquired immune deficiency syndrome; C, comparative; D, descriptive; HIV, human immunodeficiency virus; HRU, healthcare resource utilisation; IV AM, intravenous antimicrobials; NA, not applicable; MA, meta-analysis; PS, Propensity-score; SLE, systemic lupus erythematosus; SOC, standard of care.

[a]At time of anifrolumab initiation and comparator matching.

[b]Latency period.

[c]Other censoring criteria: loss to follow-up for disenrollment/de-registering, death, or end of the study period/date of data extraction.

10.2 Setting

The study will include longitudinal patient-level data from large data sources in four countries in Europe: Denmark, France, Germany, and Spain. These data sources have been selected based on the results from feasibility assessment. Details of the feasibility and rationale for database selection are provided in Section 10.4.

10.2.1 Study time periods

The study time period for analysis will be based on availability of information from the data sources and on the date of market availability for anifrolumab. The **start of the study period** will be the market launch date of anifrolumab in each country (Table 3); this considers that all data sources included in the study are available for at least 12 months before that date (12 months correspond to the minimum look-back period before index date for confounders and/or risk factors).

The **end of study period**, defined as the last possible day of follow-up when all patients still in the study are censored, will likely differ between countries and will depend on length of data lag in each country at the time when the last data extraction is performed (Table 3). The rationale for this choice is to include all data available from relevant data sources to capture a sufficient number of outcomes and exposures for the primary outcomes at study.

Table 3 Relevant dates of the study by country

Country	Start of study period[a]	Start of enrolment[b] Date when first patient can be enrolled	End of enrolment for SI outcomes[c] Date when last patient can be enrolled	End of enrolment for M outcomes[d] Date of last patient enrolled	End of study period for SI outcomes[e] Last possible day of follow-up, when all patients still included are censored	End of study period for M outcomes[f] Last possible day of follow-up, when all patients still active are censored
Denmark	04 May 2022	04 May 2022	30 April 2025	31 May 2028	31 May 2025	31 May 2029
France	19 April 2022	19 April 2022	30 April 2025	31 May 2028	31 May 2025	31 May 2029
Germany	11 March 2022	11 March 2022	30 April 2025	31 May 2028	31 May 2025	31 May 2029
Spain	May 2023 (Tbc)	May 2023 (Tbc)	30 April 2025	31 May 2028	31 May 2025	31 May 2029

Abbreviations: SI, serious infection; M, malignancy; Tbc, to be confirmed.

[a]Anifrolumab market launch date.

[b]Start of enrolment is same for the serious infections and malignancy cohorts.

[c]For infections the last patient will be included 1 month before the end of study period.

[d]For malignancies the last patient will be included 12 months before the end of study period.

[e]Calculated assuming that the final report is due on 30 Nov 2028, assuming a two-year lag time in data availability. Needs to be adapted by country after feasibility study.

[f]Calculated assuming that the final report is due on 30 Nov 2032, assuming a two-year lag time in data availability. Needs to be adapted by country after feasibility study.

10.2.2 Participants

10.2.2.1 Participants for the main analysis

For data extraction and the creation of study cohorts, a sequential approach will be used as presented in Figure 4 and detailed below. This approach applies to the creation of the cohorts for the main analyses of the primary, secondary, and exploratory objectives.

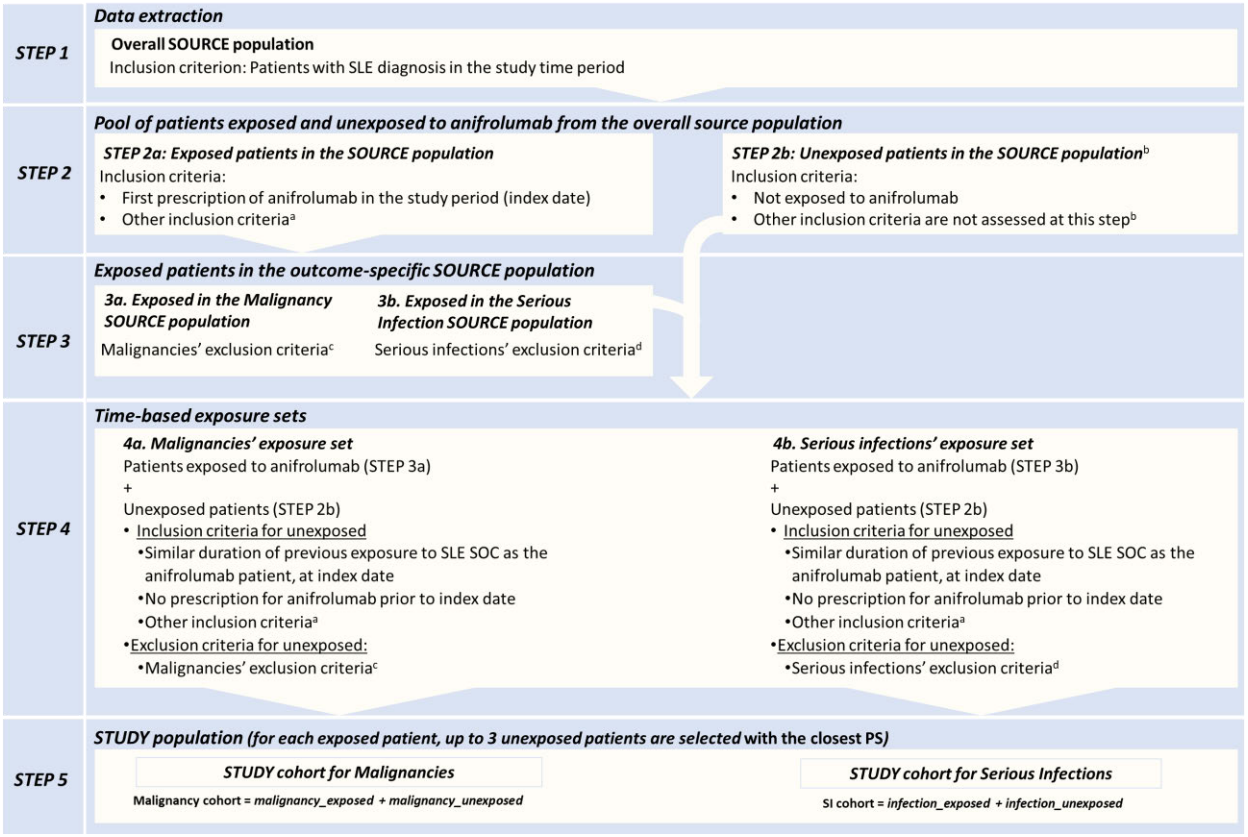

Figure 4 Overview of the data extraction and definition of the study populations

PS: Propensity-Score; SLE: systemic lupus erythematous; SI: serious infection; SOC: standard of care.

[a]Other inclusion criteria:

- A minimum data availability of 12 months prior to index date.
- Age ≥18 years, at index date.
- SLE severity: patients with moderate to severe SLE at index date.
- SLE activity: patients with at least a flare in the 6 months prior to index date.

[b]Inclusion and exclusion criteria for unexposed patients can only be applied at the creation of the exposure sets (STEP 4) because the time scale will be defined on the SLE duration of the exposed patients. Comparators do not have an index date before the identification of eligible anifrolumab patients.

[c]Malignancies' exclusion criteria:

- A diagnosis of any malignancy prior to index date.

[d]Serious infections' exclusion criteria

- A diagnosis of any malignancy prior to index date.
- A diagnosis of HIV/AIDS or congenital immunodeficiency prior to index date.
- Organ or bone marrow transplant prior to index date.
- Serious infection in the previous 6 months.

STEP 1 (Data extraction) – Overall source population

Inclusion criteria:

- Patients with SLE diagnosis (10th Revision International classification of diseases [ICD-10] codes M32.X) in the study time period.

STEP 2 – Identification of patients exposed and unexposed to anifrolumab in the overall source population

From the overall source population, exposed patients are selected. All patients not exposed to anifrolumab remain eligible to be comparators. Patients who are later exposed to anifrolumab are eligible to be comparators until then.

Step 2a. Exposed patients in the source population

Inclusion criteria:

- First prescription of anifrolumab in the study period (no anifrolumab prescription prior to index date): date of first anifrolumab prescription will be the **index date**.
- A minimum data availability of 12 months prior to index date.
- Age ≥18 years at index date.
- SLE severity (based on the SLE severity algorithm, Section 10.3.3.3): patients with moderate to severe SLE at index date[3].
- SLE activity (based on the SLE activity algorithm, Section 10.3.3.3): patients with at least a flare (uncontrolled SLE) in the 6 months prior to index date.

Step 2b. Unexposed patients in the source population

Inclusion and exclusion criteria for unexposed patients can only be applied after identifying eligible exposed patients (at step 4) because unexposed patients do not have an index date before that (the time scale will be defined on the SLE duration of the exposed patients).

STEP 3 – Identification of patients exposed to anifrolumab for the outcome-specific source population

At step 3, the *malignancy and serious infection source populations* will be created.

Step 3a. Exposed patients in the malignancy source population

Additional exclusion criteria to be applied to the exposed patients:

- A diagnosis of any malignancy prior to index date.

[3] According to the SLE severity algorithm, most moderate to severe patients will be those with a previous exposure to SOC indicated for moderate to severe disease. A very small group of patients, defined as having moderate/severe SLE based on the existence of SLE-related comorbidities, will not have a prescription of SOC for moderate/severe SLE.

Step 3b. Exposed patients in the serious infection source population

Additional exclusion criteria to be applied to the exposed patients:

- A diagnosis of any malignancy prior to index date.
- A diagnosis of HIV/AIDS or congenital immunodeficiency prior to index date.
- Organ or bone marrow transplant procedure prior to index date.
- A diagnosis of serious infection in the previous 6 months.

STEP 4 – Time-based exposure sets

This step is defined to create the time-based exposure sets, from the outcome-specific source populations. For each patient exposed to anifrolumab (identified in steps 3a and 3b) all unexposed patients from the source population (step 2b) that meet the following criteria will be included as unexposed patients.

Step 4a. Malignancy time-based exposure set

Patients exposed to anifrolumab from the malignancy source population (step 3a) and patients unexposed to anifrolumab (step 2b). Inclusion criteria for patients unexposed to anifrolumab (exposed to SLE SOC):

- At least a prescription of SOC indicated for moderate to severe SLE (Table 14).
- Duration of the previous exposure to SLE SOC similar to the SLE SOC duration of the corresponding exposed patient (+/- 45 days [wider time intervals may be considered if matches cannot be obtained using this time window]), at index date. The **index date** for the patient unexposed to anifrolumab will be the SLE SOC prescription date that will result in length of the SLE SOC treatment closer to SLE SOC treatment of the corresponding exposed patient.
- No prescription for anifrolumab prior to index date.
- A minimum data availability of 12 months prior to index date.
- Age ≥18 years at index date.
- SLE severity (based on the SLE severity algorithm, Section 10.3.3.3): patients with moderate to severe SLE at index date.
- SLE activity (based on the SLE activity algorithm, Section 10.3.3.3): patients with at least a flare (uncontrolled SLE) in the 6 months prior to index date.

Exclusion criteria for patients unexposed to anifrolumab (exposed to SLE SOC):

- A diagnosis of any malignancy prior to index date.

Step 4b. Serious infections' time-based exposure set

Patients exposed to anifrolumab from the serious infection source population (step 3b) and patients unexposed to anifrolumab (step 2b). Inclusion criteria for patients unexposed to anifrolumab (exposed to SLE SOC):

- At least a prescription of SOC indicated for moderate to severe SLE (Table 14).
- Duration of the previous exposure to SLE SOC similar to the SLE SOC duration of the corresponding exposed patient (+/- 45 days, [wider time intervals may be considered if matches cannot be obtained using this time window]), at index date. The **index date** for the patient unexposed to anifrolumab will be the SLE SOC prescription date that will result in length of the SLE SOC treatment closer to SLE SOC treatment of the corresponding exposed patient.
- No prescription for anifrolumab prior to index date.
- A minimum data availability of 12 months prior to index date.
- Age ≥18 years at index date.
- SLE severity (based on the SLE severity algorithm, Section 10.3.3.3): patients with moderate to severe SLE at index date.
- SLE activity (based on the SLE activity algorithm, Section 10.3.3.3): patients with at least a flare (uncontrolled SLE) in the 6 months prior to index date.

Exclusion criteria for patients unexposed to anifrolumab (exposed to SLE SOC):

- A diagnosis of any malignancy prior to index date.
- A diagnosis of HIV/AIDS or congenital immunodeficiency prior to index date.
- Organ or bone marrow transplant procedure prior to index date.
- A diagnosis of serious infection in the previous 6 months.

STEP 5 – Propensity score matching to define the study populations

From the malignancy and serious infection time-based exposure sets, the respective study cohorts will be created. For each exposed patient, up to three unexposed patients (exposed to SLE SOC) with the closest PS are selected to create the final combinations of exposed-unexposed patients.

For the purpose of the evaluation of malignancies as composite outcome (primary outcome) and separately for specific types of malignancies (secondary outcomes), the *Malignancy* cohort will include sub-cohorts defined by the exposure to anifrolumab (exposed or unexposed to anifrolumab): *malignancy_exposed and malignancy_unexposed* (Table 4).

For the purpose of the evaluation of serious infections as composite outcome (primary outcome), separately for opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (secondary outcomes), and to evaluate the risk of recurrent infections leading to hospitalisation (exploratory outcomes), the *serious infection* cohort will include sub-

cohorts defined by the exposure to anifrolumab (exposed or unexposed to anifrolumab): *infection_exposed and infection_unexposed* (Table 4).

Table 4 Cohorts, sub-cohorts by objective

Objective	Main features	Input cohort/population	Sub-cohorts' abbreviation[a]
Primary cohort *malignancy* (*malignancy_exposed* + *malignancy_unexposed*)			
Primary objective 1 Secondary objective 6	Estimate the incidence of new malignancies outcome (composite and separately).	***Malignancy cohort***	***malignancy_exposed*** ***malignancy_unexposed***
Primary objective 2 Secondary objective 7	Estimate hazard ratio of new malignancies outcome (composite and separately).		
Secondary objective 5	Describe cohort demographic and clinical characteristics.		
Primary cohort *serious infections* (*infection_exposed* + *infection_unexposed*)			
Primary objective 3 Secondary objectives 8, 9 Exploratory objective 11	Estimate the incidence of serious infections outcome (composite and separately). Estimate the incidence of all infections leading to hospitalisation	***Serious infection cohort***	***infection_exposed*** ***infection_unexposed***
Primary objective 4 Secondary objective 10 Exploratory objective 12	Estimate hazard ratio of serious infections outcome (composite and separately). Estimate hazard ratio of all infections leading to hospitalisation		
Secondary objective 5	Describe cohort demographic and clinical characteristics.		

[a]*Exposed* and *unexposed* defined by the exposure to anifrolumab: exposed or unexposed to anifrolumab, respectively.

10.2.2.2 Participants for sensitivity analyses, per type of SLE SOC (biologics and non-biologics)

For the primary outcomes (objectives 1 to 4), sensitivity analyses will be performed to compare patients exposed to anifrolumab with two groups of patients exposed to SLE SOC: patients exposed to SLE SOC biologics and patients exposed to SLE SOC non-biologics. Additional sub-cohorts will be re-assessed from the *overall source population* (obtained in step 1, Section 10.2.2.1). Patients initiating anifrolumab will be matched with comparable patients not exposed to anifrolumab but exposed to SLE SOC biologic drugs (belimumab or rituximab, including biosimilars) and with those exposed to SLE SOC non-biologics.

Subgroup cohorts (for malignancy and serious infection outcomes) (Table 5) will consider the same inclusion and exclusion criteria described for the main analyses (Section 10.2.2.1) from step

2 until step 4. However, at step 2 (for exposed to anifrolumab) and at step 4 (for unexposed to anifrolumab) the following additional criteria will be applied:

- Exposed patients: exclusion of patients with a prescription of SLE SOC biologics (belimumab or rituximab) in the previous 12 months.
- Unexposed to anifrolumab patients, exposed to SLE SOC biologics: inclusion of patients with a prescription of SLE SOC biologics in the previous 12 months regardless of other SLE SOC).
- Unexposed to anifrolumab patients, exposed to SLE SOC non-biologics: inclusion of patients with a prescription of SLE SOC and exclusion of those with a prescription of SLE SOC biologics in the previous 12 months.

Table 5 Subgroup cohorts for sensitivity analyses by SLE SOC treatment

Outcome	Input population	Exposed and unexposed units	Additional criteria to be applied at STEP 2 to the input population	Sub-cohorts created at STEP 4
Malignancies	*Overall source population*	Exposed to anifrolumab	EXCLUSION: Patients exposed to SLE SOC biologics in the previous 12 months	*malign_sub_exp*
		Unexposed to anifrolumab (exposed to SLE SOC biologics)	INCLUSION: Patients with SLE SOC including a biologic drug in the previous 12 months	*malign_sub_unexp_bio*
		Unexposed to anifrolumab exposed to SLE SOC non-biologics	EXCLUSION: Patients exposed to SLE SOC biologics in the previous 12 months	*malign_sub_unexp_nonbio*
Serious Infections	*Overall source population*	Exposed to anifrolumab	EXCLUSION: Patients exposed to SLE SOC biologics in the previous 12 months	*inf_sub_exp*
		Unexposed to anifrolumab (exposed to SLE SOC biologics)	INCLUSION: Patients with SLE SOC including a biologic drug in the previous 12 months	*inf_sub_unexp_bio*
		Unexposed to anifrolumab exposed to SLE SOC non-biologics	EXCLUSION: Patients exposed to SLE SOC biologics in the previous 12 months	*inf_sub_unexp_nonbio*

Abbreviations: SLE: systemic lupus erythematous; SOC: standard of care.

10.3 Variables

Variables used in this study are divided into exposure of interest (Section 10.3.1), outcome parameters of interest (Section 10.3.2), and participants characteristics and potential confounding variables (Section 10.3.3). The availability and contents of different specific variables is expected to vary between data sources. Accordingly, the inclusion, selection, and definition of specific variables may vary across data sources. Specific variable definitions will be detailed and provided as part of local protocols and the statistical analysis plan (SAP).

In this protocol, the 2019 WHO International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) has been used as the coding system for definition of diagnoses, and procedures [98].

International non-proprietary names are used as nomenclature for prescription drugs. World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system will be used for all prescription drugs in this protocol.

The ICD-10 and ATC codes used in this protocol for variable definitions will be amended to the relevant coding systems, as appropriate for the respective data sources, and will be provided in the SAP.

10.3.1 Exposure definition and variables

Exposure to the study drugs will be ascertained from recordings of outpatient visits, procedures, prescriptions dispensed at community pharmacies, and insurance claims registrations as available in the different data sources. Data availability regarding unit dose, frequency of administration, duration of therapy (start and stop dates), and dose adjustments was part of the feasibility assessment and detailed in Section 10.4.

10.3.1.1 Study drugs

SLE standard treatments can include a variety of drugs used alone or in combination, including antimalarials, glucocorticoids, immunosuppressants (synthetic and biologics), immunoglobulins and plasmapheresis (Table 14).

10.3.1.1.1 EXPOSED GROUP (ANIFROLUMAB)

The exposure of interest is anifrolumab (brand name SAPHNELO). According to the drug indication, anifrolumab is expected to be prescribed as an add-on therapy to SLE SOC. Due to the long study duration, the therapeutic indication for anifrolumab and method of administration may change over time. This may result in future use of anifrolumab without SOC indicated for moderate to severe SLE or in other forms of anifrolumab administration (e.g., subcutaneous administration). Therefore, to capture all patients exposed to anifrolumab, no requirement for concomitant SLE SOC use will be applied. Anifrolumab will be identified using the ATC code L04AA51 (or the appropriate country-specific coding system), irrespective of the administration route.

10.3.1.1.2 STANDARD OF CARE FOR MODERATE TO SEVERE SLE

In current study, SOC indicated for moderate and severe SLE, is defined as the use of any one of the following (either in addition to antimalarials and/or low dose corticosteroids or not) [33, 42, 58]:

- Medium or high dose corticosteroids (prednisolone equivalent dose ≥7.5 mg/day) either through oral or intravenous (IV) routes; **or**
- Immunosuppressants:
    - synthetic (e.g., azathioprine, methotrexate) or specific (e.g., janus kinase inhibitors such as tofacitinib); **or**
    - biologics (e.g., belimumab, rituximab): **or**
- Plasmapheresis; **or**
- IV immunoglobulins.

The selection of drugs included in the code list for SOC indicated for moderate and severe SLE is detailed in Table 14. It includes all drugs that moderate and severe SLE patients could be exposed to (including antimalarials), based on 2019 EULAR guidelines [33], published literature [49, 50, 60, 64, 75] and inputs from medical advisors. Drugs that are not in any of the provided references, or that failed in SLE clinical trials have not been included. Furthermore, the list does not consider emerging therapeutic agents (in Phase 2/3 development), as the efficacy of these therapeutic agents in the management of SLE have not been established.

Additional drugs with indication for moderate to severe SLE that are launched in any of the study countries during the study period may be considered as part of SLE SOC. Any changes in the SLE SOC code list will be communicated to PRAC in the interim reports.

10.3.1.2 Exposure assessment

Exposure will be classified using an on-treatment approach, i.e., patients will be considered exposed until the end of treatment episode or censoring. Specific criteria for malignancies and infections cohorts are detailed in Section 10.3.1.2.1 and Section 10.3.1.2.2, respectively.

Treatment episodes for patients exposed to anifrolumab

The first anifrolumab treatment episode will be considered[4]. The treatment episode is the continuous time from the date of the first prescription or administration (depending on the available data) until discontinuation plus the window of clearance (Figure 5).

Discontinuati**on** date will be calculated from the treatment start date plus the days covered by therapy if no subsequent prescription is registered after that period. **Days covered by therapy** will be based on the recommended dosing frequency for anifrolumab, i.e., it will be 30 days (4 weeks). For patients exposed to anifrolumab, duration of treatment episode will be defined regardless of concomitant use of SLE SOC.

The **window of clearance** will be defined as the time for concentration to fall below the lowest level of quantification (LLoQ) for 95% of patients. The anifrolumab window of clearance will be defined as 16 weeks.

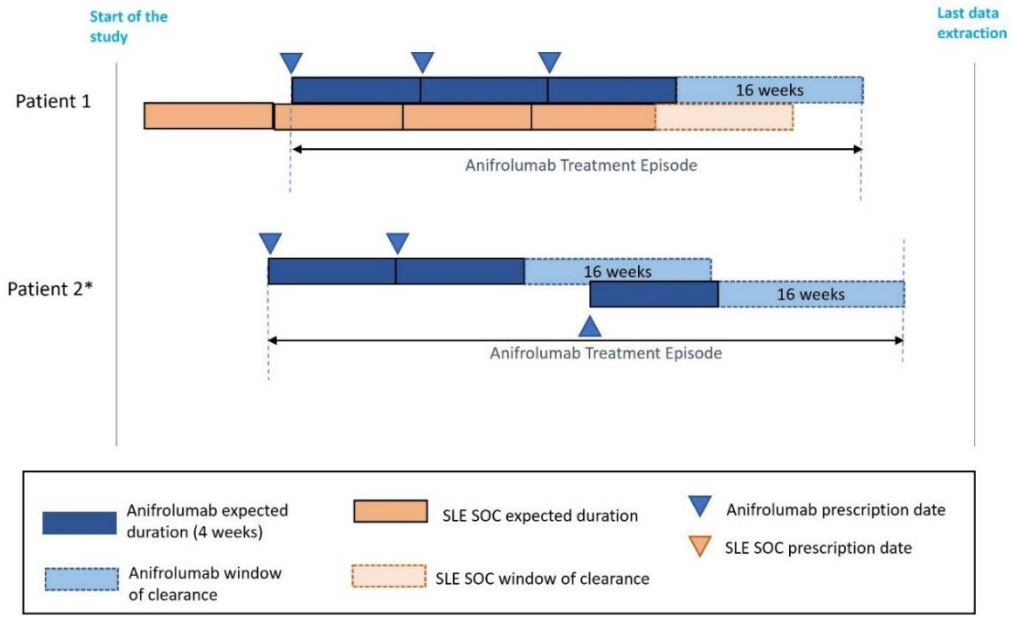

Figure 5 Treatment episodes definition for patients exposed to anifrolumab

* No concomitant SLE SOC was presented for simplicity.

Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

[4]Only first treatment is included because after anifrolumab discontinuation patients using SLE SOC may not be comparable with the non-anifrolumab users. Anifrolumab will be used as maintenance therapy and previous Randomised Controlled Trials' (RCT) results [7, 92] showed low frequency of discontinuation (until 3 years of treatment). The main reasons for anifrolumab discontinuation are expected to be adverse events (such as allergic reactions and infections) and lack of effectiveness of the drug [7], which are not likely to result in anifrolumab re-initiation. Thus, the number of anifrolumab re-starters is expected to be low and patients are likely to be different from first users. Additionally, it is not known if the risk of adverse events returns to baseline after anifrolumab discontinuation and how different are patients' characteristics after anifrolumab discontinuation.

Treatment episodes for patients unexposed to anifrolumab – exposed to SLE SOC

The **first treatment episode** is the continuous time from the date of first prescription of a SLE SOC treatment after diagnosis of moderate to severe SLE until the first date of discontinuation of that treatment plus the window of clearance (Figure 6). The index date will be assigned as the date of prescription within the time interval of the anifrolumab index date for the corresponding exposed patient (Section 10.2.2.1). Different SLE SOC drugs used (as add-on or switching between drugs) will not be counted as a different treatment if prescribed before the end of the window of clearance (patients 2 and 3 in Figure 6).

Discontinuation date will be calculated from the treatment start date plus the days covered by therapy if no subsequent prescription is registered after that period. **Days covered by therapy** are specific for each drug and will be estimated by the expected supply duration. For biologics, the period covered by a prescription will be based on the recommended dosing frequency for each biologic.

The **window of clearance** is specific for each drug and will be defined as five times the terminal half-life of the SLE SOC, or the time for concentration to fall below the lowest level of quantification (LLoQ) for 95% of patients where applicable.

After that period, if no SLE SOC prescriptions are registered, patient will be censored. Additionally, start of anifrolumab will dictate the end of SLE SOC treatment episode (patient 4, Figure 6). At the time of anifrolumab initiation patients will be considered as part of the group of patients exposed to anifrolumab.

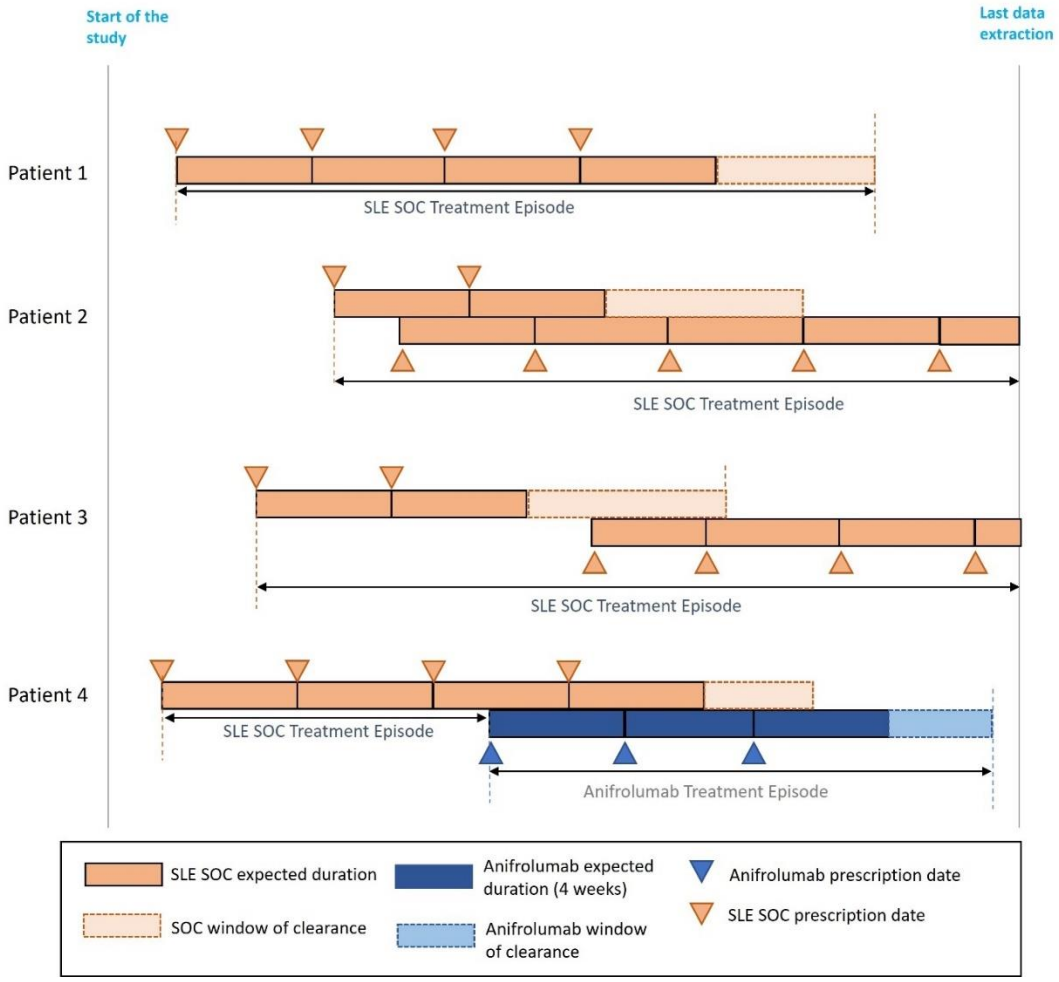

Figure 6 Treatment episodes definition for patients unexposed to anifrolumab (SLE SOC)
Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

10.3.1.2.1 FOLLOW-UP FOR THE MALIGNANCY COHORT

For the primary and secondary objectives related to malignancies, follow-up will start after a 12-months latency period after the index date (Figure 7). The latency period will be used to accommodate for the period between the exposure to drug and the diagnosis of cancer [72]. During this period, a malignancy diagnosis will not be considered an outcome of interest because of the low probability of being related with anifrolumab or other SOC new exposure. Additionally, a 12-month at risk window after the end of the treatment episode will capture malignancies diagnosed soon after drug discontinuation to avoid possible bias caused by not being able to pinpoint the discontinuation date more accurately. Thus, follow-up ends at the end of treatment episode plus 12 months, occurrence of the first malignancy or at any of the **censoring** events (i.e., loss to follow-up for disenrollment/de-registering, death, or end of the study period/date of data extraction), whichever occurs first.

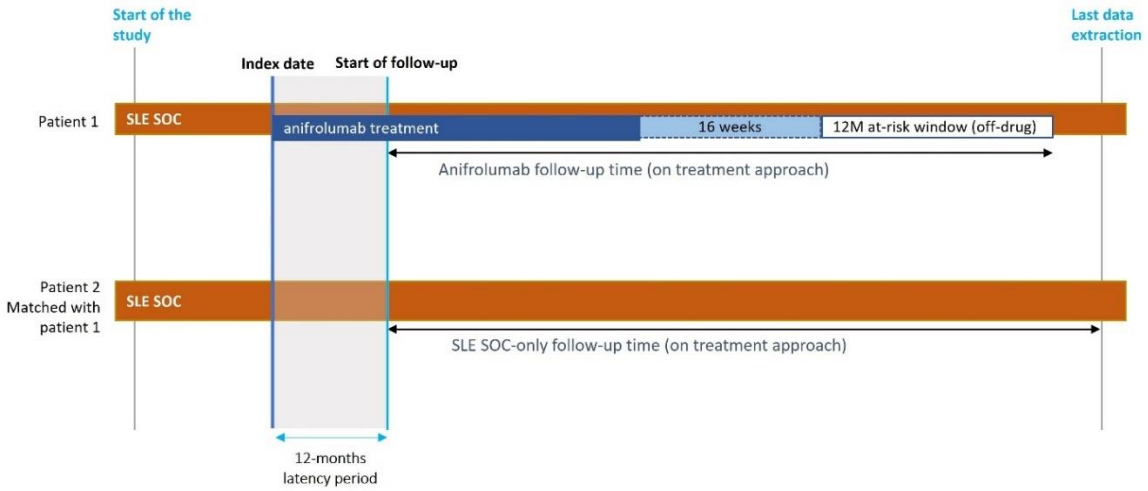

Figure 7 Follow-up assessment for the malignancy cohort (main analysis)
Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

10.3.1.2.2 FOLLOW-UP FOR THE SERIOUS INFECTION COHORT

For the serious infection primary and secondary objectives, follow-up starts at index date and ends at the end of the treatment episode (Figure 8), occurrence of a serious infection or at any of the **censoring** events (loss to follow-up for disenrollment/de-registering, death, or end of the study period/date of data extraction), whichever occurs first.

For the exploratory objective, follow-up ends at the end of treatment episode or any of the censoring events: loss to follow-up for disenrollment/de-registering, death, or end of the study period/date of data extraction, whichever occurs first.

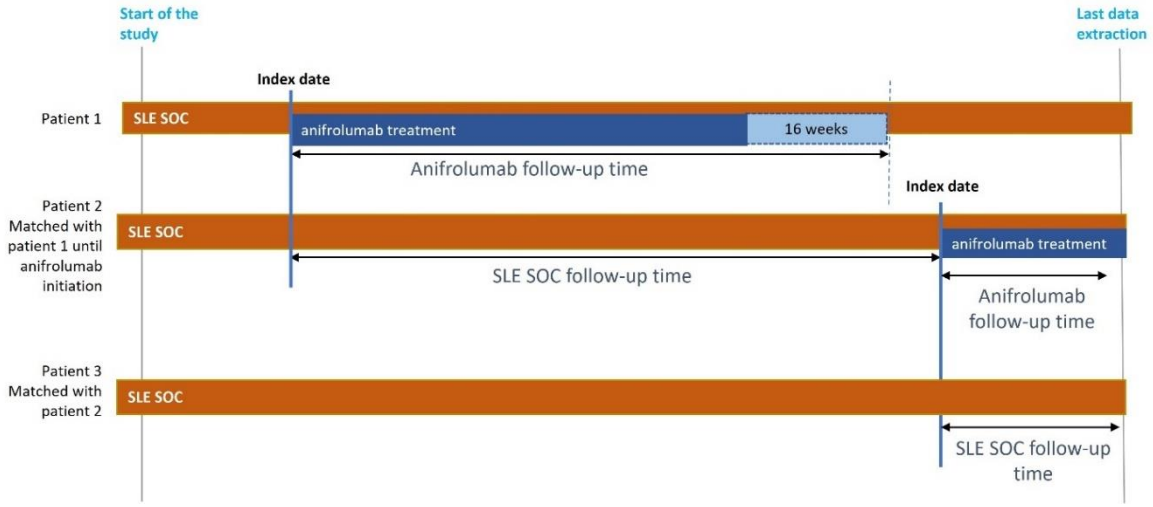

Figure 8 Follow-up assessment for the serious infection cohort (main analysis)
Abbreviations: SLE, systemic lupus erythematosus; SOC, standard of care

10.3.2 Outcome definition and variables

Outcomes will be identified in healthcare databases, prescriptions, and registries as available in the different countries. Any diagnosis variables available in the data sources will be considered.

10.3.2.1 Malignancies

As the **primary outcome**, new malignancies will include any first haematological, solid, or skin malignancies registered in the databases in the follow-up period. Benign tumours will not be included. Incident malignancies, identified by a diagnosis listed in Table 15, will be defined as new malignancies; subsequent malignancy diagnoses will not be considered.

As **secondary outcomes**, specific types of the first malignancy diagnosis will be considered. Three groups of malignancies will be considered as separate outcomes (Table 15, objectives 6 and 7): haematological, solid, and skin cancers. Within each outcome, the frequency of specific malignancies [5] (Table 15) (e.g., for haematological malignancies: non-Hodgkin's lymphoma, leukaemia, etc.; for solid cancers: lung, thyroid, breast, etc.) will be described.

If a patient is diagnosed with two or more malignancies during the study period, the follow-up time up to the occurrence of the first malignancy will be considered.

10.3.2.2 Serious infections

Serious infections are generally defined as those that result in death, are life-threatening; require inpatient hospitalisation or prolongation of existing hospitalisation; require treatment with IV antimicrobials (e.g., antibiotics, antifungals, antivirals); result in persistent or significant disability/incapacity; or are, based upon appropriate medical judgement, important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above [22, 27]. It may not be possible to identify all serious infections using this definition since it is not possible to assess some of its components from the secondary data sources e.g., if a particular infection prolonged an existing hospitalisation or led to disability.

Thus, for current study, the **primary outcome** serious infection will be defined as infections leading to hospitalisation, use of IV antimicrobials, or death. It will be defined as either of:

- Infections leading to hospitalisation:
    - Infection diagnosis as part of a hospitalisation episode (including primary and secondary diagnoses) (Table 16) [8, 78]
    - Infection diagnosis in primary or secondary care settings up to 7 days before hospitalisation (Table 16) [9, 79]

[5]The specific malignancies were defined based on the previously described increased or decreased risk among SLE patients when compared to the general population [12, 13, 84].

- Infections requiring treatment with IV antimicrobials:
    - Prescription/administration of IV antimicrobials (Table 19) [46, 51]
- Infection-related death:
    - Recorded diagnosis of infection (Table 16) in primary or secondary care settings with record of death within the subsequent 30 days [30].

Detailed operational definitions to identify the availability of serious infections data in different data sources as disease coding systems used will be defined in the SAP.

The first serious infection after index date will be included. Date of each serious infection episode will be the date of infection leading to hospitalisation, use of IV antimicrobials or death, whichever occurs first. The frequency of each serious infection component – infection leading to hospitalisation, requiring treatment with IV antimicrobials and infection-related deaths – will be described as a **secondary** objective (secondary objective 8) and comparative analyses on each component will be conducted as sensitivity analysis, where possible (Section 10.7.1.7).

As **secondary outcomes**, opportunistic serious infections, other serious infections, pneumonia (overall, fatal and non-fatal) will be analysed separately (objectives 9 and 10)[6]. Additionally, the proportion of serious infections due to COVID-19 infection will be described for patients exposed and unexposed to anifrolumab.

The definition of opportunistic infections may be challenging. To define opportunistic infections detailed clinical information is often needed and, at some level almost all agents could be considered opportunistic in that they are typically more likely to occur, or present more severely in immunosuppressed patients [99]. Therefore, classifying infections as opportunistic using secondary data is challenging. In recognition of this challenge, efforts have been made by a consensus committee (which included infectious disease, public health, and pulmonary physicians with subject matter expertise in mycobacterial, fungal, viral, bacterial or parasitic infections, as well as rheumatology physicians) to harmonize a list of infections that could be considered as opportunistic for use in clinical trials and observational studies involving biologics and other disease modifying antirheumatic drugs. The consensus list of infections was based on a systematic review of several observational studies, clinical trials, case series, and expert opinion by the committee [99].

In this study, opportunistic infections are defined based on the list of infections provided by the consensus committee with two considerations: all infections that could be mapped to ICD-10 codes

[6]Opportunistic infections are reported to be frequent among patients with autoimmune diseases. *Herpes zoster* has the highest incidence rate (IR), although frequently not considered a serious infection [47]. This is in line with results from anifrolumab RCTs that also describe *herpes zoster* as a frequent infection, together with respiratory tract infections [29]. Other classification of serious infections (by pathogen: bacterial, viral, fungal, etc) was considered but discounted, because the probability of pathogen misclassification is high in the selected data sources. Furthermore, in the available healthcare coded registries in about one third of infections the infections pathogen was not identified [76].

with certainty (Table 17) have been included; and infections (e.g., shigella) which require invasive or disseminated presentations in order to be considered opportunistic, for which there are no specific ICD-10 codes for invasive disease have been excluded.

Within all serious infections, a subset of other clinically relevant serious infections will be analysed, including respiratory tract infections (including pneumonia), sepsis, COVID-19, urinary tract infections and infections during pregnancy (Table 18).

Pneumonia will be defined regardless of the microbiologic aetiology (Table 18). Pneumonia will be analysed as a composite outcome of all identified cases and separately for fatal and non-fatal cases. Fatal pneumonia cases will be defined according to the above proposed definition of infection-related death, i.e., cases with record of death in the 30 days after the diagnosis date. All cases that do not meet this definition will be considered non-fatal.

All infections leading to hospitalisation (the first and recurrent episodes) will be considered as **exploratory outcomes**. A recurrent episode of infection will be defined as an infection leading to hospitalisation (code list available in Table 16) occurring more than 30 days after the hospital discharge date of the previous infection leading to hospitalisation.

10.3.3 Participants' characteristics and potential confounders/risk factors

The variables presented in Table 6 will be considered to describe the cohorts' characteristics (objective 5), as selection criteria or as adjustment variables for confounding control. The final choice of characteristics, risk factors and confounders will depend on the availability of data (e.g., malignancy family history) and clinical relevance. After feasibility assessment, ethnicity was excluded as a covariate since it was not available in any of the data sources (Table 26). Specific definitions will be presented in detail in the SAP.

At baseline, the variables presented in Table 6, will be considered to create the PS, since they may influence the decision of prescribing anifrolumab or other SLE SOC drugs and are considered potential risk factors for each outcome. Confounding variables will be retrieved at index date or in the look-back period as presented in Figure 2 and Figure 3.

In the following sections, specific confounders for malignancies will be presented, followed by serious infections confounders and SLE disease severity and activity. A summary of the variables for each cohort is presented in Table 6.

Table 6 Participant characteristics and confounding variables for each study cohort: malignancy and serious infection[7]

	Study cohort	
	Serious infections	**Malignancies**
Demographic characteristics		
Cohort entry year	✓	✓
Age	✓	✓
Sex	✓	✓
Socioeconomic status (including education)	✓	✓
Lifestyle characteristics		
Smoking	✓	✓
Alcohol/substance abuse	✓	✓
Height, weight, or body mass index (kg/m^2)	✓	✓
General Medical History		
Comorbidities relevant for SLE patients (Table 20)	✓	✓
Malignancy family history		✓
Procedures with radiation exposure		✓
Prior virus/infections (risk factors for malignancies) (Table 22)		✓
Previous infection (serious and non-serious infection)	✓	
Vaccines and passive immunity drugs (Table 23)	✓	
Comedication [polypharmacy] (Table 24)	✓	✓
SLE disease history and profile		
Disease duration, months (time from diagnosis to study entry)	✓	✓
Disease severity components	✓	✓
Disease activity	✓	✓
SLE standard of care (Table 14)	✓	✓

Abbreviations: SLE, systemic lupus erythematosus.

10.3.3.1 Potential confounders for the malignancy cohort

For the analysis of malignancies, potential confounders include demographics and lifestyle characteristics (as presented in Table 6), SLE history (including SLE severity, activity as detailed below) and other clinical characteristics. Some infections may be important risk factors for specific types of malignancies [6, 63] (Table 22), such as Human Papillomavirus (HPV) infection and the risk associated with cervical cancer [84] or the emergence of the oncogenic Epstein-Barr virus. HPV vaccine will be considered as reducing the risk of cervical, oropharyngeal, and anal cancer occurrence.

[7]Some data sources may not have available some of the relevant variables.

Comorbidities recognised as risk factors for cancer development will be considered, namely cardiovascular diseases [44, 45], diabetes [94], liver disease [87], kidney disease [86], chronic respiratory disease [25, 55], among others (Table 20). Likewise, several drugs have been associated with changes in the risk of cancer and will be included as covariates, namely antidiabetics [91], antihypertensives [20], antithrombotic agents [43, 53] and other recognised carcinogenic drugs (Table 24).

Furthermore, increased inflammatory activity is purported to be associated with malignancy risk. In addition to considering SLE severity and activity, other comorbidities may increase inflammatory status, namely other autoimmune diseases (excluding SLE), acquired immunodeficiencies, and chronic infections. Exposure to specific SLE drugs, such as prednisolone, cyclophosphamide, rituximab, azathioprine or cyclosporin, has also been purported to be associated with cancer development [3, 11, 100]. Adjustment for prior use of cyclophosphamide or rituximab are already taken into account when controlling the SLE severity as these drugs are used to define severe SLE. Within the group of other immunosuppressants, recognised carcinogenic drugs will be considered separately.

Family history of cancer, and radiation exposure are known risk factors of cancer and can also influence the clinical decision on the SLE prescribed drug and therefore will be considered if available in the data sources. Screening for specific malignancies (e.g., cervical, breast cancer) is not expected to prevent the occurrence of cancer but anticipate diagnosis. However, data on screening procedures may not be available in all data sources to include them as potential confounders in the study. If high quality information is available in a particular data source, then screening variables may be included in the country-specific analysis.

10.3.3.2 Potential confounders for the serious infection cohort

For the analysis of serious infections, potential confounders include demographics and lifestyle characteristics (as presented in Table 6), SLE history (including SLE severity, activity as detailed below) and other clinical characteristics.

Previous diagnosis of chronic infections (such as hepatitis B, hepatitis C, herpes simplex virus, among others [15] and other comorbidities may be important confounders of the association between anifrolumab and the occurrence of a serious infection. Thus, previous diagnoses of diabetes [35, 67, 81, 101], cardiovascular diseases [32], chronic renal disease [23, 30, 35, 67, 81], severe liver disease [30, 35, 48, 67], chronic respiratory diseases [30, 35, 55, 67, 101], autoimmune diseases (excluding SLE) [101], and immunodeficiencies [30] will be considered as confounders (Table 20). Before treatment, a vaccination plan against important infections is recommended for SLE patients, aiming at decreasing the risk of the serious infection [35]. Thus, vaccine administration for *Haemophilus influenzae B*, Hepatitis A and B, *Herpes zoster*, Influenza, Severe acute respiratory syndrome coronavirus 2, together with Meningococcal C and Pneumococcal vaccines (Table 23) will be included as potential confounder. Passive immunity drugs, such as immunoglobulins and monoclonal antibodies (e.g., varicella/zoster immunoglobulin, hepatitis B immunoglobulin, tixagevimab, and cilgavimab) will also be considered (Table 23).

Patients with previous infections are at an increased risk of a subsequent infection. Although patients with a serious infection in the previous 6 months will be excluded, the occurrence of non-serious infections and serious infections for more than 6 months will be considered as potential confounders. Non-serious infection will be defined as the occurrence in the previous 12 months of either a diagnosis code for infection on a primary care or outpatient setting, or community-dispensed antimicrobials (Table 19), without hospitalisation or use of IV antimicrobials.

Previous exposure to SLE SOC is associated with an increased risk of infections. Prior use of SLE drugs will be accounted for when considering the SLE severity and activity, namely the recent start of a SLE drug as captured by the activity algorithm.

10.3.3.3 Potential confounders for both cohorts

SLE disease severity and activity

Disease severity and activity are not directly available in secondary data sources included in this study, since validated indexes that assess disease severity and activity are not systematically used in routine practice and therefore not recorded in most data sources. Thus, this study will use algorithms [39, 56], that have been previously used in other settings, including in one European data source. The algorithms are based on previous use of SLE SOC drugs (Table 14) (including drugs mainly used to manage flares, such as non-steroidal anti-inflammatory drugs [NSAIDs]), SLE-related comorbidities (Table 21) and HRU.

SLE disease severity will be assessed as the highest severity experienced by a patient in the baseline period (12 months prior to index date) and could be categorised in three groups: mild, moderate, and severe [56] if meeting at least one of the criteria depicted in Figure 9 during the baseline period.

The severity algorithm will be used in the selection of the study population (Figure 4). The patients with mild SLE will be excluded. Individual components of the severity algorithm will be considered to create the PS at baseline.

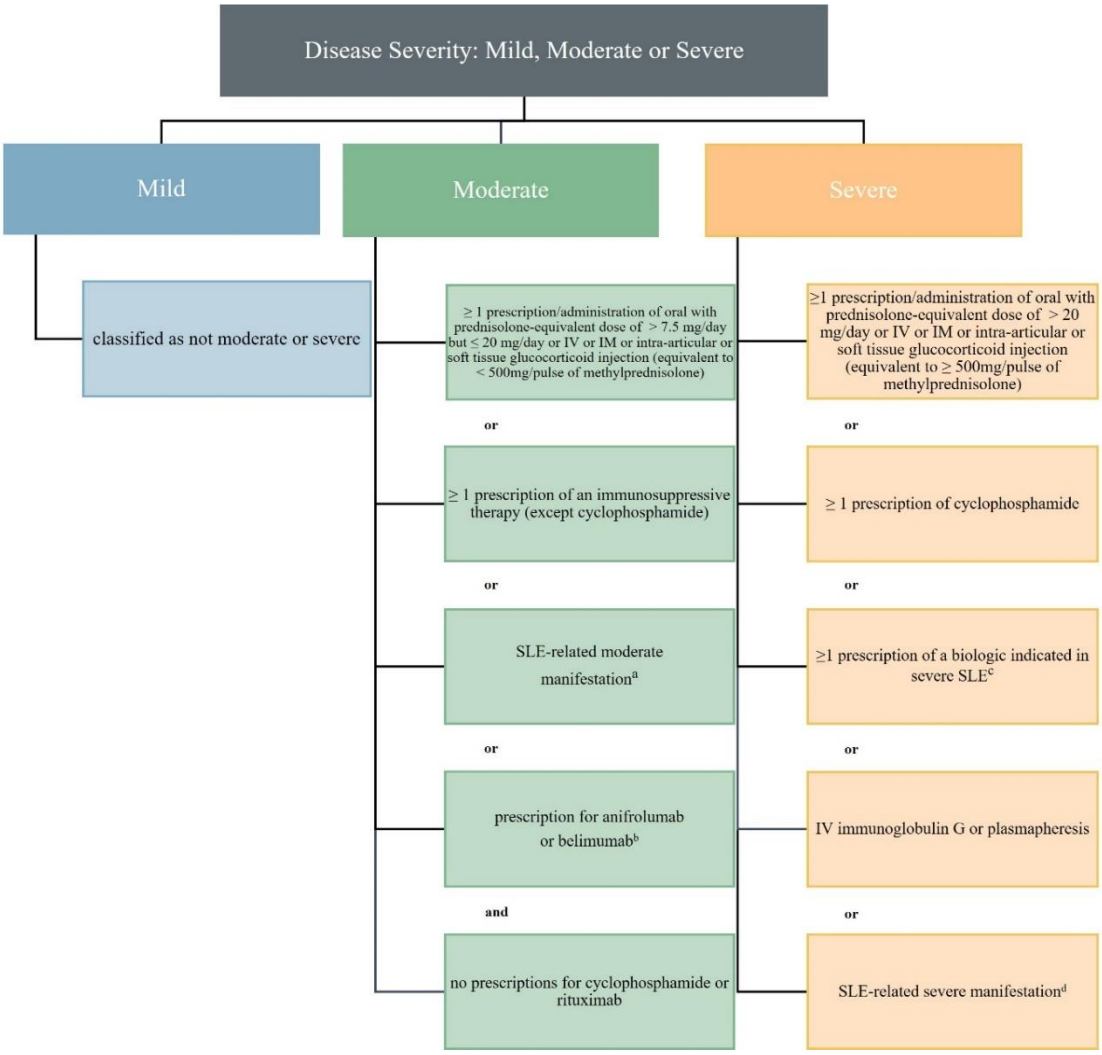

Figure 9 SLE disease severity algorithm

(Patients with mild SLE will be excluded from the study)

a. SLE-related moderate comorbid manifestations: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, haemolytic anaemia, hepatitis (non-viral), ischaemic necrosis of bone, nephritis, renal impairment other than nephritis or end-stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis vasculitis (excluding aortitis).

b. If a severe condition exists, the patient(s) will be moved to the severe category.

c. Rituximab (including biosimilars).

d. SLE-related severe comorbid manifestations: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end-stage renal disease, optic neuritis, pulmonary haemorrhage, stroke/transient ischaemic attack.

SLE-related comorbid conditions are provided in Table 21.

Abbreviations: IM; intramuscular; IV, intravenous; SLE, systemic lupus erythematosus.

SLE disease activity

Periods of increased disease activity could be categorised as mild, moderate, or severe flare [56], if meeting at least one of the criteria depicted in Figure 10. Each component of the activity algorithm will be considered in current study: initiation of any of the drugs described in Figure 10, admission to the emergency department with a SLE-related comorbidity or SLE-related hospitalisation.

SLE activity will be considered among patients that have active SLE (Figure 4). For that, patients will be defined as uncontrolled (i.e., one or more flares in the previous 6 months, regardless of the severity of the flare) if at least one of the components of the algorithm is present: initiation of a new SLE SOC (except biologics), use of NSAIDs or other drugs considered in the management of flares, use of emergency department or hospitalisation due to a SLE-related comorbidity. Additionally, individual components will be used to create the PS at baseline.

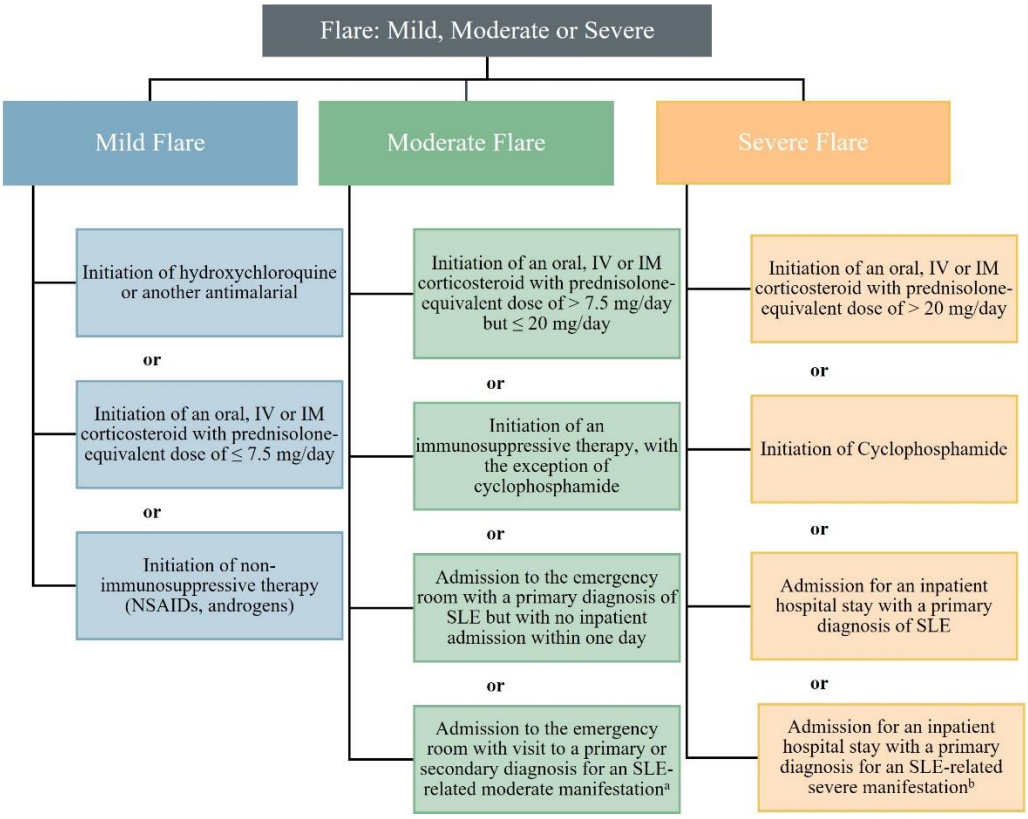

Figure 10 SLE disease activity algorithm

a. SLE-related moderate manifestations: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, haemolytic anaemia, hepatitis (non-viral), ischaemic necrosis of bone, nephritis, renal impairment other than nephritis or end-stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis vasculitis (excluding aortitis).

b. SLE-related severe manifestations: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end-stage renal disease, optic neuritis, pulmonary haemorrhage, stroke/ transient ischaemic attack.

Initiation: treatment is considered to be 'initiated' if there were no filled prescriptions for that class of medication in the 60 days prior to the medication fill [39].

Flares based on hospitalisation: the start date of the flare is the date that the patient was admitted to the hospital, unless the patient was admitted to emergency room (with any diagnosis) during the previous day; if patients had an emergency room admission the day prior to the hospitalisation, the date of the emergency admission will be considered to be the start date of the flare [56].
Length of flare: 30 days. If a flare of higher severity (moderate or severe) occurs during the 30 days, the length of the flare is limited to the time of the start of the higher severity flare.
SLE-related comorbid conditions are provided in Table 21.
Abbreviations: IM, intramuscular; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

10.4 Data sources

A feasibility assessment was conducted between June 2022 and January 2023 to assess the suitability of the proposed data sources to address this study's research question and objectives. Information was collected from the data source holders and supplemented by desktop research. Data sources from **eight countries** (Denmark, Finland, France, Germany, Spain, Sweden, UK, USA) and **five SLE specific registries** (SLE Registry Germany, Spanish Society of Rheumatology systemic lupus erythematosus registry [RELESSER], Swedish Rheumatology Quality Register [SRQ], OM1 Lupus Registry from the USA and the Systemic Lupus Erythematosus International Collaborating Clinics [SLICC]) were assessed in the feasibility assessment. Of the eight countries evaluated, four countries were selected: Denmark, France, Germany, and Spain. None of the SLE specific registries evaluated in the feasibility assessment was selected for inclusion in this study. A summary of the rationale for inclusion/exclusion of each data source evaluated in the feasibility assessment is presented in Table 25 of the Appendix 4 Data Sources' details. Data sources were selected based on the ability to capture anifrolumab and SLE SOC use, the study outcomes and the potential size of the study population. The same data sources were assessed for the suitability to examine the research objectives for malignancy and serious infections. The following information was collected for each data source during the feasibility assessment:

- Characteristics of the data source
- Access requirement
- Availability and coding systems of drugs, medical diagnoses, procedures, and laboratory measurements
- Availability and completeness of variables (exposure, outcomes, and covariates)
- Estimated number of SLE diagnosed patients
- Estimate of anifrolumab treated SLE patients in the preceding 12 months (applicable for USA data sources only)

As anifrolumab was approved in 2022 in most European countries, information on the availability of anifrolumab use is limited and unavailable in some data sources. Due to the limited availability of information on anifrolumab exposure data, exposure to biologics indicated for a similar population and with a similar administration route (belimumab IV infusion) was used as a proxy

to evaluate the ability of the data source to capture anifrolumab exposure information when the drug is available in the respective countries.

Considering the estimated sample size required for this study, it is anticipated that the selected data sources will provide the sufficient sample size required to address the research questions (see Section 10.5). If it is determined at the time of interim reports, that the selected data sources will not provide the required sample size, mitigation approaches will be considered. These mitigation approaches include the use of additional data sources (which were deemed feasible but not currently selected), and extension of the study period.

10.4.1 Description of the selected data sources

A summary of the selected data sources, the availability of exposure and outcome variables is presented in Table 7, below.

Table 7 Summary of feasibility of selected data sources

Country	Start of data availability	Country coverage	Data lag, months	Availability of exposure [a]		Availability of outcomes[b]			
						Serious Infections			Malignancies
				Anifrolumab[c]	SLE SOC	Exposure to IV antimicrobials	Serious Infection code	Registry of death	
Denmark, National Registers	1977	100%	2-13	Yes	Yes	Yes	Yes, for secondary care[d]	Yes	Yes
France, SNDS	2006 (inpatient) 2008 (outpatient)	98.9%	12	Yes	Yes, outpatient, except voclosporin[e] and mepacrine[e]	Yes	Yes, for hospitalisations	Yes	Yes, for hospitalisations
Germany, SHI	2008	5.5%	12	Yes, outpatient visits	Yes, outpatient, except mepacrine[e]	Yes, for outpatient visits	Yes	Yes	Yes
Spain, SIDIAP	2010	10.2%	6	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations; IV: Intravenous; SHI: Statutory Health Insurance; SIDIAP: System for the development of primary care research database; SLE: systemic lupus erythematosus; SNDS: National Health Data System; SOC: Standard of care.

[a] Drugs are coded using ATC coding system in all data sources

[b] Outcomes are coded using ICD-10 coding system (with German modification for Germany), except IV antimicrobials that are coded using ATC coding system

[c] Exposure to anifrolumab was based on the availability/information on biologics and belimumab (Benlysta) as a proxy for utilisation of anifrolumab.

[d] Hospitals, emergency rooms, and specialty outpatient clinics

[e] These drugs are not marketed in the country.

10.4.1.1 Denmark: Danish National Registers

Danish National Registers have a 100% coverage of the country (around 5.8 million individuals). In general, the healthcare registers at the Danish Health Data Authority are updated monthly with a data access lag time of approximately 2 months. However, the study requires linkage to socio-economic registers data which are stored at Statistics Denmark and updated annually (after the end of December). The lag time to access this linked data varies from 3 to 15 months.

- **Danish Civil Registration System**

The Danish Civil Registration System or Central Person Register (CPR) is operated by the Danish Ministry of the Interior. The Danish Civil Registration System was introduced in 1968 and contains information on demographics (age, sex, geographical region), migration and vital statistics data (date of birth and date of death) for all Danish residents. Every individual in Denmark is provided with a unique personal identification number (CPR number) at birth or upon immigration which allows for follow-up until death or emigration. The CPR number forms the basis for the precise, deterministic linkage of individual-level data between all patient-level registers and databases in Denmark, allowing the creation of a study database with individual-level data.

- **Danish Register of Medicinal Product Statistics**

The Danish Register of Medicinal Product Statistics (*Lægemiddelstatistikregisteret* [RMPS]) contains patient-level data on all prescription drugs filled by patients at community pharmacies. The register contains information on the date of purchase, item number, product name, ATC code, strength per unit, quantity of the WHO's defined daily doses (DDD) per package and number of packages filled. Data are available from 1995 onwards. Since April 2004, information on the medical indication for prescription and the daily prescribed dose by the prescribing physician is also available. However, the completeness and validity of these fields (medical indication and daily prescribed dose) are affected by the consideration that these data elements are not compulsory.

- **Danish National Hospital Medication Register**

The Danish National Hospital Medication Register (*Sygehusmedicinregisteret* [SMR]) contains information on drugs administered to patients while admitted to hospital or during outpatient visits. It contains the date and time of drug administration, the dose administered via number of units and strength per unit, product name, ATC code, and department information. Thus, this register complements the RMPS. Data have been captured since May 2018 and were made available for research in 2022. As this is a new register, data completeness, particularly for the early years may have some missingness.

- **Danish National Patient Register**

The Danish National Patient Register (Danish NPR) is managed by the Danish Health Data Authority. It was established in 1977 and is considered to have a high degree of completeness and validity. It covers patients admitted to hospitals, emergency rooms, and specialty outpatient clinics

(secondary care). Since 2007 the register has included information on all patients in Danish hospitals including private hospitals. However, reporting from private hospitals and clinics are not considered complete.

The Danish NPR includes the following information: CPR number, local municipality, admission and discharge information, the date of any incidents over the course of an illness, diagnosis (Danish adaptation of ICD-10), examinations and treatment procedures - including surgery coded with Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures (Nordisk Medicinal-Statistisk Komité [NOMESCO]) codes.

- **Danish Cancer Register**

The Danish Cancer Register contains patient-level data on incident cancers in the Danish population. Data must be reported to the register according to an executive order by The National Board of Health. Data are available from 1943 and onwards, however, reporting was voluntary until March 1987. The register contains information on date of diagnosis, location, classification of malignant tumours (TNM [“Tumour”, “Node”, and “Metastasis” categories] - a classification system to describe the amount and spread of malignant tumours in a patient’s body), and histological classification of cancer. Information from the NPR, the Cause of Death Register, and the Danish Pathology Register is used to increase completion and accuracy of data collection in the process of updating the Cancer Registry. Validation of the Cancer Register and selected clinical cancer databases was reported in 2012 by the authorities with histological verification of 92-96% of the tumours, and even close to 100% in some cancer types, including melanoma, breast, lung, and colon cancer.

The register is updated once a year after December with a lag of approximately 13 months. Since 2004, the 3rd edition of the international classification of diseases for oncology (ICD-O-3) has been used as the classification system. The ICD-7 classification was used until 1977. Between 1978 and 2003, ICD-O-1 was used.

- **Danish Cause of Death Register**

The Danish Cause of Death Register (CDR) contains information on date and cause of death. The information from the death certificate, including place of death, information about any autopsy, and municipality of residence is transferred to the Cause of Death register. Date of death is available from 1970 and onwards. The register is updated once a year after December with a lag of approximately 13 months.

- **The National Health Insurance Service Register**

The National Health Insurance service register (*Sygesikringsregisteret* [NHISR]) contains information on services supported by public health insurance and provided by general practitioners (GPs) and specialists in private practice outside the secondary setting at hospitals. Information on the weekly invoicing of the costs covered by the public health insurance is included in the register.

However, individual diagnoses and treatment information are not available. Data are available from 1990 and onwards.

- **Socio-economic registers at Statistics Denmark**

The socio-economic registers cover a wide range of information on residents in Denmark. These include annual income by individual or family, highest achieved education, occupation, proportion of time outside employment due to sick leave etc., and information on individuals receiving different types of disability aid. Socio-economic registers at Statistics Denmark are updated annually, typically after December.

Study-specific data

In Denmark, market launch of anifrolumab occurred in May 2022 (Table 3). It is assumed that information on anifrolumab will be available in SMR as it is administered in hospital settings, and information on belimumab (a proxy) is captured in this registry. ATC codes and Danish brand names allow the distinction between biologics. Information on SLE SOC dispensed in retail pharmacies is available through RMPS (since 1995) and drugs administered in hospital are available through SMR.

Data on malignancies (overall and sub-types) are captured through ICD-O diagnoses codes from the Cancer Registry. Serious infections are identified at the secondary care level through primary ICD-10 diagnoses, i.e., identified if infections are the reason for contact with the hospital. Data are not available for conditions managed only by a GP or a specialist in private practice. ICD-10 codes allow the identification of specific types of serious infections. Data on prescription/administration of IV antimicrobials are also available in the SMR. Dates of diagnoses, hospitalisation admission, discharge and date of death (regardless of the setting where occurs) are available.

Data on covariates are generally available (Table 26), except for Body Mass Index (BMI) (including weight or height), alcohol consumption, smoking and vaccination history. Procedures with radiation exposure may be available if procedure codes are registered. Previous infections may be available if the diagnosis occurred in secondary care.

10.4.1.2 France: National Health Data System

The French National Health Data System (*Système National des Données de Santé* [SNDS]) is the largest and most comprehensive healthcare dataset available in Europe. It covers 99% of the total French population - around 66 million patients [14]. Individuals enter SNDS at birth or by immigration and exit at death or emigration.

SNDS includes anonymised administrative and healthcare claims data from the French national health care insurance system databases. In particular, data from several databases are available [83]:

- the French National Health Insurance database (*Système national d'information interrégimes de l'Assurance maladie* [SNIIRAM]), available since 2008;

- the French hospital discharge summaries *(Programme de Médicalisation des Systèmes d'Information* [PMSI]), available since 2006;
- the national death registry (*Centre d'épidémiologie sur les causes médicales de Décès* [CépiDC]).

Since 2008, SNIIRAM includes the outpatient reimbursed health expenditures database (*données de consommation interrégimes* [DCIR]), which allows capturing consumption of care.

Reimbursed drugs dispensed through retail pharmacies are available through DCIR and drugs are identified by their ATC code. The date of dispensing, quantity, and brand name are also available. Information on route of administration is available and dose may be estimated from DDD. Information on drug indication is only possible for the inpatient setting, derived from diagnoses.

Hospital administered treatments are available through PMSI, if they are part of the list of high-cost drugs (*medicaments listed en sus*). Inclusion in the list allows the reimbursement of drugs, in addition to the hospital episode reimbursement.

Through the PMSI, SNDS includes medical summaries of all hospitalisations from private or public hospitals, including date of stay, medical procedures, devices implanted during the hospital stay, primary diagnosis (main reason for admission) and related diagnosis. These data are encoded according to the ICD-10.

SNDS contains data on the presence and diagnosis date of long-term chronic disease (LTD). LTD is used together with PMSI to identify patients, namely those with SLE. Patients with LTD are eligible for 100% reimbursement of healthcare expenditure. The request for attribution of LTD is made by the general practitioner and it is not mandatory. Thus, it may be missing, for instance, if the medical expenses are already covered by another chronic disease or the treatment is not expensive. Diagnoses are coded using ICD-10.

SNDS also includes demographic data (including age, sex, place of residence, complementary universal health coverage status (as proxy to socio-economic status), date of death), health encounters, dispensations, medical devices, and laboratory tests (without results) [14].

Data from DCIR and PMSI are annually updated and can be linked for each patient. At the time of the feasibility assessment, data were available until the end of 2021.

Study-specific data

In France, market launch for anifrolumab occurred in April 2022 (Table 3). A favourable reimbursement decision has been made by the health assessment authorities in France. Therefore, it is anticipated that anifrolumab will likely be included in the list of high-cost drugs and thus, will be captured in PMSI.

Data on SLE SOC drugs are available, except for voclosporin and mepacrine, which are not marketed in France. Some drugs, such as methotrexate, mycophenolate mofetil, cyclophosphamide, and cyclosporine are available if the oral forms are used. Chloroquine was in

use until the end of September 2022, when the last product was withdrawn from the market. Furthermore, rituximab and immunoglobulin G – administered as IV at the hospital – are available as they are part of the list of high-cost drugs. Only the pen formulation of belimumab, delivered in retail pharmacies, is captured.

Data on overall and specific malignancies are captured through coded diagnoses at the hospital level. This is also true for serious infections in which diagnoses allow for the identification of specific types of serious infections. Data on prescription/administration of IV antimicrobials are available for inpatients if antimicrobials are part of the list of expensive drugs. Dates of diagnoses (inpatients), hospitalisation, discharge and death are available.

Data on covariates are generally available (Table 26), except for BMI (including weight or height), alcohol consumption, and smoking. Vaccination data are captured if reimbursed.

10.4.1.3 Germany: Statutory Health Insurance Providers Claims

In Germany, insurance claims from approximately 8-10 different statutory health insurance (SHI) providers are collected by Team Gesundheit. SHI is a requirement for individuals with a permanent place of residence in Germany, even for short-term stays. Since 2012, all individuals in Germany have a specific identifier which would not change throughout lifetime. SHI covers 89% of German population; data available through the Team Gesundheit represents 5-6% of the German population, representative in terms of age, gender and region. This data source has been used for different research purposes, including oncology [18, 36] and rheumatic diseases treated with biologic agents [102].

Data on medications cover prescriptions in primary care and community pharmacy dispensing. Data on medication use in inpatient setting are not available. Data on drugs administered in outpatient visits at the hospital are captured, unless the hospital visit is reimbursed as diagnosis-related group (DRG). In that case it will not be possible to know which drug was administered as only one generic code will be available. Drug indication is not available since there is no active link between diagnosis and the prescribed therapy. Dose can be derived from the quantity prescribed and the period between prescription dates. Prescription and dispensation dates are available, but not for over-the-counter products and substances not reimbursed.

The database contains information from primary care and in- and outpatient hospital care. Data on physician visits, specialist code of the treating physician (e.g., gastroenterology), and hospitalisations are available. For inpatient stays, primary diagnoses and secondary diagnoses are available, primary diagnoses are a proxy for “cause of hospitalisation”.

Diagnosis information is available and captured using the ICD-10 coding system with German modification (GM). Data on surgical and medical procedures are recorded using the GM of the ICD-10-PCS (ICD-10 Procedure Coding System) and the operation and procedure classification system (*Operationen und Prozedurenschlüssel* [OPS]). Due to the nature of the claims data, information on data that are not subject to reimbursement are not visible in the database. For

example, information on symptoms captured by ICD-10 coding would have little or no coverage as they are usually not subject to reimbursement.

Similarly, information on a conducted diagnostic test is only available if being subject to reimbursement. Test results are not available from the claims data. Sociodemographic information is partially available. However, data on lifestyle factors are not recorded.

SHI data in Germany are updated yearly. The estimated lag time (from the time data are recorded until available for research) is currently 15-16 months or more. At the time of feasibility assessment (June 2022) data for the period between January 2011 up to December 2020 were available; data from 2022 will be available in 2024.

Study-specific data

In Germany, market launch for anifrolumab occurred in March 2022 (Table 3). Anifrolumab is expected to be captured, since belimumab data are available through prescription or dispensation. Administration during hospital stay is not captured.

Data on SLE SOC exposure is considered available for most drugs since 2011, except for mepacrine which is no longer available in Germany. Data on prescribed outpatient therapy are available. Data on biologics are available through prescription data on German national drug code unique identifier (*Pharmazentralnummer* [PZN]) level and some OPS inpatient codes.

Data on malignancies (overall and sub-types) and serious infections (overall and sub-types) are available for inpatients and outpatients if coded trough ICD-10 GM. Date of death is available. Intravenous antimicrobials can be captured from the prescriptions and dispensations in outpatient visits.

Data on covariates are generally available (Table 26), except for vaccination (substance not captured), BMI (including weight or height), alcohol consumption and smoking. Procedures with radiation exposure may be available if procedure codes are registered.

10.4.1.4 Spain: Information System for the Development of Primary Care Research

The information system for the development of primary care research database (*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària* [SIDIAP]), was established in 2010 and is under the organisation of the Catalan Institute of Health and the Primary Care Research Institute Jordi Gol. The SIDIAP database is frequently used for research purposes, and it includes a representative sample of patients attended by general practitioners. It is a regional register covering approximately 6 million people (around 80% of the individuals living in the Catalan region), which represents about 10.2% of the total Spanish population.

The SIDIAP data consists of primary care electronic medical records as well as other complementary databases with data available from 2006. Health care information is entered automatically into the e-records software (e-CAP). Since e-CAP is used by the most important health providers of the Catalan Health Department, SIDIAP is representative of both the urban and

rural areas of Catalonia. Individuals enter the SIDIAP database at birth or immigration and exit by death or emigration.

Information on all prescribed and dispensed drugs is obtained from the joint database of CatSalut with Catalan pharmacies. Drug indications are available for a few drugs which registration of the indication is required. Dose and DDDs are available in pharmacy invoice records. Dates of prescription are available for reimbursed drugs obtained in pharmacies. Other data sources can be linked to the SIDIAP data providing additional information, such as hospital admissions (from the *conjunt mínim de dades bàsiques d'hospitalització*), hospital outpatient medications (*Medicació Hospitalària de Dispensació Ambulatòria* [MHDA]) and the mortality register from which causes of death can be retrieved.

The database includes information on physician visits (date and type), diagnoses, results of laboratory analyses, as well as lifestyle factors such as history of smoking and BMI.

In the SIDIAP database, the length of data lag is approximately 6 months, and the database is updated twice a year (January and July). The time lag between when care is given and its capture in the data source is normally 6 months. Prior to data extraction, ethical approval and data holder permits must be obtained. The SIDIAP will perform scientific and ethical review and it will perform the data analysis locally.

Study-specific data

Anifrolumab use is expected to be captured, as data on biologics (including IV belimumab use) are available in SIDIAP since 2010 through hospital outpatient medications. Data on SLE SOC exposure are available.

Data on malignancies (overall and sub-types) and serious infections (overall and sub-types) are available. Infection diagnosis and date of death are available. Previous infections may be available if the diagnosis occurred in primary care.

Data on covariates are generally available (Table 26), including data for BMI, alcohol consumption, and smoking. Alcohol consumption and smoking are coded using internal codes. Data on procedures with radiation exposure are not available.

10.5 Study size

10.5.1 Expected number of SLE patients exposed to anifrolumab

Due to the recency of anifrolumab approval in the EU (14 February 2022), data on its uptake in the selected data sources for the duration of the study enrolment period (up to April 2025 for serious infections, and May 2028 for malignancies) is not available. Therefore, estimates of the number of expected anifrolumab patients in each data source for each year of the study were made based on country-level assumptions of the prevalence of SLE, proportion of patients with moderate to severe SLE, proportion of patients who have non-renal SLE, proportion of non-renal SLE

patients who are treated, a gradual uptake of anifrolumab from 1% in the initial years after market approval to 13-16% in 2028 and population coverage of each selected data source. Details of these assumptions and the annual number of exposed patients in each data source are provided in Appendix 4.3. **Number of SLE patients exposed to anifrolumab**and Table 27.

The average number of patients with SLE expected to be identified in the data sources every year (potential pool of comparators) and the total number of new patients exposed to anifrolumab identified during the enrolment period in each study cohort and data source are summarised in Table 8. For the serious infections and malignancies' cohorts, 1,435 and 3,506 patients newly exposed to anifrolumab may be captured, respectively[8].

Table 8 Expected size of the SLE population exposed to anifrolumab in the selected data sources

Country, data source	Average number of SLE patients per year[a]	Expected number of patients initiating anifrolumab	
		Malignancies' cohort (Enrolment: 2022-2028)	Serious infections' cohort (Enrolment: 2022-2025)
Denmark, National Registers	1,122	183	89
France, SNDS	15,501	2,695	1,005
Germany, SHI	1,224	216	126
Spain, SIDIAP	2,944	412	216
All		**3,506**	**1,435**

Abbreviations - SHI: Statutory Health Insurance; SIDIAP: System for the development of primary care research database; SLE: systemic lupus erythematosus; SNDS: National Health Data System
[a]Estimated as the annual average number of patients in each data source with moderate to severe, non-renal SLE treated with SLE SOC for the period 2022 to 2028 (more details in Appendix 4.3. **Number of SLE patients exposed to anifrolumab**).

10.5.2 Minimum sample size required

As the main analysis for the primary outcomes (i.e., serious infections and malignancies) will involve a meta-analysis pooling the estimates across all data sources, a meta-analytic approach in sample size estimation was used for each outcome separately. Simulations were used to compute the estimated power to detect pre-specified HR values representing the average population treatment effect (mean) for the anifrolumab exposed group compared to the unexposed group for pre-specified sample sizes. In addition, the minimum sample sizes required to achieve 80% power under specific assumptions were estimated.

[8] The number of SLE patients provided by the data sources is slightly higher than the estimated average. Thus, current estimates are expected to be a conservative measure of the number of included patients. At the time of interim reports, the number of SLE patients and the assumptions of anifrolumab uptake will be assessed to address the need of protocol adjustments to meet the necessary sample size.

Assumptions and parameters

The main objective of this study is to estimate and compare the risks between the study cohorts in terms of two outcomes – serious infections and malignancies.

Keeping this in mind, the sample analysis methodology relies on estimating power to detect any treatment associated risks between the study cohorts. In this case, we assumed pre-specified HR values of 1.5, 1.8 and 2, as the average population treatment effect (mean) and for variability of this HR, we use two values of assumed standard deviation, 0.1 and 0.2. The idea here is to have a population-level treatment effect distribution of HR with mean values of 1.5 or 1.8 or 2.0, such that from this distribution, every data source randomly samples a unique HR value per simulation run. This approach ensures the variability and heterogeneity which we expect to see from data sources which then necessitates the use of random effects meta-analysis to account for them during the final analysis of this study. Two matching ratios of exposed to non-exposed, 1:1 and 1:3, were chosen. Background rates for the primary outcomes were also varied based on published literature of incidence in the general population and in an SLE population.

Background rates

Computations were carried out with two conservative incidence rates for each outcome. Results using the incidence rates in the general population can be considered as a lower bound for the achieved power/minimum required sample sizes. Results using the incidence rates in SLE population can be considered as an upper bound for the achieved power/minimum required sample sizes.

For the malignancy outcome: There are several estimates for incidence rates (IR) of malignancy in the literature. Since this study involves cohorts situated within Europe, IR estimates based on data available within Europe for the general population and an SLE specified population were used (Table 9 and Table 10, respectively).

- Based on data from the European Cancer Information System, in 2012 the overall incidence of malignancy in the general population was 5.26 per 1000 person-years in the UK [31].
- In a multicentre study of a patient cohort from the Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology, IR for malignancy in patients with SLE was 6.31 per 1000 person-years [19].

For the serious infection outcome: There are several estimates for IRs of serious infection in the literature. Since this study involves cohorts situated within Europe, we used IR estimates based on data available from Europe. The IR estimates in the general population and in SLE patients specified below were used for the power calculations (Table 11 and Table 12).

- In a study from the Swedish Lupus Linkage cohort, newly diagnosed patients with SLE (2006–2013) and general population comparators were followed for serious infection until

2016. Rates of serious infections in the general population were 9.6 per 1000 person-years and 39.8 per 1000 person-years amongst SLE patients [81]. The definition used for serious infection outcome in this study was hospitalisation with infection as the primary diagnosis using ICD codes from the National Patient Registry of Sweden inpatient database.

Simulation steps

For a given matching ratio (exposed: non-exposed) and a given IR, simulations were carried out for a range of overall exposed sample sizes (total sample size of exposed patients across data sources). For each overall sample size (e.g., n = 3000 exposed patients), a proportion of the overall population (country-level sample size) was assigned to each data source (proportions are presented in Table 13). These proportions are based on estimated final sample sizes for the different data sources given the relative sizes of each data source and the prevalence of SLE in each study country. The SLE prevalence in each data source was obtained by literature review (see references in Table 13) The following steps were repeated 1,000 times to get 1,000 simulated 95% CIs for HRs.

Using the simsurv package, survival times were simulated for each data source from a Weibull distribution assuming proportional hazards. The average population-level treatment effect chosen was from a pre-specified list of values – 1.5, 1.8 or 2 with assumed variances of SD(HR) = 0.1 and 0.2. The provided sample sizes were taken as the exposed sample size and the non-exposed sample size was calculated as matching ratio * country-level sample size. The average follow-up times were 2 years for serious infections and 5 years for malignancies.

The estimated data source level log(HRs) for exposure status, standard errors and 95% CI were computed by fitting a cox proportional hazards model to the simulated data. The data source level log(HRs) and their standard errors were entered in a random-effect meta-analysis model to compute the pooled HR and its 95% CI. The inverse-variance method was used with the R meta package.

Finally, the proportion of 1,000 simulated runs where the meta-analysis p-value < 0.05, representing the power, was computed. Power was estimated for each pre-specified sample size of exposed group under two different outcome-specific IRs and two allocation ratios (1:1 and 1:3) for three assumed average treatment effects, HRs – (1.5, 1.8 and 2) (Log(HR) values of 0.405, 0.588 and 0.693 in lognormal space respectively) with SD[HR)] – 0.1 (expressed as the geometric coefficient of variation of log(HR) - 0.066, 0.056, 0.05 for three HRs respectively) and 0.2 (expressed as the geometric coefficient of variation of log(HR) - 0.132, 0.11, 0.099 for three HRs respectively In addition, the exact sample size required to achieve 80% power was estimated (Table 13).

The tables below show the power achieved for different pre-specified sample size values for the two main outcomes – serious infections (Table 9 and Table 10) and malignancy (Table 11 and Table 12) obtained from the simulation as described above.

Table 9 Meta-analysis level power to detect pre-specified target HR under different study size and assumptions of malignancy incidence – allocation ratio 1:1

Malignancy IR	Number of exposed to anifrolumab	Power for detecting a HR of 1.5 & SD(HR) =0.1	Power for detecting a HR of 1.5 & SD(HR) =0.2	Power for detecting a HR of 1.8 & SD(HR) =0.1	Power for detecting a HR of 1.8 & SD(HR) =0.2	Power for detecting a HR of 2 & SD(HR) =0.1	Power for detecting a HR of 2 & SD(HR) =0.2
5.26 per 1000 person-years	500	0.122	0.152	0.284	0.279	0.390	0.395
	1000	0.263	0.287	0.542	0.548	0.687	0.680
	1500	0.421	0.381	0.697	0.657	0.813	0.811
	2000	0.477	0.483	0.772	0.756	0.864	0.851
	2500	0.554	0.507	0.843	0.809	0.926	0.897
	3000	0.621	0.579	0.874	0.843	0.928	0.914
	3500	0.679	0.638	0.902	0.889	0.955	0.951
	4000	0.717	0.669	0.922	0.903	0.961	0.960
	4500	0.762	0.710	0.938	0.934	0.988	0.983
	5000	0.811	0.788	0.955	0.962	>0.999	>0.999
	5500	0.852	0.833	0.961	>0.999	>0.999	>0.999
6.31 per 1000 person-years	500	0.179	0.169	0.334	0.325	0.474	0.463
	1000	0.309	0.332	0.624	0.584	0.794	0.740
	1500	0.439	0.428	0.765	0.741	0.882	0.842
	2000	0.561	0.531	0.816	0.808	0.903	0.910
	2500	0.632	0.570	0.872	0.869	0.936	0.918
	3000	0.662	0.622	0.899	0.899	0.954	0.939
	3500	0.731	0.663	0.923	0.922	0.962	0.958
	4000	0.761	0.717	0.941	0.944	0.988	0.977
	4500	0.811	0.794	0.975	0.957	0.991	>0.999
	5000	0.847	0.829	0.991	0.976	>0.999	>0.999

Abbreviation – HR: hazard ratio; IR: incidence rate; SD: standard deviation

Table 10 Meta-analysis level power to detect pre-specified target HR under different study size and assumptions of malignancy incidence – allocation ratio 1:3

Malignancy IR	Number of exposed to anifrolumab	Power for detecting a HR=1.5 &SD(HR) =0.1	Power for detecting a HR of 1.5 & SD(HR) =0.2	Power for detecting a HR of 1.8 & SD(HR) =0.1	Power for detecting a HR of 1.8 & SD(HR) =0.2	Power for detecting a HR of 2 & SD(HR) =0.1	Power for detecting a HR of 2 & SD(HR) =0.2
5.26 per 1000 person-years	500	0.310	0.364	0.581	0.631	0.735	0.729
	1000	0.497	0.503	0.768	0.792	0.901	0.870
	1500	0.629	0.610	0.881	0.852	0.933	0.935
	2000	0.670	0.683	0.933	0.897	0.967	0.969
	2500	0.762	0.701	0.938	0.936	0.978	0.978
	3000	0.786	0.754	0.956	0.944	0.985	0.979
	3500	0.818	0.781	0.969	0.959	0.994	0.991

Malignancy IR	Number of exposed to anifrolumab	Power for detecting a HR=1.5 &SD(HR) =0.1	Power for detecting a HR of 1.5 & SD(HR) =0.2	Power for detecting a HR of 1.8 & SD(HR) =0.1	Power for detecting a HR of 1.8 & SD(HR) =0.2	Power for detecting a HR of 2 & SD(HR) =0.1	Power for detecting a HR of 2 & SD(HR) =0.2
6.31 per 1000 person-years	4000	0.853	0.795	0.981	0.975	0.991	0.991
	4500	0.883	0.818	>0.999	>0.999	>0.999	>0.999
	500	0.362	0.358	0.642	0.658	0.785	0.783
	1000	0.555	0.511	0.835	0.817	0.914	0.911
	1500	0.657	0.632	0.915	0.902	0.959	0.955
	2000	0.723	0.694	0.938	0.920	0.979	0.963
	2500	0.781	0.763	0.968	0.937	0.986	0.981
	3000	0.841	0.780	0.971	0.959	0.986	0.988
	3500	0.879	0.814	0.983	0.980	0.994	0.995
	4000	0.888	0.815	0.984	0.979	0.997	0.996

Abbreviation – HR: hazard ratio; IR: incidence rate; SD: standard deviation

Table 11 Meta-analysis level power to detect pre-specified target HR under different study size and assumptions of serious infections incidence – allocation ratio 1:1

Serious Infections IR	Number of exposed to anifrolumab	Power for detecting a HR of 1.5 & SD(HR) =0.1	Power for detecting a HR of 1.5 & SD(HR) =0.2	Power for detecting a HR of 1.8 & SD(HR) =0.1	Power for detecting a HR of 1.8 & SD(HR) =0.2	Power for detecting a HR of 2 & SD(HR) =0.1	Power for detecting a HR of 2 & SD(HR) =0.2
9.6 per 1000 person-years	500	0.087	0.099	0.161	0.165	0.288	0.304
	1000	0.192	0.218	0.418	0.433	0.548	0.553
	1500	0.289	0.305	0.590	0.599	0.749	0.731
	2000	0.377	0.368	0.711	0.675	0.811	0.803
	2500	0.433	0.426	0.762	0.719	0.871	0.854
	3000	0.529	0.484	0.819	0.791	0.903	0.875
	3500	0.560	0.509	0.838	0.817	0.926	0.902
	4000	0.617	0.566	0.879	0.857	0.936	0.932
	4500	0.689	0.697	0.901	0.881	0.966	0.956
	5000	0.761	0.754	0.959	0.948	>0.999	0.977
	5500	0.822	0.804	>0.999	0.982	>0.999	>0.999
39.8 per 1000 person-years	500	0.375	0.392	0.665	0.692	0.809	0.804
	1000	0.635	0.582	0.885	0.851	0.945	0.930
	1500	0.732	0.710	0.946	0.925	0.978	0.968
	2000	0.825	0.771	0.975	0.948	0.987	0.985
	2500	0.868	0.826	0.973	0.968	0.996	0.987

Abbreviation – HR: hazard ratio; IR: incidence rate; SD: standard deviation

Table 12 Meta-analysis level power to detect pre-specified target HR under different study size and assumptions of serious infections incidence – allocation ratio 1:3

Serious Infections IR	Number of exposed to anifrolumab	Power for detecting a HR of 1.5 & SD(HR) =0.1	Power for detecting a HR of 1.5 & SD(HR) =0.2	Power for detecting a HR of 1.8 & SD(HR) =0.1	Power for detecting a HR of 1.8 & SD(HR) =0.2	Power for detecting a HR of 2 & SD(HR) =0.1	Power for detecting a HR of 2 & SD(HR) =0.2
9.6 per 1000 person-years	500	0.265	0.256	0.474	0.516	0.621	0.617
	1000	0.409	0.433	0.716	0.706	0.832	0.813
	1500	0.520	0.500	0.813	0.779	0.897	0.902
	2000	0.586	0.606	0.876	0.854	0.955	0.937
	2500	0.662	0.644	0.905	0.893	0.958	0.955
	3000	0.714	0.657	0.930	0.908	0.976	0.972
	3500	0.750	0.722	0.962	0.923	0.985	0.972
	4000	0.800	0.753	0.965	0.941	0.985	0.974
	4500	0.816	0.801	0.971	0.964	>0.999	>0.999
39.8 per 1000 person-years	500	0.583	0.569	0.852	0.829	0.943	0.925
	1000	0.789	0.716	0.958	0.947	0.981	0.985
	1500	0.882	0.835	0.977	0.975	0.995	0.987

Abbreviation – HR: hazard ratio; IR: incidence rate; SD: standard deviation

For the malignancy outcome, using an allocation ratio of 1:3, an average follow-up time of 5 years, and an IR of 6.31 per 1000 person-years, the minimum required sample size to achieve 80% power for detecting a pre-specified true HR of 1.5 (geometric mean of 0.425 in lognormal space) from an effect distribution with SD(HR) of 0.2 (geometric coefficient of variation of 0.132 in lognormal space), is approximately **3,195** anifrolumab patients across all countries.

For serious infections, using an allocation ratio of 1:3, an average follow-up time of 2 years, and an IR of 39.8 per 1000 person-years, the minimum required sample size to achieve 80% power for detecting a pre-specified true HR of 1.5 (geometric mean of 0.425 in lognormal space) from an effect distribution with SD(HR) of 0.2 (geometric coefficient of variation of 0.132 in lognormal space), is approximately **1,312** anifrolumab patients across all countries.

The proportional share for each data source was based on the expected number of SLE patients as presented in section 10.5.1. These proportions along with the required country-level sample size to achieve 80% power to detect a pre-specified HR of 1.5 (geometric mean of 0.405 in lognormal space) from an effect distribution with SD(HR) of 0.2 (geometric coefficient of variation of 0.132 in lognormal space) with a 1:3 matching is presented in Table 13.

Considering the estimated number of patients initiating anifrolumab during the study period (3,506 for the malignancies cohort, and 1,435 for the serious infections cohort Table 8) and the required sample size presented above (3,195 for the malignancies cohort and 1,312 for the serious infections

cohort), there is a reasonable assumption that the final study report milestones as specified in this protocol can be met. However, the assumptions used in the calculation of the exposed anifrolumab patients will be evaluated at the first progress report (31 May 2026) and first interim report (31 May 2027). If the assumptions do not hold, the final study report milestones will be re-evaluated, and potential mitigation steps will be explored.

Table 13 Minimum sample size needed for malignancy and SI outcomes (overall and in each data source)

Country	Share of country in study (%)	Minimum required sample size (anifrolumab patients) for the Malignancy outcome with IR = 6.31 per 1000 py	Minimum required sample size (anifrolumab patients) for the SI outcome with IR = 39.8 per 1000 py
Denmark	5.89%	188	77
France	74.56%	2,382	978
Germany	5.40%	173	71
Spain	14.16%	452	186
Total	**100.00%**	**3,195**	**1,312**

Abbreviation – HR: hazard ratio; IR: incidence rate; SD: standard deviation

10.6 Data management

IQVIA (who will perform the PASS on behalf of AstraZeneca) will take responsibility for application for the study permits, obtaining necessary approvals (ethical or otherwise), and access to the study data. Generally, the data will be stored and analysed in accordance with local policy. All data used in this study will be in the form of electronic records, and the data holders collect and manage data according to their own standards.

The identification of the study population will be conducted by the individual data source holders according to the specifications given in Section 10.2.2. After the identification of the study population from different data sources, study data from each data source will be extracted. The data extraction will be conducted by the individual data source holders. After data are extracted, the data holders will make data accessible to IQVIA, according to data permits in each respective country. The details of the data permits will be confirmed when the data permits are granted. If the data permits allow, individual level data will be accessed by IQVIA. However, individual level data from some of the data holders (SHI (Germany) and SIDIAP (Spain)) cannot be accessed by IQVIA but will be managed and analysed by the data provider (Team Gesundheit (Germany) and Primary Care Research Institute Jordi Gol (Spain)). All individual level data accessible to IQVIA will have original personal identifiers replaced with a study identification number. Thus, IQVIA will not have access to data that allow individuals to be directly identified.

IQVIA will adhere to all local and regional laws on data protection and privacy. IQVIA will also adhere to IQVIA standard operating procedures, and data management for this study will be conducted using standard IQVIA processes. IQVIA will maintain appropriate data storage,

including periodic backup of files and archiving procedures and will comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans, and performing quality checks for all scripts.

The general principles for data management and statistical analyses will be described in detail in the SAP. Therein all data checks to be performed on completeness, plausibility, and consistency of collected data will be described in detail with identification of data discrepancies. IQVIA will perform all data management and statistical analyses using statistical software (SAS version 9.4 or later, or R [version 3.5.0 or later]) or STATA. The data providers conducting the data management and statistical analysis for the study will store the datasets and analytic scripts according to the data provider's procedures. Full audit trail starting from raw data obtained from register holders and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses will be kept for inspection for five years after publication of results. The study may be inspected by AstraZeneca's independent representative(s), scientific committee, or by the competent authorities.

10.7 Data analysis

A full description of the analytical approach will be developed and described in the SAP. Details on data derivations, category definitions, analyses, handling of missing data, and presentation of the study results will be provided in SAP. SAP will be finalised prior to the conduct of the study analyses.

All study results will be presented separately for each country in the study reports, as appropriate when data become available. The final study report will include all descriptive, comparative, exploratory and sensitivity analyses as well as the meta-analysis for all the data sources.

10.7.1 Statistical methods

10.7.1.1 Time-based exposure sets and propensity score matching

Base cohort

The base cohort will be defined using SLE diagnosis within the study period as the inclusion criteria. Anifrolumab exposed patients in the base cohort will consist of individuals who had prior exposure to SLE SOC drugs. Hence, the base cohort will be formed of all patients who have used SLE SOC, some adding-on anifrolumab as incident user, and the others continuing SLE SOC alone.

Time-based exposure sets

Time-based exposure sets will be defined to determine the time-points at which comparability will be established. Time on SLE SOC (i.e., time from the first prescription of SLE SOC for moderate to severe SLE) will be considered as a marker of disease course. For each exposed patient, a time-

based exposure set will be created including all unexposed patients with similar time on SOC as the exposed at the time of anifrolumab initiation. Anifrolumab and SLE SOC prescriptions dates will be used to anchor the exposure sets from the base cohort [88]. The detailed process of time-based exposure set creation is presented in Section 10.1 and in Section 10.2.2.1.

Time-conditional propensity score-based matching

Time-conditional propensity scores will be used to compute, for each patient in each time-based exposure set, the propensity of being exposed to anifrolumab (vs. staying on SLE SOC) as a function of patient characteristics at the exposure risk set date. Variables identified as potential confounders included in Table 6 will be considered for inclusion in the time-conditional propensity score. The steps involved in creation of time-based exposure sets and PS matching are below:

1. In the base cohort, each patient is treated as a possible comparator in the beginning until exposure of anifrolumab or censoring due to other reasons.
2. The index date for patients in the exposed group is their anifrolumab first exposure date.
3. On a timescale of time since start of SLE SOC, for each timepoint where a patient is exposed to anifrolumab, the set of eligible comparators is formed based on time since the start of SLE SOC.
4. All patients who are not yet on anifrolumab are eligible for being a comparator. Eligible comparators must have a prescription of SLE SOC within +/- 45 days (wider time intervals may be considered if matches cannot be obtained using this time window) of the respective anifrolumab exposure date, on the time scale of time since start of SOC. The closest SOC prescription date to the anifrolumab exposed patient's index date will be selected as an index date for the matched comparator patient. Patients who are not yet on anifrolumab can therefore be included in several time-based exposure sets.
    a. For example, if the exposed patient initiates anifrolumab 180 days since start of SLE SOC, eligible comparators with a SOC prescription between 135 days and 225 days since start of SLE SOC will be included in the time-based exposure set.
5. For all patients, time-varying PS covariates (for example, SLE severity, SLE activity, comorbidity status, BMI, age etc.) will be updated at each time point corresponding to a time-based exposure set (i.e., at index date).
6. The time-conditional propensity score will be fit as a single time-dependent Cox proportional hazards regression or conditional logistic regression model (as appropriate given the data), using all the time-varying and fixed covariates from all the exposure sets.
7. Within each time-based exposure set, the model fitted from step 6 will be used to compute time-conditional PS values for the anifrolumab exposed patient and its eligible set of comparators.
8. For positivity purposes, within each time-based exposure set, the time-conditional PS value of the exposed patient should be within the range of the time-conditional PS values of the unexposed patients. If this is not the case, the exposure set is eliminated.

9. Matching will be done chronologically from SLE SOC start. Up to 3 matches will be selected amongst the SLE SOC comparators within the time-based exposure set based on whose PS scores are the closest to the score of the anifrolumab initiator. Matched comparators will be removed from all subsequent time-based exposure sets.
10. The effectiveness of this matching will be assessed. Covariate distributions before and after matching and the associated balance diagnostics will be reported.

Further details regarding the PS computation and matching procedure will be provided in the SAP.

10.7.1.2 General considerations and descriptive analysis

The following relates to secondary and exploratory objectives 5, 11 and to any other descriptive analysis conducted in the study.

For the descriptive analysis of continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1^{st}) and upper (3^{rd}) quartiles, as well as 5^{th} and 95^{th} percentiles will be presented. For categorical variables, the numbers, and percentages of observations for each of the categories will be presented in descriptive analysis. The number of patients and percentages with missing data for each variable will be reported. Further details on methodology will be provided in the SAP.

In the descriptive analysis, the total number of patients at risk and the number of events for each study outcome in the exposed to anifrolumab and SLE SOC comparator groups will be tabulated both before and after PS based adjustments [5, 89]. Descriptive tables will also include the SOC treatments received, number of flares in 6 months prior to study entry and time since last flare by exposure status. Covariate balance will be assessed by examining the distribution of variables in the cohorts and estimating standardised differences for each variable between the anifrolumab-exposed and the comparator cohort. In case large differences in standardised differences are present, modifications to the time-conditional propensity score or to the matching algorithm will be considered. Modification could include using the alternative model for fitting the PS model (Cox regression vs conditional logistic regression) or implementing a calliper when selecting the time-conditional matched comparators in step 9. Further details will be provided in the SAP:

The measures of study outcomes, with associated 95% CI, will be estimated for the exposed to anifrolumab and unexposed groups.

In all regression analyses, guidelines for appropriate fitting of any logistic or cox regression model recommend a minimum of ten outcome events per term (where term may be any linear covariate, non-linear predictor, or interaction term). In the primary analysis, including the primary and secondary objectives, if sufficient outcome events are not available, regression results should be interpreted with caution with regards to bias and precision. In addition, descriptive statistics of the occurrence and duration of all infections leading to hospitalisation, in moderate/severe SLE

patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), will also be provided (objective 11). For this, the number, proportion of patients, median time to recurrent serious infection, duration of hospitalisation for each recurrent serious infection and death will be tabulated for both treatment cohorts.

10.7.1.3 Estimation of crude incidence rates

The following relates to primary and secondary objectives 1, 3, 6, 8 and 9 and exploratory objective 11.

Using the exposure definition mentioned in Section 10.3.1, the crude IRs for each outcome (malignancy and serious infections) within the relevant sub-cohort will be expressed as number of cases per 1,000 patient-years at risk. Only the event under study in each of the sub-cohorts will be considered. For example, a patient with an incident serious infection event who subsequently is newly diagnosed with a malignancy event will contribute with both event groups of interest to the study.

Crude cumulative IRs of serious infection will be calculated over these time periods of interest - 30, 180, and 365 days from index date. For malignancy outcome, the time periods used for calculating crude cumulative IR will be: 1-year, 3-year and 5year since the start of follow-up after the 12-month latency period.

The crude cumulative IR will be calculated as the number of malignancies during the cumulative interval of interest, divided by the total person-years at risk in the period. It will be presented per 1000 person-years at risk, with the associated 95% CI. In addition, plots of cumulative incidence function will also be presented, calculated using the Nelson-Aalen non-parametric method, over the study period for all the outcomes under consideration.

10.7.1.4 Comparative analysis

The following relates to primary and secondary objectives 2, 4, 7, 10 and exploratory objective 12.

For objectives 2, 4, 7 and 10, cox proportional hazard regression models will be used to estimate the HR within the matched populations with a robust sandwich covariance matrix to account for the same patient contributing anifrolumab exposed person-time and SOC-exposed person-time. HRs and the corresponding 95% CIs will be reported. The proportional hazard assumption will be verified for each study exposure. The final objective-specific outcome models for the PS-matched cohort analyses will include any variables found to be imbalanced after the PS matching.

For objective 12, based on the descriptive analysis and on the availability of sufficient patients across data sources, a comparative analysis will be conducted to compare the average risk (hazard) of recurrent infections (up to 4th serious infection only) in patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). Further details on the methodology will be available in SAP.

10.7.1.5 Confounding variables

All confounders listed previously in Section 10.3.3, will be assessed once for each patient at their index dates.

10.7.1.6 Meta-analyses

In addition to data source level analyses, results will also be combined in a meta-analysis. Meta-analysis will be performed only for the primary study objectives. The meta-analysis will be performed using aggregated data from all study countries, assuming the country-specific analyses are available for pooling. Prior to conducting the meta-analysis, heterogeneity across the study countries will be assessed using:

- Cochran's Q test (significance level: 0.1). Q is calculated as the weighted sum of squared differences between individual studies and the pooled value across data sources.
- The I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). I^2 is calculated as follows:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Where Q is Cochran's statistic and 'df' is its degrees of freedom. The I^2 is a statistic that estimates the percentage of variance in effects attributable to study heterogeneity rather than sampling error.

- τ^2 statistic: Utilises the Q value to calculate the excess variation across data sources

If high levels of heterogeneity are found to exist, the study design and characteristics in the included local studies will be reviewed and the possible source of heterogeneity discussed. The country-level logHRs and their standard errors will be entered in a random-effect inverse-variance model. Data source-specific results and the overall combined estimate will be presented in forest plots including effect size and 95% CI for each study country included in the analysis. In a sensitivity analysis, the meta-analysis will be done using a fixed-effect model.

Further details regarding the meta-analysis will be presented in the SAP.

10.7.1.7 Sensitivity analyses

Sensitivity analyses will be conducted for the primary objectives related to malignancies and/or serious infections.

- For both serious infections and malignancies: Patients exposed to anifrolumab will be compared with two groups of patients exposed to SLE SOC: a) patients exposed to SLE SOC biologics (belimumab and rituximab, including biosimilars) and b) patients exposed to SLE SOC non-biologics.

- For malignancies: As the definition of the latency period is subjective, two other latency periods will be evaluated: no latency period and 24 months latency period.
- For serious infections: A comparative analysis of the incidence for each component of the serious infection definition (i.e., infection leading to hospitalisation, use of intravenous antimicrobials and infection-related death) will be conducted, comparing the incidence among patients exposed to anifrolumab versus comparable moderate/severe SLE patients on SOC. However, as these comparative analyses may be limited by small sample size for each of the components of the serious infections' definition, the analyses will only be conducted if feasible.
- Meta-analysis: The main analysis uses a random effects model to pool the effect estimates across data sources assuming that there is heterogeneity amongst the included data sources (i.e., the true effect is different between the data sources). To assess the robustness of this assumption, the meta-analysis will be conducted with a fixed effects model and its results reported as a sensitivity analysis.

10.7.1.8 Handling of missing data

The following relates all objectives and all sub-cohorts.

Missing data are those where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the extracted data may not be interpretable, or where the value must be assumed to be missing because of data inconsistency or out-of-range results. Methods commonly used in non-interventional studies for handling missing data, such as imputation, complete case analysis or indicator for missing values, will be considered. The SAP will describe the full details on handling missing data that will include the methods for identifying where missing data methods should be applied, the techniques for identifying the type of missing information and the appropriate imputation methods to be used, if any.

Variables which are only recorded if an event, test, or diagnosis occurs are not eligible for missingness analysis although we acknowledge that these may be missing. For example, if there is no record of an event, it must be assumed that that event did not occur rather than assuming the data are missing because in registry data the fact that a patient did not have the event, is not recorded. All variables relying on the presence of a diagnostic code (i.e., ICD-10) fit this definition.

Lifestyle factors such as smoking, obesity, and alcohol/substance abuse have been identified as having a high possibility of missingness in this study due to the reliance of recording as diagnostic codes or in a specialised registry, therefore we may be unable to adjust estimates for those confounders.

10.8 Quality control

This study will be conducted according to the rules of good pharmacoepidemiology practices (GPP) and the Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 1) EMA/813938/2011 Rev 1. All aspects of the study from protocol development to the reporting of the results will be conducted within the work-framework of IQVIA Quality Management System and in accordance with the following manual, operating procedures, and work instructions.

According to the policies and procedures above a quality control plan for the study will be developed and executed, which will include quality control on study methodology, SAP, programming, data management and analysis, and study report including study results and conclusions. Furthermore:

- The principle of the independence of quality control applies.
- IQVIA project management will ensure that individuals responsible for the execution of specific quality control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the quality control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.
- The executed quality control plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team.
- The project management team will also ensure that IQVIA employees assigned to the project are trained on protocol and project-specific procedures, as per IQVIA procedure.

The study will be conducted as prescribed in this protocol. Revisions to the protocol would be approved by the principal investigator and AstraZeneca. All changes to the protocol shall be documented as protocol amendments and when necessary, such protocol amendments are delivered to relevant ethics committees and register holders.

The study protocol has been written following the Code of Conduct by the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) (European Medicines Agency, 2018). The protocol also follows the key elements of the Guideline for GPPs by International Society for Pharmacoepidemiology (ISPE).

IQVIA, the principal investigator, the MAH and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

For information on storage of records, archiving of the statistical programming will be performed to generate the results and possible audits. Due to the study type (observational study using secondary databases) on-site monitoring will not be performed.

10.9 Limitations of the research methods

Study design

- **Prevalent user bias** can result from comparing patients with different SLE disease course in terms of the risk of the outcomes [88], namely in different duration of SLE drugs that might also increase the risk of malignancies and serious infections. A new-user design, comparing patients initiating anifrolumab with patients initiating other SOC indicated for moderate to severe SLE, could minimise bias. However, it is not feasible to answer the study research question because anifrolumab does not have an active comparator, since it is indicated as an add-on therapy to patients with uncontrolled SLE despite SOC. To minimise this bias, time-based risk sets will be defined to identify patients exposed and unexposed to anifrolumab with previous exposure to SOC with similar duration. Additionally, patients matched using PS scores allows for balancing the exposure groups in terms of several characteristics that might also affect the probability of the outcomes of interest.

- In this study, there is an **immortal time** for the group exposed to anifrolumab because patients need to survive or be event free to initiate the drug, but patients only exposed to SOC do not. Immortal time bias is minimised by the time-based risk sets creation in which patients are matched on similar previous SOC duration. Additionally, comparators will be selected at the time of anifrolumab initiation (regardless of future anifrolumab initiation). If comparators were patients that did not initiated anifrolumab during the entire study period immortal time would be included.

- Confounding **by indication** may occur because adding anifrolumab may be due to changes in the severity or disease activity. To minimise bias, the study only includes patients with uncontrolled, moderate to severe SLE. Additionally, patients exposed and unexposed to anifrolumab will be matched on SOC duration and on PS.

- **Bias from depletion of susceptibles** might occur when patients at higher risk of the outcome, particularly serious infections, are excluded from the population still at risk, and exclusions differ between the groups being compared. If serious infections are more likely to occur shortly after drug initiation [81], at index date unexposed patients might have a lower risk of serious infections than anifrolumab exposed patients. This bias may be minimised by the analytical plan to match based on disease severity and activity.

Sample size and representativeness

- The inclusion of several countries contributes to the sample size and representativeness of European anifrolumab users. However, SLE clinical management may occur in healthcare settings that are not part of some of the data sources (e.g., private care) which could result in the exclusion of potential eligible patients. Possible selection bias may occur if patients in the other settings are different from those included in terms of outcome risk. However, in the included countries, anifrolumab is more likely to be available in secondary care (hospitals or SLE specialised clinics) which would minimise selection bias.

- SLE is not a very common disease. The selection of patients with moderate to severe uncontrolled disease and matching with a comparator cohort with a similar SOC duration may increase internal validity. However, it is possible that some anifrolumab exposed patients who do not have suitably matched comparators may have to be excluded from the study. Despite this exclusion, it is assumed that these patients may be too different from the general moderate/severe SLE patient population in the real-world setting.

Data sources and data availability (overall)

- Automated healthcare databases are appropriate for real-world studies because of the recording of prescription and clinical data in the absence of a specific research question. However, the accuracy of the analyses to answer any given research question depends to some degree on the accuracy of the available information. Data collected for administrative purposes may have incomplete medical information which is not directly related to reimbursement (e.g., body mass index). This can affect the measurement of variables that may be important covariates for the assessment of the association between anifrolumab use and the occurrence of serious infections and malignancies. To minimise the risk of including incomplete information, all retrieved data will be reviewed for possible inconsistences or implausible information.

- Some data sources have relatively long lag times. Denmark, France and Germany have particularly long lag periods (up to 13 months in Denmark and 12 months in France and Germany), which could limit availability of data. However, an assumption of a data lag time of approximately 2 years will be implemented to maximise capturing available data.

- Missing information might also vary between the data sources. Whenever applicable, missing information will be reported.

- When the outcome for a specific analysis has less than five cases/observations, the specific result and other potentially related results may not be reported as such in all the included databases, as it could lead to the identification of patients. This may be a potential limitation for analyses that require stratification, such as the detailed number of specific malignancies. Furthermore, minimum and maximum values cannot be reported.

- For data sources with data only available for recent years, the date of SLE diagnosis or the first SLE SOC prescription may be left-censored. This might result in misclassification of SLE duration or previous SLE SOC duration. However, in this study, no differential misclassification is assumed within country-specific data sources.

- All relevant variables for the definition of the PS and for further adjustment will be included in the analyses. However, information on individual covariates may not be available in all databases, such as body mass index, smoking or alcohol consumption. This and possible unknown confounding variables may result in residual confounding of the study results.

Exposure assessment

- Anifrolumab is a novel drug. Thus, the drug uptake in the countries and populations covered in the data sources may be slow at the beginning of the study period and is likely to increase closer to the end of the study.

- Anifrolumab is not indicated for the treatment of severe, active central nervous system lupus or severe, active lupus nephritis [29]. These conditions were not considered as exclusion criteria to capture all patients that might be using anifrolumab in real-world context (even if not indicated for). Clinical manifestations related with lupus nephritis and central nervous system lupus will be included as part of the severity algorithm and PS and thus, patients exposed to anifrolumab and to SLE SOC will be matched on these conditions.

- The end of anifrolumab treatment takes into account the window of clearance which is based on time for concentration to fall below the LLoQ in 95% of patients. Patients with only one dose of anifrolumab may have shorter clearance (10 weeks) [2]. Although the use of only one dose is not expected in many patients, it might result in overestimation of the risk related with the use of anifrolumab since patients might be considered exposed to the drugs even if anifrolumab is no longer in the body.

- The definition of the window of clearance for all the other SLE SOC is based on pharmacokinetic data from different sources, which may lack consistency and reliability and result in misclassification of the SLE SOC duration. However, the number of patients not exposed to any SLE SOC is expected to be small due to SLE severity. Thus, the impact of treatment duration misclassification may be minimal as, for most patients, the end of follow-up is likely to be defined by the occurrence of other censoring criteria (malignancy/serious infection, end of study period, death, or disenrollment).

- Drug exposure will be assessed from prescription, dispensing or drug administration data sources. For each, accuracy of drug exposure classification, namely the date of treatment initiation and discontinuation, may be different according the oral/IV administration mode of SLE SOC, and between countries:

    - In the outpatient setting, where most anifrolumab administrations are likely to occur, the ability to distinguish infused drugs may be challenging. However, included data sources use ATC or other coding system to capture drugs used in outpatient setting, minimising under-detection of anifrolumab and misclassification. However, changes in the coding system and/or reimbursement decisions, namely of outpatient visits for anifrolumab infusion (such as in Germany or France), may impact exposure definition.

    - In France, the ability to capture data on anifrolumab use depends on the moment the drug integrates the high-cost drug list. Under-detection of anifrolumab exposure may result in misclassification of the exposure status.

    - In Germany, if a patient is hospitalised and was given anifrolumab, information about such administration would not be available. This may result in misclassification of the start or end

of treatment and consequent censoring. However, since the end of treatment is defined 16 weeks after drug discontinuation, misclassification is expected to occur mainly among patients experiencing very long hospitalisations. Not all SLE SOC drugs are marketed in all countries (e.g., voclosporin not marketed in France). This will not affect within country analyses but may impair inter-country comparability.

- Depending on the mode of administration, not all SLE SOC drugs are captured in the data sources. In France, some drugs are only available if used in oral forms. Patients prescribed IV drugs may be misclassified in terms of the start/end of SLE SOC and regarding SLE severity. E.g., If IV cyclophosphamide is more likely to be prescribed than the oral form, patients with severe SLE might be misclassified as having moderate SLE. This will limit comparability between exposed and unexposed patients with moderate disease. However, the use of propensity scores including several other patient characteristics may minimise misclassification.

Outcome assessment: serious infections and malignancies

- One of the mechanisms by which SLE patients are at increased risk of serious infections and malignancies is mediated by the exposure to immunosuppressant therapies [13, 41, 84]. High doses of glucocorticoids or other immunosuppressants such as azathioprine, mycophenolate mofetil or cyclophosphamide are recognised risk factors for serious infections and malignancies [13, 41, 84]. If patients exposed to anifrolumab are more likely to have been previously exposed to any of these drugs than those in the comparator group, an apparent increased risk associated with anifrolumab will be observed. To minimise this bias, the type and duration of SLE SOC previously used will be considered for the PS creation and thus, patients will be matched on similar previous exposure. However, residual confounding may be present.

Outcome assessment: serious infections

- Not all serious infections are captured by current definition because some of the serious infection components are not available in secondary data sources (e.g., if a particular infection prolonged an existing hospitalisation or led to disability). Thus, the incidence of serious infections may be underestimated.

- The use of different databases (coded hospitalisations, drug prescriptions, death registries) is likely to improve sensitivity of the outcome [8], by identifying serious infections that are managed in different settings (because of the type of infection, countries' healthcare structure or access to care). Infection-related diagnoses in inpatient administrative data sources showed sensitivity ranging from 4.4–100%, depending on the type of infection (e.g., low sensitivity for sepsis), source of data, population included, and the algorithms used [8]. By considering several infection diagnoses and including diagnoses in any position (primary and secondary diagnosis) sensitivity is increased. However, specificity might decrease as infections not related with drug exposure might be more often captured. Although the definition used is likely to have high sensitivity to

capture all serious infections, data from different databases may not be available in all countries, impairing comparability.

- In France, data on IV antimicrobials may not be captured because only expensive drugs administered in the hospital setting are captured. Additionally, only data on hospitalisation diagnoses are available and it is not possible to capture data on infections coded in primary care that resulted in a hospitalisation (if that hospitalisation does not include an infection diagnosis).
- In Germany, data on inpatient IV antimicrobials administration are not captured.
- The Danish National Registries only capture data on diagnoses from secondary care (emergency, inpatient, and specialty outpatient care) and if the infection is coded as the reason for healthcare encounter.

To account for possible misclassification, narrow definitions of serious infection will be used as sensitivity analyses for the primary outcomes, by assessing and comparing the incidence of each component of the serious infection definition. However, these analyses may not be feasible if sample sizes are small for each of these serious infection components. Additionally, the management of serious infections in each country may differ, limiting generalizability.

- Identification opportunistic infections may require detailed clinical information – that may not be available in secondary data [99]. Despite this challenge, in a diagnostic validation study which aimed to evaluate the reliability of identifying opportunistic infections (tuberculosis, listeriosis, aspergillosis, histoplasmosis, cryptococcosis, pneumocystis carinii, systemic candidiasis and cytomegalovirus) using ICD-10 codes in an administrative claims data, the positive predictive value (PPV) varied between 20% for systemic candidiasis to 100% for cryptococcosis. The PPV for all the opportunistic outcomes investigated, excluding systemic candidiasis was greater than 66%. As a composite outcome, excluding candidiasis, the PPV was 76% [80].

- There are varying definitions of opportunistic infections. While it may be challenging to identify one formal definition, a comprehensive list of potential opportunistic infections, which represents a systematic review-informed consensus opinion by infectious disease and rheumatology experts, relevant in rheumatology has been ratified by a consensus committee [99]. The consensus committee acknowledge that while this list is neither complete nor absolutely "correct", the presence of the infections in this list may be indicative of an altered host immunity playing an aetiological role in the setting of biologic therapy. The limitation in the use of this list from the consensus committee for this study is that not all conditions on the list have ICD codes (hepatitis B reactivation, invasive Shigella infection, invasive Campylobacter infection and BK virus causing polyomavirus-associated nephropathy). Therefore, these infections will not be captured. Additionally, some unspecific codes (e.g., pneumonia with no defined pathogen, other sepsis) will not be defined as opportunistic. This will increase the specificity of the opportunistic serious infections definition but may result in decreased sensitivity of the outcome.

- Date of death will be identified by linking data to administrative records or mortality registries available in the study countries. The added sensitivity of including death registries for patients with a prior infection diagnosis (regardless of cause of death) may come at the expense of decreased specificity by considering deaths that might occur 30 days after an infection diagnosis but are not related with the infection episode.

Outcome assessment: malignancies

- Most malignancies have long latency periods in the absence of immunosuppression [66]. Although immunosuppression shortens the latency period [100], current study follow-up time may be short (seven years will be the maximum duration between first enrolled patient and the end of follow-up) to identify some malignancies. Thus, the incidence may be underestimated. However, haematological malignancies are expected to be the most frequent cancer types among SLE patients [12, 13, 84]. For those, latency periods are likely to be shorter.

- Previous research suggests that biologics are associated with an increased risk of malignancies [100]. Therefore, cancer screenings (e.g., for breast or cervical cancers) and closer surveillance may be reinforced among patients exposed to biologics, namely anifrolumab [16]. If so, anifrolumab patients may have a diagnosis at an earlier time point than it would have been if it had been diagnosed by its clinical appearance. This may result in an increased risk of malignancy in anifrolumab patients. However, patients exposed to SLE SOC may also be exposed to other biologics or known carcinogenic drugs (such as cyclophosphamide) which may result in similar adherence to cancer screenings, minimising surveillance bias [41].

Capturing malignancies using claims data may be prone to misclassification because unconfirmed cases may be captured. Since no population-based cancer registry is used for France (SNDS), Germany (SHI) and Spain (SIDIAP), misclassification may occur. Additionally, in France, malignancies are only captured for patients that were hospitalised. Although virtually all patients may be hospitalised at some stage of the disease, under-detection may occur.

SLE severity and activity

- Disease severity and activity scales (e.g., Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K score]) are frequently used in randomised controlled trials but are not routinely recorded in secondary data sources and therefore were not included. Activity could also be addressed by considering specific biomarkers (e.g., C3, C4) which are unlikely to be systematically used and available. To minimise the lack of available data, severity and activity algorithms that were previously defined [39, 56] will be used, incorporating information that is used in routine practice: scale-up of SLE treatment strategies, SLE clinical manifestations and HRU.

- SLE severity is mainly related with organ damage, and it may reflect disease duration and activity. The algorithm to be used in current study was developed from existing validated tools and clinical knowledge and it was previously validated against a measure of SLE activity

(SLEDAI-2K) in a database from the USA [85]. In the European setting, the algorithm was only used in Clinical Practice Research Datalink (CPRD) [56]. However, performance may be different in other settings.

- SLE severity algorithm showed 86% sensitivity and 68% specificity for classifying moderate/severe vs. mild SLE [85]. Thus, misclassification might occur. For example, a patient with moderate disease who have a severe flare may not be distinguished from a patient who have severe disease if the criterion to define flare severity was the initiation of high dose corticosteroid (>20 mg/day) (exposure to one or more prescription of high dose corticosteroid defines severe disease). Even so, severity is assessed prior to anifrolumab exposure and patients will be similar in other characteristics. Thus, misclassification is not expected to be differential in patients exposed and unexposed to anifrolumab.

- The presence of a coded diagnosis with no concomitant exposure to medication prior to index date may misclassify patients in terms of SLE severity and activity. This might be minimised by including patients with previous SLE SOC use and restricting SLE severity and activity definition for the 12- and 6-months period before index date. Additionally, the number of patients who satisfy the various criteria for moderate/severe disease and active disease will be described to ascertain the potential for misclassification.

- Distinction between clinical manifestations (i.e., acute conditions) that define active SLE from comorbidities may not be possible for some of the diagnoses included in the activity algorithm (e.g., renal impairment). Although active disease will be assessed for a shorter look-back period of 6 months, misclassification is possible.

10.10 Other aspects

10.10.1 Quality assurance

In compliance with regulatory requirements, AstraZeneca, a third party on behalf of AstraZeneca, or regulatory agencies may conduct quality assurance audits/ inspections at any time during or following a study. The participating data sources must agree to allow auditors/inspectors direct access to all study related documents, apart from patient-level data, according to national legislation in participating countries and internal guidelines of the participating databases. The database representative must also agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

Before the data delivery to IQVIA, the data holders should have collected and managed data according to their own standards. After the data are delivered to IQVIA by the data holders, IQVIA will process the data and perform basic quality checks. For the data sources providing aggregate-level data to IQVIA, data will be processed, and basic quality checks based on the defined data quality indicators will also be performed prior to aggregation of the data.

Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

10.10.2 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant regulatory authorities and may require submission or notification to the relevant data source institutional review board (IRB)/independent ethics committee or regulatory authorities where required by pertinent regulations. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

10.10.3 Study management

This study will be performed by IQVIA, with guidance, input, review, and approval of AstraZeneca, including development of materials, data management, analysis, and reporting.

11 PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the guidelines for GVPs and GPP issued by the ISPE, the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws, and regulations.

11.1 Independent ethics committee/institutional review board

The study protocol will be submitted to the responsible IRB/Independent Ethics Committee for its review/approval whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to Ethics Review Boards and regulatory authorities as required by local laws and regulations.

When the approval has been granted, the formal procedure of applying for access to and retrieval of patient-level health information can be performed to each governing health authority in the respective countries. A prerequisite for approval from an IRB is that the research project is thoroughly described in a study protocol with a clear scientific objective and purpose.

The overall ethical review and data access time is expected to vary between 3 and 18 months, depending on the data source/country.

This study is non-interventional, and analysis is based on secondary data use. No identifying data are collected or stored by IQVIA in any of the planned approaches.

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will adhere to the ISPE GPP guidelines. This is a non-interventional study design which is based on secondary data use. Expedited reporting of adverse events and adverse drug reactions is not required.

13 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

13.1 Progress reports

Study progress will be reported in Periodic Safety Update Reports.

13.2 Interim analyses and reporting

Two interim reports will be submitted for serious infections and malignancies primary outcomes (one for serious infections and malignancies and one for malignancies only). The first interim report will be finalised on 31 May 2027. The second interim report will be finalised on 31 May 2030.

13.3 Final analyses and reporting

The final study reports are planned for 30 November 2028 for serious infections and 30 November 2032 for malignancies and would include all descriptive, comparative, exploratory and sensitivity analyses as well as the meta-analysis combining data from all the data sources included in the study.

The interim/progress report(s) and the final study report will be written in accordance with the GVP guidelines module VIII (EMA/813938/2011).

In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), information about this PASS will be entered into the publicly available EU PAS register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

13.4 Publications

Based on the study report, the principal investigator and co-investigators (together referred to as “investigators”; members of the responsible parties and possible other contributors approved by the responsible parties) will prepare (a) scientific manuscript(s) for academic publication. The responsible parties decide the publication forums.

The investigators will inform AstraZeneca in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require pre-submission review and approval by AstraZeneca.

The principal investigator and AstraZeneca are committed to ensuring that authorship for all publications comply with the criteria defined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors, updated April 2010. It is stated that each

author should have participated sufficiently in the work to take public responsibility for the content. These conditions apply equally to external investigators and to employees of the Sponsor.

Within 3 months following the study report, an abstract of the study findings will be made available to the public through the EU PAS Register (The European Union electronic Register of Post-Authorisation Studies). According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial, or personal interests. AstraZeneca is entitled to view the final results and interpretations prior to submission for publication in the EU PAS Register, and to comment these without unjustifiably delaying the publication. AstraZeneca will maintain the right to delay publication in order to protect intellectual property rights. The principal investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period due to pending response from the peer-review process.

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APPENDICES

Appendix 1 List of stand-alone documents

None

Appendix 2 ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15 October 2018

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				7.
	1.1.1 Start of data collection[9]	☒	☐	☐	
	1.1.2 End of data collection[10]	☒	☐	☐	
	1.1.3 Progress report(s)	☒	☐	☐	
	1.1.4 Interim report(s)	☒	☐	☐	
	1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
	1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	9.
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
	2.1.2 The objective(s) of the study?	☒	☐	☐	
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	10.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10.1

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

[10] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	10.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	10.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	10.2.2
4.2	Is the planned study population defined in terms of:				10.2
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	10.1; 10.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	10.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	10.9
5.3	Is exposure categorised according to time windows?	☒	☐	☐	10.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	10.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	10.3.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	10.3.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	10.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	10.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	10.3.2; 10.9
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	10.3.3; 10.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	10.1; 10.3.3; 10.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	10.3.; 10.9

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	10.7.1

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	10.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	10.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	10.4 Appendix 4.2
9.2	Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	10.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, comorbidity, co-medications, lifestyle)	☒	☐	☐	10.4 Appendix 4.2
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	10.4 Appendix 3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	10.4 Appendix 3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	10.4 Appendix 3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	10.7.1
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	10.5
10.3	Are descriptive analyses included?	☒	☐	☐	10.7.1.2
10.4	Are stratified analyses included?	☒	☐	☐	10.7.1
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	10.7.1.5
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	10.7.1.1; 10.7.1.7
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	10.7.1.8
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	10.7.1.7

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	10.6; 10.10.1
11.2	Are methods of quality assurance described?	☒	☐	☐	10.10.1
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	10.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	10.9
12.1.2 Information bias?	☒	☐	☐	10.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	10.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	10.2; 10.4.1; 10.5; 10.9; Appendix 4

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	11.
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6; 11.

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	6; 10.10.2

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13.
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.4

Comments:

Abbreviations: ENCePP, European network of centres for pharmacoepidemiology & pharmacovigilance; EU PAS, European Union post-authorisation safety studies; IT, information technology; N/A, not applicable; WHO, World Health Organisation.

Name of the main author of the protocol: Mickael Arnaud

Date: 28/April/2023

Signature: _____

Appendix 3 Exemplar code lists

Code lists will be finalised in the SAP.

Table 14 Drug classes and active substances used in SLE SOC

Drug/Procedure	ATC codes
Antimalarials	
Chloroquine	P01BA01
Hydroxychloroquine	P01BA02
Quinacrine (mepacrine)	P01AX05
Glucocorticoids	
Dexamethasone	H02AB02
Methylprednisolone	H02AB04
Prednisolone	H02AB06
Prednisone	H02AB07
Triamcinolone	H02AB08
Immunosuppressive agents	
Biologic immunosuppressants	
Anifrolumab (drug of interest)	L04AA51
Belimumab	L04AA26
Rituximab (including reference product and biosimilars)	L01FA01
Synthetic immunosuppressants	
Anakinra	L04AC03
Apremilast	L04AA32
Azathioprine	L04AX01
Baricitinib	L04AA37
Cyclophosphamide	L01AA01
Cyclosporine	L04AD01
Leflunomide	L04AA13
Methotrexate	L04AX03
Mycophenolic acid/sodium[1]	L04AA06
Sirolimus	L04AA10
Tacrolimus	L04AD02
Thalidomide	L04AX02
Tofacitinib	L04AA29
Voclosporin	L04AD03
Immunoglobulins	
Immunoglobulin G	J06BA02
Plasmapheresis	
Plasmapheresis (procedure)	B05AX03

Table 15 Exemplar code list of malignancies

		ICD-10 codes
All malignancies		C00-C96 D00-D09
Specific groups [12, 13, 84]	**Malignancies**	
Haematological malignancies	**All** haematological (malignant neoplasms of lymphoid, haematopoietic and related tissue)	C81-C96
	Leukaemia	C91-95
	Lymphoma	C81-88, C96
	Hodgkin's lymphoma	C81
	Non-Hodgkin's lymphoma	C82-86, C96
	Multiple myeloma and malignant plasma cell neoplasms	C90
Solid malignancies	**All**	C00-13, C15-16, C18-23, C25, C32-34, C45, C50-54, C56, C60-62, C64-65, C67, C70-73
	Bladder	C67
	Breast	C50
	Cervix uteri	C53
	Endometrium	C54.1
	Oesophagus	C15
	Gastric	C16
	Liver	C22
	Lung	C33-34
	Oropharynx	C09-10
	Larynx	C32
	Ovary	C56
	Prostate	C61
	Renal	C64-65
	Thyroid	C73
	Vagina	C52
	Vulva	C51
Skin malignancies	**All** (melanoma and other malignant neoplasms of skin)	C43-C44

Abbreviations: ICD-10, international statistical classification of diseases tenth revision.

Table 16 Exemplar code list of serious infections (composite outcome)

	ICD-10 codes
All serious infections (composite) [81]	A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0, H60.1, H60.2, H60.3, H66, H67, H70, I30.1, I40.0, J00-J22, J34.0, J36, J38.3, J39.0, J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, L00-L04, L05.0, L08, N10-N12, N13.6, N15.1, N15.9, N30.0, N30.8, N34.0, N39.0, N41.2, N43.1, N45, N48.2, N61, N70-N74, N75.1, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98, R65.0, R65.1, B34.2, B97.2, J12.81, J12.82, U07.1, U07.2, U10

Abbreviations: ICD-10, international statistical classification of diseases tenth revision

Table 17 Exemplar code list of opportunistic serious infections

Group	Subgroup	Clinical Code Description	ICD-10
Bacterial	Salmonella	Salmonella sepsis	A02.1
		Localized salmonella infections	A02.2
	Tuberculosis	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15
		Respiratory tuberculosis, not confirmed bacteriologically or histologically	A16
		Tuberculosis of nervous system	A17
		Tuberculosis of other organs	A18
		Miliary tuberculosis	A19
	Leprosy	indeterminate leprosy	A30.0
		Tuberculoid leprosy	A30.1
		Borderline tuberculoid leprosy	A30.2
		Borderline leprosy	A30.3
		Borderline lepromatous leprosy	A30.4
		Lepromatous leprosy	A30.5
		Other forms of leprosy	A30.8
		Leprosy, unspecified	A30.9
	Infection due to other mycobacteria	Pulmonary mycobacterial infection	A31.0
		Cutaneous mycobacterial infection	A31.1
		Other mycobacterial infections	A31.8
		Mycobacterial infection, unspecified	A31.9
	Listeriosis	Listerial meningitis and meningoencephalitis	A32.1
		Listerial sepsis	A32.7
		Other forms of listeriosis	A32.8
	Nocardiosis	Pulmonary nocardiosis	A43.0
		Cutaneous nocardiosis	A43.1
		Other forms of nocardiosis	A43.8
		Nocardiosis, unspecified	A43.9
	Systemic bartonellosis	Systemic bartonellosis	A44.0
	Legionnaires disease	Legionnaires disease	A48.1
		Nonpneumonic Legionnaires disease [Pontiac fever]	A48.2
	Vibriosis (invasive disease due to Vibrio vulnificus)	Vibrio vulnificus as the cause of diseases classified to other chapters	B98.1
Viral	Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy	A81.2
	Herpes simplex	Herpesviral gingivostomatitis and pharyngotonsillitis	B00.2
		Herpesviral meningitis	B00.3
		Herpesviral encephalitis	B00.4

Group	Subgroup	Clinical Code Description	ICD-10
		Herpesviral ocular disease	B00.5
		Disseminated herpesviral disease	B00.7
	Herpes Zoster	Zoster encephalitis	B02.0
		Zoster meningitis	B02.1
		Zoster with other nervous system involvement	B02.2
		Zoster ocular disease	B02.3
		Disseminated zoster	B02.7
		Zoster with other complications	B02.8
		Zoster without complication	B02.9
	Hepatitis C progression	*Chronic viral hepatitis C (B18.2) or Fibrosis and cirrhosis of liver (K74) after a record of Acute hepatitis C (B17.1)*	
	CMV	Cytomegaloviral pneumonitis	B25.0
		Cytomegaloviral hepatitis	B25.1
		Cytomegaloviral pancreatitis	B25.2
		Other cytomegaloviral diseases	B25.8
		Cytomegaloviral disease, unspecified	B25.9
		Cytomegaloviral mononucleosis	B27.1
Fungal	Candidiasis	Pulmonary candidiasis	B37.1
		Candidiasis of other urogenital sites	B37.4
		Candidal meningitis	B37.5
		Candidal endocarditis	B37.6
		Candidal sepsis	B37.7
	Coccidioidomycosis	Acute pulmonary coccidioidomycosis	B38.0
		Chronic pulmonary coccidioidomycosis	B38.1
		Pulmonary coccidioidomycosis, unspecified	B38.2
		Cutaneous coccidioidomycosis	*B38.3*
		Coccidioidomycosis meningitis	B38.4
		Disseminated coccidioidomycosis	B38.7
		Other forms of coccidioidomycosis	B38.8
		Coccidioidomycosis, unspecified	B38.9
	Histoplasmosis	Acute pulmonary histoplasmosis capsulati	B39.0
		Chronic pulmonary histoplasmosis capsulati	B39.1
		Pulmonary histoplasmosis capsulati, unspecified	B39.2
		Disseminated histoplasmosis capsulati	B39.3
		Histoplasmosis capsulati, unspecified	B39.4
		Histoplasmosis duboisii	B39.5
		Histoplasmosis, unspecified	B39.9
	Blastomycosis	Acute pulmonary blastomycosis	B40.0
		Chronic pulmonary blastomycosis	B40.1
		Pulmonary blastomycosis, unspecified	B40.2
		Cutaneous blastomycosis	B40.3

Group	Subgroup	Clinical Code Description	ICD-10
		Disseminated blastomycosis	B40.7
		Other forms of blastomycosis	B40.8
		Blastomycosis, unspecified	B40.9
	Paracoccidioides infection	Pulmonary paracoccidioidomycosis	B41.0
		Disseminated paracoccidioidomycosis	B41.7
		Other forms of paracoccidioidomycosis	B41.8
		Paracoccidioidomycosis, unspecified	B41.9
	Sporotrichosis (including Sporothrix schenckii)	Pulmonary sporotrichosis	B42.0
		Lymphocutaneous sporotrichosis	B42.1
		Disseminated sporotrichosis	B42.7
		Other forms of sporotrichosis	B42.8
		Sporotrichosis, unspecified	B42.9
	Chromomycosis and phaeomycotic abscess	Phaeomycotic brain abscess	B43.1
		Subcutaneous phaeomycotic abscess and cyst	B43.2
	Aspergillosis	Invasive pulmonary aspergillosis	B44.0
		Other pulmonary aspergillosis	B44.1
		Tonsillar aspergillosis	B44.2
		Disseminated aspergillosis	B44.7
	Cryptococcosis	Pulmonary cryptococcosis	B45.0
		Cerebral cryptococcosis	B45.1
		Osseous cryptococcosis	B45.3
		Disseminated cryptococcosis	B45.7
	Zygomycosis	Pulmonary mucormycosis	B46.0
		Rhinocerebral mucormycosis	B46.1
		Gastrointestinal mucormycosis	B46.2
		Disseminated mucormycosis	B46.4
	Mycetoma	Eumycetoma	B47.0
		Actinomycetoma	B47.1
		Mycetoma, unspecified	B47.9
	Other mycoses, not elsewhere classified (including Penicillium marneffei and Pneumocystosis)	Rhinosporidiosis	B48.1
		Allescheriasis	B48.2
		Geotrichosis	B48.3
		Penicillosis	B48.4
		Pneumocystosis	B48.5
		Opportunistic mycoses	B48.7
	Unspecified	Unspecified mycosis	B49
Parasitic	Leishmaniasis	Visceral leishmaniasis	B55.0
	Chagas disease	Acute Chagas disease with heart involvement	B57.0
		Acute Chagas disease without heart involvement	B57.1
		Chagas disease (chronic) with heart involvement	B57.2

Group	Subgroup	Clinical Code Description	ICD-10
		Chagas disease (chronic) with digestive system involvement	B57.3
		Chagas disease (chronic) with nervous system involvement	B57.4
		Chagas disease (chronic) with other organ involvement	B57.5
	Toxoplasmosis	Toxoplasma oculopathy	B58.0
		Toxoplasma hepatitis	B58.1
		Toxoplasma meningoencephalitis	B58.2
		Pulmonary toxoplasmosis	B58.3
		Toxoplasmosis with other organ involvement	B58.8
		Toxoplasmosis, unspecified	B58.9
	Strongyloidiasis	Intestinal strongyloidiasis	B78.0
		Disseminated strongyloidiasis	B78.7
	Cryptosporidiosis	Cryptosporidiosis	A07.2
	Microsporidiosis	Other specified protozoal intestinal diseases	A07.8
		Other specified protozoal diseases	B60.8

Abbreviations: ICD-10, international statistical classification of diseases tenth revision; CMV, cytomegalovirus infection

Table 18 Exemplar code list of other relevant serious infections (including pneumonia)

Subgroup	Clinical Code Description	ICD-10
Pneumonia [a]	Influenza with pneumonia, virus not identified	J11.0
	Viral pneumonia, not elsewhere classified	J12
	Pneumonia due to Streptococcus pneumoniae	J13
	Pneumonia due to Haemophilus influenzae	J14
	Bacterial pneumonia, not elsewhere classified	J15
	Pneumonia in diseases classified elsewhere	J17
Acute bronchitis and bronchiolitis	Acute bronchitis	J20
	Acute bronchiolitis	J21
Acute upper respiratory infections	Acute nasopharyngitis [common cold]	J00
	Acute sinusitis	J01
	Acute pharyngitis	J02
	Acute tonsillitis	J03
	Acute laryngitis and tracheitis	J04
	Acute obstructive laryngitis [croup] and epiglottitis	J05
	Acute upper respiratory infections of multiple and unspecified sites	J06
COVID-19	Coronavirus infection, unspecified site	B34.2
	Coronavirus as the cause of diseases classified to other chapters	B97.2
	Pneumonia due to SARS-associated coronavirus	J12.81
	Pneumonia due to coronavirus disease 2019	J12.82
	COVID-19, virus identified	U07.1
	COVID-19, virus not identified	U07.2
	Multisystem inflammatory syndrome associated with COVID-19	U10
Sepsis	Streptococcal sepsis	A40
	Other sepsis	A41
	Systemic Inflammatory Response Syndrome of infectious origin without organ failure	R65.0
	Systemic Inflammatory Response Syndrome of infectious origin with organ failure	R65.1
Urinary tract infection	Acute tubulo-interstitial nephritis	N10
	Acute cystitis	N30.0
	Other cystitis	N30.8
	Urethral abscess	N34.0
	Urinary tract infection, site not specified	N39.0
	Gonococcal infection of lower genitourinary tract without periurethral or accessory gland abscess	A54.0
	Gonococcal infection of lower genitourinary tract with periurethral and accessory gland abscess	A54.1
	Gonococcal pelviperitonitis and other gonococcal genitourinary infections	A54.2
Infections During Pregnancy	Infections of genitourinary tract in pregnancy	O23
	Other infection during labour	O75.3
	Puerperal sepsis	O85

Subgroup	Clinical Code Description	ICD-10
	Other puerperal infections	O86
	Infections of breast associated with childbirth	O91
	Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium	O98

Abbreviations: ICD-10, international statistical classification of diseases tenth revision

[a] Pneumonia will be additionally analysed as a separate secondary outcome

Table 19 Exemplar code list of antimicrobials

Antimicrobials	ATC codes for Intravenous antimicrobials	ATC codes for all antimicrobials dispensed at the community pharmacy*
Anthelmintics	-	P02
Antibacterials and antiinfectives	J01	J01, D06, S01A, S01C, S02A, S03C, G01
Antimycobacterials	J04	J04
Antimycotics and antifungals	J02	J02, D01
Antiprotozoals (except antimalarials)	-	P01A, P01C
Antivirals	J05	J05, D06BB, S01AD

Abbreviations: ATC, anatomical therapeutic chemical.

* To define previous occurrence of non-serious infection.

Table 20 Exemplar code list for comorbidities relevant for SLE patients

	Diagnosis	ICD-10 codes
SLE-specific risk adjustment index [97] *	Cerebrovascular disease	I60-I69
	Chronic renal failure [30, 35, 67, 81]	N18
	Congestive heart failure	I50.0
	Diabetes [35, 67, 81, 101]	E10-E14
	Moderate or severe liver disease [30, 35, 67, 81]	K70-K77
	Myocardial infarction	I21, I22
	Nephritis	N00, N01, N03, N05
	Pericarditis [51]	I30, I32
	Peripheral vascular disease	I73
	Pleuritis [51]	A15.6, A15.7, A16.5, A16.7
	Thrombocytopenia [51]	D69.6, D69.5, D69.4
Other comorbidities	Autoimmune diseases excluding SLE (e.g., rheumatological, inflammatory bowel disease and multiple sclerosis) [101]	L40, I73.0, M15.0, M35.0, K50, K51, G35
	Immunodeficiencies (excluding congenital and HIV) [30]	D80-D89
	Cardiovascular diseases (atrial fibrillation, coronary artery disease, hypertension) [46, 67, 81]	I48, I25.1, I10-I15
	Chronic respiratory diseases [30, 35, 67, 101]	J40-J47
	Gastrointestinal conditions (e.g., peptic ulcer disease, gastro-oesophageal reflux disease, dyspepsia, helicobacter pylori infection, Barrett's oesophagus, gastritis and duodenitis, chronic pancreas disease, chronic liver disease, gallstones)	K21, K22.7, K25-K29, K30, K76.9, K80-K82, K86, B98.0

Abbreviations: HIV, human immunodeficiency virus; ICD-10, international statistical classification of diseases tenth revision.
*Three variables were removed from the index because they are exclusion or censoring criteria: HIV, metastatic disease, any malignancy.

Table 21 Exemplar code list for SLE-related comorbidities (SLE severity and activity algorithms)[11]

	Group	Conditions	ICD-10 codes
Moderate comorbid conditions	Cardiovascular cardiorespiratory system	Haemolytic anaemia	D55-D59
		Myocarditis	I40
		Pericarditis	I30
		Pleurisy/pleural effusion	J90 J91
		Vasculitis (excluding aortitis)	M05.2
	Hepatic and gastrointestinal	Acute pancreatitis	K85
		Hepatitis (non-viral)	K72.0
		Lupus enteritis/colitis	
	Musculoskeletal	Avascular ischaemic necrosis of bone	M87
	Neurological	Demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy	G36-G37
		Mononeuropathy/polyneuropathy	G56-G64
		Myelopathy	G99.2
		Pseudotumor cerebri	G93.2
		Seizure	R56.8
	Renal	Nephritis	N10, N11
		Renal impairment (other than nephritis or end-stage renal disease)	S37.0, N18 (excl. N18.5)
	Ocular	Chorioretinitis	H30.9
		Episcleritis/scleritis	H15
Severe comorbid conditions	Cardiovascular cardiorespiratory system	Aortitis	I79.1
		Arterial/venous thrombosis	I82
		Cardiac tamponade	I31.9
		Pulmonary haemorrhage	R04.8
		Stroke (cerebral infarction)	I63
		Transient ischaemic attack	G45
	Hepatic and gastrointestinal	Intestinal pseudo-obstruction	K56.0
	Neurological	Acute confusional state/psychosis	F05.1, F05.9
		Aseptic meningitis	G02.0, A87.0, G01
		Cranial neuropathy	S04

[11]SLE severity and severity algorithms defined in Section 10.3.3.3 [39, 56].

	Group	Conditions	ICD-10 codes
	Ocular	Optic neuritis	H46
	Renal	End-stage renal disease	N18.5
		Renal failure	N17, N19
Additional conditions to be considered to define moderate and severe flares (SLE activity algorithm only)	Other	Arthritis/arthralgia	M25.5
		Dry eye/tear film insufficiency	H04.1
		Rash	R21
		Low white blood cell count (leukopenia, neutropenia, lymphocytopenia)	R72
		Lymph node enlargement	R59
		Myalgia/myositis	M79.1
		Urticaria	L50

Abbreviations: ICD-10, international statistical classification of diseases tenth revision.

Table 22 Exemplar code list of virus/infections considered risk factors for malignancies[12]

Prior infection diagnosis	ICD-10 codes
Epstein-Barr virus	D82.3
Hepatitis B virus	B16
Hepatitis C virus	B17.1, B18.2
HIV	B20-B24
HTLV-I	B33.3, G04.1, Z22.6, B97.3
Human papillomavirus	B97.7
Kaposi's sarcoma herpesvirus	C46

Abbreviations: HIV, human immunodeficiency virus; HTL V-I, human T-cell lymphotropic virus type 1; ICD-10, international statistical classification of diseases tenth revision.

[12] virus/infections considered risk factors for malignancies [6, 63].

Table 23 Exemplar code list of vaccines and immunoglobulins[13]

	ATC codes
Haemophilus influenzae B	J07AG
Hepatitis A and hepatitis B	J07BC
Herpes zoster	J07BK
Human papillomavirus*	J07BM
Influenza	J07BB
Meningococcal C	J07AH07
Pneumococcal	J07AL
Severe acute respiratory syndrome coronavirus 2	J07BX03
Immunoglobulins, normal human	J06BA
Specific immunoglobulins (e.g., varicella/zoster, hepatitis A, measles immunoglobulins)	J06BB (except J06BB01: anti-D (rh) immunoglobulin)
Antibacterial monoclonal antibodies: raxibacumab, bezlotoxumab	J06BC02, J06BC03
Antiviral monoclonal antibodies (palivizumab; motavizumab; tixagevimab and cilgavimab; nirsevimab**; casirivimab and imdevimab**)	J06BD

Abbreviations: ATC, anatomical therapeutic chemical.
*For the malignancy cohort this is the only vaccine to be considered. ** No ATC code is available at the moment (August 2022).

[13] Recommended vaccines for SLE patients [54, 93].

Table 24 Exemplar code list of comedication polypharmacy

Comedication	SI	Malignancies	ATC codes
Agents acting in the renin-angiotensin system		x	C09
Alkylating agents (excluding cyclophosphamide)		x	L01A (excluding L01AA01)
Anabolic agents for systemic use		x	A14
Antiepileptics		x	N03
Antihypertensives		x	C02
Antiobesity preparations, excl. diet products		x	A08
Antithrombotic agents		x	B01, A01AD05, N02BA01
Aspirin (acetylsalicylic acid)		x	A01AD05, B01AC06, N02BA01, M01BA03
Beta blocking agents		x	C07
Bisphosphonates		x	M05BA, M05BB
Calcium channel blockers		x	C08
Cisplatin		x	L01XA01
Corticosteroids for systemic use, except SLE-related	x	x	H02, H02A, H02B, except the ones provided in Table 14
Diuretics		x	C03
Anti-inflammatory and antirheumatic products		x	M01A, M01B, M01C
Doxorubicin		x	L01DB01
Drugs used in diabetes		x	A10
Etoposide in combination with cisplatin and bleomycin		x	L01CB01; L01DC01
Hypnotics and sedatives, Anxiolytics		x	N05C, N05B
Immunostimulants	x		L03
Immunosuppressive agents except SLE-related	x		L04, L04A, L04AA, L04AX, except the ones provided in Table 14
Intrauterine and intravaginal hormonal contraceptives		x	G02BB, G02BA03
Lipid modifying agents (including statins)		x	C10
Methylhydrazines (procarbazine) (excluding nitrogen mustard, vincristine, procarbazine and prednisone and other combined chemotherapy including alkylating agents)		x	L01XB (excluding L01XB01; L01AA)
NSAIDs for systemic use		x	M01A
Other Carcinogenic drugs (e.g., Pioglitazone, Reserpine, Metronidazole, Chloroform, etc.) *		x	A10BG03, A10BD09, A10BD12, A14A, C02AA02, C02LA01, C02LA51, C02LA71, C02AA52, C04AX02, D01AE13, D05AD02, G04BX06, H03BA02, J01BA01, G01AA05, D10AF03, D06AX02,

Comedication	SI	Malignancies	ATC codes
			S01AA01, S02AA01, S03AA08, J01EB08, A01AB17, D06BX01, G01AF01, J01XD01, P01AB01, N01AB02, N02BE03, N02BE53, N02BE73, N03AB02, N03AB52, P03AX03, V10XA, V09XA
Podophyllotoxin derivatives (etoposide and teniposide)		x	L01CB
Sex hormones and modulators of the genital system		x	G03
Tamoxifen		x	L02BA01

Note: codes for "L01 – Antineoplastics" are unlikely to be present considering these are mainly administrated to cancer patients who are excluded of the cohort.

*As defined by the American Cancer Society [3].

Abbreviations: ATC, anatomical therapeutic chemical; NSAIDs, non-steroidal anti-inflammatory drugs; SI, serious infections; SLE, systemic lupus erythematosus.

Appendix 4 Data Sources' details

Appendix 4.1. Included data sources

Table 25 Data sources included in the feasibility assessment

Country	Data source	Assessed in Feasibility Assessment	Selected for this Study	Rationale for decision / Considerations
Denmark	National Registers	Yes	Yes	- Hospital administration of drugs has been captured since 2018 and has been available for research in 2022 - Study outcomes are available (if coded in secondary care) - Available linkage to the population-based cancer registry - Potential to provide a relatively large number of anifrolumab users compared to some other Nordic countries
Finland	National Registers	Yes	No	- Suitable for current study. - Data source not selected for inclusion because other larger European data sources are available.
France	National Health Data System (SNDS)	Yes	Yes	- Anifrolumab exposure is likely to be captured. Anifrolumab is expected to be integrated in the list of high-cost drug by the French National Authority for Health and therefore included in the data source. - Study outcomes are available (from inpatient setting) - Potential to provide a large number of anifrolumab users (largest European data source)
Germany	Statutory Health Insurance Claims (SHI)	Yes	Yes	- Anifrolumab will be captured as administered in outpatient visits, unless the visit is reimbursed as a diagnosis-related group (not being able to distinguish administered drugs). However inpatient administration of anifrolumab is not available in this data source - Study outcomes are available (except for inpatient IV drugs antimicrobials administration) - Potential to provide a relatively large number of anifrolumab users
	SLE Registry	Yes	No	- Pregnancy registry
Spain	Information System for the Development of Primary Care Research (SIDIAP)	Yes	Yes	- Anifrolumab will be captured - Study outcomes are available - Possible linkage to the population-based cancer registry

Country	Data source	Assessed in Feasibility Assessment	Selected for this Study	Rationale for decision / Considerations
	Spanish Society of Rheumatology systemic lupus erythematosus registry (*Registro de Lupus Eritematoso Sistémico de la Sociedad Española de Reumatología* [RELESSER])	Yes	No	- Not possible to capture dates of drug prescription/administration or diagnoses - Limited information on outcomes, e.g., malignancies are captured if cancer is the cause of death
Sweden	National Registers	Yes	No	- Anifrolumab exposure is not captured because anifrolumab use is expected to occur in the hospital setting. However, it would be possible to have data from 3-4 hospitals where EMR extraction and linkage with National registries is performed, limiting generalizability - This will serve as a back-up data source if minimum sample size is not reached and the data is linked to the Swedish Rheumatology Registry (see below)
	Swedish Rheumatology Quality Register (SRQ)	Yes	No	- Suitable for current study because anifrolumab is captured and linkage to the national registries is possible - Coverage and representativeness of the SLE population are unavailable - Back-up data source if minimum sample size is not reached
UK	CPRD-Hospital Episode Statistics (HES) General practice online database (GOLD)	Yes	No	- Anifrolumab will be available if coded by the GP from hospital letter. However, the level to which the data is transcribed from referral/feedback letters is likely to be limited. Direct hospital prescribing or administration information is not available in CPRD-HES
USA	HealthCore Integrated Research Database (HIRD)	Yes	No	- Suitable for current study - Back-up data source if minimum sample size is not reached
	Optum Research Database (ORD)	Yes	No	- Suitable for current study - Back-up data source if minimum sample size is not reached
	Consumer Value Stores (CVS) Aetna	Yes	No	- Suitable for current study - Back-up data source if minimum sample size is not reached
	OM1 Lupus Registry	Yes	No	- Suitable for current study - Back-up data source if minimum sample size is not reached

Country	Data source	Assessed in Feasibility Assessment	Selected for this Study	Rationale for decision / Considerations
International	The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)	Yes	No	- The SLICC database stopped active collection of data in July 2022, therefore exposure data for the study period (2022-2032) is unavailable. Variables required for serious infections ascertainment are not included in current cohort data

Appendix 4.2. Covariates

Table 26 Availability of baseline characteristics and covariates

Databases/Countries	Denmark	France	Germany	Spain
	National Registers	SNDS	SHI	SIDIAP
Baseline characteristics/covariates	**(Availability Yes/No, other text: Partial)**			
Age	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes
Location	Yes	Yes	Yes	Yes
Ethnicity	No	No	No	No
Body Mass Index	No	No	No	Yes
Comorbidities /disease history	Yes	Yes	Yes	Yes
Prior exposure to immunosuppressive drugs	Yes	Yes	Yes	Yes[a]
Vaccination	No	Only if reimbursed	No, substance not captured	Yes, ATC codes
Procedures with radiation exposure	Partial (NPR)[b]	Yes	Partial (ICD-10 codes)	No
Prior Infection	Yes[c]	Yes	Yes	Yes
Alcohol consumption	Partial[d]	No	No	Yes
Smoking Status	No	No	No	Yes
Date at SLE diagnosis	Yes	Yes	Yes	Yes
Number of healthcare visits, for any reason	Yes	Yes	Yes	Yes
Start and end date of hospitalisations	Yes	Yes	Yes	Yes
Emergency department visits	Yes	Yes	Yes[e]	Yes
Number of outpatient/primary care contacts	Yes	Yes	Yes	Yes

Abbreviations: ATC: Anatomical Therapeutic Chemical; ICD-10: 10th Revision International Classification of Diseases; NPR: National Patient Register; SHI: Statutory Health Insurance; SIDIAP: System for the development of primary care research database; SLE: systemic lupus erythematosus; SNDS: National Health Data System.

[a]Except administered during hospitalisation.

[b]Yes, except for in hospital administered. Should be an external source linkage.

[c]If the diagnosis is made at hospital. Diagnoses from GPs and specialist in private practice are not available.

[d]Only available if patient is in treatment for alcohol abuse/alcoholism and has been in contact with a hospital regarding this.

[e]Diagnosis of emergency care visit not available.

Appendix 4.3. Number of SLE patients exposed to anifrolumab

For each year and data source, estimates of prevalent SLE patients and SLE patients newly exposed to anifrolumab were calculated. The following steps were taken:

1. The number of SLE patients per country (eligible to be exposed to anifrolumab) was estimated considering the following assumptions (based on literature reviews, estimates obtained from local marketing companies, and out-sourced studies from a variety of vendors):
   a. Prevalence of SLE: 12-months prevalence;
   b. Proportion of non-renal SLE: 78% of SLE diagnosed patients present non-renal SLE or mild renal involvement [34, 95];
   c. Proportion of SLE patients with pharmacological treatment: 90%;
   d. Proportion of patients with moderate to severe SLE: 60-70% [33].
2. The number of SLE patients in the data source was obtained by multiplying the number of SLE patients in each country by the data source coverage (the average number of SLE patients per year was estimated for the entire enrolment period).
3. The number of SLE patients in the data source exposed to anifrolumab was obtained by multiplying the number of SLE patients in the data source by the expected anifrolumab uptake:
   a. Anifrolumab uptake considered that, at peak (ten years after market launch, 2032), 40-50% of SLE patients would be treated with biologics;
   b. Among those, 40-50% would be exposed to anifrolumab.
4. Finally, each year, the number of patients initiating anifrolumab was calculated as the difference between the number of patients exposed to anifrolumab in that year and the number of patients exposed to anifrolumab in the previous year.

Table 27 presents the results of the described estimates, namely the annual number of new users of anifrolumab each year in each data source.

Table 27 Number of anifrolumab patients per year and data source

		2022	2023	2024	2025	2026	2027	2028	Average number of SLE patients per year[a]	Total Exposed Patients for Each Study Outcome: M (2022-28)	Total Exposed Patients for Each Study Outcome: SI (2022-25)
Denmark, National registries (100% population coverage)	**Country-level**										
	Number of patients with SLE[b]	1,110	1,114	1,118	1,122	1,125	1,129	1,133			
	Expected anifrolumab uptake (%)	1%	3%	5%	8%	11%	14%	16%			
	Data source estimates										
	Number of patients with SLE[c]	1,110	1,114	1,118	1,122	1,125	1,129	1,133	**1,122**		
	Number of SLE patients exposed to anifrolumab[d]	14	33	60	89	125	160	183			
	Number of SLE patients **initiating** anifrolumab[e]	**14**	**19**	**27**	**29**	**36**	**35**	**23**		**183**	**89**
France, SNDS (98.9% population coverage)	**Country-level**										
	Number of patients with SLE[b]	14,772	15,066	15,066	15,066	16,550	16,584	16,616			
	Expected anifrolumab uptake (%)	0%	2%	4%	7%	11%	14%	16%			
	Data source estimates										
	Number of patients with SLE[c]	14,609	14,900	14,900	14,900	16,367	16,401	16,433	**15,501**		
	Number of SLE patients exposed to anifrolumab[d]	<10	226	536	1,005	1,865	2,299	2,695			
	Number of SLE patients **initiating** anifrolumab[e]	**<10[f]**	**226**	**310**	**469**	**860**	**434**	**396**		**2,695**	**1,005**
Germany, SHI (5.5% population coverage)	**Country-level**										
	Number of patients with SLE[b]	22,347	22,321	22,285	22,259	22,234	22,222	22,173			
	Expected anifrolumab uptake (%)	1%	3%	7%	10%	13%	16%	18%			
	Data source estimates										
	Number of patients with SLE[c]	1,229	1,227	1,225	1,224	1,222	1,222	1,219	**1,224**		
	Number of SLE patients exposed to anifrolumab[d]	15	41	80	126	163	200	216			
	Number of SLE patients **initiating** anifrolumab[e]	**15**	**26**	**40**	**45**	**37**	**37**	**16**		**216**	**126**
Spain, SIDIAP (10.2% population coverage)	**Country-level**										
	Number of patients with SLE[b]	27,713	27,689	27,660	27,628	30,166	30,467	30,772			
	Expected anifrolumab uptake (%)	0%	2%	5%	8%	8%	12%	13%			
	Data source estimates										
	Number of patients with SLE[c]	2,826	2,824	2,821	2,818	3,076	3,107	3,138	**2,944**		
	Number of SLE patients exposed to anifrolumab[d]	<10	46	129	216	235	363	412			
	Number of SLE patients **initiating** anifrolumab[e]	**<10[f]**	**46**	**83**	**86**	**20**	**128**	**49**		**412**	**216**
								Total number of new anifrolumab patients		**3,506**	**1,435**

Abbreviations: M, malignancy; SHI: Statutory Health Insurance; SIDIAP: System for the development of primary care research database; SLE: systemic lupus erythematosus; SNDS: National Health Data System; SI, serious infection

[a] Estimated as the average number of patients with SLE in the data source from 2022 to 2028

[b] Based on 12-month prevalence estimate. Estimate provided is the number of patients with non-renal, moderate to severe SLE who receive pharmacological treatment

[c] Number of SLE patients in the country multiplied by the coverage of the data source

[d] Number of SLE patients in the data source multiplied by the anifrolumab uptake

[e] Number of SLE patients exposed to anifrolumab in the current year minus the number of SLE patients exposed to anifrolumab in the previous year

[f] These numbers were approximated to 0 in the estimation of total anifrolumab exposed patients.

PROTOCOL SIGNATURE FORM

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[redacted]

Institution: AstraZeneca AB

[redacted]

[redacted]

Institution: AstraZeneca AB

[redacted]

[redacted]

Institution: AstraZeneca AB

Principal Investigator: Mickael Arnaud, PhD

Associate Director Epidemiologist IQVIA
mickael.arnaud@iqvia.com

Principal Investigator Signature:

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