PASS Protocol	
Active substance	Anifrolumab
Product reference	EMEA/H/C/004975
Version number	EMA Version 3.0
Date	28 August 2023

A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB, 151 85 Sodertalje, SWEDEN
MAH contact person	[redacted] [redacted] AstraZeneca [redacted]

SAPHNELO™ (anifrolumab) is a trademark of the AstraZeneca group of companies.

Electronic record of all signatures from designees is provided on the signature page

Approved by:

[redacted]

Institution: AstraZeneca AB

[redacted]

Institution: AstraZeneca AB

[redacted]

Institution: AstraZeneca AB

Title	A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab
Protocol version identifier	EMA Version 3.0
Date of last version of protocol	10 March 2023
EU PAS Register number	Study not yet registered
Active substance	Anifrolumab (L04AA51)
Medicinal product	SAPHNELO
Product reference	EMEA/H/C/004975
Procedure number	Not Applicable
Marketing authorisation holder(s)	AstraZeneca AB, 151 85 Sodertalje, SWEDEN
Joint PASS	No
Research question and objectives	**Primary objectives** 1. To describe and estimate the risk of **Major Congenital Malformations (MCM)** in live and non-live offspring from a. women with moderate/severe systemic lupus erythematosus (SLE), exposed to anifrolumab during the first trimester of pregnancy b. comparable population of women with moderate/severe SLE, exposed to standard of care (SOC) and unexposed to anifrolumab during the first trimester of pregnancy 2. To estimate the relative risk of **MCM** in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy 3. To describe and estimate the risk of **select pregnancy loss outcomes** (composite of

	spontaneous abortion and stillbirth) in pregnancies ooccurring in a. women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy 4. To estimate the relative risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy **<u>Secondary objectives</u>** 5. To describe demographic and clinical characteristics of: a. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy b. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy c. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab anytime during pregnancy d. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy 6. To describe and estimate the risk of **minor Congenital Malformations (mCM)** in live and non-live offspring from

	a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy 7. To estimate the relative risk of **mCM** in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab any time during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy 8. To describe and estimate the risk of **adverse pregnancy outcomes** separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy 9. To estimate the relative risk of **adverse pregnancy outcomes** separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

	10. To describe and estimate the risk of **adverse birth outcomes** (preterm birth, small for gestational age (SGA)) in live offspring from a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy 11. To estimate the relative risk of **adverse birth outcomes** (preterm birth, SGA) in live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy **<u>Exploratory objectives</u>** 12. To describe and estimate the risk of **adverse outcomes related to infant growth** up to one year of age of live offspring from: a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy 13. To describe and estimate the risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE a. exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) b. exposed to SOC during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3)

	and unexposed to anifrolumab anytime during pregnancy 14. To estimate the relative risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) compared to women with moderate/severe SLE exposed to SOC in the same pregnancy trimesters and unexposed to anifrolumab anytime during pregnancy 15. To describe and estimate the risk of **MCM** *by target body system organ class* in live and non-live offspring from a. women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy
Country (-ies) of study	France, Germany, Finland, Denmark, and United States of America

Author(s)	[redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted] [redacted] [redacted] IQVIA [redacted]

1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ATC	Anatomical Therapeutic Chemical Classification System
CPRD	Clinical Practice Research Datalink
CRO	Contract Research Organisation
DAPI	Dynamic Assessment of Pregnancies and Infants
DDD	Defined Daily Dose
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethics Review Boards
EU	European Union
EULAR	European League Against Rheumatism
FDA	United States Food and Drug Administration
GM	German modification
GPP	Good Pharmacoepidemiology Practices
HCU	Health Care Utilisation
HES	Hospital Episode Statistics
IV	Intravenous
ICD	International Statistical Classification of Diseases and Related Health Problems
IPTW	Inverse probability treatment weighting
LLOQ	Lowest Level of Quantification
LMP	Last menstrual period
LMP2	Last menstrual period + 2 weeks
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major Congenital Malformations
mCM	Minor Congenital Malformations
NHISR	National Health Insurance Service Register
NPR	National Patient Register
PASS	Post-Authorisation Safety Study
PIN	Personal Identity Number
PMSI	Programme de médicalisation des systèmes d'information
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity score
QC	Quality Control
RR	Risk ratio

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SC	Subcutaneous
SGA	Small for gestational age
SHI	Statutory Health Insurance
SID	Study Identification Number
SLE	Systemic Lupus Erythematosus
SOC	Standard of Care
SSC	Study Steering Committee
USA	United States of America
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Responsible parties	Contact details
Principal investigator	Ana Cristina Santos, MPH PhD Senior Epidemiologist IQVIA Lagoas Park Edificio 3, 2740-266, Lisbon, Portugal
Marketing Authorisation holder	AstraZeneca AB [redacted]

3.1 Study Steering Committee

A Study Steering Committee (SSC) will be established, and a Study Steering Committee Charter will be in place that describes the SSC roles and responsibilities.

The SSC composition will aim to provide a good balance of expertise, by including experts from immunology, gynaecology, teratology, epidemiology, and patient representatives. Collectively these experts will have the scientific, medical, patient perspective, and study management experience to design, conduct the study, and evaluate the study results appropriately. AstraZeneca's representatives, selected based on their expertise, will also participate in SSC meetings as invited observers.

The SSC will provide scientific advice and guidance with regard to the study methodology (design, data collection and analysis), including with respect to protocol revision and amendments, as well as clinical input aspects of the study.

The SSC is responsible for overseeing the conduct of the study and making recommendations if needed, discussing study results and communication plan.

4. ABSTRACT

Title

A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab

Rationale and background

Systemic Lupus Erythematosus (SLE) is a chronic, complex autoimmune disease with unknown aetiology. There is considerable individual variability in SLE manifestations. Therefore, there is no single treatment paradigm. A tailored, multidisciplinary strategy is required that adjusts to patients' individual clinical manifestations. Evidence supporting the involvement of the type I interferon pathway in SLE, has led to the development of anifrolumab. Anifrolumab is a human monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1). Anifrolumab was approved by the Food and Drug Administration (FDA) on 30th July 2021 for the treatment of adult patients with moderate to severe SLE, who are receiving standard therapy. Anifrolumab 300 mg solution for infusion was approved via a centralised procedure in the European Union (EU) on 14th February 2022, as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy (EMEA/H/C/004975/0000). As SLE disproportionately affects women of childbearing potential compared to men, it is conceivable that anifrolumab exposure during pregnancy may occur.

While there is considerable data detailing the harmful effects of increased level of interferons during pregnancy, there is limited data on the effect of blockade of interferon signalling in pregnancy. Current literature suggests that there is a lack of developmental defects in mice following the blockade of interferon signalling. However, results from a pre- and postnatal developmental toxicity study conducted on cynomolgus monkeys, suggested a non-statistically significant higher incidence of embryo-foetal loss among anifrolumab exposed monkeys. The relevance of these findings to humans is not known. Although, for exposures up to approximately 28 times the maximum recommended human dose on an AUC basis, no maternal or postnatal developmental effects were observed.

As part of the original marketing authorisation application to the European Medicines Agency (EMA), AstraZeneca included a proposal within the European Union Risk Management Plan, to conduct a non-interventional multi-country post-authorisation safety study to characterise the use of anifrolumab in women with SLE. Consequently, this non-interventional voluntary post-authorisation safety study (PASS) was designed to fill the evidence gaps on the safety of anifrolumab exposure during pregnancy.

Research question and objectives

The aim of this study is to describe congenital malformations, adverse pregnancy and birth outcomes in pregnancies/offspring from women with moderate/severe SLE exposed to anifrolumab during pregnancy and to compare with outcomes in women with moderate/severe SLE who are exposed to other SOC but not anifrolumab. Adverse outcomes related to infant growth up to one year of age will also be investigated.

Primary objectives

1. To describe and estimate the risk of **Major Congenital Malformations** (**MCM**) in live and non-live offspring from
    a. women with moderate/severe SLE, exposed to anifrolumab during the first trimester of pregnancy
    b. comparable population of women with moderate/severe SLE, exposed to standard of care (SOC) and unexposed to anifrolumab during the first trimester of pregnancy
2. To estimate the relative risk of **MCM** in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy
3. To describe and estimate the risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in
    a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy
    b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy
4. To estimate the relative risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

Secondary objectives

5. To describe demographic and clinical characteristics of
    a. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy
    b. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy

c. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab anytime during pregnancy

d. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

6. To describe and estimate the risk of **minor Congenital Malformations** (**mCM**) in live and non-live offspring from

    a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy

    b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy

7. To estimate the relative risk of **mCM** in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

8. To describe and estimate the risk of **adverse pregnancy outcomes** separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from

    a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy

    b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy

9. To estimate the relative risk of **adverse pregnancy outcomes** separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

10. To describe and estimate the risk of **adverse birth outcomes** (preterm birth, small for gestational age (SGA)) in live offspring from

    a. women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy

b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy

11. To estimate the relative risk of **adverse birth outcomes** (preterm birth, SGA) in live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

Exploratory objectives

12. To describe and estimate the risk of **adverse outcomes related to infant growth** up to one year of age of

    a. live offspring from women with moderate/severe SLE, exposed to anifrolumab anytime during pregnancy

    b. live offspring from a comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab anytime during pregnancy

13. To describe and estimate the risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE

    a. exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3)

    b. exposed to SOC during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) and unexposed to anifrolumab anytime during pregnancy

14. To estimate the relative risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) compared to women with moderate/severe SLE exposed to SOC in the same pregnancy trimesters and unexposed to anifrolumab anytime during pregnancy

15. To describe and estimate the risk of **MCM** by target body system organ class in live and non-live offspring from

    a. women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy

    b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy

Study design

The study will utilise a non-interventional longitudinal population-based retrospective cohort design. It will be conducted using secondary data derived from multiple databases which record longitudinal medical data. The data sources include registries in Finland, Denmark, France, Germany and the United States of America (USA). The unit of analysis is a pregnancy in women with moderate/severe SLE. Therefore, a woman may contribute more than one pregnancy to the study.

The two primary outcomes of interest are a composite of MCM diagnosed in the offspring at the end of the pregnancy or until one year of age, based on the ICD-10 diagnostic codes (or other country specific coding system), as recorded in the data sources; and select pregnancy loss outcomes (a composite of spontaneous abortion and stillbirth), diagnosed in the woman from last menstrual period + 2 weeks (LMP2) up to end of pregnancy.

The secondary outcomes of interest are a composite of mCM (diagnosed in the offspring at the end of the pregnancy or until one year of age), adverse pregnancy outcomes (diagnosed in the woman from LMP2 up to end of pregnancy), adverse birth outcomes (diagnosed in the offspring at birth), investigated separately.

For congenital malformation (CM), birth, and infant outcomes, the population of study will be limited to offspring for whom mother-offspring record linkage is available within each data source. However, for pregnancies that end in a spontaneous abortion, an elective termination of pregnancy, or stillbirth where there is a diagnosis of MCM in the mother's record, mother-offspring linkage will not be required.

The exposure of interest is *in utero* exposure to anifrolumab and/or *in utero* exposure to SLE SOC between LMP2 (derived from last menstrual period or, if missing, gestational age) and end of pregnancy or occurrence of the outcome of interest (whichever comes first). For the primary outcome of MCM, the exposure ascertainment period is restricted to the etiologically relevant period of the first trimester. Exposure information will be derived from outpatient visits and/or prescription data, as recorded in the data source for each country. Country-specific cohorts of eligible women or woman/offspring units will be identified for each outcome.

A group of pregnant women comparable to the exposed, with moderate/severe SLE, will be selected as the comparator group. Moderate and severe SLE patients when compared to non-SLE population are at increased risk of adverse outcomes, because of SLE disease activity and the effect of SLE-related medication use. Therefore, the choice of this internal comparison group has been made to minimise confounding by SLE disease severity/activity and medications.

Descriptive analyses of the population under study, the risk in the exposed and unexposed cohorts, and the relative risk of the primary and secondary outcomes of the study will be provided for pregnancies/offspring of women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy (for MCM during the first trimester) compared with a comparator group of

women with moderate/severe SLE exposed to SLE SOC and unexposed to anifrolumab anytime during pregnancy (for MCM during the first trimester).

Aggregated country-specific results for the primary objectives will be combined (if feasible) via a meta-analytic approach, providing a pooled estimate across all data sources.

Population

Study time period

The start of the study period will be the market launch date of anifrolumab in each country, as follows: 11 March 2022 for Denmark, market launch date to be confirmed for Finland, 19 April 2022 for France, 11 March 2022 for Germany, 23 August 2021 for the USA. The end of study period, defined as the last possible day of follow-up when all patients still active are censored, is likely to differ between countries. It will depend on the length of data lag in each country at the time of last data extraction (31 March 2031).

Participants

To address the research questions eligible cohorts will be identified through a nested selection process. An *overall source population* will be created for data extraction *(STEP 1)* and split into *exposed to anifrolumab* ***source*** *population* and *unexposed to anifrolumab* ***source*** *population (STEP2).*

Then criteria common to exposed and unexposed to anifrolumab source populations will be applied to create post-data extraction *exposed to anifrolumab* ***study*** *population* and *unexposed to anifrolumab* ***study*** *population (STEP 3)* from which the cohorts of analyses will be derived *(STEP 4)*.

Since this is a non-interventional observational study, minimal inclusion and exclusion criteria are desirable to minimise potential selection bias and represent real world clinical practice.

Variables

Exposure

The exposure of interest is anifrolumab, irrespective of administration route. *In utero* exposure to anifrolumab (as an add-on therapy to SLE SOC, hereafter referred to as polytherapy) will be compared to non-exposure to anifrolumab (exposed to only SLE SOC).

Exposure to SLE SOC (with the exclusion of anifrolumab) will be assessed from conception (defined as LMP2), until end of first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for all other outcomes, under the assumption that once treatment is started, it continues throughout pregnancy (throughout the first trimester for the outcome of MCM). A look back period of 5-half-lives of the relevant drugs will be considered. This is to account for

prescriptions/dispensations/administrations prior to LMP2 that could lead to *in utero* exposure of the offspring.

Exposure to anifrolumab will be assessed from LMP2 until end of the first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for all other outcomes, or until censoring. Considering the window of clearance of anifrolumab (16 weeks), all patients who receive prescriptions/dispensations/administrations of anifrolumab in the 16 weeks prior to LMP2 or during the first trimester of pregnancy will be considered exposed in the first trimester for the MCM outcome. Patients who receive prescriptions/dispensations/administrations of anifrolumab in the 16 weeks prior to LMP2 or anytime during pregnancy will be considered exposed for all other outcomes.

Offspring whose mother had no anifrolumab prescription/dispensations/administration in the 16 weeks prior to LMP2 or during the first trimester for the outcome of MCM, or during pregnancy for all other outcomes, will be considered unexposed.

Pregnancies exposed to confirmed teratogenic drugs prior to LMP2 until end of first trimester (for MCM outcome) or end of pregnancy (all other pregnancy outcomes), with a look back period of 5-half-lives of the relevant drug, in both the exposed and unexposed groups, will be excluded.

Outcomes

Primary outcomes

The primary outcomes of interest are MCM (defined as a composite of all major MCMs) occurring in live or non-live offspring and select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth).

MCM are defined as defects of prenatal origin that have either cosmetic or functional significance to the child's health, development, or survival. In this study, MCM ascertainment will be based on the presence of an ICD-10 code (or other database specific coding system [codes to be adapted to the coding systems used in each of the data sources]) in the database. These ICD-10 codes will be classified according to the EUROCAT (Description of the Congenital Anomaly Subgroups in EUROCAT Guide 1.5 classification scheme, as four of the five countries are in Europe. As a sensitivity analysis, all congenital malformations will be mapped to the Metropolitan Atlanta Congenital Defects Program (MACDP) USA-based classification system for MCM.

The MCM ascertainment period is defined as:

- for live births, from birth until 1 year of age
- for non-live births (spontaneous abortion and stillbirth) an ICD-10 code of MCM as the diagnosis at end of pregnancy
- for elective terminations, an ICD-10 code of an MCM as the reason for the termination at termination of pregnancy

The select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) will be defined as the presence of at least one of the following criteria:

- an ICD-10 code of spontaneous abortion (unintended loss of an intrauterine pregnancy which is less than 22 weeks of gestation for the European data sources; less than 20 weeks for the USA data sources)
- an ICD-10 code of stillbirth (unintended foetal death occurring at or after 22 weeks of gestation for the European data sources; at or after 20 weeks for the USA data sources)

Secondary outcomes

Minor congenital malformations (mCM)

mCM among live and non-live offspring are a structural anomaly or dysmorphic feature which does not impair viability or require intervention or treatment. mCM will be defined as a composite outcome. In this study, mCM ascertainment will be based on the presence of an ICD-10 code (or other database specific coding system [codes to be adapted to the coding systems used in each of the data sources]) in the database. These ICD-10 codes will be classified according to the EUROCAT (Description of the Congenital Anomaly Subgroups in EUROCAT Guide 1.5) classification scheme, as four of the five data countries are in Europe.

Adverse pregnancy outcomes

Adverse pregnancy outcomes of interest in this study are spontaneous abortions, ectopic pregnancy, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy and emergency caesarean section. In addition, a composite outcome of foetal loss, defined as the presence of at least one of the following: spontaneous abortions, ectopic pregnancy, elective termination of pregnancy and stillbirth will be investigated.

Adverse birth outcomes

Adverse birth outcomes of interest in this study are preterm birth and SGA.

Exploratory outcomes

Select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) will be analysed by exposure period according to specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) and MCM will be classified by body system organ class according to the EUROCAT categories Guide 1.5.

Adverse outcome related to growth up to one year of age will be a dichotomous variable defined as a composite outcome based on the presence of at least one of the following conditions: abnormal head circumference growth, stunting, or wasting. The period of assessment will be from birth until the end of the first year after birth.

Data sources

The study will make secondary use of existing data from five countries which have been selected based on a feasibility assessment conducted between July 2022-January 2023. The selected countries are:

- Denmark
- Finland
- France
- Germany
- USA

Study size

Sample size and power calculations were carried out separately for each of the primary outcomes of interest (MCM and select pregnancy loss outcomes) at the meta-analysis level. First, the **total number of SLE pregnancies** in the data sources were estimated using either the annual number of SLE pregnancies obtained in the feasibility assessment or the number of annual live births captured by the data sources (with assumptions on database coverage and proportion of live births/pregnancies in SLE patients) in cases where the data sources did not provide estimates in the feasibility assessment.

From the total number of SLE pregnancies, **the number of anifrolumab exposed pregnancies** in moderate-to-severe SLE women that would be eligible for the study was estimated using the following assumptions: 50% SLE pregnancies occur in women with moderate-to-severe SLE; 80% of SLE pregnancies are unexposed to confirmed teratogenic drugs; 80% of all anifrolumab exposed pregnancies are exposed to anifrolumab during the first trimester of pregnancy; varying anifrolumab exposure of 5% and 10% among pregnant SLE women. Under an assumption of 10% anifrolumab exposed SLE pregnancies and a final study report milestone submission date of 2032, the expected number of anifrolumab exposed pregnancies in the selected data sources which would be eligible for analysis is **353** (USA-Carelon Research 102, USA-DAPI 114, Denmark 8, Finland 6, France 116, Germany 7) **for the MCM outcome** and **497** (USA-Carelon Research 163, USA-DAPI 162, Denmark 11, Finland 7, France 145, Germany 9) **for the select pregnancy loss outcome**.

Given the estimated number of anifrolumab exposed pregnancies in moderate-to-severe SLE women, the **expected number of events for the primary objectives** to be observed were estimated using a prevalence of 7% for MCM and a prevalence of 20% for select pregnancy loss.

Only the data sources where at least one primary outcome (MCM or select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth)) event is expected to be observed will

be considered for the meta-analysis. Under the assumptions of 10% anifrolumab exposed SLE pregnancies and a final study report milestone of 2032, USA-Carelon Research, USA-DAPI, and France will contribute to the meta-analysis for MCM. USA-Carelon Research, USA-DAPI, France, and Denmark will contribute to the meta-analysis for the select pregnancy loss outcome.

Using the data sources expected to contribute to meta-analysis, a non-inferiority margin of a risk ratio (RR) of 2.5 and exposed versus non-exposed patient allocation ratios of 1:2 and 1:3, the minimum required sample size for the primary study outcomes with 80% power was calculated. Based on these assumptions, **the sample size required** to achieve 80% power to rule out a RR of 2.5 or greater for the MCM outcome is **210** (assuming a 1:2 matching ratio) **or 183** (assuming a 1:3 matching ratio) anifrolumab exposed pregnancies. For the composite outcome spontaneous abortion and stillbirth, the sample size required to achieve 80% power to rule out a RR of 2.5 or greater is **72** (assuming a 1:2 matching ratio) **or 61** (assuming a 1:3 matching ratio) anifrolumab exposed pregnancies.

In addition to the a priori calculations for sample size requirement, **the power** to rule out a threshold RR of 2.5 for primary study outcomes with exposed:unexposed allocation ratios of 1:2 and 1:3, given the estimated number of anifrolumab exposed moderate-to-severe SLE pregnancies (under a 10% exposure assumption), and a final study report milestone of 2032 using the data sources expected to contribute to meta-analysis was also calculated. Based on the estimated numbers, the meta-analysis for the MCM would have an **expected power** of 96% (assuming a 1:2 matching ratio) or 98% (assuming a 1:3 matching ratio). For the select pregnancy loss outcome the meta-analysis would have an expected power of >99% in both the 1:2 and 1:3 matching scenarios.

All assumptions that have been used in these estimations will be evaluated during the first and second interim reports, and the study milestones will be adjusted, if necessary, to ensure a sufficient sample is obtained to address the research objectives.

Data analysis

The data analysis for each study objective will be performed separately for each data source.

In this study, propensity score (PS) adjustment will be performed to control for confounding. PS matching will used in this study if it does not significantly reduce the sample size, otherwise PS weighting will be used. The PS adjustment will be performed separately within each data source and for each study cohort. The PS will be obtained using a logistic regression or other modelling method (e.g., gradient boosting) as seen appropriate for the data. All the potential confounders considered for inclusion in the PS model will be estimated before or at LMP2, or before or at the start of exposure, as seen relevant for the confounder. The maximum number of the confounders to be included in the PS model will be one fifth of the minimum number of exposed or unexposed patients in the study cohort. The PS adjustment will be performed only if the PS model can be fit on the available data and if the PS model fit is reasonable. Covariate balance will be assessed

before and after PS adjustment by examining the distribution of variables in the study sub-cohorts and estimating standardized differences for each variable between the study sub-cohorts. If PS adjustment is not suitable for the data, no adjusted estimates of the study outcomes will be provided in the study results.

Descriptive analysis will be performed in the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab to estimate the cumulative incidence (i.e., risk), with associated 95% confidence intervals (CIs), of MCM (objective 1 & 15), select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) (objective 3 & 13), mCM (objective 6), adverse pregnancy outcomes (objective 8), adverse birth outcomes (objective 10), and adverse outcome related to infant growth up to one year of age (objective 12). The measures of study outcomes will be estimated before and after application of PS adjustment to obtain crude and adjusted estimates, respectively. Additionally, the description of the time from birth to MCM ascertainment will be conducted in live and non-live offspring from women who had moderate/severe SLE and were exposed or unexposed to anifrolumab during the first trimester of pregnancy. The time to MCM ascertainment will be calculated from birth and limited up to 1 year after birth. The time to MCM ascertainment will be estimated both before and after application of PS adjustment to obtain crude and adjusted estimates, respectively. Kaplan-Meier curves (and their 95% CIs) will be used for characterizing the time from birth to MCM ascertainment. Descriptive analysis will also be conducted for study objective 5 to describe the demographic and clinical characteristics of the live and non-live offspring and their mothers in the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab. For continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1st) and upper (3rd) quartiles, as well as 5th and 95th 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. Additionally, the number and proportion of mothers who received anifrolumab in the preconception period will be reported. The timing of anifrolumab administrations in the preconception period will also be reported.

For the comparison of the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab within the study cohorts, the RRs will be estimated. The RRs will be estimated if there is at least one event of the relevant outcome observed per exposure group. Both crude and adjusted RRs, with associated 95% CIs, will be estimated for the study outcomes of MCM (objective 2), select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) (objective 4 & 14), mCM (objective 7), adverse pregnancy outcomes (objective 9), adverse birth outcomes (objective 11). The crude RRs will be estimated before PS adjustment, and the adjusted RRs will be estimated after PS adjustment. If covariate balance is not achieved through PS adjustment, additional adjustment by using unbalanced covariates in the outcome regression model (log-binomial or robust, modified Poisson) will be considered. Additionally, any other potential covariates (or risk factors) that are not included into the PS model but are hypothesised to be associated with the study outcomes may be used as covariates for the statistical models.

The meta-analysis for the primary objectives will be performed using effect size estimates from all study countries for which the adjusted RRs will be estimated. Results of the meta-analysis will be derived using a fixed-effect model since the true effect is expected to be the same in all study countries. Prior to conducting the meta-analyses, heterogeneity across the study countries will be assessed. Considerable heterogeneity would indicate that the study results should be interpreted as inconclusive. 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

A progress report is planned 12 months after Pharmacovigilance Risk Assessment Committee (PRAC) endorsement of protocol (currently assumed to be Q4 2023). It will contain a status update of database applications and any relevant amendments pertaining to database applications.

Two interim reports will be submitted 36 and 72 months after the progress report.

Interim report 1 will contain descriptive analyses relevant to primary and secondary objectives, for data sources where relevant data is available for reporting. Descriptive analysis conducted in interim report 1 will be blinded to exposure. Interim report 2 will include all descriptive and comparative analyses using all available data at the time of reporting. Exploratory analyses, sensitivity analyses and meta-analyses will not be included in interim report 2.

The final study report is planned for 31 March 2032 and will include all descriptive, comparative, exploratory, sensitivity, and meta-analytic analyses for all data sources from all available data at that time.

- Protocol PRAC approval: Planned date 14 December 2023[1]
- Registration EU PASS: Planned date 31 March 2024 (after PRAC endorsement of protocol and before data extraction)
- Progress report: Planned date 31 December 2024
- Anticipated date of first data extraction: Planned date 31 May 2025
- Interim report 1: Planned date 31 December 2027
- Interim report 2: Planned date 31 December 2030
- Last data extraction: Planned date 31 March 2031
- Final report of study results: Planned date 31 March 2032 (15 months after Interim report 2)

[1] This date is an assumption of PRAC approval of the protocol. All subsequent dates are dependent on the actual date of protocol approval by PRAC.

5. AMENDMENTS AND UPDATES

Table 1: Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	<<*DD Month YYYY*>>			
2	<<*DD Month YYYY*>>			
3	<<*DD Month YYYY*>>			

6. MILESTONES

A progress report is planned 12 months after Pharmacovigilance Risk Assessment Committee (PRAC) endorsement of the protocol (currently assumed to be Q4 2023). It will contain a status update of database applications and any relevant amendments pertaining to database applications. Database access may take between 7 to 18 months; therefore, the progress report may not include patient numbers from each data source.

Two interim reports will be submitted at 36 and 72 months after the progress report. The first interim report will contain descriptive analyses relevant to primary and secondary objectives using all available data at the time of the report. In this report, a descriptive summary of the study outcomes will be provided for the overall study population but blinded to exposure status. The second interim report will contain all descriptive and comparative analyses relevant to the primary and secondary objectives, using ***all available*** data at the time of reporting. Study outcomes will be provided for the exposure categories. Interim report 2 will not include analyses related to exploratory objectives, sensitivity analyses, or meta-analyses.

The final study report is planned for 31 March 2032 and will include all descriptive, comparative, exploratory, sensitivity, and meta-analytic analyses for all the data sources (Table 2).

Assuming an allocation ratio of 1:2 between anifrolumab exposed and unexposed, minimum sample sizes of 210 anifrolumab users for the MCM outcome and 72 anifrolumab users for the select pregnancy loss outcome would be needed to rule out a target threshold RR of 2.5 with 80% power (see Section 9.5.2). Under the assumption of a final study report milestone of 31 March 2032, and an anifrolumab exposure of 10% in moderate-to-severe SLE pregnancies, the total anticipated number of anifrolumab exposed patients in the selected data sources during the study time period is 353 for the MCM outcome and 497 for the select pregnancy loss outcomes. With these numbers the expected power to rule out a RR of 2.5 is ≥ 96% for the primary study outcomes (for more details on sample size estimations, see Section 9.5). These assumptions will be reviewed in each interim report and study milestones will be adjusted if necessary to ensure a sufficient sample size is obtained.

Table 2: Study milestones

Milestone	Planned date[2]
Protocol PRAC approval	14 December 2023
Registration in the EU PAS Register	31 March 2024
Study progress report	31 December 2024
Start of data collection	31 May 2025
Interim report 1	31 December 2027
Interim report 2	31 December 2030

[2] This date is an assumption on the planned PRAC approval of the protocol. All the subsequent dates are also planned and dependent on the date of protocol approval by PRAC.

Milestone	Planned date[2]
End of data collection	31 March 2031
Final report of study results	31 March 2032

7. RATIONALE AND BACKGROUND

7.1 Disease Burden of SLE

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, rheumatic disease. The clinical course of SLE is fluctuating and is characterised by periods of exacerbations and reduced activity or less commonly remission (90). This multisystem disease is characterised by the production of autoantibodies and the occurrence of tissue damage arising from inflammation and the deposition of immune complexes, as well as side effects of SLE treatments (91). There is significant heterogeneity in the clinical and biological manifestations of SLE 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.

Epidemiological studies on SLE show marked gender, age, racial, temporal, and regional variations. Females are disproportionally more affected than males, with estimated female: male ratios ranging from 8:1 to 15:1 and peak incidence occurring between the ages of 15 and 45 years (90, 91). Disease burden is estimated to be 2 to 3 times higher in people of African and Asian descent compared to people of Caucasian descent (89).

Globally, the incidence of SLE ranges from 0.3-23.7 cases per 100,000 person years (90). In the European Union (EU) and the United States of America (USA), incidence of SLE is estimated to range from 3.3-5.0, and 1.8-23.7 per 100,000 person years respectively (90). Prevalence estimates of SLE are 6.5-178.0 per 100,000 persons globally, 40.0-143.7 per 100,000 persons in the USA and 25.4-91.0 per 100,000 persons in Europe (90). The prevalence of SLE has been increasing in recent years in the USA and United Kingdom (UK) (92, 118).

Systemic lupus is a complex disease with unknown aetiology. Identified risk factors include inherent genetic susceptibility, environmental triggers (sunlight/UV light, infection, smoking, alcohol), and immune system dysregulation (16, 25, 30, 75, 77).

7.2 Current Treatment Paradigm

Given the individual variability in SLE manifestations, there is no single treatment paradigm. A tailored, multidisciplinary strategy is required that adjusts 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, reduction of disease activity and optimisation of health-related quality of life (43). The American College of Rheumatologists (ACR) guidelines for SLE management have not been updated in over 20 years. Therefore, EULAR recommendations are commonly adopted in clinical practice in the USA.

For mild disease, first line treatments include antimalarials (e.g., hydroxychloroquine) and oral glucocorticoids (e.g., prednisone). Treatment options for moderate/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's biosimilars) are considered in severe, organ-threatening refractory cases (43).

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 (69). Long-term use of hydroxychloroquine can cause retinopathy and poor adherence to treatment remains an issue (43). Glucocorticoids are powerful immunosuppressants 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 to long-term morbidity and early cardiovascular mortality (85, 95, 96) and the risk of irreversible organ damage increases with glucocorticoid dose (87, 110). The use of non-specific conventional immunosuppressants is associated with an increased risk of infection, malignancy, and cardiovascular disease (7, 53, 54, 100). Furthermore, these conventional immunosuppressants are not effective in all patients for all manifestations of SLE (87, 110).

Despite the considerable progress in the identification of effective biological therapies for the management of immune-mediated conditions, such as rheumatoid arthritis and inflammatory bowel disease, not much progress has been made in the identification of specifically targeted treatments for SLE (8, 101). In the EU and the USA, 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, was approved by the EMA in 2011, for the treatment of adult patients with active, autoantibody positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (33). It targets one pathway – the B-Lymphocyte stimulator (BLyS) cytokine pathway which affects B cell survival, maturation and differentiation into autoantibody producing cells (31). SLE patients are likely to have different underlying immunopathological pathways driving their SLE disease manifestations (32). As such, belimumab is not effective in all patients. Anifrolumab, a human monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1) was developed based on the evidence supporting the role of type I interferon pathway in SLE (48). It was approved in the USA and the EU as an add-on therapy for the treatment of adult patients with moderate to severe SLE, despite standard therapy in July 2021 and February 2022, respectively (38). Approval 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 (BILAG)–based Composite Lupus Assessment (BICLA), compared to patients who received placebo (48, 79).

7.3 SLE Treatment in Pregnancy

Pregnancy in women with SLE carries a higher maternal and foetal risk compared with pregnancy in healthy women (1, 12, 103). During pregnancy, the risk factors associated with adverse

outcomes include active/disease flares, active nephritis and use of glucocorticoids (especially at a maintenance above 10-20mg/day of prednisone equivalent) (12, 20, 116) . Therefore, the treatment of active SLE during pregnancy is guided by the disease severity and degree of organ involvement, like the approach for patients in the nonpregnant state (12, 20, 116).

It is currently recommended that treatment should not be withheld in pregnancy; however, some medications used to treat SLE may cross the placenta to cause foetal harm (3). Thus, the risks and benefits of treatment during pregnancy must be weighed against the risk of SLE activity having a deleterious effect on the mother and the foetus.

The most used medication to treat patients with SLE during pregnancy is hydroxychloroquine (3). Evidence from a controlled study and other non-randomized evidence supports a beneficial role of hydroxychloroquine in controlling disease activity and preventing flare-ups during pregnancy (3). Glucocorticoids, azathioprine, calcineurin inhibitors (ciclosporin A, tacrolimus) may be used based on the availability of data suggesting an acceptable benefit/risk ratio, although they may carry a small risk of causing foetal harm (3). In moderate to severe flares, additional modalities may be considered such as high dose glucocorticoid (including pulse intravenous (IV) therapy), IV immunoglobulin and plasmapheresis (3).

Mycophenolate mofetil, methotrexate, and leflunomide are contraindicated in pregnancy because of either their definitive or suspected teratogenic effects (3). The use of cyclophosphamide during the first trimester is contraindicated because of the risk of foetal loss. However, it may be used for the management of severe, life-threatening, or refractory manifestations during the second or third trimester (3). Ideally these therapeutic agents should be replaced with medications compatible with pregnancy 6 months prior to conception (3).

Data on the use of biologics anifrolumab and belimumab in pregnancy are limited, therefore current recommendations indicate that these drugs should not be used unless the benefit outweighs the risk to the foetus (3, 33, 38).

7.4 Knowledge Gaps

For ethical reasons, pregnant or lactating females were excluded from all anifrolumab clinical studies. For the same reasons, treatment with anifrolumab was discontinued for any patient who became pregnant during the clinical trials. Therefore, there are no data on patients receiving anifrolumab throughout the entirety of their pregnancy or their offspring.

While there is considerable data detailing the harmful effects of increased level of interferons during pregnancy, there is limited data on the effect of blockade of interferon signalling in pregnancy (14). Current literature suggests that there is a lack of developmental defects in mice following the blockade of interferon signalling. However, results from a pre- and postnatal developmental toxicity study conducted on cynomolgus monkeys, suggested a non-statistically significantly higher incidence of embryo-foetal loss among anifrolumab exposed monkeys. The relevance of these findings to humans is not known. Although, for exposures up to approximately

28 times the maximum recommended human dose on an AUC basis, no maternal, or postnatal developmental effects were observed (38).

7.5 Regulatory Commitment

As part of the original marketing authorisation application to the EMA, and in response to the non-clinical findings on the safety of anifrolumab exposure in pregnancy, AstraZeneca included a proposal within the European Union Risk Management Plan, to conduct a non-interventional multi-country post-authorisation safety study to characterise the use of anifrolumab in women with SLE during planned and unplanned pregnancies. The study design and objectives were subsequently modified in response to the scientific comments provided by the PRAC (specifically the Day 120 and Day 180 responses), to describe pregnancy and infant outcomes in women with SLE who received treatment with anifrolumab during pregnancy; and to compare these estimates to estimates obtained for pregnant women with SLE who did not receive anifrolumab during pregnancy.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to describe congenital malformations, adverse pregnancy, and birth outcomes in pregnancies/offspring from women with moderate/severe SLE exposed to anifrolumab (indicated as an add-on therapy to the standard of care (SOC)) and compare the occurrence of these outcomes to outcomes observed in women with moderate/severe SLE whose pregnancies are not exposed to anifrolumab (but are on other SLE SOC) (55).

8.1 Objectives

Primary objectives

1. To describe and estimate the risk of **MCM** in live and non-live offspring from
    a. women with moderate/severe SLE, exposed to anifrolumab during the first trimester of pregnancy
    b. comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy
2. To estimate the relative risk of **MCM** in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy
3. To describe and estimate the risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in
    a. women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy
    b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy
4. To estimate the relative risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

Secondary objectives

5. To describe demographic and clinical characteristics of
    a. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy

b. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy
c. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab anytime during pregnancy
d. live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

6. To describe and estimate the risk of **minor Congenital Malformations (mCM)** in live and non-live offspring from

    a. women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy
    b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

7. To estimate the relative risk of **mCM** in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

8. To describe and estimate the risk of **adverse pregnancy outcomes** separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from

    a. women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy
    b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

9. To estimate the relative risk of **adverse pregnancy outcomes** separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

10. To describe and estimate the risk of **adverse birth outcomes** (preterm birth, small for gestational age (SGA)) in live offspring from

    a. women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy

b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

11. To estimate the relative risk of **adverse birth outcomes** (preterm birth, SGA) in live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy

Exploratory objectives

12. To describe and estimate the risk of **adverse outcome related to infant growth** up to one year of age of live offspring from
    a. women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy
    b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy
13. To describe and estimate the risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in
    a. women with moderate/severe SLE exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3)
    b. comparable population of women with moderate/severe SLE exposed to SOC during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) and unexposed to anifrolumab anytime during pregnancy
14. To estimate the relative risk of **select pregnancy loss outcomes** (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimesters 1&2&3) compared to women with moderate/severe SLE exposed to SOC in the same pregnancy trimesters and unexposed to anifrolumab anytime during pregnancy
15. To describe and estimate the risk of **MCM** by target body system organ class in live and non-live offspring from
    a. women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy
    b. comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy

9. RESEARCH METHODS

9.1 Study design

The study will be performed using a non-interventional longitudinal population-based retrospective cohort design. It will be conducted using secondary data derived from multiple databases in Denmark, Finland, France, Germany, and USA. The unit of analysis is individual pregnancies in women with moderate/severe SLE. Therefore, each woman may contribute multiple occurrences of pregnancies to the study.

There are two primary outcomes of interest: **composite of MCM** and **select pregnancy loss outcomes.** The ascertainment period for MCM is from the end of the pregnancy until one year of age, while the ascertainment period for select pregnancy loss outcomes is from LMP2 until end of pregnancy. The study design schemas for these outcomes are provided in Figure 1 (MCM) and Figure 2 (select pregnancy loss outcomes) below.

The secondary outcomes of interest are mCM, adverse pregnancy outcomes, and adverse birth outcomes. The outcome ascertainment periods for these secondary outcomes are from birth until one year of age (mCM), from LMP2 until end of pregnancy (adverse pregnancy outcomes) and at birth (adverse birth outcomes). The study design schemas are presented in Figure 1 (mCM), Figure 2 (adverse pregnancy outcomes) and Figure 3 (adverse birth outcomes).

The exploratory outcomes of interest are adverse outcomes related to infant growth. The ascertainment period for this outcome is from birth until 1 year of age. The study design schema is presented in Figure 4. In addition to this exploratory outcome, analysis for the select pregnancy loss outcome (composite of spontaneous abortion and stillbirth) by specific trimester of anifrolumab exposure (details as provided in Section 9.3.1), and the risk of MCM by target body organ system classification according EUROCAT (41) will be conducted.

For congenital malformation (CM), birth and infant outcomes, the population of study will be limited to offspring for whom mother-offspring record linkage is available within each data source. However, for pregnancies that end in a spontaneous abortion, an elective termination of pregnancy or stillbirth where there is a diagnosis of MCM, mother-offspring linkage will not be required.

The exposure of interest is *in utero* exposure to anifrolumab (see Section 9.3.1) and/or *in utero* exposure to SLE SOC between last menstrual period + 2 weeks (LMP2) (derived from last menstrual period or, if missing, gestational age) and:

1. for MCM, end of first trimester
2. for all other outcomes, end of pregnancy

or occurrence of the outcome of interest (whichever comes first).

Exposure information will be derived from outpatient visits and/or prescription data, as recorded in the data source for each country. Country-specific cohorts of eligible women or

woman/offspring units will be identified, depending on the outcome of interest. A summary of the study design is presented in Table 3.

Table 3: Summary of study design

Topic	Outcome	Population	Inclusion assessment window	Exposure assessment period	Index date	Follow-up	
						Offspring	Mother
Congenital anomalies	MCM	Live and non-live offspring	min 12 months prior to LMP2	from LMP2 to end of first trimester of pregnancy[1]	LMP2	from LMP2 to max 1y of age	NA
Select pregnancy loss outcomes	Composite of spontaneous abortion and stillbirth	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Congenital anomalies	mCM	Live and non-live offspring	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	from LMP2 to max 1y of age	NA
Adverse pregnancy outcomes	Ectopic pregnancy	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse pregnancy outcomes	Spontaneous abortion	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse pregnancy outcomes	Elective termination of pregnancy	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse pregnancy outcomes	Stillbirth	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse pregnancy outcomes	Composite of foetal loss	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse pregnancy outcomes	Infections requiring hospitalisation during pregnancy	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse pregnancy outcomes	Emergency caesarean section	All pregnancies	min 12 months prior to LMP2	from LMP2 to end of pregnancy[1]	LMP2	NA	end of pregnancy
Adverse birth outcomes	Preterm birth	Live offspring	min 12 months prior to LMP2	from LMP2 to end of pregnancy	birth	NA	NA
Adverse birth outcomes	Small for gestational age	Live offspring	min 12 months prior to LMP2	from LMP2 to end of pregnancy	birth	NA	NA
Adverse infant growth	Infant growth	Live offspring	min 12 months prior to LMP2	from LMP2 to end of pregnancy	birth	from birth to max 1y of age	NA

[1] The exposure window is considered from conception (defined as LMP2) to the end of pregnancy (first trimester only for MCM) or censoring, whichever occurs first.

Abbreviations used in the table: NA, Not applicable; Min, Minimum; Max, Maximum; 1 y, 1 year of age; LMP2, Date of conception (last menstrual period + 2 weeks)

For the main analysis, a comparable group of pregnant women, with moderate/severe SLE, will be selected as the comparator group. The current indication for anifrolumab use is as an add-on therapy for moderate/severe SLE. Therefore, the most suitable comparator population is a population of women with moderate/severe SLE. Additionally women with moderate/severe SLE are at increased risk of adverse outcomes during pregnancy, (as a result of SLE disease severity, SLE disease activity and effects of medication use) compared to non-SLE pregnant women (27). However, as treatment with anifrolumab may reduce SLE severity, it is possible that not all anifrolumab exposed pregnancies would be of moderate/severe severity. Therefore, a sensitivity analysis which includes all anifrolumab users (regardless of disease severity) will be conducted. Details of this sensitivity analysis are provided in Section 9.7.5.

Aggregated country-specific results for the primary objectives will be combined via a meta-analytic approach, providing a pooled estimate across all data sources.

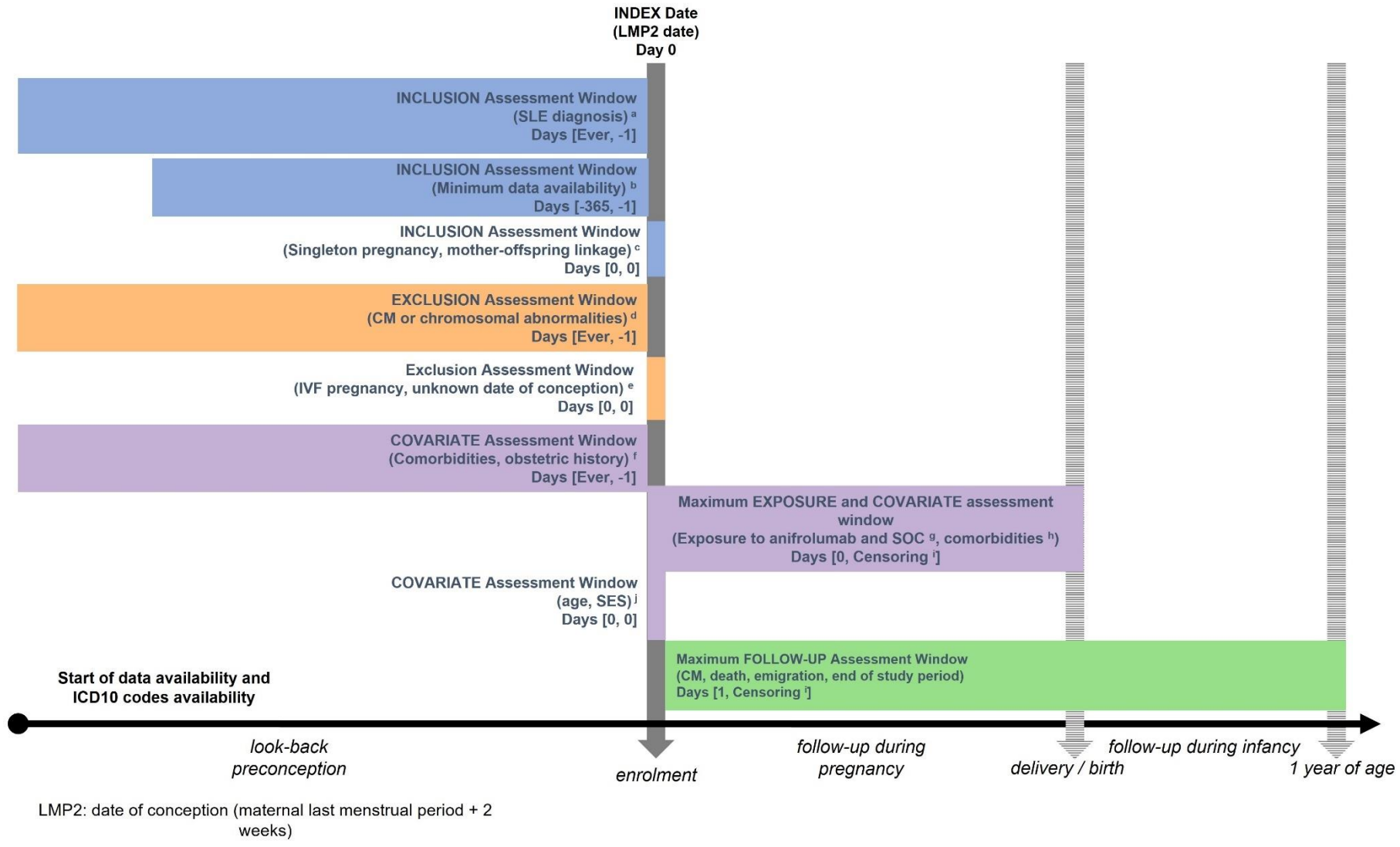

Figure 1: Overview of the study design, for MCM and mCM

a. Diagnosis of SLE in the mother before pregnancy
b. Women with a continuous enrolment in the database for ≥ 12 months prior to conception (defined as LMP2)

c. Singleton pregnancy, mother-offspring linkage. Mother-offspring linkage will not be required for spontaneous abortion, stillbirth, and ectopic pregnancy where the diagnosis/reason provided is MCM
d. Women with a history of CM or chromosomal abnormalities
e. Pregnancy associated with in vitro fertilisation (IVF), pregnancy with unknown date of conception
f. Comorbidities and covariates measured prior to index date may include maternal diabetes, maternal pre-pregnancy body mass index (BMI), obstetric history
g. Exposure to SLE SOC will be assessed in the exposed and comparator groups at LMP2 with a look-back period of 5-half-lives of relevant drug. Exposure to anifrolumab will be assessed from LMP2 until end of the first trimester of pregnancy for MCM outcome and anytime during the pregnancy for mCM outcome with a maximum look-back period of 16-weeks (time for anifrolumab concentration to fall below the LLOQ for 95% of patients) prior to LMP2
h. Comorbidities and covariates measured during pregnancy may include maternal smoking, alcohol and substance abuse, gestational diabetes
i. First of the following: diagnosis of CM, death, emigration, end of study period (reaching the age of 1 year), and administrative data cut off
j. Covariates measured at index date may include maternal socioeconomic status (SES), age at LMP2

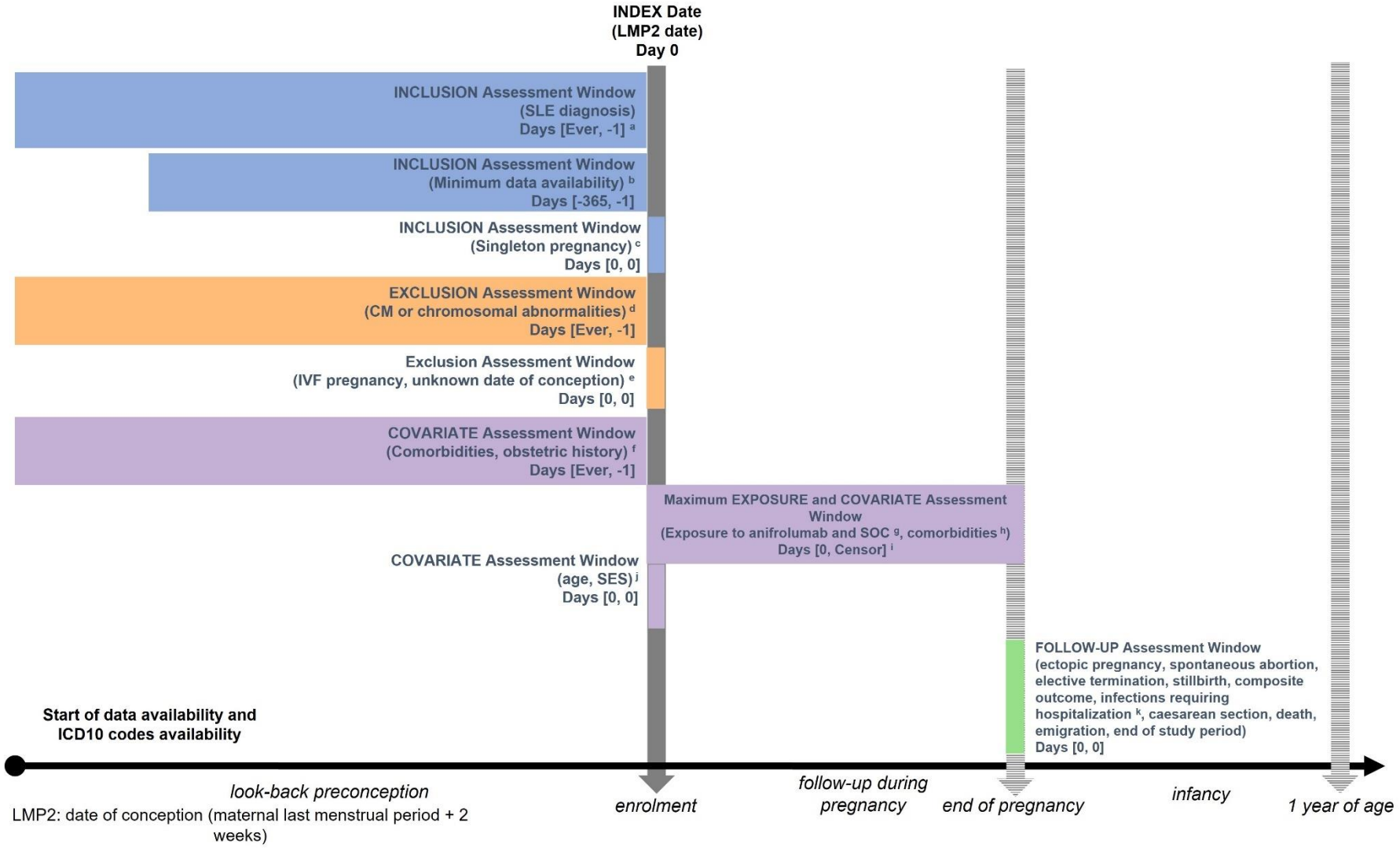

Figure 2: Overview of the study design, for adverse pregnancy outcomes

a. Diagnosis of SLE before pregnancy
b. Women with a continuous enrolment in the database for ≥ 12 months prior to conception (defined as LMP2)

c. Singleton pregnancy, mother-offspring linkage. Mother-offspring linkage will be required for ectopic pregnancy, spontaneous abortion, elective termination, stillbirth, infections requiring hospitalisation, caesarean section
d. Women with a history of CM or chromosomal abnormalities
e. Pregnancy associated with in vitro fertilisation (IVF), date of conception cannot be established
f. Comorbidities and covariates measured prior to index date may include maternal diabetes, maternal pre-pregnancy BMI, obstetric history
g. Exposure to SLE SOC will be assessed in the exposed and comparator groups at LMP2 with a look-back period of 5-half-lives of relevant drug. Exposure to anifrolumab will be assessed from LMP2 until end of pregnancy with a maximum look-back period of 16-weeks (time for anifrolumab concentration to fall below the LLOQ for 95% of patients) prior to LMP2
h. Comorbidities and covariates measured during pregnancy may include maternal smoking, alcohol and substance abuse, gestational diabetes
i. First of the following: ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) composite of foetal loss (considering the presence at least one of the following: spontaneous abortion, ectopic pregnancy, elective termination of pregnancy and stillbirth), infections requiring hospitalisation during pregnancy, emergency caesarean section, death, emigration, end of study period (end of pregnancy)
j. Covariates measured at index date may include maternal socioeconomic status (SES), age at LMP2
k. For infections requiring hospitalisation during pregnancy, follow-up is from enrolment until the end of pregnancy

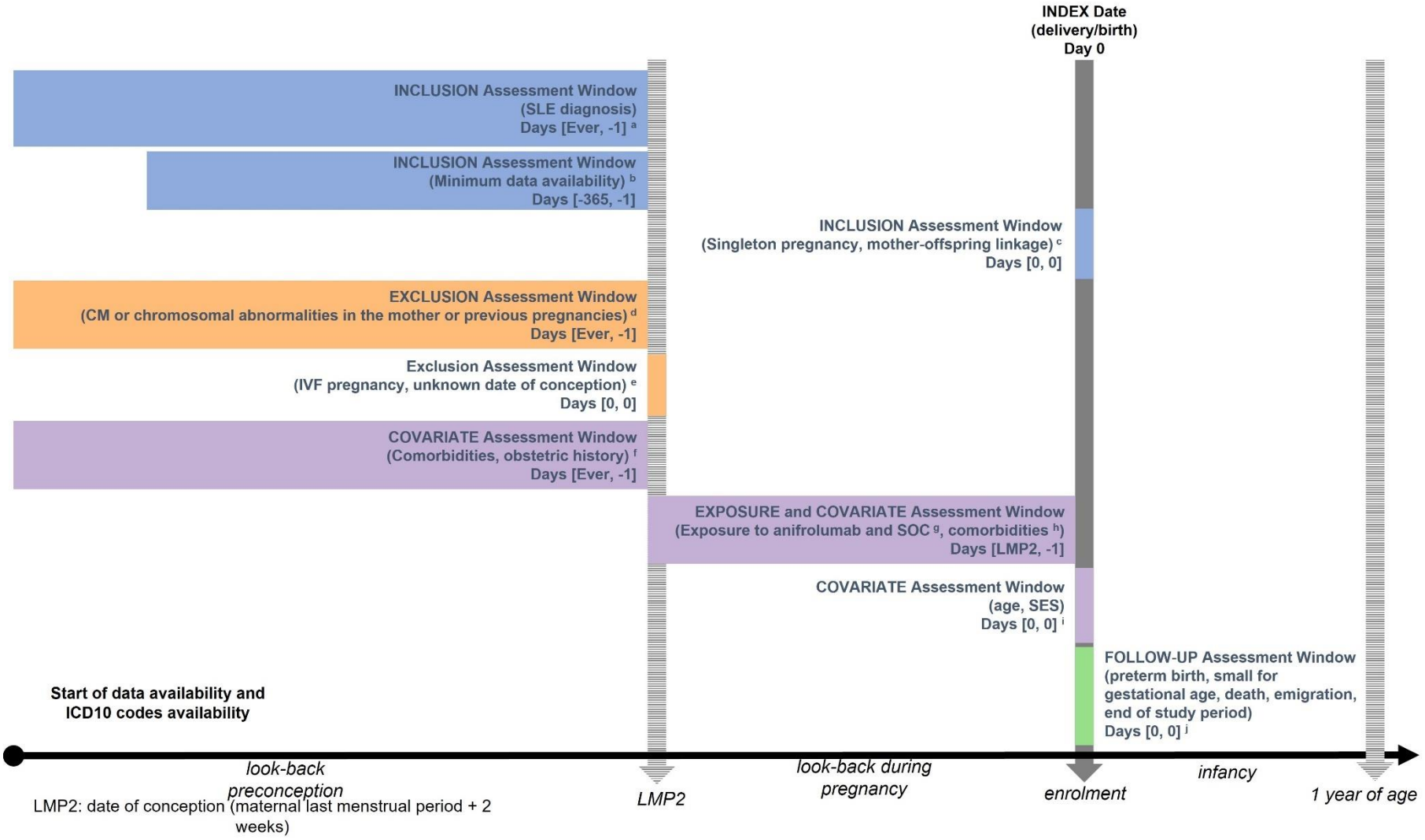

Figure 3: Overview of the study design, for adverse birth outcomes

a. Diagnosis of SLE before pregnancy
b. Women with a continuous enrolment in the database for ≥ 12 months prior to conception (defined as LMP2)
c. Singleton pregnancy, mother-offspring linkage

d. Women with a history of CM or chromosomal abnormalities (information related to history of CM and chromosomal abnormalities can also be retrieved from clinical records (birth and maternal clinical records) regarding the current pregnancy)
e. Pregnancy associated with in vitro fertilisation (IVF), date of conception cannot be established
f. Comorbidities and covariates measured prior to index date may include maternal diabetes, maternal pre-pregnancy BMI, obstetric history
g. Exposure to SLE SOC will be assessed in the exposed and comparator groups at LMP2 with a look-back period of 5-half-lives of relevant drug. Exposure to anifrolumab will be assessed from LMP2 until end of pregnancy with a maximum look-back period of 16-weeks (time for anifrolumab concentration to fall below the LLOQ for 95% of patients) prior to LMP2
h. Comorbidities and covariates measured during pregnancy may include maternal smoking, alcohol and substance abuse, gestational diabetes
i. Covariates measured at index date may include maternal socioeconomic status (SES), age at LMP2
j. First of the following: preterm birth, small for gestational age, death, emigration, end of study period (delivery/birth)

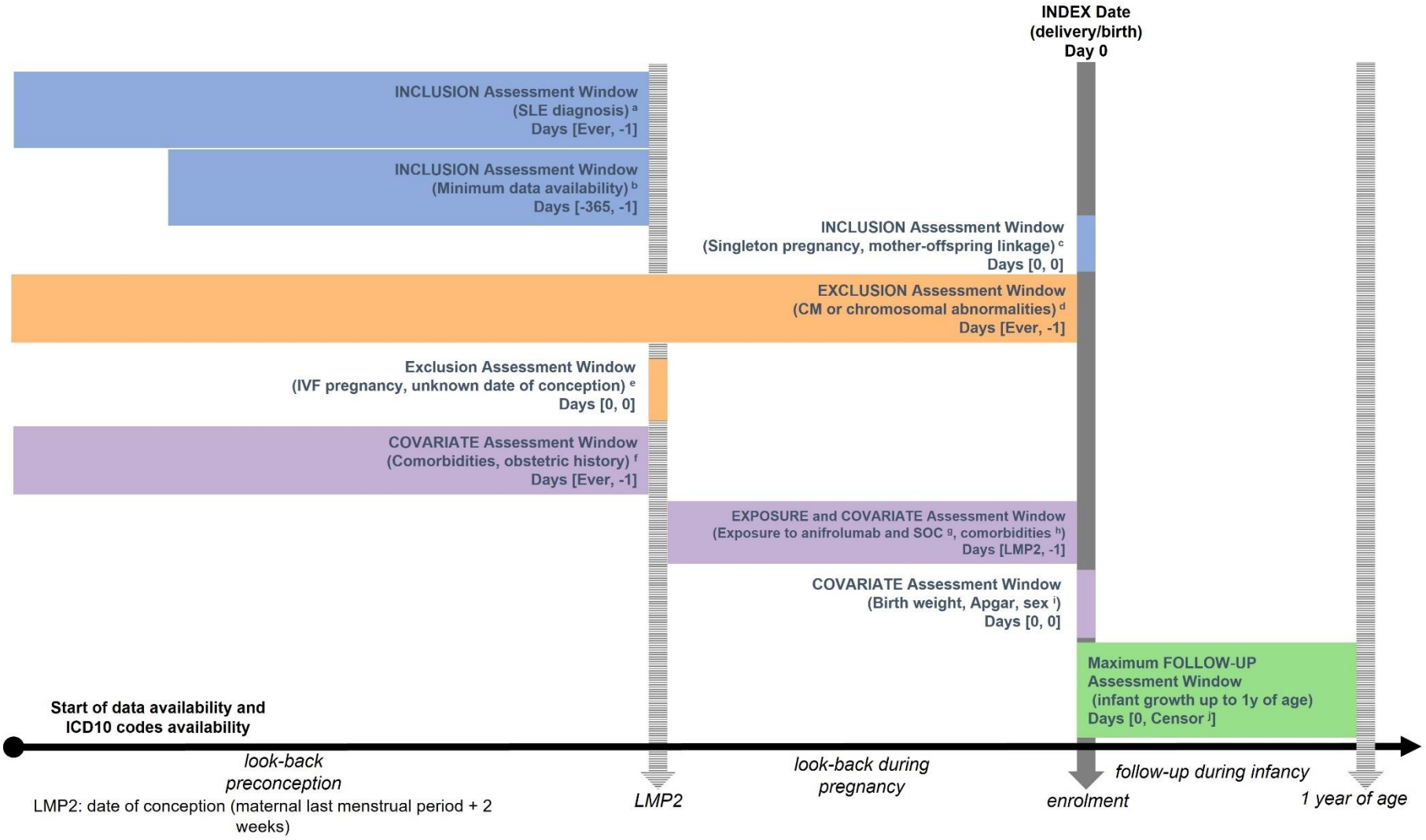

Figure 4: Overview of the study design, for adverse outcomes related to infant growth up to 1 year of age

a. Diagnosis of SLE before pregnancy
b. Women with a continuous enrolment in the database for ≥ 12 months prior to conception (defined as LMP2)
c. Singleton pregnancy, mother-offspring linkage
d. Women with a history of CM or chromosomal abnormalities
e. Pregnancy associated with in vitro fertilisation (IVF), date of conception cannot be established
f. Comorbidities and covariates measured prior to index date may include maternal diabetes, maternal pre-pregnancy BMI, obstetric history
g. Exposure to SLE SOC will be assessed in the exposed and comparator groups at LMP2 with a look-back period of 5-half-lives of relevant drug. Exposure to anifrolumab will be assessed from LMP2 until end of pregnancy with a maximum look-back period of 16-weeks (time for anifrolumab concentration to fall below the LLOQ for 95% of patients) prior to LMP2
h. Comorbidities and covariates measured during pregnancy may include maternal smoking, alcohol and substance abuse, gestational diabetes
i. Covariates measured at index date may include birth weight, Apgar score and sex of the infant
j. First of the following: adverse growth outcome, death, emigration, end of study period (reaching the age of 1 year)

9.2 Setting

A total of 6 large longitudinal patient-level data sources have been selected for this study, representing 5 countries: Denmark, Finland, France, Germany, and USA.

The included data sources are:

- Danish national health and socioeconomic registries (Denmark)
- Finnish national health and socioeconomic registries (Finland)
- National Health Data System (SNDS) (France)
- Rheuma-Kindwunsch und Schwangerschaft (RHEKISS) (Germany)
- Carelon Research (formerly known as Health Core Integrated Research Database - HIRD) (USA)
- Optum DAPI (USA)

9.2.1 Study time period

The overall study time period will span from 12 months (minimum look back period) prior to the country-specific anifrolumab market launch date until the latest available data at the last data extraction date. The **start of the study period** will be the market launch date of anifrolumab in each country (Table 4)

The **end of study period**, defined as the last possible day of follow-up when all patients still active are censored (30 September 2028 for Denmark, Finland, France and Germany; 30 September 2030 for USA). This will likely differ between countries as it is dependent on the length of data lag in each country at the time when the last data extraction is performed (Table 4). The rationale for this choice is to include all data available from relevant data sources to capture a sufficient number of outcomes, exposures, and linked mother-offspring pairs for the primary outcome at study, as reported in Section 9.4.

Table 4: Relevant dates of the study by country

Country	**Start of study period** Anifrolumab market launch date	**Start of enrolment** [1] Date of first patient enrolled	**End of enrolment** [2] Date of last patient enrolled	**End of study period** [3] Last possible day of follow-up, when all patients still active are censored
Denmark	11 March 2022	11 March 2022	29 September 2028	30 September 2028
Finland	Not launched	TBC	29 September 2028	30 September 2028
France	19 April 2022	19 April 2022	29 September 2028	30 September 2028
Germany	11 March 2022	11 March 2022	29 September 2028	30 September 2028

Country	**Start of study period** Anifrolumab market launch date	**Start of enrolment** [1] Date of first patient enrolled	**End of enrolment** [2] Date of last patient enrolled	**End of study period** [3] Last possible day of follow-up, when all patients still active are censored
USA	23 August 2021	23 August 2021	29 September 2030[4]	30 September 2030[4]

1 For *adverse birth outcomes* and *adverse outcomes related to infant growth* up to 1 year of age, due to the index date being birth/delivery, start of enrolment will begin 9 months after anifrolumab market launch date to allow for the observation of exposure during pregnancy.

2 For *CM outcomes* the last pregnancy will be included on 29 December 2026 (to allow for 9 months of pregnancy and 1 year after birth to be potentially observed).
For *adverse pregnancy outcomes* the last pregnancy will be included on 29 December 2027 (to allow for 9 months of pregnancy to be potentially observed).
For *adverse outcomes related to infant growth* up to 1 year of age the last offspring will be included on 29 September 2027 (to allow for 1 year after birth to be potentially observed).
For *adverse birth outcomes* the last offspring will be included on 29 September 2028 (no follow-up applicable).

3 Calculated assuming that the final report is due on 31 March 2032 and assuming a lag time of up to 2 years in data availability.

4 Due to shorter lag times in the USA data sources (see Section 9.4.1), an extra two years of data collection has been assumed

9.2.2 Participants

To address the research questions, eligible cohorts will be identified through a nested selection process (Figure 5). An *overall source population* will be created for data extraction *(STEP 1)* and split into *exposed to anifrolumab source population* and *unexposed to anifrolumab source population (STEP2).*

Then criteria common to exposed and unexposed to anifrolumab source populations will be applied to create post-data extraction *exposed to anifrolumab study population* and *unexposed to anifrolumab study population (STEP 3)* from where the cohorts of analyses will be derived *(STEP 4)*.

Since this is a non-interventional observational study, minimal inclusion and exclusion criteria are desirable to minimise potential selection bias and represent real world clinical practice.

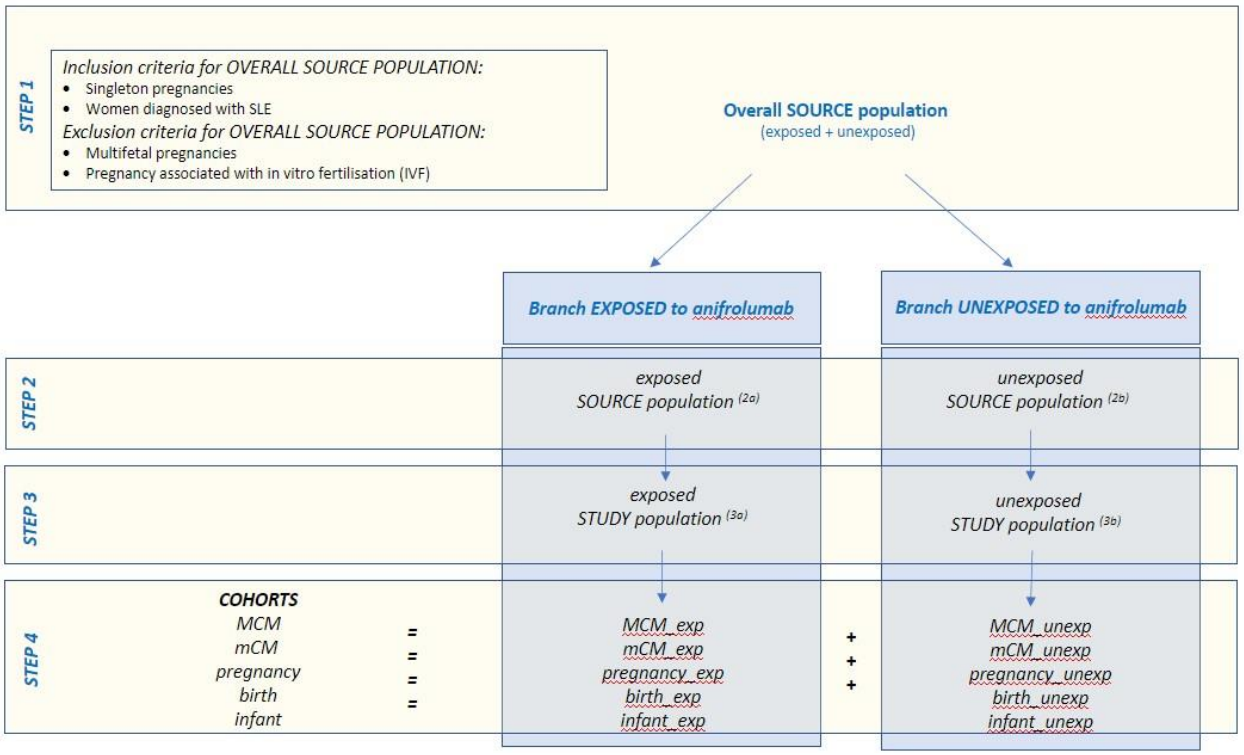

Figure 5: Overview of the data extraction and selection of the population

(2a) Inclusion criteria for EXPOSED SOURCE POPULATION:

- Women with a continuous enrolment in the database for ≥ 12 months prior to LMP2
- Women diagnosed with SLE before pregnancy
- Women exposed to anifrolumab (polytherapy, added to SLE SOC) during pregnancy and/or 16-week period prior to LMP2

Exclusion criteria for EXPOSED SOURCE POPULATION:

- Pregnancies whose date of conception cannot be established

(2b) Inclusion criteria for UNEXPOSED SOURCE POPULATION:

- Women with a continuous enrolment in the database for ≥ 12 months prior to LMP2
- Women diagnosed with SLE before pregnancy
- Women treated with SLE SOC during pregnancy

Exclusion criteria for UNEXPOSED SOURCE POPULATION:

- Women treated with anifrolumab during pregnancy and/or 16-week period prior to LMP2
- Pregnancies whose date of conception cannot be established

(3a; 3b) Inclusion criteria for EXPOSED and UNEXPOSED STUDY POPULATION:

- Women with moderate to severe SLE

Exclusion criteria for EXPOSED and UNEXPOSED STUDY POPULATION:

- Women with a history of CM or chromosomal abnormalities (according to available records), before delivery
- Women prescribed a confirmed teratogenic drug prior to LMP2 with a time period of 5-half-lives of relevant drug or during pregnancy

Exclusion criteria for STEP 4 are reported in Table 5.

STEP 1

Inclusion criteria for data extraction to create an *overall source population:*

- Singleton[3] pregnancies
- Women diagnosed with SLE

Exclusion criteria for data extraction to create an *overall source population*:

- Pregnancy associated with in vitro fertilisation (IVF)[4]

STEP 2

Step to create *exposed to anifrolumab source population* and *unexposed to anifrolumab source population*, from the overall source population (created in STEP 1).

STEP 2A - exposed to anifrolumab source population

Additional inclusion criteria to be applied after data extraction to create an *exposed source population*:

- Women with a continuous enrolment[5] in the database for ≥ 12 months prior to LMP2
- Women diagnosed with SLE before pregnancy
- Women exposed to anifrolumab (polytherapy, added to SLE SOC) during pregnancy and/or 16-week period prior to LMP2[6]

Additional exclusion criterion to be applied after data extraction to create an *exposed source population:*

- Pregnancies whose date of conception cannot be established

[3] Singleton pregnancies will be identified based on the coding system (e.g., ICD-10) used in the data sources (see Table 18). All pregnancies will be assumed to be singleton if there is no ICD-10 or procedural code that suggests the pregnancy is multifetal. For RHEKISS singleton pregnancy will be identified with the MedDRA code for single pregnancy. Multifetal pregnancies will be excluded because they share the same maternal exposure and it is not known how medication can be absorbed, distributed, and metabolised by each of the foetuses. Moreover, CMs as well as adverse pregnancy and birth outcomes occur more frequently in twin and triplet pregnancies than in singleton pregnancies, regardless of the exposure to the drug at study.

[4] IVF pregnancies will be excluded due to issues related to the lack of information regarding maternal covariates in cases where a donor egg was used. Further, a higher incidence of adverse pregnancy and birth outcomes (e.g., gestational diabetes, gestational hypertension, preterm labour, low birthweight) have been reported in IVF pregnancies compared to spontaneously conceived controls (118, 121).

[5] For example, a patient can be considered continuously enrolled in a specific time period if that patient had a contact with healthcare services (such as drug prescription or hospitalisation) prior to that period and if emigration or death were not notified after this contact. Criteria to define continuous enrolment in the database are country specific and will be detailed in the SAP.

[6] The exposure period of interest for MCM outcomes is the first trimester of pregnancy and for all other outcomes, anytime during pregnancy. In order to account for potential prescriptions/dispensations/administrations that could lead to an intake during the period of interest, all prescriptions/dispensations/administrations that are recorded in the 16 weeks (time for anifrolumab concentration to fall below the LLOQ for 95% of patients) prior to LMP2 will be considered (2).

STEP 2B – unexposed to anifrolumab source population

Additional inclusion criteria to be applied after data extraction to create an *unexposed source population* (mirroring the exposed SLE source population, except for the exposure itself):

- Women with a continuous enrolment[7] in the database for ≥ 12 months prior to LMP2
- Women diagnosed with SLE before pregnancy
- Women treated with SLE SOC during pregnancy[8]

Additional exclusion criteria to be applied after data extraction to create an *unexposed source population* (mirroring the exposed source population, except for the exposure itself):

- Women treated with anifrolumab during pregnancy and/or during the 16-week period prior to LMP2
- Pregnancies whose date of conception cannot be established

STEP 3

Step to create *exposed to anifrolumab study population* and *unexposed to anifrolumab study population.*

STEP 3A and 3B – exposed and unexposed to anifrolumab study population

Additional inclusion criteria to be applied to the exposed and unexposed source population for creating a post-data extraction overarching *exposed and unexposed study population* with only moderate to severe SLE (mirroring the exposed study population, except for the exposure itself):

- Women with moderate to severe SLE (severity assessment is based on the SLE severity algorithm, see Figure 7)

Additional exclusion criteria to be applied to the exposed and unexposed source population for creating a post-data extraction overarching *exposed and unexposed study population* (mirroring the exposed study population, except for the exposure itself):

- Women with mild SLE (severity assessment is based on the SLE severity algorithm, see Figure 7)

[7] For example, a patient can be considered continuously enrolled in a specific time period if that patient had a contact with healthcare services (such as drug prescription/administration or hospitalisation) prior to that period and if emigration or death were not notified after this contact. Criteria to define continuous enrolment in the database are country specific and will be detailed in the SAP.
[8] Exposure to SLE SOC will be assessed from LMP2 until end of first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for all other outcomes. A look-back period of 5-half-lives of relevant drugs will be considered.

- Women with a history of CM or chromosomal abnormalities and genetic syndromes (according to available records)[9], before delivery
- Women prescribed a confirmed teratogenic drug prior to LMP2 until end of first trimester (for MCM outcome) or end of pregnancy (all other pregnancy outcomes), with a look back period of 5-half-lives of relevant drug, in both the exposed and unexposed groups (see Table 20)

To address the research questions related to the primary, secondary, and exploratory outcomes, cohorts and subgroups will be created. Additional selection criteria, to form the relevant population for each specific outcome, will be applied (*STEP 4*).

STEP 4 - Cohorts and sub-cohorts

For the purpose of the evaluation of MCM (primary outcome), the *MCM* cohort will be derived from the study populations (Table 5) and will include live and non-live offspring from mothers diagnosed with SLE (regardless of the exposure to anifrolumab, i.e., sub-cohorts *MCM_exp+MCM_unexp).*

For the purpose of the evaluation of mCM (secondary outcome), the *mCM* cohort will be derived from the study populations (Table 5) and will include live and non-live offspring from mothers diagnosed with SLE (regardless of the exposure to anifrolumab, i.e., sub-cohorts *mCM_exp+mCM_unexp).*

For the purpose of the evaluation of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth; primary outcome), and secondary outcomes (adverse pregnancy outcomes), the *pregnancy* cohort will be derived from the study populations (Table 5) and will include pregnant women diagnosed with SLE (regardless of the exposure to anifrolumab, i.e., sub-cohorts *pregnancy_exp+pregnancy_unexp).*

For the purpose of the evaluation of adverse birth outcomes (secondary outcomes), the *birth* cohort will be derived from the study populations (Table 5) and will include live offspring from mothers diagnosed with SLE (regardless of the exposure to anifrolumab, i.e., sub-cohorts *birth exp+birth_unexp*).

For the purpose of the evaluation of adverse outcomes related to infant growth up to one year of age, the *infant* cohort will be derived from the study populations (Table 5) and will include live offspring from mothers diagnosed with SLE (regardless of the exposure to anifrolumab, i.e., sub-cohorts *infant_exp+infant_unexp).*

[9] Several CMs in the mother are due to genetic syndromes/ microdeletions and chromosomal abnormalities which are heritable. These genetic syndromes/microdeletions are also causally associated with the outcomes of interest. The list of these syndromes/microdeletions and chromosomal abnormalities are provided in Appendix D. Exemplar Codelists.

Additional inclusion and exclusion criteria to derive the abovementioned cohorts and sub-cohorts are listed in Table 5.

Table 5: Cohorts and sub-cohorts as described in STEP 4, by objective

Objective	Main features	Input Cohort/ Population	Sub-cohort Abbreviation	Additional criteria to be applied to the input Cohort/ Population
Primary cohort MCM (*MCM_exp+MCM_unexp*)				
Primary objective 1 & 2; Secondary objective 5a-b Exploratory objective 15	Describe and estimate the risk and relative risk of MCM. Describe cohort demographic and clinical characteristics. *Among live and non-live offspring*	***Exposed study population***	***MCM_exp***	INCLUSION: • MCM: Pregnancies exposed to anifrolumab during the first trimester of pregnancy (+16 weeks prior to LMP2) • All pregnancies ending in spontaneous abortion, elective termination of pregnancy and stillbirth, regardless of linkage mother-offspring within the study period • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Adopted children (where information is available)
Primary objective 1 & 2; Secondary objective 5a-b Exploratory objective 15	Describe and estimate risk and relative risk of MCM. Describe cohort demographic and clinical characteristics. *Among live and non-live offspring*	***Unexposed study population***	***MCM_unexp***	INCLUSION: • All pregnancies ending in spontaneous abortion, elective termination of pregnancy and stillbirth, regardless of linkage mother-offspring within the study period • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Pregnancies exposed to anifrolumab during the first trimester (+16 weeks prior to LMP2) (see Section 9.3.1) • Adopted children (where available)

Objective	Main features	Input Cohort/ Population	Sub-cohort Abbreviation	Additional criteria to be applied to the input Cohort/ Population
Secondary cohort mCM (mCM_exp+mCM_unexp)				
Secondary objective 5c-d, 6 & 7;	Describe and estimate the risk and relative risk of mCM. Describe cohort demographic and clinical characteristics. *Among live and non-live offspring*	***Exposed study population***	***mCM_exp***	INCLUSION: • mCM: Pregnancies exposed to anifrolumab anytime during pregnancy (+16 weeks prior to LMP2) • All pregnancies ending in spontaneous abortion, elective termination of pregnancy and stillbirth, regardless of linkage mother-offspring within the study period • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Adopted children (where available)
Secondary objective 5c-d, 6 & 7	Describe and estimate risk of and relative risk of mCM. Describe cohort demographic and clinical characteristics. *Among live and non-live offspring*	***Unexposed study population***	***mCM_unexp***	INCLUSION: • All pregnancies ending in spontaneous abortion, elective termination of pregnancy and stillbirth, regardless of linkage mother-offspring within the study period • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2) (see Section 9.3.1) • Adopted children (where available)
Primary and Secondary cohort *pregnancy_* (*pregnancy_ exp+ pregnancy_ unexp*)				
Primary objective 3 & 4	Describe and estimate risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth), adverse	***Exposed study population***	***pregnancy_exp***	INCLUSION: • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2)

Objective	Main features	Input Cohort/ Population	Sub-cohort Abbreviation	Additional criteria to be applied to the input Cohort/ Population
Secondary objective 5c-d, 8 & 9 Exploratory objective 13 & 14	pregnancy outcomes, separately and as a composite of foetal loss Estimate relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth), adverse pregnancy outcomes, separately and as a composite of foetal loss. Describe cohort demographic and clinical characteristics. *Among pregnant women*			• Ectopic pregnancies (except for ectopic pregnancy outcome)
Primary objective 3 & 4 Secondary objective 5c-d, 8 & 9 Exploratory objective 13 & 14	Describe and estimate risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth), adverse pregnancy outcomes, separately and as a composite of foetal loss. Estimate relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth), adverse pregnancy outcomes, separately and as a composite of foetal loss. Describe cohort demographic and clinical characteristics. *Among pregnant women*	***Unexposed study population***	***pregnancy_unexp***	EXCLUSION: • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2) (see Section 9.3.1) • Ectopic pregnancies (except for ectopic pregnancy outcome)
Secondary cohort *birth* (*birth_exp+ birth_unexp*)				
Secondary objective 5c-d, 10 & 11	Describe and estimate risk of adverse birth outcomes. Estimate relative risk of adverse birth outcomes. Describe cohort demographic and clinical characteristics. *Among live offspring*	***Exposed study population***	***birth_exp***	INCLUSION: • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2) • Pregnancies with linkage mother-offspring within the study time period

Objective	Main features	Input Cohort/ Population	Sub-cohort Abbreviation	Additional criteria to be applied to the input Cohort/ Population
Secondary objective 5c-d, 10 & 11	Describe and estimate risk of adverse pregnancy outcomes. Estimate relative risk of adverse pregnancy outcomes. Describe cohort demographic and clinical characteristics. *Among live offspring*	***Unexposed study population***	***birth_unexp***	INCLUSION: • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2) (see Section 9.3.1) • Adopted children (where available)
Exploratory cohort *infant* (*infant_exp+ infant_unexp*)				
Secondary objective 5c-d; Exploratory 12	Describe and estimate the risk adverse outcomes related to infant growth. Describe cohort demographic and clinical characteristics. *Among live offspring*	***Exposed study population***	***infant_expSLE***	INCLUSION: • Live offspring • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2) • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Adopted children (where available) • Preterm offspring born <37 gestational weeks
Secondary objective 5c-d; Exploratory 12	Describe and estimate the risk adverse outcomes related to infant growth. Describe cohort demographic and clinical characteristics. *Among live offspring*	***Unexposed study population***	***infant_unexpSLE***	INCLUSION: • Live offspring • Pregnancies with linkage mother-offspring within the study time period EXCLUSION: • Pregnancies exposed at any time to anifrolumab (+16 weeks prior to LMP2) (see Section 9.3.1) • Adopted children (where available) • Preterm offspring born <37 gestational weeks

9.3 Variables

Variables used in this study are subdivided into exposure of interest (see Section 9.3.1), outcome parameters of interest (see Section 9.3.2), and participants characteristics and potential confounding variables and risk factors (see Section 9.3.3).

In this protocol, the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) has been used as the coding system for the definition of the outcome variables, other relevant diagnoses, and procedures.

International non-proprietary names are used as nomenclature for prescription drugs. World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system has been 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 statistical analysis plan (SAP).

Appendix D. Exemplar Codelists provides an exemplar list of codes for exposure variables, outcome variables, and other variables for which either ATC codes and/or ICD-10 are used. The list of codes will be finalised in the SAP.

9.3.1 Exposure definition and measures

Study drugs

Exposure to anifrolumab and other SLE SOC drugs (see Table 19) will be ascertained from recordings of outpatient visits, procedures, prescriptions, prescriptions dispensed at community pharmacies, or insurance claims registrations, as available in the different data sources.

According to the drug indication, anifrolumab is expected to be prescribed as an IV infusion as part of polytherapy (i.e., add-on therapy to other SLE SOC drugs). However, due to the long study duration, the method of administration may change over time. Therefore, for the main analysis, the objectives will be evaluated in pregnancies exposed to anifrolumab in the polytherapy setting, regardless of administration route.

Despite that anifrolumab is indicated as an add on therapy, it is possible that some patients, either due to incomplete information on medication or off-label use, anifrolumab may be observed to have monotherapy. Therefore, a sensitivity analysis including anifrolumab exposure both as monotherapy and polytherapy will be performed. Details of this sensitivity analysis is provided in Section 9.7.5.

Drug classes used in SLE SOC include antimalarials, glucocorticoids, immunosuppressants (both synthetic and biologic), immunoglobulins and plasmapheresis (43, 55, 71) (Table 19).

Co-medications (43, 55) (prescription drugs other than SLE SOC drugs in Table 19) are reported in Table 27.

Classification of in utero exposure to SLE drugs and co-medications

The **window of clearance** is defined as 5 times the terminal half-life of the drug for SLE SOC and/or co-medication[10], or, in certain cases, such as biologics, time for concentration to fall below the lowest level of quantification (LLOQ) for 95% of patients. LLOQ is 16 weeks for anifrolumab (2), 14 weeks for belimumab (60) and 15 weeks for rituximab (84).

Particular care will be taken in the definition and classification of *in utero* exposure of the offspring (i.e., through treatment received by the mother during or in the 16 weeks before pregnancy for anifrolumab, 14 weeks for belimumab, 15 weeks for rituximab, and 5-half-lives for other SLE SOC drugs).

Exposure to SLE SOC and/or co-medication (excluding biologics) will be assessed from LMP2 until end of first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for all other outcomes. A look back period of 5-half-lives of relevant drugs will be considered. This is to account for prescription/dispensations/administrations prior to LMP2 that gave rise to *in utero* exposure of the offspring.

SLE SOC and/or co-medications are assumed to be continued throughout pregnancy. It is common for SLE to be more active during pregnancy with a high prevalence of flares (11, 12, 28, 63, 67). The risk of adverse outcomes among pregnant women who have SLE is related to disease severity (e.g., involvement of the kidneys) and activity during pregnancy (29, 39), thus it is expected that SLE treatment would occur even in pregnancy. A sensitivity analysis accounting for actual use of SLE SOC during pregnancy is presented in Section 9.7.5.

Exposure to anifrolumab will be assessed from LMP2 until end of the first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for all other outcomes (see Section 8.1), or until censoring, regardless of duration of exposure. Considering anifrolumab window of clearance (16 weeks, see definition above), all patients who receive prescriptions/dispensations/administrations of anifrolumab in the 16 weeks prior to LMP2 or during pregnancy will be considered exposed (2).

Offspring whose mother had no anifrolumab prescription/dispensations/administration in the 16 weeks prior to LMP2 or during the first trimester for the outcome of MCM, or during pregnancy for all other outcomes, will be considered unexposed.

Although, the foetus is most at risk during the period of organogenesis (i.e., during the first trimester of pregnancy), exposures during other gestational time periods may also be associated with adverse outcomes (e.g., spontaneous abortion, stillbirth, or other pregnancy complications). The identification of critical windows of exposure *in utero* provides clues to possible mechanisms of the pregnancy loss and provides guidelines for protection of the foetus. An exploratory analysis focusing on the effect of *in utero* exposure to anifrolumab in different trimesters of pregnancy on the

[10] The respective half-lives of SLE SOC and co-medications will be provided in the SAP.

occurrence of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth will be assessed:

- **Exposed during pregnancy by trimesters** – *in utero* exposed to anifrolumab will be determined for each pregnancy trimester (dichotomous variables) and combined into a pattern of exposure by trimester (Table 6). The exposure by trimester will be defined as:
    - in each trimester, offspring whose mother had at least one prescription/dispensations/administration of anifrolumab leading to an exposure period overlapping with a specific trimester(s), will be classified as exposed (yes/no) (Table 6);
    - offspring whose mother had no anifrolumab prescription/dispensations/administration in the 16 weeks (anifrolumab window of clearance) prior to LMP2 or during all pregnancy, with the assumption of continuing treatment with SOC, will be classified as non-exposed (yes/no) (Table 6).

Table 6: Maternal exposure status by trimester, offspring *in utero* exposed to anifrolumab (polytherapy) vs offspring *in utero* exposed to SLE SOC

Exposed group				Comparator group		
1st trimester	2nd trimester	3rd trimester		1st trimester	2nd trimester	3rd trimester
anifrolumab (+ SOC)	SOC [1]	SOC [1]	VS	SOC	SOC [1]	SOC [1]
anifrolumab (+ SOC)	anifrolumab (+ SOC)	SOC [1]	VS	SOC	SOC	SOC [1]
anifrolumab (+ SOC)	anifrolumab (+ SOC)	anifrolumab (+ SOC)	VS	SOC	SOC	SOC
SOC	anifrolumab (+ SOC)	anifrolumab (+ SOC)	VS	SOC	SOC	SOC
SOC	SOC	anifrolumab (+ SOC)	VS	SOC	SOC	SOC

Abbreviations used in the table: SOC, Standard of care; VS, Versus

[1] SOC might not be applicable if pregnancy ends early

Definition of exposure period

Women exposed to anifrolumab during pregnancy are included in the exposed groups regardless of the exposure status before pregnancy. The maximum exposure period is from LMP2 to delivery/birth. The maternal exposure period during pregnancy is not considered to be fixed. This is because pregnancy duration is not exactly the same for all pregnancies (full-term birth is considered between 37 to 42 weeks of gestation). Also, exposure period can end earlier with a censoring event (e.g., elective termination of pregnancy).

The definition of exposure period relies on available information on the date of prescription/dispensation/administration, the expected supply (i.e., package size, the number of packages prescribed/dispensed), and the estimated window of drug clearance (for anifrolumab, the time for concentration to fall below the LLOQ for 95% of patients is 16 weeks from last administration). The exposure period starts on the date when the drug was administered or

prescribed/dispensed (if information on the date of dispensation is not available, the start of the exposure period will be defined based on the date when the prescription was issued). The end date of the exposure period is calculated by adding the estimated window of clearance and expected supply to the prescriptions/dispensations/administrations date (Figure 6).

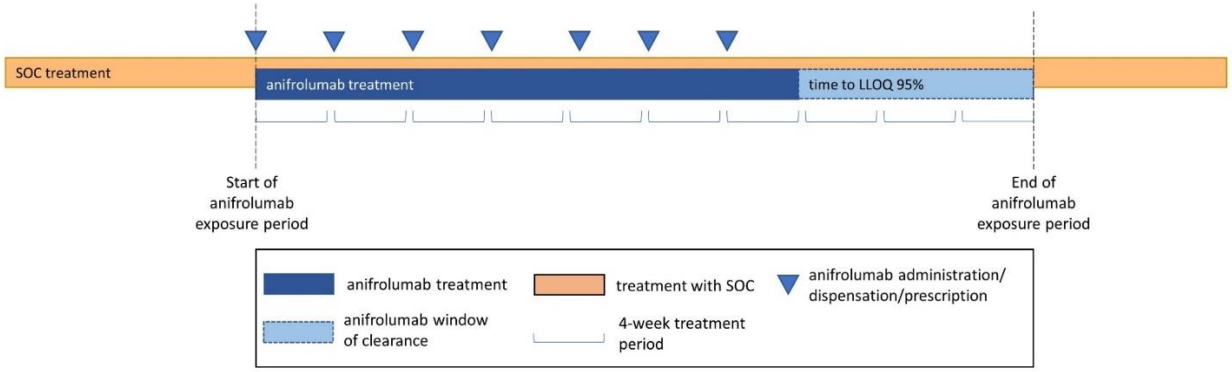

Figure 6: Anifrolumab exposure period

9.3.2 Outcome definition and measures

In line with the study objectives (see Section 8.1), the study's primary, secondary and exploratory outcomes are defined below. Study outcomes will be identified based on the coding system used in the data sources (ICD-10 CM for the USA data sources, ICD-10 for Denmark, Finland and France; MedDRA codes for Germany). ICD-10 codes are provided in Appendix D. Exemplar Codelists.

The maternal death rate in women with SLE as well as the infant death rate of women with SLE are reported to be low and thus, the maternal and infant death rates are expected to be low in this study (21, 99).

Primary outcomes

During the outcome ascertainment period, which will span from the index date to the exit date for each offspring, outcome events will be identified in registers and data sources using ICD-10 or equivalent codes (ICD-10 CM for the USA data sources, ICD-10 for Denmark, Finland, and France; MedDRA codes for Germany). For the primary outcome the **index date/start of follow-up**, included in the enrolment, will be defined as the LMP2 (as defined in Section 9.1) from which the foetus/offspring will be followed up for the outcome of interest. The **exit date/end of follow-up** will be defined as the first of the following: end of the study period, death, emigration (where available), loss to follow-up (disenrollment/de-registering), reaching the age of 1 year or date of first diagnosis of the outcome at study.

MCM (defined as a composite of all major MCMs) among live and non-live offspring: The first primary outcome of interest is MCM occurring in live or non-live offspring. MCM is defined as defects of prenatal origin that have either cosmetic or functional significance to the child's health, development, or survival. MCM ascertainment will be based on the presence of an ICD-10 code (or other database specific coding system [codes to be adapted to the coding systems used in each of the data sources]) in the database. These ICD-10 codes will be classified according to the EUROCAT (Description of the Congenital Anomaly Subgroups in EUROCAT Guide 1.5) classification scheme, as four of the five data sources are in Europe (41). As there are some differences in the classification of MCMs by different classification schemes, the USA CDC definition of MCM as an abnormality of body structure or function that is present at birth, is of prenatal origin (i.e., birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention as implemented by the Metropolitan Atlanta Congenital Defects Program (MACDP) will also be implemented as a sensitivity analysis (see Section 9.7.5) (15, 24). The list of the MCM and their respective ICD-10 codes are presented in Table 22a using the EUROCAT classification. The MACDP 6-digit code defect list for major congenital malformations is presented in Table 22b.

The MCM ascertainment period is defined as:

- for live births, from birth until 1 year of age
- for non-live births (spontaneous abortion and stillbirth) an ICD-10 of MCM as the diagnosis at end of pregnancy
- for elective terminations, an ICD-10 code of an MCM as the reason for the termination at termination of pregnancy.

Select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) among all pregnancies

The second primary outcome of interest is select pregnancy loss outcomes, a composite of spontaneous abortion and stillbirth (Table 24).

For the select pregnancy loss outcomes, the **index date/start of follow-up**, will be defined as the LMP2 (as defined in Section 9.1) from which the pregnancy will be followed until the outcome of interest. The **exit date/end of follow-up**[11] will be defined as the end of the study period, death, emigration (where available), loss to follow-up (disenrollment/de-registering), or date of first diagnosis of the outcome at study, or delivery, whichever is the earliest.

The select pregnancy loss outcomes will be defined as the presence of at least one of the following criteria:

- ICD-10 code of spontaneous abortion [12] (unintended loss of an intrauterine pregnancy) which is less than 22 weeks of gestation for the European data sources (40); less than 20 weeks for the USA data sources (64);
- ICD-10 code of stillbirth [13] (unintended foetal death occurring at or after 22 weeks of gestation for the European data sources (78); at or after 20 weeks for the USA data sources (64).

Secondary outcomes

During the outcome ascertainment period, outcome events will be identified based on ICD-10 CM codes for the USA, ICD-10 for Denmark, Finland and France; MedDRA codes for Germany recorded in patient registries.

Minor congenital malformations

For this outcome the **index date/start of follow-up**, will be defined as the LMP2 (as defined in Section 9.1) from which the foetus/offspring will be followed up for the outcome of interest. The **exit date/end of follow-up** will be defined as the end of the study period, death, emigration (where available), loss to follow-up (disenrollment/de-registering), reaching the age of 1 year or date of first diagnosis of the outcome at study, whichever is the soonest.

[11] Specific outcome censoring rules will be applied. For spontaneous abortion outcome specific end of follow-up will be 22 weeks of gestation for the European data sources or 20 weeks for the USA data sources further details will be specified in the SAP.

[12] The legal requirements and conventional definitions for spontaneous abortion vary by country. The definition used by the data source will be applied. The National Center for Health Statistics (NCHS) and the Center for Disease Control and Prevention (CDC) define spontaneous abortion in the USA as a pregnancy termination before 20 weeks of gestation or a foetus weighing 500 grams at birth. The ICD-10 defines spontaneous abortion as "the loss of pregnancy from natural causes before the 20th week of pregnancy". The WHO defines spontaneous abortion as "termination of pregnancy by expulsion of the embryo or foetus before 22 weeks of pregnancy or below 500 g of weight." The EurPeristat defines spontaneous abortion as the termination of a pregnancy before 22 weeks of gestation.

[13] The legal requirements and conventional definitions for stillbirth vary by country. The definition used by the data source will be applied. Stillbirth is defined as foetal death whose birth weight is of 350 g or more, or if weight is unknown, of 20 completed weeks gestation or more, by the CDC. Stillbirth is defined by the WHO and ICD-10 as the death of a foetus before complete expulsion or extraction from its mother after reaching a birth weight of 500 grams or gestational age of 22 weeks. The EurPeristat defines stillbirth as the death after 22 completed weeks of gestation.

mCM among live and non-live offspring: are a structural anomaly or dysmorphic observable feature which does not impair viability or require intervention or treatment. mCM will be defined as a composite, classified according to EUROCAT (Description of the Congenital Anomaly Subgroups in EUROCAT Guide 1.5) (41). The list of the mCM and their respective ICD-10 codes are presented in Table 23.

Adverse pregnancy outcomes

For the adverse pregnancy outcomes, the **index date/start of follow-up**, included in the enrolment, will be defined as the LMP2 (as defined in section 9.1) from which the pregnancy will be followed up for the outcome of interest. The **exit date/end of follow-up**[14] will be defined as the end of the study period, death, emigration (where available), loss to follow-up (disenrollment/de-registering), or date of first diagnosis of the outcome at study, or delivery, whichever is the earliest. The list of the adverse pregnancy outcomes[15] and their respective ICD-10 codes are presented in Table 24.

- **Spontaneous abortions**[12]**:** unintended loss of an intrauterine pregnancy which is less than 22 weeks of gestation for the European data sources (40); less than 20 weeks for the USA data sources (64);
- **Ectopic pregnancy:** occurs when a fertilised egg implants outside of the uterus, usually in one of the fallopian tubes.
- **Elective termination of pregnancy:** is defined as the intentional termination of pregnancy at any time in gestation for any reason. When possible, reasons for elective termination are captured and classified as elective termination of pregnancy for foetal anomaly or for other reasons.
- **Stillbirth**[13]**:** unintended foetal death occurring at or after 22 weeks of gestation for the European data sources (78); at or after 20 weeks for the USA data sources (64).
- **Composite of foetal loss:** will be defined as the presence of at least one of the following: spontaneous abortion, ectopic pregnancy, elective termination of pregnancy and stillbirth.
- **Infections requiring hospitalisation during pregnancy:** infections requiring hospitalisation during pregnancy will be considered as the occurrence of the first event of a hospitalisation for an infection diagnosis, as primary diagnosis. The list of the infections considered, and their respective ICD-10 codes are presented in Table 24.
- **Emergency caesarean section:** surgical procedure involving the incision of the walls of the abdomen and uterus for delivery of an offspring that occurs when vaginal delivery is

[14] Specific outcome censoring rules will be applied. For spontaneous abortion and ectopic pregnancy there will be outcome specific end of follow-up dates. For spontaneous abortion outcome specific end of follow-up will be 22 weeks of gestation as for the ectopic pregnancy end of follow-up will be 16 weeks of gestation further details will be specified in the SAP.

[15] To maximize the capture of non-live births for spontaneous abortion, elective termination, and stillbirth, an exhaustive list of codes related to pregnancies as well as to outcomes will be used, i.e., every code will be included.

discontinued due to unexcepted complications during labour, such as the occurrence of foetal distress (105).

Adverse birth outcomes

For the adverse birth outcomes, the **index date**, included in the enrolment, will be defined as the delivery/birth date from which the offspring will be followed up for the outcome of interest. The **exit date/end of follow-up** will be defined as the end of the study period, death, emigration (where available), loss to follow-up (disenrollment/de-registering), or 1 day after delivery/birth, whichever is the soonest. The list of the adverse birth outcomes and their respective ICD-10 codes are presented in Table 25.

- **Preterm birth**: defined as live births less than 37 weeks of gestation (<37 weeks)
- **SGA**: is defined as a birth weight lower than the 10th percentile of the distribution of birth weights among live births, by gestational age and sex, using a validated global reference for foetal weight and birthweight (76).

Exploratory outcomes

For the exploratory outcomes, the **index date/start of follow-up** and **exit date/end of follow-up** for MCM will be defined as in Section 9.3.2 MCM will be classified also by body system organ class according to the EUROCAT categories Guide 1.5 (section 3.3 in EUROCAT Subgroups of congenital anomalies) (41).

The full list of ICD-10 codes for MCM of interest can be found in Table 22.

Adverse outcomes related to infant growth up to 1 year of age

For the adverse outcomes related to infant growth, the **index date/start of follow-up**, included in the enrolment, will be defined as birth date from which the offspring will be followed up for the outcome of interest. The **exit date/end of follow-up** will be defined as the end of the study period, death, emigration (where available), loss to follow-up (disenrollment/de-registering), reaching the age of 1 year or date of first diagnosis of the outcome at study, whichever is the soonest.

Infant growth up to one year of age:

- Length (any time point during the first year of life – as available)
- Weight (any time point during the first year of life – as available)
- Head circumference (any time point during the first year of life – as available)

Adverse outcome related to growth up to one year of age will be a dichotomous variable defined as a composite outcome based on the presence of at least one of the following conditions: abnormal head circumference growth, stunting, or wasting. The period of assessment will be during the first year of life and the outcome will be assessed whenever anthropometric measurements are

available. The offspring will be classified as subnormal growth if meeting at least one of the recommended WHO cut off values below at any time during the first year of life (119):

- <-2 SD z-score (equivalent to 2.3rd percentile) of head circumference-for-age based in the WHO 2006 growth charts.
- <-2 SD z-score (equivalent to 2.3rd percentile) of length-for-age to define stunting based in the WHO 2006 growth charts.
- <-2 SD z-score (equivalent to 2.3rd percentile) of weight-for-length to define wasting, based in the WHO 2006 growth charts (119).

9.3.3 Participant's characteristics and potential confounders/risk factors

A broad range of characteristics and risk factors, related to mother and offspring, will be considered. These include, but are not limited to, demographic and clinical characteristics and concomitant comorbidities and medications (Objective 5). The final choice of characteristics, risk factors and confounders will depend on the availability of data and clinical relevance.

- **Demographic characteristics of the live offspring (at birth)**: gender, gestational age, birth weight, Apgar score.
- **Demographic characteristics of mothers with SLE (before or at start of exposure)**: maternal age, maternal socioeconomic status, and maternal ethnicity.
- **Maternal lifestyle characteristics (before or at LMP2)**: smoking prior pregnancy, alcohol abuse prior pregnancy, substance abuse prior pregnancy, maternal weight and height or BMI (kg/m^2) prior to pregnancy.
- **Maternal clinical characteristics**: SLE-related comorbid conditions, SLE SOC, SLE activity algorithm, co-medications (non-SLE SOC), selected autoimmune conditions (**before or at start of exposure**). Pre-pregnancy diabetes, pre-pregnancy hypertension (**before or at LMP2**).
- **Health Care Utilisation (HCU) (before or at LMP2)** in the 12 months prior to LMP2 will be use as proxy of burden of maternal comorbidities: number prenatal visits, number of outpatients and primary care visits, use of emergency department, hospitalisations (number of days, number of hospitalisations), type of health care providers visited.
- **Obstetric history (before or at LMP2)**: gestational diabetes, pre-pregnancy pre-eclampsia, previous spontaneous abortion, previous stillbirth, previous preterm birth, and previous SGA birth.

The list of potential risk factors and confounders for the analysis of *MCM and mCM, adverse pregnancy outcomes and adverse birth outcomes* are summarised below in Table 7, with further details in Table 21. Factors listed as exclusion criteria for the selection of study population are

omitted from the potential risk factors (Table 5). The list of the ICD-10 codes for substance abuse, alcohol abuse, and diabetes, are presented in Table 28, Table 29, Table 30, respectively.

Table 7: Potential confounders/risk factors of risk of MCM and mCM, adverse pregnancy outcomes and adverse birth outcomes in the offspring exposed *in utero* to anifrolumab vs unexposed *in utero* to anifrolumab

	CM	Adverse pregnancy outcomes						Adverse birth outcomes	
	MCM/mCM	Ectopic pregnancy	Spontaneous abortion	Elective termination of pregnancy	Stillbirth	Infections requiring hospitalisation during pregnancy	Emergency C-section	Preterm birth	SGA
Mother									
Age at conception (LMP2)	×	×	×	×	×	×	×	×	×
Socioeconomic status (before or at start of exposure)	×	×	×	×	×	×	×	×	×
Health care utilisation (before or at LMP2)	×	×	×	×	×	×	×	×	×
SLE-related comorbid conditions (before or at start of exposure)	×	×	×	×	×	×	×	×	×
SLE SOC (before or at start of exposure)	×	×	×	×	×	×	×	×	×
SLE activity algorithm (before or at start of exposure)	×	×	×	×	×	×	×	×	×
Autoimmune conditions (before or at start of exposure)	×		×	×	×		×	×	×
Co-medications (non-SLE SOC) (before or at start of exposure)	×	×	×	×	×	×	×	×	×
Smoking (before or at LMP2)	×	×	×	×	×	×	×	×	×
Alcohol abuse (before or at LMP2)	×	×	×	×	×	×	×	×	×
Substance abuse (before or at LMP2)	×	×	×	×	×	×	×	×	×
Gestational diabetes (before or at LMP2)								×	×
Pre-pregnancy obesity (before or at LMP2)	×		×		×		×	×	×
History of pre-eclampsia (before or at LMP2)	×				×				
Pre-pregnancy hypertension (before or at LMP2)	×				×	×	×	×	×

	CM	Adverse pregnancy outcomes						Adverse birth outcomes	
	MCM/mCM	Ectopic pregnancy	Spontaneous abortion	Elective termination of pregnancy	Stillbirth	Infections requiring hospitalisation during pregnancy	Emergency C-section	Preterm birth	SGA
Mother									
Pre-pregnancy diabetes (before or at LMP2)	×		×		×	×	×	×	×
Previous spontaneous abortions (before or at LMP2)	×		×	×	×			×	
Previous stillbirth (before or at LMP2)	×				×				
Previous preterm birth (before or at LMP2)								×	
Previous SGA (before or at LMP2)									×
Offspring									
Year of conception	×	×	×	×	×	×	×	×	×

- Omitted from this list are potential risk factors and/or potential mediators between SLE treatments and CM that are exclusion criteria in this study (as defined in Section 9.2.2):
    - *mother*: history of CM or chromosomal abnormalities and genetic syndromes before delivery and women prescribed a confirmed teratogenic drug (including but not limited to warfarin, angiotensin converting enzyme inhibitors, antineoplastic agents, isotretinoin, misoprostol, or thalidomide), at LMP2 with a look back period of 5-half-lives of relevant drug, to account for prescriptions/dispensations/administrations that may have led to exposure during pregnancy.
    - *offspring*: adopted children.

SLE Severity and Activity Identification

As anifrolumab is currently indicated for moderate and severe SLE, to select a comparable population, only pregnant women with moderate to severe SLE will be included in the main analysis.

Disease severity and activity are not directly obtained from secondary data sources, since validated indices that assess disease severity and activity are not systematically used in routine practice and therefore not recorded in most data sources. In this study, algorithms developed for use in secondary data base studies will be used (50, 66). The algorithm was derived in a USA claims data source (OPTUM) based on literature and clinical consultation. It combines elements of cumulative damage (exemplar code list provided in Table 26) and/or usage of SLE medications (exemplar code list provided in Table 19) based on the Systemic Lupus Erythematosus Disease Index (SLEDAI), Systemic Lupus Activity Measure (SLAM), British Isles Lupus Assessment Group Index (BILAG) indices, and a consensus of expert clinical opinion. The algorithm has been previously used in other settings and validated in the OPTUM research database (106). The validation was performed by comparing the Garris (50) SLE severity algorithm to the highest SLE Disease Activity Index-2000 (SLEDAI-2K) score in 100 patients with SLE treated at Brigham and Women's Hospital Lupus Center (2008–2010), over a 1-year period for each person, using SLEDAI-2K categories of mild (<3), moderate (3-6), and severe (>6). For classifying moderate/severe disease vs. mild, the algorithm has a sensitivity of 85.7%, specificity of 67.6%, positive predictive value (PPV) of 81.8%, and negative predictive value (NPV) of 73.5% (106).
In this study, adaptations, based on expert rheumatologist advice, have been made to the Garris et. al. disease severity algorithm (50, 66, 106). These adaptations are the inclusion of the additional criteria based on IV, intramuscular, intra-articular, and soft tissue glucocorticoid injection, and the prescription of the biologics anifrolumab or belimumab, IV immunoglobulin G or plasmapheresis. For the SLE disease activity algorithm, IV and intramuscular corticosteroid were added to the severe and moderate disease activity. The prednisolone-equivalent dose was modified from 60 mg/day (severity algorithm) and 40 mg/day (activity algorithm) to 20 mg/day for both algorithms (Figure 7 and Figure 8).

The highest SLE severity classification experienced by a patient in the baseline period (maximum look-back period of 12 months prior to LMP2) and highest activity (maximum look-back period of 6 months prior to LMP2 and at the end of each trimester for the adverse birth outcomes) will be assessed using the severity and activity algorithms (Figure 7 and Figure 8). The severity algorithm will be used in the selection of the study population (see Figure 5) and each single component of the severity and activity algorithms will be considered for confounding adjustment.

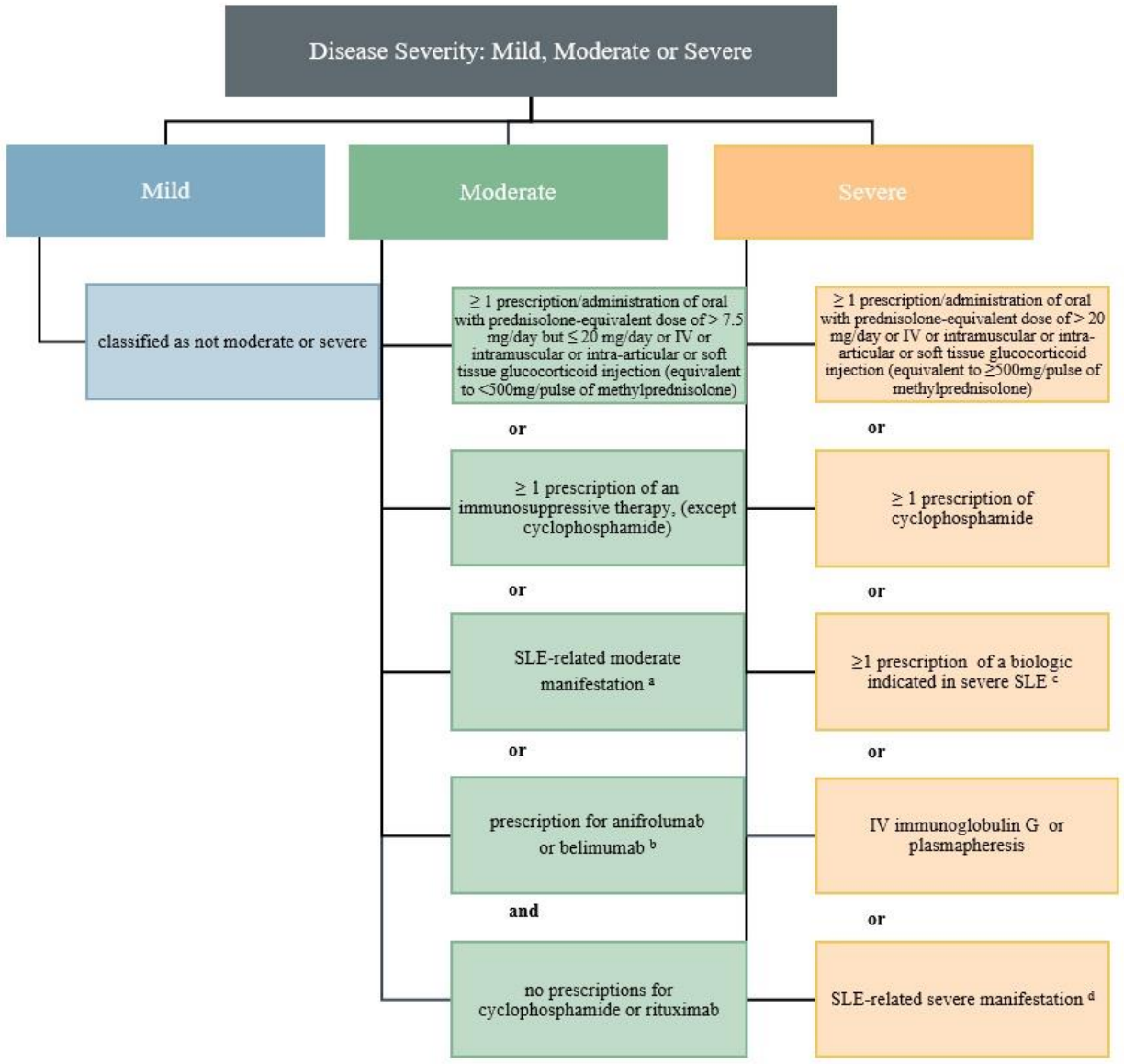

Figure 7: SLE disease severity algorithm[16]

a. SLE-related moderate manifestations: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic 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 reference product and biosimilars)
d. 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 (TIA)

[16] SLE-related manifestations further details are provided in Table 26. Abbreviations: IV, Intravenous; SLE, Systemic lupus erythematosus.

Periods of increased disease activity (flares, Figure 8) are categorised as mild, moderate and severe (66), if meeting one or all of the following criteria (Figure 8), and will be assessed as the highest disease activity experienced by a patient in the baseline period (maximum look-back period of 6 months prior to LMP2). Periods of increased SLE disease activity will also be assessed at the end of each trimester for the adverse birth outcomes. Other markers of disease activity will be retrieved whenever available: results of complements (C3, C4) (5, 43) or anti-double stranded DNA (anti-dsDNA) (43).

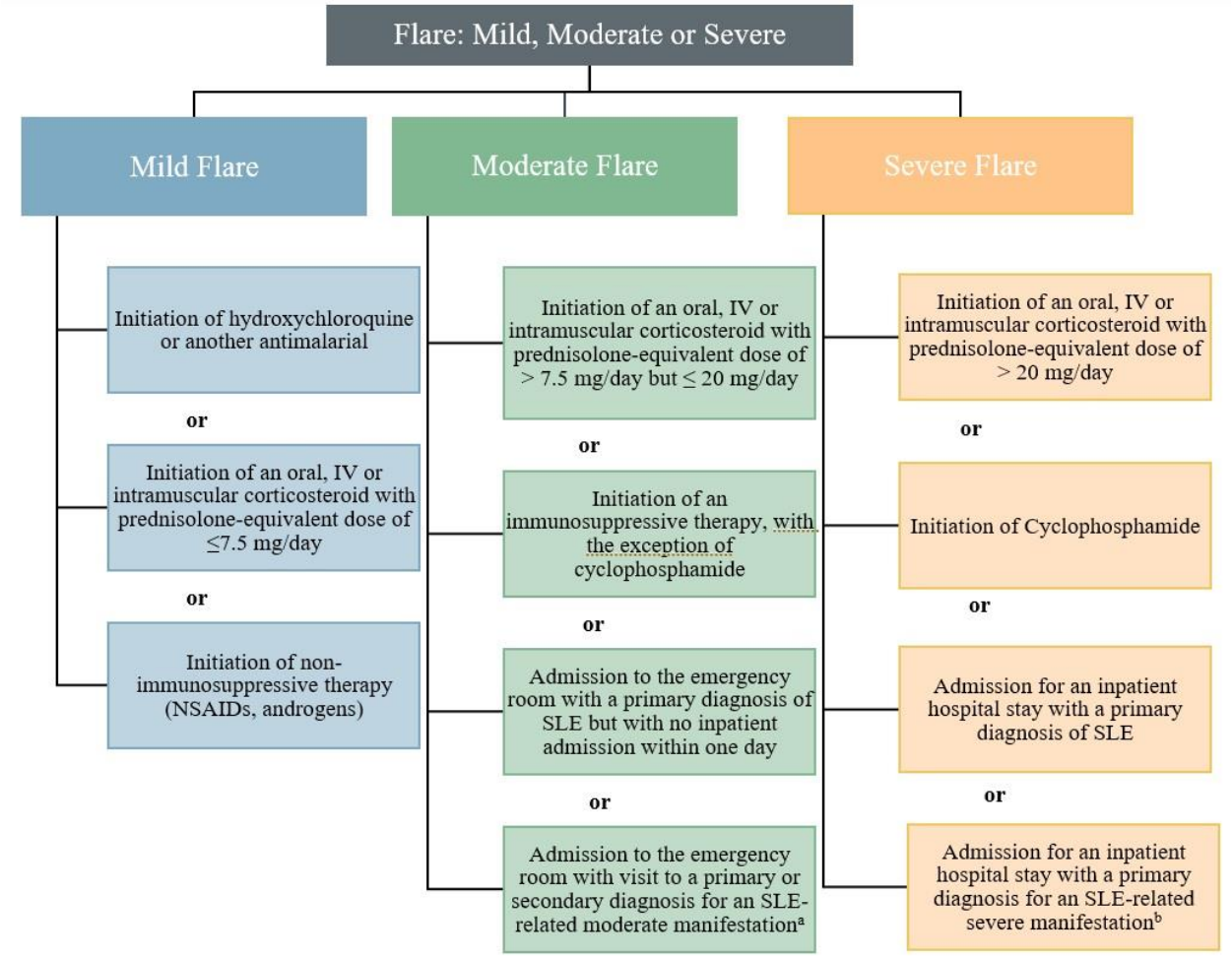

Figure 8: SLE disease activity algorithm[17]

a. SLE-related moderate manifestations: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic 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)

[17] SLE-related manifestations further details are provided in Table 26. Abbreviations: IV, Intravenous; NSAIDs, Non-steroidal anti-inflammatory drugs; SLE, Systemic lupus erythematosus.

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/TIA

Additional considerations

Exposure to co-medications. *In utero* exposure (16 weeks prior to LMP2 to account for prescriptions/dispensations/administrations that may have led to exposure during pregnancy) to co-medications (122) (provided in Appendix D. Exemplar Codelists) will be assessed and considered for confounding adjustment.

Exposure to co-medications will be ascertained from recordings of outpatient visits, procedures, prescriptions, prescriptions dispensed at community pharmacies and insurance claims registrations as available in the different data sources. Co-medication will be identified using ATC codes (provided in Table 27). The list of co-medication of SLE-related comorbidities was based on literature (43, 55) and complemented by clinical experts' recommendations. The availability of information on exposure was explored as part of the feasibility assessment.

Exposure to co-medications in the 16 weeks prior to LMP2 will be investigated and considered as a risk factor for the primary and secondary outcomes. A polypharmacy index will be created. There is no consensus definition of polypharmacy (72). In this study, polypharmacy will be considered as a continuous variable, reflecting the cumulative number of the prescribed medications from other therapeutic classes (other than those specified for the treatment of SLE described in Section 9.3.1), within an interval of interest. This polypharmacy index will be considered for confounding adjustment. The rationale for considering polypharmacy as a potential risk factor is based on some evidence that polypharmacy may be associated with adverse events during pregnancy. Factors which may contribute to the foetal risk in polypharmacy include the pathophysiology of the underlying co-morbid conditions, adverse drug effects and the potential for drug-to-drug interaction (72, 111). In addition, polypharmacy may be an indication of severity of disease, with SLE manifestations in multiple organ systems requiring treatment (102).

Maternal age at conception. Maternal age at conception is considered a major risk factor for the studied outcomes. Multiple epidemiological studies have found a relation between advanced maternal age at conception and congenital malformations (57), adverse pregnancy (46), birth and infant outcomes (52). Although maternal age is not directly associated to the exposure of interest, it is associated with the severity of the disease and with the selected outcomes, thus this variable will be considered for confounding adjustment.

Gestational age. Is measured from the first day of the LMP and expressed in weeks and days, completed weeks, or in days. Gestational age is usually calculated from the reported LMP (depends on recall of the LMP and assumes that ovulations occurred on average 2 weeks after LMP). If gestational age is calculated from LMP, 2 weeks will be added to the time interval to estimate the conception date (LMP2). For data sources in which the LMP is missing, date of conception (equivalent to LMP2) will be estimated based on date of birth and gestational age at birth. In

countries where gestational age is calculated from conception, gestational age (in days) will be subtracted from the date of birth to obtain the date of conception.

Foetal biometric measures from ultrasounds are increasingly being used to confirm or adjust LMP. Current recommendations from the American College of Obstetricians and Gynaecologist, the Society for Maternal-Foetal Medicine, Euro-Peristat Network recommend use of the best obstetric estimate rather than LMP alone. Hence, in Europe, and USA, estimate of gestational age is based on ultrasound dating, and rarely based on LMP alone due to reporting errors (23). Thus, gestational age will be assessed using the best obstetric estimate available. Gestational age is rarely available for ectopic pregnancies or miscarriages.

9.4 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 four SLE specific registries (SLE Registry Germany, Spanish Society of Rheumatology systemic lupus erythematosus registry [RELESSER], OM1 Lupus Registry and The Systemic Lupus Erythematosus International Collaborating Clinics [SLICC]) were assessed in the feasibility assessment. Of these data sources, six were selected: Carelon Research (USA), DAPI (USA), Finnish National Registries, Danish National Registries, SNDS (France), RHEKISS (Germany). A summary of the rationale for inclusion/exclusion of each data source evaluated in the feasibility assessment is presented in Table 14 of Appendix C. 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 following information were collected on 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 pregnancies occurring in SLE patients
- Estimate of number of pregnancies in SLE patients who were prescribed anifrolumab in the preceding 12 months (applicable for USA data sources only)

As anifrolumab was granted market authorisation in the EU in 2022 and approved in the USA in 2021, information on the availability of anifrolumab use is limited or 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 when it becomes available in the respective countries.

Considering the estimated sample size required for this study, it is estimated that the selected data sources will provide a sufficient sample size to address the research questions (see Section 9.5). 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.

9.4.1 Overall description of the databases

9.4.1.1 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 lag time of approximately 2 months. However, the study requires linkage to socio-economic registers, 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.

- **The 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 civil registration 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.

- **The National Health Insurance Service Register**

The National Health Insurance Service Register (*Sygesikringsregisteret* [NHISR]) records information on services supported by public health insurance and provided by general practitioners 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 (available in other registers). Data is available from 1990 onwards.

- **The Danish Register of Medicinal Product Statistics**

The Danish Register of Medicinal Product Statistics (*Lægemiddelstatistikregisteret* [RMPS]) holds patient-level data on all prescription drugs dispensed via 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 a 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.

- **The 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 may not be complete from the early years (may have some missingness).

- **The 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 register 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 adaption of the ICD-10), examinations and treatment information - including surgery coded with Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures (Nordisk Medicinal-Statistisk Komité [NOMESCO]) codes, as well as supplementary information regarding births.

- **The Register of Laboratory Results for Research**

Information on laboratory tests at the country's large clinical biochemical and clinical immunological laboratories is collected in the National Laboratory Database daily. Tests performed in general practice and sent to a hospital laboratory for analysis are also included. This information is transferred to the Register of Laboratory Results for Research (RLRR). If a patient, has proactively denied consent to exchange lab results, then the results are not transferred to the RLRR. Two types of tests are included: a) analysis of blood, urine, joint fluids and spinal fluids for the purpose of preventing, diagnosing and controlling the treatment of human diseases; b) blood type determination and examination of blood e.g., pregnancy, immune disorders and certain infections. The register contains information on type of test, value, unit and date of sampling. Data from the five regions in Denmark has gradually been included in the register since late 2013. In addition, some historical data from before 2013 has also been transferred to the register.

Completeness is not reported but expected to be high. The RLRR is estimated to have reached 100% coverage by 2020. Only laboratory tests encoded with Nomenclature for Property and Unit (NPU) terminology are transferred from National Laboratory Database to the RLRR (currently approximately 95% of all laboratory tests). RLRR is updated weekly from the National Laboratory Database.

- **The Danish Medical Birth Registry (MBR)**

The Danish Medical Birth Registry (MBR) contains data on all live and stillbirths in Denmark since 1973. The registry contains high validity data on the actual birth, the outcome of the birth and whether there were complications during labour. The registry also includes information about the parents, including their municipality of residence, and their civil status and CPR numbers.

The MBR consists of a main table with index pregnancy (one line for each infant in the same pregnancy) as the key identifier and information on the identity on both parents by CPR number, diagnosis (ICD-10 codes) and possible complications, potential risk factors and number of prenatal visits. Any congenital abnormalities are retrospectively added to the table if identified within the first year of life. All subsequent health events reported by diagnoses and surgical interventions can be found in the NPR. All deaths of mother or infant within the first 365 days after delivery are registered including the age in days when the infant died.

- **The Danish Cause of Death Register (CDR)**

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 CDR. Date of death is available from 1970 onwards. The register is updated once a year after end of December with a lag of approximately 13 months.

- **The 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 end of December.

Study-specific data availability

The estimated annual number of pregnancies in women with SLE eligible for the MCM analysis and the select pregnancy loss outcomes analysis is 12 and 16, respectively (see Section 9.5.1 and Table 9).

Mother-offspring linkage is available since 1973, and all live births and stillbirths after 22 weeks of gestational age can be linked. This linkage is achieved using a deterministic approach.

Anifrolumab received marketing authorisation in Denmark in February 2022 and had a market launch in March 2022 (Table 4). It is provided to patients without any additional out of pocket costs. In Denmark, it is assumed that anifrolumab would be captured in SMR as it is administered at the hospital and administration of belimumab was captured in the registry.

Information on drugs dispensed through retail pharmacies (captured in the RMPS since 1995), drugs prescribed in hospital or in other institutional care (captured in the RMPS) and drugs administered in hospital (captured in the SMR since 2018) are available. ATC codes and Danish brand names enable the distinction between biologics.

All study outcomes of interest are available or partially available (Table 16), as well as maternal characteristics, other baseline characteristics and covariates (Table 17).

9.4.1.2 Finland

- **The Finnish Population Information System**

Every permanent resident of Finland (resident for at least one year) has a unique personal identity number (PIN). All national registers described below, record information using this unique number. This enables linkage of the different registers when permitted by patient consent or local regulation. The PIN is assigned by the Finnish Population Information System which is maintained by the Digital and Population Data Services Agency. The registry collects basic demographic information (age, sex, area of residence, date of death), sociodemographic characteristics, and migration. The registry data has been saved in an electronic format since 1971. Monthly updates are available, and the lag time is one month.

- **The Care Register for Health Care**

The register holder of the Care Register for Health Care (HILMO) is the Finnish Institute for Health and Welfare (THL). The data are available from 1994. HILMO contains data on both in- and outpatient secondary care. It has information on hospitalisation duration, diagnoses (ICD-10 codes), medical procedures, emergency room visits, and type of admission. HILMO also has data on day surgeries, patients discharged from inpatient care, number of patients in inpatient care in health centres and hospitals. However, there is no data available on hospital administered medication, which is captured in the electronic medical records. The reporting delay time is nine months. Therefore, the data from a given year is released for research in September of the following year.

- **The Register of Primary Health Care Visits**

The register holder of the Register of Primary Health Care Visits (AvoHILMO) is THL. The data are available from 2011 and occupational health and private sector were added in 2019. This register includes data from healthcare centres and institutions providing primary healthcare. Data on the time and place of the primary healthcare visits, reason for visit/diagnose (ICP-2 codes) and

procedures are recoded. The reporting delay time is nine months. Therefore, the data from a given year is released for research in September of the following year.

- **The Finnish National MBR**

Finnish national MBR is managed by THL and has data since 1987. The register contains data on all birth events, both live and stillborn in Finland with birth weight of at least 500 grams and gestational age of at least 22 + 0 weeks. Information on the mother, the infant and the course of pregnancy is also collected e.g., maternal diagnoses (ICD-10 codes), details of parturition, previous pregnancies and deliveries, infants' weight and height. Data on infants is collected until day seven. Since 2004, there is also a data file on small preterm infants that contains additional information of all live births in Finland with a birth weight of less than 1501 grams or gestational age less than 32 + 0 weeks. Data is collected to this data file until infant's age corresponds to 42 weeks' gestation. The registry has a lag time of around six months and new data is released annually in the summer.

- **The Register of CMs**

Register of CMs is managed by THL and has data since 1963. The register contains data on children who have been diagnosed with at least one major congenital chromosomal or structural anomalies. There is also data on other congenital anomalies such as congenital hypothyroidism and teratomas, detected or suspected in stillborn and live born infants and foetuses. Data on autopsy and other examinations are collected as well. Anomalies are recorded in accordance with the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) guidance and ICD-10 codes. The congenital anomalies are recorded and followed during the first year of the child. The current lag time is three years, but the data holders have plans to reduce the lag time to two years.

- **The Register on Induced Abortions**

Register on Induced Abortions is managed by THL and has data since 1983. Data on all legally done induced abortions in Finland is collected. Healthcare units performing the procedures are mandated by law to report abortions. The variables recorded include grounds for the induced abortion, duration of pregnancy and method of termination and other practices. The register also collects data on the mother, such as number of previous pregnancies and method of contraception. The data from the previous year is available in November-December of the following year.

- **The Cause of Death Register**

The Cause of Death Register is managed by the Statistics Finland since 1971. It contains data on demographics, cause of death (ICD-10 codes) and time of death of all permanent residents in Finland. The complete data is collected from death certificates and the data from the previous year is available in January next year. The date of death is available earlier with a 5-month lag time.

- **The Prescription registers**

In Finland, there are 2 different prescription registers, the traditional prescription register and the e-prescription register. The traditional prescription register is managed by the Social Insurance Institute and has data since 1994. It covers only dispensed, reimbursed drugs. The e-prescription register is also held by Social Insurance Institute but managed by THL. The e-prescription register was founded in 2010 and electronic prescriptions became mandatory for all healthcare sectors in 2017. It covers all dispensed prescribed drugs (reimbursed and non-reimbursed). The variables include e.g., date of purchase and trade name, ATC code. Strength and package size of the drug product can be requested from the e-register.

- **The Finnish Electronic Medical Records**

Finnish Electronic Medical Records (EMRs) contain most of the specialist health care in their region. The research data is obtained from the hospitals' electronic patient records by using extraction of structured data and/or text mining. Start date for data collection varies between wellbeing services counties. The three biggest districts are Hospital District of Helsinki and Uusimaa (1,7 million residents in this region), Wellbeing services county of Pirkanmaa (500,000 residents), and Wellbeing services county of Southwest Finland (almost 500,000 residents). The Hospital District of Helsinki and Uusimaa is responsible for arranging secondary care in the Uusimaa region. Variables that are recorded in the hospital districts' EMR depends on which county is selected. Most of them include diagnosis, procedures, clinical notes, laboratory test results and hospital administered medication. Data lag time depends on the county which needs to be selected for the studies. EMR data is linkable to other Finnish data sources and can be applied for with the same data permit as other data sources.

- **Statistics Finland**

Statistics Finland collects demographic, socioeconomic, including educational level data of the Finnish population.

Study-specific data availability

The estimated annual number of pregnancies in women with SLE eligible for the MCM analysis and the select pregnancy loss outcomes analysis is 10 and 12, respectively (see Section 9.5.1 and Table 9).

Mother-offspring linkage is available since 1987, and all live births and stillbirths after 22 weeks of gestational age or with a birth weight over 500g can be linked. This linkage is achieved using a deterministic approach.

Anifrolumab received marketing authorisation in Finland in February 2022 but has not yet had a market launch. Finland´s wellbeing counties have their own or a combined procurement agreement for hospital administered drugs. In this procurement agreement, it is decided which specific products will be used for that specific procurement period. If the drug (e.g., anifrolumab) is listed in the procurement agreement, it will be provided to patients without any additional out of pocket costs.

In Finland, information on drugs prescribed in hospital or in other institutional care and drugs administered in hospital or in other institutional care are available with possible unavailability in case of small patient counts (<5). In Finland, prescriptions and dispensing of oral and subcutaneous (SC) biologics are available from prescription registers, hospital administered medication, including anifrolumab, are available from EMRs. ATC codes will allow the distinction between biologics.

In Finland, all study outcomes of interest are available or partially available (Table 16), as well as maternal characteristics, other baseline characteristics and covariates (Table 17).

9.4.1.3 France

The French National Health Data System (Système National des Données de Santé (104) is the largest and most comprehensive healthcare dataset available in Europe. It covers 99% of the French population, approximately 66 million patients (9). 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. The SNDS is composed of:

- 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]).

These databases can be linked by a unique patient identifier (104).

Since 2008, SNIIRAM includes the outpatient reimbursed health expenditures (*données de consommation interrégimes* [DCIR]) which allows studying consumption of care. Data from DCIR (outpatient care) and PMSI (inpatient care) can be linked for follow-up across different settings of care including outpatient practice and hospital admissions related to administration of medications, surgery, and obstetrics.

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) (9). Information on occupational diseases and sick leaves are also available (104).

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 availability

The estimated annual number of pregnancies in women with SLE eligible for the MCM analysis and the select pregnancy loss outcomes analysis is 178 and 223, respectively (see Section 9.5.1 and Table 9).

Mother-offspring linkage is available since 2012, and all live births and stillbirths can be linked (10). This linkage is achieved using a deterministic approach.

In France, anifrolumab received marketing authorisation in February 2022 and entered the market in April 2022 (Table 4).

In France, reimbursed drugs dispensed through retail pharmacies are available. 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 use is available until the end of September 2022, when the last product was withdrawn from the market. Data on biologics is available from 2008 for outpatient (DCIR) and inpatient (PMSI) settings. For hospital administered drugs, only expensive drugs are captured in SNDS. Rituximab and immunoglobulin G – administered as IV in the hospital sector – are available as they are part of the list of high-cost drugs. Exposure to anifrolumab can only be captured provided it is among the high-cost drug list. Anifrolumab was on the high-cost drug list from 28 June 2021 to 12 May 2022 and was thus captured during that period. Health authority assessment procedures to determine reimbursement approach for anifrolumab is currently ongoing. The suitability of France as a data source, will be re-evaluated when a decision on reimbursement has been made, as this will influence the ability of SNDS to capture the exposure of interest.

In France, all study outcomes of interest are available or partially available (Table 16), as well as maternal characteristics, other baseline characteristics and covariates (Table 17).

9.4.1.4 Germany

Rheuma-Kindwunsch und Schwangerschaft (RHEKISS)

The nationwide register RHEKISS has been recording the course and outcome of pregnancies in patients with a confirmed diagnosis of an inflammatory rheumatic disease since 2015 (74). Patients can be included either when they wish to have children or in early pregnancy (up to 20 week of pregnancy). The aim of the register is to collect data on the course of the auto-inflammatory diseases before, during and after pregnancy and to collect information on anti-rheumatic drug therapies during pregnancy.

RHEKISS is a prospective observational cohort study. At baseline, socio-demographics, prior pregnancies, comorbidities, treatment, disease activity and severity as well as antibody status are reported. During pregnancy, rheumatologists and patients report drug treatments, course of the maternal disease, development of foetus and complications once per trimester. After delivery, the pregnancy outcome and child development during the first two years of life are collected (45).

Data includes:

- Therapy before conception, during pregnancy and after birth
- Course of the rheumatic disease before conception, during pregnancy and after birth
- Complications in pregnancy
- Outcome of the pregnancy
- State of health of mother and child at and after birth
- Child development in the first two years of life
- The observation period is a maximum of 5 years if inclusion occurs when the patient wishes to have children

RHEKISS is a joint project of the German Rheumatism Research Center Berlin and the Rheumatism Center Rhein-Ruhr e.V., Düsseldorf. Around 150 internal rheumatologists contribute to RHEKISS.

Study-specific data availability

Estimated annual number of pregnancies in women with SLE eligible for the MCM analysis and the select pregnancy loss outcomes analysis is 10 and 13, respectively (see Section 9.5.1 and Table 9).

In RHEKISS, mother and infant data are reported and recorded simultaneously, mother-offspring linkage is inherent in the data collection mechanism.

In Germany, anifrolumab received marketing authorisation in February 2022 and entered the market in March 2022 (Table 4). Reimbursement for anifrolumab was granted from April 2022 onwards.

In RHEKISS, both reimbursed and non-reimbursed drugs prescribed for outpatient use are available and over the counter drugs, taken by patients, are partially available. All anti-rheumatic drug treatments, including anifrolumab, are captured regardless of care setting. Data on biologics (including belimumab) is available since 2015 through rheumatologist reports.

In RHEKISS, all study outcomes of interest are available or partially available (Table 16), as well as maternal characteristics, other baseline characteristics and covariates (Table 17).

9.4.1.5 The United States of America

Carelon Research (formerly known as HealthCore Integrated Research Database - HIRD)

Carelon Research is a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. Carelon Research contains a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from one of the largest commercially insured populations in the USA drawn from nearly 73 million unique individuals with medical coverage and nearly 59 million with medical and pharmacy claims information. Member enrolment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and healthcare utilisation may be tracked for health plan members in the database dating back to January 2006, and with diagnoses recorded in ICD-10 since October 2015.

The HealthCore Integrated Research Environment will be used to link the claims data in Carelon Research to complementary data sources including, but not limited to, inpatient and outpatient medical records, national vital statistics records (e.g., National Death Index for date and cause of death), and disease registries.

Study-specific data availability

The estimated annual number of pregnancies in women with SLE eligible for the MCM analysis and the select pregnancy loss outcomes analysis is 112 and 179, respectively (see Section 9.5.1 and Table 9).

Mother-offspring linkage is available since 2006, and approximately 73% of live births can be linked. This linkage is achieved using a deterministic approach.

In the USA, anifrolumab received FDA approval in July 2021 and entered the market in August 2021.

In Carelon Research, information on drugs dispensed through retail pharmacies is available. In outpatient and inpatient settings, data on drugs taken by oral route may not be available, whereas data on drugs administered as a procedure would be available via procedure codes. Additionally,

data on administered drugs may be captured via abstraction from requested medical records (available for a subset of patients) or asked via a patient survey.

In Carelon Research, all study outcomes of interest are available or partially available (Table 16), as well as maternal characteristics, other baseline characteristics and covariates (Table 17).

Optum Dynamic Assessment of Pregnancies and Infants (DAPI)

The Optum DAPI is sourced from a large proprietary administrative health care claims research database that covers members of a large national health insurer affiliated with Optum. The database contains medical and pharmacy claims, outpatient clinical laboratory results, socioeconomic measures, and patient enrolment data, dating back to 1994. The DAPI and Carelon Research databases draw from different insurance providers. Therefore, duplications could occur in instances where a patient is covered by both insurers (as primary or secondary), in which case the duplicate will be identified by hashing identifiers or linkage. However, duplication of data on events will not be expected as patients will be sourced from claims, which are derived from different insurance providers.

Within the Optum data source, these administrative claims data can be used to identify pregnancies and link the health care data of mothers with that of their infants. Data of mothers and infants is linked through a family identifier and by matching the dates of delivery and infant's birth. The fraction of identified deliveries that cannot be matched to an infant is likely due to the infant being carried under a different health insurance from the mother, in other instances, this is due to pregnancies that did not end in a delivery. Because the linkage is made within an identifiable health insurance database affiliated with Optum, Optum can (with appropriate approvals) access medical records for mothers or infants to ascertain covariate information and/or to confirm outcomes.

Study-specific data availability

The estimated annual number of pregnancies in women with SLE eligible for the MCM analysis and the select pregnancy loss outcomes analysis is 125 and 178, respectively (see Section 9.5.1 and Table 9).

Mother-offspring linkage is available since 1994 and 85% of live births can be linked. This linkage is achieved using a deterministic approach.

In the USA, anifrolumab received FDA approval in July 2021 and entered the market in August 2021.

In DAPI, information on drugs dispensed through retail pharmacies is available. In outpatient and inpatient settings, data on drugs taken by oral route may not be available, whereas data on drugs administered as a procedure would be available via procedure codes.

In DAPI, all study outcomes of interest are available or partially available (Table 16), as well as maternal characteristics, other baseline characteristics and covariates (Table 17).

Table 8: Summary of data sources and countries for this study

Country	Start of data availability	Coverage	Number of pregnancies in women with moderate to severe SLE per year[1]	Data lag (months)	Availability of exposure		Availability of outcomes				Rationale for the decision
					Anifrolumab[2]	SOC	CM[3]	Adverse pregnancy outcomes[4]	Adverse birth outcomes[5]	Infant growth outcome	
Denmark (National Registers)	Between 1970 and 2018[6]	100%	20	2-13	Available	Available	Available	Available	Available	Partial: - Length and weight are captured in the Children Database - No data on development available except for specific diagnoses	- Ability to capture anifrolumab exposure and primary outcomes
Finland (National Registers)	Between 1961 and 2019[6]	100%	16	1-24	Available	Available	Available	Partial: - Infections requiring hospitalisation during pregnancy	Available	Partial: - Height and weight might be available from HILMO and AvoHILMO	- Ability to capture anifrolumab exposure and primary outcomes
France (SNDS)	2008 (DCIR) 2006 (PMSI)	98.9%	263	12	Partial: - Only pen formulation of Belimumab delivered in retail pharmacies are captured. - Only hospital administered drugs listed as high-cost drugs are captured	Partial: - Vocosporin and mepacrine not available - Only hospital administered drugs listed as high-cost drugs are captured	Available	Partial: - Spontaneous abortion - Elective termination of pregnancy	Available	Partial: - Data on infant development is not available	- Ability to capture anifrolumab exposure (if included in the list of high-cost drugs) and primary outcomes[7]
Germany (RHEKISS)	2015	NA[8]	25	No	Available	Available	Available	Available	Available	Available	- Ability to capture anifrolumab exposure and primary outcomes

Country	Start of data availability	Coverage	Number of pregnancies in women with moderate to severe SLE per year[1]	Data lag (months)	Availability of exposure		Availability of outcomes				Rationale for the decision
					Anifrolumab[2]	SOC	CM[3]	Adverse pregnancy outcomes[4]	Adverse birth outcomes[5]	Infant growth outcome	
USA (Carelon Research)	2006	7%[9]	225	3	Available	Available	Available	Available	Available	Available	- Ability to capture anifrolumab exposure and primary outcomes - Number of pregnancies captured
USA (DAPI)	2007	4%[10]	223	3-6	Available	Available	Available	Available	Available	Partial: - May be extracted from medical records for subset of patients	- Ability to capture anifrolumab exposure and primary outcomes - Number of pregnancies captured

Abbreviation used in the table: NA, Not available; CM, Congenital malformation; SOC, Standard of care; SLE, Systemic lupus erythematosus; UK, United Kingdom; USA, United States of America; MCM, Major congenital malformation; mCM, minor congenital malformation; ICD-10 GM, International Classification of Diseases 10th Revision German Modification; SGA, Small for gestational age; DCIR, Données de Consommation Inter-Régimes; PMSI, Programme de médicalisation des systèmes d'information

[1] Estimates for the annual number of pregnancies in women with SLE was directly provided by Carelon Research, DAPI and RHEKISS. For the other data sources, an estimate for the annual number of pregnancies in women with SLE was computed (see Section 9.5.1).
[2] Exposure to anifrolumab was based on the availability/information of biologics (in general) and belimumab (Benlysta) as a proxy for utilisation of anifrolumab.
[3] Refers to major and minor congenital malformations.
[4] Refers to ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, and caesarean section.
[5] Refers to preterm birth and small for gestational age.
[6] Varies by the component registers.
[7] Only high-cost hospital administered drugs are captured in SNDS. Therefore, exposure to anifrolumab can only be captured provided it is among the list of high-cost drugs.
[8] RHEKISS is a nationwide, multi-centre registry for pregnancies in rheumatology and includes rheumatologist and patient reported data in the form of electronic case reports. As of July 2022, the registry includes 1907 patients (about 270 patients per year from 2015 onwards).
[9] Approximately 20% of USA population (75 million) have ever been recorded by Carelon Research, and approximately 7% of USA population (21 million) are actively enrolled.
[10] Approximately 21% of USA population (70 million) have ever been recorded by ORD, and approximately 4% of USA population (13 million) are actively enrolled.

9.5 Study size

In this study, both sample size and power calculations were calculated separately for each of the primary outcomes (MCM and select pregnancy loss outcomes) at the meta-analysis level. The assumptions and methods used for the sample size and power calculations are introduced in Section 9.5.1. In the sample size estimation, the minimum required sample size to achieve 80% power to rule out a target threshold risk ratio (RR) of 2.5 at the meta-analysis level was calculated (see Section 9.5.2). For the power calculations, the expected power to rule out a target threshold RR of 2.5 at the meta-analysis level was computed based on the expected number of exposed pregnancies in the data sources during the planned study period (see Section 9.5.3).

9.5.1 Assumptions and methods for the sample size and power calculations

In this study, the number of SLE pregnancies in the data sources were estimated using the reported annual number of SLE pregnancies obtained from the feasibility assessment. In data sources where this was not available, it was estimated based on the number of annual live births captured by the data sources (details are provided in Section 9.5.1.2)

From the total number of SLE pregnancies, the number of anifrolumab exposed pregnancies and the expected number of primary study outcome events in moderate-to-severe SLE women that would be eligible for the study were estimated using assumptions on the primary study outcome prevalence and the proportion of patients expected to fulfil the inclusion criteria for the study.

Only the data sources where at least one primary study outcome (MCM or select pregnancy loss outcomes) event is expected to be observed would be considered for the meta-analysis. Using the data sources expected to contribute to the meta-analysis, the minimum required sample size to rule out a threshold RR for primary study outcomes with 80% power was calculated. In addition to the required sample size calculation, power calculations to rule out a threshold RR for the primary study outcomes using the estimated number of anifrolumab exposed SLE pregnancies in the data sources expected to contribute to the meta-analysis were performed. Further details on the assumptions used for the calculations are provided in the following sections.

9.5.1.1 Assumptions used for the sample size and power calculations

To estimate the number of anifrolumab exposed SLE pregnancies and the expected number of primary study outcome events in data sources that would be eligible for the analysis in this study, the following assumptions were used:

- **A prevalence of 7% for MCM outcome.** Prevalence of MCM in pregnancies in women with moderate-to-severe SLE was estimated based on a literature search. Among moderate/severe SLE patients exposed to belimumab, birth defect prevalence estimates of 5.6% to 21.7% were observed in post hoc summary of clinical studies and a prospective

pregnancy registry, respectively (86) A prevalence of 6.4% of congenital malformations was observed in renal SLE pregnancies (51) These proxy estimates of MCM in moderate-to-severe SLE align with the observed population based prevalence estimates ranging from 7.4% to 13.6% (114) among women diagnosed with SLE (117).

- **A prevalence of 20% for the composite of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth).** Prevalence of the composite outcome of select pregnancy loss (spontaneous abortion and stillbirth) in moderate-to-severe SLE pregnancies ranged from 15.3% to 30% (51, 81, 86). For the individual outcomes, the prevalence estimates ranged from 1.8% to 3.7% for stillbirths (51, 103, 120), and the prevalence estimate was 16% (12.1% to 19.9%) for spontaneous abortions (103). Based on the intended objective to evaluate embryo-foetal loss, a composite outcome of spontaneous abortion and stillbirth has been used.
- **Proportion of SLE pregnancies occurring in women with moderate-to-severe disease of 50%.** There is limited information on the proportion of SLE pregnancies that occur in women with moderate-to-severe disease. The proportion of moderate-to-severe disease at the time of diagnosis among the general SLE population is estimated to be 50% (66, 80). Literature regarding medication patterns for SLE pregnant women suggests that 40-45% use immunosuppressors and/or biologics, which may be a proxy indicator of moderate/severe disease (12, 67). Thus, in this study, an assumption of 50% was used.
- **Proportion of unexposed to confirmed teratogenic SLE SOC and/or non-SLE SOC drugs of 80%.** It is estimated that 80% of the SLE pregnancies are not exposed to SLE SOC and non-SLE SOC confirmed teratogenic drugs before conception, with a time period of 5-half-lives of relevant drug (see list of confirmed teratogenic drugs and half-lives in Table 20), or during pregnancy. This estimate is based on the reported use of SLE SOC and/or non-SLE SOC drugs in SLE population (47, 48).
- **Proportion of anifrolumab exposure during the first trimester of pregnancy of 80%.** The majority of the anifrolumab exposed pregnancies are expected to be unplanned and exposed to anifrolumab only in the early stages of the pregnancy, as the current recommendations indicate that anifrolumab should only be used during pregnancy if the benefit outweighs the risk to the foetus (86). We therefore used the assumption that 80% of all anifrolumab exposed pregnancies are exposed to anifrolumab during the first trimester of pregnancy.
- **Proportion of anifrolumab exposed pregnancies in women with moderate-to-severe SLE of 5% and 10%.** Based on market forecasts, uptake of anifrolumab in the general SLE population is expected to grow from 5% within two years of market launch to 20% by 5 years after market launch. Given the uncertainty of how these forecasts apply to SLE women of child-bearing potential and to use in pregnant SLE women, we used a conservative lower bound (5%) and a more realistic midpoint value (10%) for the proportion of pregnancies in women with moderate-to-severe SLE exposed to anifrolumab.

In addition, to estimate the minimum required sample size and the expected power, the following assumptions were used:

- **Non-inferiority margin of RR of 2.5**. The RR of 2.5 was based on previously reported increase in risk of MCM for exposure to a major teratogenic drug (62).
- **Allocation ratio of exposed to unexposed patient ratios of 1:2 and 1:3.** Anifrolumab was approved only recently (FDA approval July 2021, date of marketing authorisation from EMA in February 2022) and the current recommendations indicate that it should only be used unless the benefit outweighs the risk to the foetus (3, 33, 38). Thus, it is expected in this study that the number of patients exposed to anifrolumab will be lower than the number of patients unexposed to anifrolumab (exposed to SLE SOC). Matching each patient in the exposed cohort to more than one patient in the unexposed cohort will increase statistical power, and thus, allocation ratios of 1:2 and 1:3 were used.

9.5.1.2 Assumptions on data sources and number of pregnancies in SLE patients

To assess the anticipated study size in each data source, the total number of pregnancies in women with SLE were estimated in the feasibility assessment. Three data sources (Carelon Research, DAPI and RHEKISS) provided estimates for the annual number of pregnancies in women with SLE. For the data sources that did not provide estimates in feasibility assessments (Denmark, Finland, France), an estimate for the annual number of pregnancies in women with SLE was computed using the following parameters and assumptions:

a) Latest available data on annual live births in the respective country of the data source (obtained from official statistical offices (42, 83));
b) Data source coverage: Proportion of the country's total population covered by the data source (information obtained from the data sources during feasibility assessment);
c) Proportion of live births occurring in SLE women among all live births. This information was only available for the USA, Denmark, and Sweden. Final estimates were obtained through different methods:
    - Denmark: average proportion from the Nordic countries (i.e., Denmark (58) and Sweden (94))
    - Finland: average proportion from the Nordic countries (i.e., Denmark (58) and Sweden (94))
    - France: average proportion from USA (21) Denmark (58) and Sweden (94);
d) Proportion of non-live births in SLE pregnancies. According to a literature review, 20% of SLE pregnancies result in non-live births (22, 70, 82, 93, 103, 113). This proportion was used for all countries.

Based on the parameters and assumptions above, the following calculations were made for the data sources (Denmark, Finland and France):

1. The number of live births in SLE women captured by the data source was calculated as the number of annual live births in the country (parameter a) multiplied by the data source

coverage (parameter b) multiplied by the proportion of live births that occur in SLE women (parameter c);

2. The number of pregnancies in SLE women captured by the data sources was calculated as the number of live births in SLE women (step 1) divided by 0.80, as 80% (obtained from parameter d) of SLE pregnancies are expected to end in a live birth. The final estimates for the annual number of pregnancies in women with SLE were 449 (Carelon Research), 445 (DAPI), 50 (RHEKISS), 41 (Denmark), 32 (Finland) and 558 (France).

Assuming 50% of SLE pregnancies occur in women with moderate-to-severe disease, the expected number of SLE pregnancies in women with moderate-to-severe disease was obtained by multiplying the number of reported or estimated pregnancies in SLE women (step 2) by 0.5. This resulted in an estimate for the annual number of pregnancies in women with moderate-to-severe SLE to be 224 (Carelon Research), 222 (DAPI), 20 (Denmark), 16 (Finland), 279 (France) and 25 (RHEKISS). Furthermore, 20% of pregnancies in women with moderate-to-severe SLE are expected to be excluded from analysis due to exposure to SLE SOC and non-SLE SOC confirmed teratogenic drugs before conception, with a time period of 5-half-lives of relevant drug (see Table 20), or during the pregnancy. Thus, the estimated annual number of pregnancies in women with moderate-to-severe SLE eligible for analysis were 179 (Carelon Research), 178 (DAPI), 16 (Denmark), 12 (Finland), 223 (France) and 13 (RHEKISS) (Table 9).

In Denmark, Finland, France and RHEKISS data sources, all live births can be linked to a pregnancy. However, in USA data sources (Carelon Research and DAPI) not all live births can be linked to the mother: 73% and 85% of the pregnancies resulting in a live birth can be linked to the offspring in Carelon Research and DAPI, respectively. Thus, the MCM analysis can only be conducted in USA data sources (Carelon Research and DAPI) using the pregnancies resulting in live birth that can be linked to the mother or resulting in a recorded pregnancy loss or non-live birth. In other data sources, all pregnancies in women with moderate-to-severe SLE are eligible for both the MCM and the select pregnancy loss outcomes analysis. The estimated annual number of pregnancies in women with moderate-to-severe SLE that are eligible for MCM analysis were 112 (Carelon Research), 125 (DAPI), 12 (Denmark), 10 (Finland), 178 (France) and 10 (RHEKISS) (Table 9).

The summary of the estimated annual number of pregnancies in women with moderate-to-severe SLE eligible for the primary outcome analysis are shown in Table 9 for each data source and anifrolumab exposure proportion scenarios. The MCM analysis will only consider the pregnancies where anifrolumab exposure occurs during the first trimester of pregnancy, and it is assumed that 80% of all anifrolumab exposed pregnancies have exposure to anifrolumab within the first trimester of pregnancy. Based on these estimates and assuming that 5% of pregnancies in moderate to severe SLE patients are exposed to anifrolumab, the total number of anifrolumab exposed patients by the end of the study time period (September 2030 in USA, September 2028 in other study countries) is estimated to be 249 (82 [Carelon Research], 81 [DAPI], 5 [Denmark], 3 [Finland], 73 [France] and 5 [RHEKISS]) patients (Table 10) for the select pregnancy loss outcome

and 175 (51 [Carelon Research], 56 [DAPI],4 [Denmark], 3 [Finland], 58 [France] and 3 [RHEKISS]) for the MCM outcome.

Under the assumption of 10% of pregnancies in moderate to severe SLE patients exposed to anifrolumab, the estimated number at the end of the study period is 497 (163[(Carelon Research], 162 [DAPI], 11 [Denmark], 7 [Finland], 145 [France] and 9 [RHEKISS] patients (Table 11) for the select pregnancy loss outcome and 353 (102 [Carelon Research], 114 [DAPI],8 [Denmark], 6 [Finland], 116 [France] and 7 [RHEKISS]) for the MCM outcome.

To identify the data sources that are likely to contribute to the meta-analysis, the probability of observing at least one MCM or select pregnancy loss outcomes event in the data source during the study period was estimated. Data sources that have a ≥90% probability of observing at least one outcome event will be considered for inclusion in the meta-analysis level study size and power calculations (cells highlighted in Table 10 and Table 11). Under the assumption of a 5% anifrolumab exposure, the data sources of Carelon Research (USA), DAPI (USA) and France each have >90% probability of observing at least one event for each primary outcome (MCM or select pregnancy loss outcomes) in the exposed group during the study time period. Under the assumption of 10% anifrolumab exposure, the data sources of Carelon Research, DAPI, Denmark and France each have >90% probability of observing at least one select pregnancy loss outcome event in the exposed group during the study time period, and the data sources of Carelon Research (USA), DAPI (USA) and France each have >90% probability of observing at least one MCM outcome event in the exposed group during the study time period (Table 11).

Assuming a two-year extension of the study period (study final report in 2034) and under the assumption of 5% anifrolumab exposure, the data sources of Carelon Research (USA), DAPI (USA) and France would each have >90% probability of observing at least one select pregnancy loss outcome or MCM event. Under an assumption of 10% anifrolumab exposure, the data sources of Carelon Research (USA), DAPI (USA), Denmark, France and RHEKISS would each have >90% probability of observing at least one event for the select pregnancy loss outcomes; and Carelon Research (USA), DAPI (USA) and France data sources would each have >90% probability of observing at least one event for the MCM outcome.

As the exact proportion of exposure to anifrolumab among pregnant SLE women is unknown at this time, these assumptions will be evaluated in the first interim report, and the study milestones will be adjusted as necessary to ensure a sufficient sample is obtained to address the research objectives.

Table 9: Estimated annual number of pregnancies in women with SLE eligible for the primary outcome analysis by the data sources and with 5% and 10% of exposure to anifrolumab among pregnant SLE women.

Data source	Annual number of pregnancies in women with moderate/severe SLE eligible for select pregnancy loss outcomes analysis	Annual number of pregnancies in women with moderate/severe SLE eligible for MCM analysis[a]	Annual number of pregnancies in women with moderate/severe SLE eligible for select pregnancy loss outcomes analysis		Annual number of pregnancies in women with moderate/severe SLE eligible for MCM analysis[a]	
			5% exposed to anifrolumab	10% exposed to anifrolumab	5% exposed to anifrolumab	10% exposed to anifrolumab
USA (Carelon Research)	179	112[1]	9	18	6[1]	11[1]
USA (DAPI)	178	125[2]	9	18	6[2]	13[2]
Denmark	16	12	1	2	1	1
Finland	12	10	1	1	1	1
France	223	178	11	22	9	18
Germany (RHEKISS)	13	10	1	1	1	1

The annual number of pregnancies in women with moderate/severe SLE eligible for the analysis are shown as integers rounded up from the exact estimates.

[a] It is estimated that 80% of all anifrolumab exposed pregnancies are eligible for MCM analysis i.e., have the exposure to anifrolumab anytime during the first trimester of pregnancy.

[1] Approximately 73% of the pregnancies resulting in a live birth can be linked to the offspring in Carelon Research. The MCM analysis can only be conducted using the pregnancies resulting in live birth that can be linked to the mother or resulting in a recorded pregnancy loss or non-live birth.

[2] Approximately 85% of the pregnancies resulting in a live birth can be linked to the offspring in DAPI. The MCM analysis can only be conducted using the pregnancies resulting in live birth that can be linked to the mother or resulting in a recorded pregnancy loss or non-live birth.

Table 10: Estimated total number of pregnancies in women with moderate-to-severe SLE exposed to anifrolumab and estimated total number of primary outcomes expected in the data sources by final study reporting year, assuming that 5% of the pregnancies in women with moderate-to-severe SLE are exposed to anifrolumab.

Final study report year	Data source	Select pregnancy loss outcomes			MCM		
		Total number of pregnancies in women with moderate/severe SLE exposed to anifrolumab eligible for analysis	Estimated number (95% CIs) of events from pregnancies in women with moderate/severe SLE exposed to anifrolumab[a]	Probability of observing at least one event from pregnancies in women with moderate to severe SLE exposed to anifrolumab[b]	Total number of pregnancies in women with moderate/severe SLE exposed to anifrolumab eligible for analysis	Estimated number (95% CIs) of events from pregnancies in women with moderate/severe SLE exposed to anifrolumab[a]	Probability of observing at least one event from pregnancies in women with moderate to severe SLE exposed to anifrolumab[b]
2032	USA (Carelon Research)	82	16 (9-25)	**>99%**	51	3 (0-8)	**98%**
	USA (DAPI)	81	16 (9-25)	**>99%**	56	3 (0-8)	**98%**
	Denmark	5	1 (0-5)	67%	4	0 (0-3)	25%
	Finland	3	0 (0-3)	49%	3	0 (0-3)	20%
	France	73	14 (7-23)	**>99%**	58	4 (1-10)	**99%**
	Germany (RHEKISS)	5	1 (0-5)	67%	3	0 (0-3)	20%
2034 (study extended by 2 years)	USA (Carelon Research)	100	20 (12-30)	**>99%**	62	4 (1-10)	**99%**
	USA (DAPI)	99	19 (11-29)	**>99%**	69	4 (1-10)	**99%**
	Denmark	7	1 (0-5)	79%	5	0 (0-3)	30%
	Finland	5	1 (0-5)	67%	4	0 (0-3)	25%
	France	94	18 (10-28)	**>99%**	75	5 (1-11)	**>99%**

Final study report year	Data source	Select pregnancy loss outcomes			MCM		
		Total number of pregnancies in women with moderate/severe SLE exposed to anifrolumab eligible for analysis	Estimated number (95% CIs) of events from pregnancies in women with moderate/severe SLE exposed to anifrolumab[a]	Probability of observing at least one event from pregnancies in women with moderate to severe SLE exposed to anifrolumab[b]	Total number of pregnancies in women with moderate/severe SLE exposed to anifrolumab eligible for analysis	Estimated number (95% CIs) of events from pregnancies in women with moderate/severe SLE exposed to anifrolumab[a]	Probability of observing at least one event from pregnancies in women with moderate to severe SLE exposed to anifrolumab[b]
	Germany (RHEKISS)	6	1 (0-5)	74%	4	0 (0-3)	25%

[a] Confidence intervals calculated using Poisson exact method.

[b] Based on 1,000,000 simulations with binomial distribution.

Table 11: Estimated total number of pregnancies in women with the moderate-to-severe SLE exposed to anifrolumab and estimated total number of primary outcomes expected in the data sources by final study reporting year, assuming that 10% of the pregnancies in women with moderate-to-severe SLE are exposed to anifrolumab.

Final study reporting year	Data source	Select pregnancy loss outcomes			MCM		
		Total number of pregnancies in women with moderate/severe SLE exposed to anifrolumab eligible for analysis	Estimated number (95% CIs) of events from pregnancies in women with moderate/severe SLE exposed to anifrolumab[a]	Probability of observing at least one event from pregnancies in women with moderate to severe SLE exposed to anifrolumab[b]	Total number of pregnancies in women with moderate/severe SLE exposed to anifrolumab eligible for analysis	Estimated number (95% CIs) of events from pregnancies in women with moderate/severe SLE exposed to anifrolumab[a]	Probability of observing at least one event from pregnancies in women with moderate to severe SLE exposed to anifrolumab[b]
2032	USA (Carelon Research)	163	32 (21-45)	**>99%**	102	7 (2-14)	**>99%**
	USA (DAPI)	162	32 (21-45)	**>99%**	114	7 (2-14)	**>99%**
	Denmark	11	2 (0-7)	**91%**	8	0 (0-3)	44%
	Finland	7	1 (0-5)	**79%**	6	0 (0-3)	35%
	France	145	29 (19-41)	**>99%**	116	8 (3-15)	**>99%**
	Germany (RHEKISS)	9	1 (0-5)	**87%**	7	0 (0-3)	40%
2034 (study extended by 2 years)	USA (Carelon Research)	199	39 (27-53)	**>99%**	124	8 (3-15)	**>99%**
	USA (DAPI)	198	39 (27-53)	**>99%**	139	9 (4-17)	**>99%**
	Denmark	14	2 (0-7)	**96%**	10	0 (0-3)	52%
	Finland	9	1 (0-5)	**87%**	8	0 (0-3)	44%
	France	187	37 (26-50)	**>99%**	150	10 (4-18)	**>99%**
	Germany (RHEKISS)	11	2 (0-7)	**91%**	9	0 (0-3)	48%

[a] Confidence intervals calculated using Poisson exact method.

[b] Based on 1,000,000 simulations with binomial distribution.

9.5.1.3 Methods for estimating required sample size and expected power

The required sample size and expected power calculations were based on the assumptions described above and were carried out separately for each primary outcome (MCM and select pregnancy loss) at the meta-analysis level. Data sources that had at least a 90% probability of having at least 1 event in each exposure group (see Table 10 and Table 11) were included in the meta-analysis.

The sample size and power calculations were performed using simulations under the assumption that the true RR is 1.0. For both sample size and power calculations, simulations were repeated 1,000 times to get 1,000 simulated 95% CIs for RRs.

The required sample size to achieve 80% power for a one-sided alpha-level of 2.5% at meta-analysis were performed using simulations as detailed below:

1. For a given overall sample size, a proportion of the overall population was assigned to each of the data sources likely to be included in the meta-analysis (proportions are presented in Table 12).
2. The number of primary outcome events in each exposure group were randomly drawn for each data source from a binomial distribution. In the binomial distribution, the number of trials was set equal to the estimated data source-level sample size and the probability of success was set to equal to the prevalence of the outcome in each exposure group, assuming that the true RR is 1 (no effect of exposure).
3. The estimated data source level log(RRs), their standard errors, and their 95% CIs were computed using a log-link Poisson regression (in place of log-binomial regression which tended to not converge) from the simulated number of events.
4. The data source level log(RRs) and their standard errors were entered in a fixed-effect meta-analysis model where pooled 95% CIs were computed. The inverse-variance method was used for the meta-analysis. The meta-analysis was run using the meta package in R (97).
5. The steps 2-4 were repeated for 1,000 times, and the proportion (which represents the achieved power) of the 1,000 simulated 95% CI upper bounds that were smaller than the target RR of 2.5 was computed.
6. The overall sample size was varied to range over positive integers for simulations, and the required sample size for this study was identified as the minimum overall sample size necessary to achieve 80% power (as defined in step 5).

The achieved power (proportion of the simulations where the upper bound of the meta-analysis RR was lower than the target RR of 2.5) was estimated based on the anticipated number of primary outcome events in each exposure groups and using simulations where the steps 2-4 (as described above) were repeated 1,000 times to get 1,000 simulated 95% CIs for RRs. The achieved power was calculated as the proportion of the 1,000 simulated 95% CI upper bounds that were smaller than the target RR of 2.5.

9.5.2 Required sample size

The required total sample size was estimated as the minimum sample size necessary to achieve 80% power for a one-sided alpha-level of 2.5% at meta-analysis level to rule out a target threshold RR of 2.5 for each primary outcome (MCM and select pregnancy loss outcomes). The minimum sample size per data source was calculated based on the expected percentage that the data source would contribute to the total sample size in the meta-analysis (Table 12).

For MCM analysis, a total number of 630 live and non-live births (210 anifrolumab and 420 comparator) using a matching ratio of 1:2, or 732 live and non-live births (183 anifrolumab and 549 comparator) using a matching ratio of 1:3 would be required to achieve at least 80% power to rule out an RR of 2.5 or greater. For the select adverse pregnancy loss outcomes analysis, a total number of 216 pregnancies (72 anifrolumab and 144 comparator) using a matching ratio of 1:2, or 244 pregnancies (61 anifrolumab and 183 comparator) using a matching ratio of 1:3 would be necessary to achieve at least 80% power to rule out an RR of 2.5 or greater.

Table 12: Data source level sample size percentages and required sample sizes assuming that only USA (Carelon Research), USA (DAPI) and France contribute to the meta-analysis of the primary outcomes.

Data source	Percentage of the total sample size in the data sources for select pregnancy loss outcomes analysis[a]	Required sample size per anifrolumab exposure group for meta-analysis of the select pregnancy loss outcomes		Percentage of the total sample size in the data sources for MCM analysis[a]	Required sample size per anifrolumab exposure group for meta-analysis of MCM	
		1:2 matching ratio	1:3 matching ratio		1:2 matching ratio	1:3 matching ratio
USA (Carelon Research)	35%	25	21	31%	66	57
USA (DAPI)	35%	25	21	35%	73	64
France	30%	22	19	34%	71	62
In Total	100%	72	61	100%	210	183

[a] Based on the estimated number of pregnancies in women with moderate/severe SLE eligible for the analysis and exposed to anifrolumab, as shown in Table 10 and Table 11.

9.5.3 Expected power

The expected power to rule out a target threshold RR of 2.5 was computed at the meta-analysis level based on the expected number of exposed pregnancies in the data sources. There are three data sources (USA (Carelon Research), USA (DAPI) and France) that contribute to the meta-analysis for the MCM outcome, irrespective of anifrolumab exposure proportion (see Table 10 and Table 11). These three data sources also contribute to the meta-analysis of the select pregnancy loss outcomes. Additionally, Denmark contributes to the meta-analysis of the select pregnancy loss outcomes if the assumption of 10% for anifrolumab exposure is used. For select pregnancy loss outcomes, the expected power to rule out an RR of 2.5 was superior to 99% in all scenarios

(Table 13). For MCM outcomes, the expected power to rule out an RR of 2.5 was equal or superior to 69% assuming 5% of exposure to anifrolumab among pregnant SLE women, and equal or superior to 96% assuming 10% of exposure to anifrolumab among pregnant SLE women (Table 13).

Table 13: Expected power in the meta-analysis of select pregnancy loss and MCM with 5% and 10% of all pregnancies in women with moderate-to-severe SLE exposed to anifrolumab.

Final study reporting year	Data sources included in the meta-analysis of select pregnancy loss	Expected power for the meta-analysis of select pregnancy loss outcomes		Data sources included in the meta-analysis of MCM	Expected power for the meta-analysis of MCM	
		1:2 matching ratio	1:3 matching ratio		1:2 matching ratio	1:3 matching ratio
5% exposure to anifrolumab						
2032	USA (Carelon Research) USA (DAPI) France	>99%	>99%	USA (Carelon Research) USA (DAPI) France	69%	72%
2034 (study extended by 2 years)	USA (Carelon Research) USA (DAPI) France	>99%	>99%	USA (Carelon Research) USA (DAPI) France	80%	84%
10% exposure to anifrolumab						
2032	USA (Carelon Research) USA (DAPI) Denmark France	>99%	>99%	USA (Carelon Research) USA (DAPI) France	96%	98%
2034 (study extended by 2 years)	USA (Carelon Research) USA (DAPI) Denmark France Germany (RHEKISS)	>99%	>99%	USA (Carelon Research) USA (DAPI) France	>99%	>99%

9.6 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 9.2. 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 is extracted, the data holders will make data accessible to IQVIA, according to data permits in each specific country. The details of the data permits will be confirmed only once 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 (e.g., Carelon Research (USA)) cannot be accessed by IQVIA but will be managed and analysed by the data provider (e.g., HealthCore). All individual-level data accessible to IQVIA will have original personal identifiers replaced with a study identification number (SID). 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. 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 programmes.

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 (Statistical Analysis System (115) version 9.4 or later, STATA or R [version 3.5.0 or later]). The data providers conducting the data management and statistical analysis for the study will store the datasets and analytic programmes 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 5 years after publication of results. The study may be inspected by the AstraZeneca's independent representative(s), scientific committee, or by the competent authorities.

9.7 Data Analysis

All data analysis will be performed separately for each data source on the study population as defined in Section 9.2.2. The study population selection process will be reported using a STROBE

(STrengthening the Reporting of OBservational studies in Epidemiology) diagram that shows cohort and sub-population exclusions step by step, as defined in Section 9.2.2.

All study results will be presented separately for each data source in the study reports, as appropriate when data become available. The full study reports for all data sources, including all descriptive, comparative, exploratory, and sensitivity analyses, as well as the meta-analysis results will be provided in the final report. The study reporting is described in detail in Section 6.

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

In this study, the missing data will be reported as part of descriptive analysis (see Section 9.7.1). 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 (35). 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.

The small number masking rules define the lower limit for the number of units that can be reported in a table. The small number masking rules vary by data sources. For example, Denmark and Finland have a limit of 5, USA (Carelon Research) has a limit of 10 and France has a limit of 11. The small number masking rules of the data sources will be considered when presenting the study results for descriptive and comparative analysis. If the small number masking rules apply, only the comparative analysis results for the relevant study outcome (and no descriptive analysis results for the relevant study outcome) will be provided to avoid inadvertent unmasking of small numbers.

9.7.1 Methods

Propensity score methodology for confounding

Methods based on propensity score (PS) are frequently used in non-interventional studies to control for confounding when estimating treatment effects (6). PS methods allow for control of measured confounding in treatment effects when the measured confounders related with the treatment are correctly modelled in the PS (107). In non-interventional studies, the widely used methods that employ PS methods in adjusting for confounders include PS matching and PS weighting using inverse probability treatment weighting (IPTW). In this study, the average treatment effect in the treated (ATT) is the estimand of interest. To estimate ATT using PS matching, each patient within the study treatment is matched either to one (i.e. 1:1 matching) or more (i.e. 1:n matching) patients who have the same or a similar PS value (65). In PS matching, the patients in the study treatment cohort who do not have a close enough match in the comparator treatment cohort need to be excluded from the analysis (65). To estimate ATT using IPTW, each subject in the study treatment cohort has a weight of one and each subject in the comparator treatment cohort has a weight of the odds of receiving the study treatment i.e. PS/(1-PS) (6). This

weighting approach is also known as standardised mortality ratio weighting, and it creates a pseudo-population of the comparator treatment cohort that has the same covariate distribution as the study treatment cohort (107). The PS weighting approach excludes patients from the original study population when there are non-overlapping PS values in the study cohorts (65). The PS weighting with IPTW is vulnerable to patients with extreme PS weights, but truncation methods will be used in this study if PS weighting is used and extreme PS weights are observed (19, 65).

In this study, PS matching will be considered as the preferable PS adjustment method. PS matching will be used if it does not significantly reduce the sample size, otherwise PS weighting will be used. In PS matching, if there are many more patients in the comparator treatment cohort than in the study treatment cohort, each patient in the anifrolumab exposed cohort may be matched to more than one patient (e.g., 1:2 or 1:3 matching) to increase statistical power.

The PS adjustment will be performed separately within each data source and for each study cohort that is derived from the study populations as defined in Section 9.2.2. In this study, the PS will be obtained using a logistic regression model or another modelling method (e.g., gradient boosting) as seen appropriate for the data. For the PS model, all the potential confounders listed in Table 7 Section 9.3.3 will be considered for inclusion. All these potential confounders will be estimated before or at conception, or before or at the start of exposure, as seen relevant for the confounder (see Section 9.3.3). Specifically, each single component of the SLE severity and activity algorithms (described in Section 9.3.3) will be considered for inclusion in the PS model. The maximum number of confounders to be included in the PS model will be one fifth of the minimum between the number of exposed or unexposed patients in the study cohort (as defined in Section 9.2.2) (17). The PS adjustment will be performed only if the PS model can be fit on the available data and if the PS model fit is reasonable (17). If PS adjustment is not suitable for the data, no adjusted estimates of the study outcomes will be provided in the study results. Further details on the PS modelling will be provided in the SAP.

To check the overlap and similarity of the PS distributions between the study sub-cohorts (exposed to anifrolumab and unexposed to anifrolumab, as defined in Section 9.2.2), the distribution of the propensity scores in the study sub-cohorts will be examined (49). To evaluate the balance of covariates within the study cohorts, the characteristics of the study sub-cohorts (exposed to anifrolumab and unexposed to anifrolumab, as defined in Section 9.2.2) will be tabulated before and after application of PS adjustment. Covariate balance will be assessed by examining the distribution of variables in the study sub-cohorts using summary statistics, and by estimating standardised differences for each variable between the study sub-cohorts (exposed to anifrolumab and unexposed to anifrolumab, as defined in Section 9.2.2). No statistical tests are planned for this comparison, but variables with standardised differences above 0.1 will be further evaluated and may lead to a re-evaluation of the PS model. Further details will be provided in the SAP.

Descriptive analysis

In the descriptive analysis, the total number of patients at risk and the number of events for each study outcome in the study sub-cohorts (exposed to anifrolumab and unexposed to anifrolumab as defined in Section 9.2.2) will be tabulated before and after application of PS adjustment, if suitable for the data. The measures of study outcomes will be estimated before and after application of PS adjustment (if suitable for the data) to obtain crude and adjusted estimates, respectively. The measures of study outcomes, with associated 95% CIs, will be estimated for the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab as defined in Section 9.2.2. In this study, cumulative incidence (i.e. incidence proportion) by exposure status to anifrolumab during pregnancy will be assessed for the following study outcomes: MCM (objective 1 & 15), select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) (objective 3 & 13), mCM (objective 6), adverse pregnancy outcomes (objective 8), adverse birth outcomes (objective 10), and adverse outcome related to infant growth up to one year of age (objective 12).

Additionally, the description of the time from birth to MCM ascertainment will be conducted in live and non-live offspring from women who had moderate/severe SLE and were exposed or unexposed to anifrolumab during the first trimester of pregnancy. The time to MCM ascertainment will be calculated from birth and up to 1 year after birth. The time to MCM ascertainment will be estimated both before and after application of PS adjustment (if suitable for the data) to obtain crude and adjusted estimates, respectively. Kaplan-Meier curves (and their 95% CIs) will be used for characterising the time from birth to MCM ascertainment. Together with the Kaplan-Meier curves, the number of patients at risk at appropriate time intervals (e.g., 7 days or as seen appropriate for the study), and the median (with 95% CI) for the time from birth to MCM ascertainment will be reported.

For study objective 5 (secondary objective), descriptive analysis will be conducted to describe the demographic and clinical characteristics of the live and non-live offspring and their mothers (defined in Section 9.3.3) in the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab as defined in Section 9.2.2. For the descriptive analysis of continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1st) and upper (3rd) quartiles, as well as 5th and 95th 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.

Additionally, descriptive summaries of the number and proportion of mothers who received anifrolumab in the preconception period will be reported. These descriptive summaries will include the total number of anifrolumab administrations per mother in the preconception period summarized as a continuous variable, and the timing of anifrolumab administrations in the preconception period summarized as the number and proportion of mothers who received anifrolumab in pre-specified time intervals (e.g., within 4 weeks before LMP, within 4-8 weeks before LMP etc., or as seen appropriate for the study data). In addition, the descriptive summaries will include the timing of the last anifrolumab administration per mother. The description of

anifrolumab administrations may also be extended to mothers who received anifrolumab during pregnancy, if appropriate for the study. Further details will be provided in the SAP.

Comparative analysis

For the comparison of the study sub-cohorts exposed to anifrolumab and unexposed to anifrolumab within the study cohorts (as defined in Section 9.2.2), the association metrics of RRs will be estimated. The RRs will be estimated if there is at least one outcome event observed per exposure group. Both crude and adjusted RRs will be reported and estimated for each relevant study outcome. The crude and adjusted RRs will be estimated before and after PS adjustment, respectively. The adjusted RRs will be reported only if PS adjustment is suitable for the data. The statistical model to be used for the estimation of the crude and adjusted RRs will be the log-binomial regression or the robust, modified Poisson regression as seen appropriate for the study data (13, 18). If covariate balance is not achieved through PS adjustment, additional adjustment by using unbalanced covariates in the outcome regression model will be considered. Additionally, any other potential covariates (or risk factors) that are not included in the PS model but are hypothesised to be associated with the study outcomes may be used as covariates for the statistical models. Further details on the statistical models will be provided in the SAP.

Meta-analysis

In addition to data source level analyses, results will be combined in a meta-analysis. Meta-analysis will be performed only for the adjusted RR estimates of the primary study objectives (MCM and selected pregnancy loss outcomes). The meta-analysis will be performed using effect size estimates from all study countries for which the adjusted RR were estimated.

Prior to conducting the meta-analyses, 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 studies.

- 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.

- The τ^2 statistic

Considerable heterogeneity would indicate that the study results should be interpreted as inconclusive.

Results of the meta-analysis will be derived using a fixed-effect model since it is expected that the effect is the same in all study countries. A random-effects model can be conducted as a sensitivity analysis if substantial heterogeneity is observed. 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. Further details will be presented in the SAP.

9.7.2 Primary objectives

The analysis for the primary study objectives will be conducted separately for each data source. In addition, meta-analysis will be performed to combine the adjusted RRs regarding the primary outcomes (i.e., MCM and select pregnancy loss outcomes) from the individual data sources where comparative analysis are performed as described in Section 9.7.1. The description of the analysis to be conducted for each primary study objective is provided in the following sections.

Objective 1

The analysis to describe and estimate the risk of MCM in live and non-live offspring from the mothers who had moderate/severe SLE and were exposed to anifrolumab during the first trimester of pregnancy or exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy (study objective 1) will be performed using the *MCM* cohort and its sub-cohorts as defined in Section 9.2.2). The crude and adjusted cumulative incidence (with corresponding 95% CI) of the MCM in live and non-live offspring from the mothers who had moderate/severe SLE and were exposed to anifrolumab during the first trimester of pregnancy or who were exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy will be estimated separately. The crude cumulative incidence (i.e., risk) will be calculated as the total number of live and non-live offspring with MCM divided by the total number of live and non-live offspring. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment, if suitable for the data. Additionally, the Kaplan-Meier plots will be generated both before and after application of PS adjustment to obtain crude and adjusted estimates for the time from birth to MCM ascertainment, respectively (as described in Section 9.7.1).

Objective 2

To estimate the relative risk of MCM in live and non-live offspring from the mothers who had moderate/severe SLE and were exposed to anifrolumab during the first trimester of pregnancy or exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy (study objective 2), the crude and adjusted RRs (with corresponding 95% CIs) will be estimated using the *MCM* cohort (as defined in Section 9.2.2). The crude RR and its 95% CI will be estimated using a regression model as specified in Section 9.7.1. The adjusted RR and its 95% CIs will be estimated by using the same regression model after applying an appropriate PS adjustment method

as described in Section 9.7.1. In addition, meta-analysis on the data source specific crude and adjusted RRs of MCM in live and non-live offspring from mothers who were exposed or unexposed to anifrolumab during pregnancy will be conducted as described in Section 9.7.1.

Objective 3

The analysis to describe and estimate the risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in all pregnancies from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 3) will be performed using the *pregnancy* cohort (as defined in Section 9.2.2). The crude and adjusted cumulative incidence (with corresponding 95% CI) of the select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) will be estimated for cases where mother was exposed to anifrolumab during pregnancy and for cases where mother was unexposed to anifrolumab during pregnancy. The crude cumulative incidence (i.e., risk) will be calculated as the total number of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) divided by the total number of pregnancies. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment, if suitable for the data.

Objective 4

To estimate the relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 4), the crude and adjusted RR (with corresponding 95% CI) will be estimated using the *pregnancy* cohort (as defined in Section 9.2.2). The crude RR and its 95% CI will be estimated using a regression model as specified in Section 9.7.1. The adjusted RR and its 95% CI will be estimated using the same regression model following an appropriate PS adjustment method as described in Section 9.7.1.

9.7.3 Secondary objectives

The analysis for the secondary study objectives will be conducted separately for each data source. The description of the analysis to be conducted for each secondary study objective is provided in the following sections.

Objective 5

To describe the demographic and clinical characteristics of the live and non-live offspring and their mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during the first trimester of pregnancy or anytime during pregnancy (study objective 5), the descriptive analysis of the demographic and clinical characteristics (as defined in Section 9.3.3) will be provided as described Section 9.7.1. The demographic and clinical characteristics of the

live and non-live offspring and their mothers will be presented separately for each study cohort and sub-cohorts as defined in Table 5 (Section 9.2.2). No statistical testing comparing the distribution of demographic and clinical characteristics distribution between the study cohorts or sub-cohorts is planned.

Objective 6

The analysis to describe and estimate the risk of mCM in live and non-live offspring from the mothers with moderate/severe SLE who were exposed or unexposed to anifrolumab during pregnancy (study objective 6) will be performed using the *mCM* cohort and its sub-cohorts as defined in Section 9.2.2. The crude and adjusted cumulative incidence (with corresponding 95% CI) of the mCM in live and non-live offspring from the mothers will be estimated separately for the case where mother had moderate/severe SLE and was exposed or unexposed to anifrolumab during pregnancy. The crude cumulative incidence (i.e., risk) will be calculated as the total number of live and non-live offspring with mCM divided by the total number of live and non-live offspring. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment described in Section 9.7.1.

Objective 7

To estimate the relative risk of mCM in live and non-live offspring from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 7), the crude and adjusted RRs (with corresponding 95% CI) will be estimated using the *mCM* cohort. The crude RR and its 95% CI will be estimated using a regression model as specified in Section 9.7.1. The adjusted RR and its 95% CI will be estimated using the same regression model following an appropriate PS adjustment method as described in Section 9.7.1.

Objective 8

The analysis to describe and estimate the risk of adverse pregnancy outcomes (as defined in Section 9.3.2) in all pregnancies from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 8) will be performed using the *pregnancy* cohort (as defined in Section 9.2.2). The crude and adjusted cumulative incidence (with corresponding 95% CI) of the adverse pregnancy outcomes (as defined in Section 9.3.2) will be calculated for cases where the mother was exposed to anifrolumab during pregnancy and for cases where the mother was unexposed to anifrolumab during pregnancy. The crude cumulative incidence (i.e., risk) will be calculated as the total number of each adverse pregnancy outcome (as defined in Section 9.3.2) divided by the total number of pregnancies. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment.

Objective 9

To estimate the relative risk of adverse pregnancy outcomes (as defined in Section 9.3.2) in pregnancies from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 9), the crude and adjusted RR (with corresponding 95% CI) will be estimated using the *pregnancy* cohort (as defined in Section 9.2.2). The crude RR and its 95% CI will be estimated using a regression model as specified in Section 9.7.1. The adjusted RR and its 95% CI will be estimated using the same regression model following an appropriate PS adjustment method as described in Section 9.7.1.

Objective 10

The analysis to describe and estimate the risk of adverse birth outcomes in live offspring from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 10) will be performed using the birth cohort (as defined in Section 9.2.2). The crude and adjusted cumulative incidence (i.e., risk) for the adverse birth outcomes will be calculated for cases where mother was exposed to anifrolumab during pregnancy and for cases where mother was unexposed to anifrolumab during pregnancy. The crude cumulative incidence (i.e., risk) will be calculated as the total number of each adverse birth outcome divided by the total number of live offspring. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment.

Objective 11

To estimate the relative risk of adverse birth outcomes in live offspring from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 11), the crude and adjusted RRs (with corresponding 95% CI) will be estimated using the *birth* cohort (as defined in Section 9.2.2). The crude RR will be estimated using a regression model. The adjusted RR and will be estimated following PS adjustment, if suitable for the data, and using a regression model.

9.7.4 Exploratory objectives

The analysis for the exploratory study objectives will be conducted separately for each data source. The description of the analysis to be conducted for each exploratory study objective is provided in the following sections.

Objective 12

The analysis to describe and estimate the risk of adverse outcome related to infant growth up to one year of age in live offspring from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during pregnancy (study objective 12) will be performed using the

infant cohort (as defined in Section 9.2.2). The crude and adjusted cumulative incidence (with corresponding 95% CI) of adverse outcome related to infant growth will be calculated for cases where mother was exposed to anifrolumab during pregnancy and for cases where mother was unexposed to anifrolumab during pregnancy. The crude cumulative incidence (i.e., risk) will be calculated as the total number of adverse outcomes related to infant growth divided by the total number of live offspring. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment.

Objective 13

To describe and estimate the risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE who were exposed or unexposed to anifrolumab in specific pregnancy trimesters (study objective 13), the pregnancy trimester specific exposure groups where the exposure to the study or comparator treatment is during a specific pregnancy trimester (trimester 1 only; trimester 1&2 only; trimester 2&3 only; trimester 3 only; all trimester 1&2&3) will be generated from the *pregnancy* cohort (as defined in Section 9.2.2). The analysis for the pregnancy trimester specific exposure groups will be performed separately by comparing each exposed group and its comparator group as shown in Table 6 in Section 9.3.1. This requires that the PS adjustment is done separately for 5 exposure group comparisons i.e., 5 different PS models will be fitted on each of the exposure group comparisons separately. Also, the crude and adjusted cumulative incidence will be calculated separately for each of the 5 exposure group comparisons (as shown in Table 6 in Section 9.3.1) to estimate the risk of the select pregnancy loss outcomes in pregnancies occurring in women with moderate/severe SLE with pregnancy trimester specific exposure to the anifrolumab. The crude cumulative incidence (i.e., risk) will be calculated as the total number of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) divided by the total number of pregnancies in pregnancy trimester specific study cohorts. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment.

Objective 14

To estimate the relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE and who were exposed anifrolumab in specific pregnancy trimester (study objective 14), the crude and adjusted RRs (with corresponding 95% CI) will be estimated separately for each specific pregnancy trimester exposure groups as defined in Section 9.7.1. The crude RR will be estimated separately for each pregnancy trimester specific exposure groups using a regression model as specified in Section 9.7.1. The adjusted RR will be estimated using the same regression model following an appropriate PS adjustment method as described in Section 9.7.1.

Objective 15

The analysis to describe and estimate the risk of MCM by target body system organ class in live and non-live offspring from the mothers who had moderate/severe SLE and were exposed or unexposed to anifrolumab during the first trimester of pregnancy (study objective 15) will be performed using the *MCM* cohort (as defined in Section 9.2.2). The crude and adjusted cumulative incidence (with corresponding 95% CI) of the MCM by target body system organ class in live and non-live offspring from the mothers will be estimated separately for cases where mother was exposed to anifrolumab during the first trimester of pregnancy and for cases where mother was unexposed to anifrolumab during the first trimester of pregnancy. The crude cumulative incidence (i.e., risk) of MCM by target body system organ class will be calculated as the total number of live and non-live offspring with MCM divided by the total number of live and non-live offspring per each target body system organ class. The adjusted cumulative incidence (i.e., risk) will be estimated following PS adjustment.

9.7.5 Sensitivity analyses

Re-definition of the pre-conception exposure window for patients who receive prescriptions/dispensations/administrations of anifrolumab in the period prior to LMP2

The rationale for this sensitivity analysis is to explore the robustness of the exposure definition to changes in the pre-conception exposure ascertainment time-window for patients who receive anifrolumab prior to LMP2. While it is reasonable to assume that an unborn child could be exposed to anifrolumab if the mother has had a dose of anifrolumab in the 16 weeks prior to conception (LMP2), based on the population pharmacokinetics of anifrolumab, where time for concentration to fall below the LLOQ for 95% of patients is 16 weeks (2), it is also plausible that the serum concentrations may be so low (or even absent) at the time of pregnancy. Therefore, using the exposure ascertainment period of 16 weeks prior to LMP2 could result in exposure misclassification. There is a possibility that this misclassification could affect the measure of association between the exposure of interest and the outcomes of interest.

Therefore, to reduce the potential risk of exposure misclassification, the following alternative pre-conception time-windows for anifrolumab exposure will be considered:

a) up to 8 weeks prior to LMP2 until end of the first trimester for the outcome of MCM, and up to 8 weeks prior to LMP2 until end of pregnancy for select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth).

b) from LMP2 until end of the first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth).

Re-definition of the pre- and post-conception exposure window for the exclusion of SLE SOC and non-SLE SOC drugs with a confirmed teratogenic effect

After 4- to 5-half-lives, the plasma concentrations of a given drug is below a clinically relevant concentration and is considered eliminated. However, after 2- to 3-half-lives, the plasma concentration can be considered (very) low (56). Further, the etiologically relevant window, where the foetus is most susceptible to teratogens, is the first trimester of pregnancy for the MCM outcome (98). The rationale for this sensitivity analysis is to explore alternative pre- and post-conception exposure windows when estimating the relative risk and adjusted relative risk of MCM and select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth):

a) Pregnancies exposed to confirmed teratogenic drugs up to 1-half-life prior to LMP2 until end of the first trimester for the outcome of MCM, and up to 1-half-life prior to LMP2 until end of pregnancy for select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth), in both the exposed and unexposed groups, will be excluded.

b) Pregnancies exposed to confirmed teratogenic drugs from LMP2 until end of the first trimester for the outcome of MCM, and from LMP2 until end of pregnancy for select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth), in both the exposed and unexposed groups, will be excluded.

Inclusion of offspring in utero exposed to SLE SOC and non-SLE SOC drugs regardless of the teratogenic effect

For the main analysis, pregnancies exposed to confirmed teratogenic drugs are excluded. However, in real world settings, patients may be exposed to other teratogens in pregnancy. Therefore, this sensitivity analysis will provide a "real-world" estimate of risk in a setting which is reflective of clinical practice.

To estimate the relative risk of MCM in live and non-live offspring from women exposed to anifrolumab during the first trimester of pregnancy compared to women with SLE exposed to SLE SOC and unexposed to anifrolumab during the first trimester of pregnancy.

To estimate the relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) from women exposed to anifrolumab anytime during pregnancy compared to women with SLE exposed to SLE SOC and unexposed to anifrolumab anytime during pregnancy.

For both primary outcomes, in the calculation of the adjusted relative risk, a PS adjustment will be performed to control for confounding including the use of confirmed teratogenic drugs.

Exposure to anifrolumab monotherapy or polytherapy added to SLE SOC

The rationale for this sensitivity analysis is two-fold. While anifrolumab is indicated as an add-on medication (i.e., polytherapy) for moderate/severe SLE, it is possible that not all SLE medications being taken by a patient are captured in the database. Therefore, patients who seem to be on monotherapy may in fact be on polytherapy.

The relative risk of MCM in live and non-live offspring from women exposed to anifrolumab (monotherapy or polytherapy added to SLE SOC, excluding SLE SOC and non-SLE SOC drugs with a confirmed teratogenic effect) during the first trimester of pregnancy, compared to women with SLE exposed to SLE SOC (excluding SLE SOC and non-SLE SOC drugs with a confirmed

teratogenic effect) and unexposed to anifrolumab during the first trimester of pregnancy, will be estimated using the same approach as for study objective 2 (primary objective) as described in Section 9.7.2.

The relative risk of select pregnancy loss outcomes (a composite of spontaneous abortion and stillbirth) from women exposed to anifrolumab (monotherapy or polytherapy added to SLE SOC, excluding SLE SOC and non-SLE SOC with a confirmed teratogenic effect) anytime during pregnancy, compared to women with SLE exposed to SLE SOC (excluding SLE SOC and non-SLE SOC with a confirmed teratogenic effect) and unexposed to anifrolumab anytime during pregnancy, will be estimated using the same approach as for study objective 4 (primary objective) as described in Section 9.7.2.

Inclusion of exposed and unexposed pregnancies, irrespective of SLE severity, in the 12 months prior to conception

The rationale for this sensitivity analysis is that treatment with anifrolumab may reduce disease severity and the disease severity algorithm may misclassify patients. Therefore, this sensitivity analysis aims to minimise bias that may be arising from these phenomena.

The relative risk of MCM in live and non-live offspring from women with SLE, irrespective of SLE severity, in the 12 months prior to LMP2 exposed to anifrolumab (excluding SLE SOC and non-SLE SOC drugs with a confirmed teratogenic effect) during the first trimester of pregnancy, compared to women with SLE, irrespective of SLE severity, in the 12 months prior to LMP2 exposed to SLE SOC (excluding SLE SOC and non-SLE SOC drugs with a confirmed teratogenic effect) and unexposed to anifrolumab during the first trimester of pregnancy, will be estimated using the same approach as for study objective 2 (primary objective) as described in Section 9.7.2.

The relative risk of select pregnancy loss outcomes (a composite of spontaneous abortion and stillbirth) from women with SLE, irrespective of SLE severity in the 12 months prior to LMP2, exposed to anifrolumab (excluding SLE SOC and non-SLE SOC drugs with a confirmed teratogenic effect) anytime during pregnancy, compared to women with SLE, irrespective of SLE severity in the 12 months prior to LMP2, exposed to SLE SOC (excluding SLE SOC and non-SLE SOC drugs with a confirmed teratogenic effect) and unexposed to anifrolumab anytime during pregnancy, will be estimated using the same approach as for study objective 4 (primary objective) as described in Section 9.7.2.

Exposure re-definition

Although it is expected that patients will generally take medications as prescribed, it is possible that patients may not fully comply with prescribed medications. Therefore, to reduce the risk of exposure misclassification, exposure to anifrolumab will be defined as having at least two claims for filled prescriptions/dispensations/administrations during the etiologically relevant exposure time window. This sensitivity analysis will be conducted for the all the primary objectives following methods described in Section 9.7.1 if sample size allows.

Unmeasured confounding for primary study outcomes

The rationale of this sensitivity analysis is to examine the robustness of the primary study outcome (MCM and select pregnancy loss outcomes) analysis results to unmeasured confounding. Quantitative bias analysis methods will be used for studying the effect of unmeasured confounding on the study results (68). The quantitative bias analysis methods will be selected depending on what is known about the potential unmeasured confounder and its relationship between the exposure and the primary study outcomes (26). If the effect of a specific confounder and its relationship between the exposure and the primary study outcomes is well understood, a simple equation may be used for quantifying the confounder's relationship to exposure and primary study outcomes. This method allows to estimate the primary study outcome analysis results after adjusting for the specific unmeasured confounder (26). This approach could be considered in cases where a specific confounder is measured in some but not all data sources (listed as a limitation in Section 9.9). In case nothing is known about a potential unmeasured confounder, methods such as the E-value approach may be considered (26). The E-value approach aims to assess how strongly an unmeasured confounder would have to be related to anifrolumab exposure and primary study outcomes to explain away (i.e., nullify) the observed association of anifrolumab exposure with the primary study outcomes (112). Further details on the methods will be provided in the SAP.

Account for actual use of SLE SOC during pregnancy

The rationale for this sensitivity analysis is to account for actual use of SLE SOC during pregnancy in estimating the risk and relative risk of primary study outcomes. For the main analysis, the SLE SOC is assumed to be continued throughout pregnancy. In this sensitivity analysis, an exact matching criterion will be added to the PS matching step of the cohort building. For a given anifrolumab exposed pregnancy, the set of potential matches will be restricted to pregnancies unexposed to anifrolumab and exposed to SLE SOC during the same trimester(s) as the exposed pregnancy was exposed to anifrolumab. For example, if a given exposed pregnancy is exposed to anifrolumab during the second and third trimester, potential matches will be restricted to unexposed pregnancies with SLE SOC exposure during the second and third trimester. After matching, the sensitivity analysis will be conducted as described for Objectives 1-4 (see Section 9.7.2).

Exposure to anifrolumab and risk of MCM using the MACDP classification system for congenital malformations

This study comprises both European and American data sources; therefore, the MACDP USA-based classification system, in addition to the EUROCAT, for MCM will be used.

The MACDP classification system categorises and defines congenital malformations differently from EUROCAT, and the results obtained from each classification system may differ. Since it is essential to consider the potential impact of different categorisations and definitions of congenital malformations on the results, a sensitivity analysis will be performed using the MACDP classification system. The rationale of this sensitivity analysis is to examine the robustness and

reliability of the association between exposure to anifrolumab and the risk of MCM using the MACDP classification (59).

9.8 Quality control

The study will be conducted according to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice (GPP) Guidelines and IQVIA standard operating procedures. At the study level, all aspects of the study from protocol development to the reporting of the results will be conducted within the framework of the IQVIA Quality Management System.

According to the policies and procedures above, a Quality Control (QC) plan for the study will be developed and executed, which will include QC on the protocol in general, study methodology, SAP, programming, data management and analysis, and study report including study results and conclusions.

Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps. The principle of the independence of QC applies.
- IQVIA project management will ensure that individuals responsible for the execution of specific QC steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the QC plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.
- Datasets and analytic programmes will be stored according to IQVIA and data holder procedures, with access restricted to authorised study personnel at the respective entities.

Also, the Project Manager of the study will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure RWI_WI_PM0035 “Real World Project-Specific Training and Staff Transition”.

The executed QC plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team.

9.9 Limitations of the research methods

Use of secondary data collected and maintained in electronic databases offers several scientific and operational advantages for conducting a pregnancy study, including specifically:

- The possibility of mitigating the information and selection bias that may affect primary data collection which involves a self-selected population of pregnant women and their infants.
- The opportunity to study all the eligible exposed and non-exposed pregnancies (i.e., no individual informed consent for this study is required) in women with SLE.
- The potential to optimise statistical efficiency with a 1:n (e.g., 1:3) match of exposed and non-exposed pregnancies.
- Additionally, national databases such as those from Nordic countries are known to be representative of the population of the country, typically containing lifetime data of patients and have demonstrably been used for research to obtain insights into the real-world use of pharmaceutical products. The presence of medical birth registries and registers of congenital malformation in some of these countries with high PPVs for adverse outcomes such as MCMs increases the internal validity of studies conducted using these national data sources.

The individual study databases have limitations typical of other real-world databases:

- Data are collected primarily for administrative purposes, so some medical information not directly related to reimbursement may be incomplete or not available at all. The accuracy of the available information may vary between data sources. This can affect the measurement of exposure to anifrolumab, the outcomes of interest and/or the covariates. To ensure that the accuracy of the retrieved information is acceptable, all data will be reviewed for possible inconsistencies or implausible information. Also, missing information may vary between data sources, and whenever applicable, missing information will be reported (please see Section 9.7).
- Information on all the study outcomes and individual covariates may not be available in all databases, in particular lifestyle variables and the up to 1-year assessment of growth of the infant.
- For some of the data sources, relatively long lag times must be considered, and these would vary by country. Thus, an assumption of a data lag time of approximately 2 years will be implemented.
- This study relies on data sources not primarily collected to conduct pregnancy outcomes studies. Accordingly, outcome misclassification due to limitations in sensitivity or specificity for the study outcomes cannot be ruled out. If this misclassification is non-differential between the exposed and unexposed cohorts, this will likely lead to bias toward the null and attenuate any true effect. Bias in other directions remains a possibility. On the

other hand, if misclassification is differential between exposed and unexposed cohorts, bias can affect the results in any direction.

- An exhaustive list of codes will be used to maximise the capture of non-live births. However, early spontaneous abortions, which usually occur in the first 6 weeks of gestation, are not commonly recorded, and this may introduce outcome misclassification. As the included women are patients with moderate/severe SLE who may more often seek medical advice due to their condition and to the SLE-related increased risk of spontaneous abortion, the misreporting of spontaneous abortions is expected to be low.
- Additionally, the likelihood that spontaneous abortions would be recorded differently in the data sources across exposed and unexposed cohorts is low. The net effect of this non-differential misclassification is a bias towards the null. As for the other adverse pregnancy outcomes, such as ectopic pregnancy or elective termination of pregnancy, these are likely to have a hospitalisation event associated, and as such, it is not likely that this would be differentially recorded in the exposed and unexposed cohorts.
- The definitions for spontaneous abortion and stillbirth vary by country. Whereas the definitions are uniform within Europe, they differ from those in the USA. As the occurrence of this outcome requires the use of ICD-10 codes recorded by individual data sources, further adjustments to harmonise the gestational age at event occurrence cannot be made.
- The definition of stillbirth includes both antepartum and intrapartum stillbirths, but they cannot be distinguished in the data and will be grouped for the purposes of analysis. However, most of the stillbirths will be antepartum (73). Rates of intrapartum stillbirth are not expected to be different between exposed and unexposed cohorts.
- For some data sources, there are reporting restrictions based on the overall number of events. For example, in Danish data sources, when the outcome for a specific analysis, has less than 5 cases/observations, the specific result and other potentially related results cannot be reported. This is because of the potential of patient identification. This may be a potential limitation for analyses that require stratifications, such as the exploratory analysis to investigate the risk of CM by target body system organ class or the risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) by different pregnancy trimesters. In this instances, minimum and maximum values cannot be reported.

Also, some study analysis limitations must be acknowledged.

- Confounding by indication is common in comparative observational studies, and as the prescription of anifrolumab will depend on the assessment of the severity or activity of the disease, confounding by indication may occur. However, in this study, mitigation strategies, such as selection of only moderate/severe SLE cases has been planned to minimise the presence of confounding by indication. Furthermore, PS methods will be applied to minimise the potential for confounding due to differences in baseline characteristics between the exposed and unexposed groups.

- Regarding SLE SOC, the recordings of exposure based on prescription or dispensation alone do not guarantee that the patient ingested or injected the medication; the recordings of prescriptions are an expression of the treating physician's recommendation of the drug, and the prescriptions dispensed at community pharmacies and insurance claims registrations are an expression of the patients' intention to follow the recommendation from the physician.
- Considering the IV infusion as the current route of administration of anifrolumab, definition of exposure may be challenging. Outpatient visits with a recording of the relevant ATC and/or procedure codes, rather than the prescribing/dispensing records may be needed to determine the exposure status of study subjects. This could potentially lead to misclassification of the exposure (i.e., use of anifrolumab may be under-detected). Such a potential bias would move the measure of association towards the null, since the exposure status of the cohorts would not be fully established, and the cohorts of exposed and non-exposed pregnancies will therefore be more similar. The feasibility assessment was used to inform the selection of data sources to minimise the impact of this potential limitation.
- It is assumed that all prescribed drugs are filled and then taken by patients in a compliant manner. Non-compliance would result in misclassification of exposure and could cause an underestimation of the association between exposure and outcome.
- SLE severity and activity algorithms were adapted from a previously published algorithm used in other settings (50), including the data sources included in this study, to meet current criteria and recommendations of medication use in SLE patients. The assumptions made for the proposed adaptations were based on the experience of the study team, including database analysis expertise and clinical knowledge, but also on literature relevant to the subject, ensuring that sound assumptions are made.
- For some of the diagnoses included in the activity algorithm, distinguishing clinical manifestations (i.e., acute illnesses) that define active SLE from comorbidities may not be possible (e.g., renal impairment). Therefore, there is a possibility of misclassifying signs of active disease as a comorbidity. The impact of this misclassification is considered minimal as adjustments will be made for disease activity as well as disease severity.
- Since anifrolumab prescribing is not recommended in pregnancy, uptake of the drug in pregnancy may be extremely limited at least in the initial years of launch post-authorisation, thus hampering the feasibility of the safety analyses with respect to study size targets.
- Misclassification may occur in the derivation of date of conception. When based on LMP, the derivation of date of conception assumes an average cycle length of 28 days and that conception occurred mid-cycle. The LMP is also subject to accuracy of recall by the woman, regularity of her cycles, and variations in the interval between bleeding and anovulation. When based on gestational age, the degree of misclassification depends on the method and accuracy of the gestational age assessment. However, the misclassification is expected to be within a range of days for most patients.

- Immortal time bias cannot be ruled out. Immortal time is the period during which the outcome of interest cannot occur because of the study design (108). In this study, there is an immortal time because a pregnancy must "survive" until initiation of treatment to be considered as exposed. Nevertheless, it is expected that most pregnant women would have exposure to anifrolumab in the first trimester, and exposure to anifrolumab initiation in the second or third trimester is not expected to be frequent. Adding to this, most outcomes that terminate a pregnancy, such as a spontaneous abortion or an ectopic pregnancy, are expected to happen in the first trimester, thus minimising the impact of this bias.
- The probability of receiving anifrolumab may be related to the length of pregnancy, to some extent. The patients with longer pregnancies have more opportunity (i.e., time) to be prescribed anifrolumab, while the patients with shorter pregnancies have less opportunity (i.e., time) to be prescribed anifrolumab. This may cause a bias in the analysis as shorter pregnancies are more likely to be included in the study cohort unexposed to anifrolumab.
- Both maternal and paternal disease history can be important predictors of the risk of adverse pregnancy outcomes because of shared environmental and genetic risk factors. For this study, no paternal data will be available because linkage to paternal data is not possible for most data sources. Therefore, offspring whose fathers have a history of CM before pregnancy will not be excluded, and no adjustments can be made for potential confounders related to fathers.
- All relevant measured covariates will be entered into the PS and/or outcome regression models (comparative analyses in objectives 2, 4, 7, 9, 11, and 14). However, given that registries may not contain information on all relevant known and unknown confounding variables, residual confounding may still be present in the study results.

9.10 Other aspects

None.

10. PROTECTION OF HUMAN SUBJECTS

This non-interventional study involves the use of pseudonymised electronic healthcare records and does not affect the treatment of the patients. The study is conducted in accordance with the ENCePP Code of Conduct (34), the Guidelines for GPP (37), the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations. AstraZeneca, the Contract Research Organisation (CRO), other participating entities and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

The CRO will receive pseudonymised data including dummy SIDs only. AstraZeneca will not have access to the patient-level data at any time of the study.

Due to data protection restrictions in the study countries (e.g., Denmark and Finland), the cells in tables with few observations need to be masked. Thus, cells in tables must include a minimum of 5 observations and summary statistics can only be calculated if a minimum of 5 observations are used. In addition, minimum and maximum values may not be reported due to the protection of subjects' privacy in specific study countries (e.g., Denmark, Finland).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This PASS is designed to investigate the risk of MCM and mCM separately, as well as adverse pregnancy, birth, and infant outcomes (up to 1 year of age) in the offspring of women with SLE exposed *in utero* to anifrolumab and SLE SOC. According to Good Pharmacovigilance Practices (GVP) Module VI.C.1.2.1.2. "Non-interventional post-authorisation studies with a design based on secondary use of data", suspected adverse reactions reporting, in the form of Individual Case Safety Reports, is not required (36). Safety data addressing the objectives of the study will be summarised in each interim report and in the final study report.

11.1 Independent Ethics Committee/Institutional Review Board

The study protocol will be submitted to the responsible Institutional Review Board/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 (ERB) 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 ERB 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Progress Report

A progress report will be submitted 12 months after the PRAC endorsement of protocol. It will contain a status update of database applications and any relevant amendments pertaining to database applications.

12.2 Interim Analyses and Reporting

Two interim reports will be submitted 36 and 72 months after the progress report. The first interim report will include a detailed status update of database applications and relevant amendments. It will also include the number of patients recorded up to the reporting period and expectations for sufficient patient inclusion to address the study question.

Ethics applications and data request processes in the countries of interest vary. Therefore, it is noteworthy that, owing to variations in data access procedures, completion of the first interim report may range from 7 to 18 months. Additionally, it will provide only descriptive analyses of relevant data sources.

The second interim report, due 72 months after the progress report, will include all descriptive and comparative analyses related to primary and secondary objectives. Note that interim report 2 will not include exploratory analysis or sensitivity analyses or meta-analyses.

12.3 Final Analyses and Reporting

The final study report is planned 15 months after the second interim report (31 March 2032) and would include all descriptive, comparative, exploratory, sensitivity, and meta-analytic analyses for all data sources. The ability to achieve this milestone would be reviewed at the first interim report, when assumptions of anifrolumab uptake among pregnant women will be assessed.

The interim/progress report(s) and the final study report will be written in accordance with the GVP guidelines module VIII, (EMA/813938/2011), and the RECORD-PE checklist (ref: https://www.record-statement.org/checklist-pe.php).

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.

12.4 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 AstraZeneca.

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.

13. REFERENCES

1. Al Arfaj, A.S. and N. Khalil, *Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia.* Lupus, 2010. **19**(14): p. 1665-1673.
2. Almquist, J., et al., *Nonlinear Population Pharmacokinetics of Anifrolumab in Healthy Volunteers and Patients With Systemic Lupus Erythematosus.* J Clin Pharmacol, 2022. **62**(9): p. 1106-1120.
3. Andreoli, L., et al., *EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome.* Annals of the Rheumatic Diseases, 2017. **76**(3): p. 476-485.
4. Apostolopoulos, D. and E.F. Morand, *It hasn't gone away: the problem of glucocorticoid use in lupus remains.* Rheumatology (Oxford), 2017. **56**(suppl 1): p. i114-i122.
5. Arriens, C., et al., *Cell-bound complement activation products associate with lupus severity in SLE.* Lupus Sci Med, 2020. **7**(1).
6. Austin, P.C. and E.A. Stuart, *Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies.* Stat Med, 2015. **34**(28): p. 3661-79.
7. Barber, M.R.W. and A.E. Clarke, *Systemic lupus erythematosus and risk of infection.* Expert Rev Clin Immunol, 2020. **16**(5): p. 527-538.
8. Baumgart, D.C. and W.J. Sandborn, *Crohn's disease.* Lancet (London, England), 2012. **380**(9853): p. 1590-1605.
9. Bezin, J., et al., *The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology.* Pharmacoepidemiology and Drug Safety, 2017. **26**(8): p. 954-962.
10. Blotière, P.O., et al., *Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: An application to antiepileptic drug use in 4.9 million pregnant women in France.* Pharmacoepidemiol Drug Saf, 2018. **27**(7): p. 763-770.
11. Braga, A., et al., *Systemic lupus erythematosus and pregnancy: A retrospective single-center study of 215 pregnancies from Portugal.* Lupus, 2021. **30**(13): p. 2165-2175.
12. Buyon, J.P., et al., *Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study.* Annals of Internal Medicine, 2015. **163**(3): p. 153-163.
13. Carter, R.E., S.R. Lipsitz, and B.C. Tilley, *Quasi-likelihood estimation for relative risk regression models.* Biostatistics, 2005. **6**(1): p. 39-44.
14. Casazza, R.L., H.M. Lazear, and J.J. Miner, *Protective and Pathogenic Effects of Interferon Signaling During Pregnancy.* Viral Immunology, 2020. **33**(1): p. 3-11.
15. CDC. *Birth Defects - Metropolitan Atlanta Congenital Defects Program (MACDP)*. 12 Mar 2021 [cited 2023 23 Jan]; Available from: https://www.cdc.gov/ncbddd/birthdefects/macdp.html.
16. Chebbi, D., et al., *Familial lupus in Tunisia: a series of 14 families.* 2020.
17. Chen, Q., et al., *Too many covariates and too few cases? - a comparative study: Too many covariates and too few cases? - a comparative study.* Statistics in Medicine, 2016. **35**(25): p. 4546-4558.

18. Chen, W., et al., *Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification.* BMC Med Res Methodol, 2018. **18**(1): p. 63.
19. Chesnaye, N.C., et al., *An introduction to inverse probability of treatment weighting in observational research.* Clinical Kidney Journal, 2022. **15**(1): p. 14-20.
20. Clark, C.A., et al., *Preterm deliveries in women with systemic lupus erythematosus.* The Journal of Rheumatology, 2003. **30**(10): p. 2127-2132.
21. Clowse, M.E., et al., *A national study of the complications of lupus in pregnancy.* Am J Obstet Gynecol, 2008. **199**(2): p. 127 e1-6.
22. Clowse, M.E., et al., *The impact of increased lupus activity on obstetric outcomes.* Arthritis Rheum, 2005. **52**(2): p. 514-21.
23. Conce, P.W., D.-M. Christine, and W. Keele, *D1.2 Core evidence elements for generating medication safety evidence for pregnancy using population-based data: Core data elements, design and analytical foundations.* 2021.
24. Correa-Villaseñor, A., et al., *The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the centers for disease control and prevention.* Birth Defects Research Part A: Clinical and Molecular Teratology, 2003. **67**(9): p. 617-624.
25. Costenbader, K.H., et al., *Cigarette smoking and the risk of systemic lupus erythematosus: A meta-analysis.* Arthritis & Rheumatism, 2004. **50**(3): p. 849-857.
26. D'Agostino McGowan, L., *Sensitivity Analyses for Unmeasured Confounders.* Curr Epidemiol Rep, 2022. **9**: p. 361–375.
27. Dao, K.H. and B.L. Bermas, *Systemic Lupus Erythematosus Management in Pregnancy.* International Journal of Women's Health, 2022. **14**: p. 199-211.
28. Davis-Porada, J., et al., *Low frequency of flares during pregnancy and post-partum in stable lupus patients.* Arthritis Res Ther, 2020. **22**(1): p. 52.
29. de Jesus, G.R., et al., *Understanding and Managing Pregnancy in Patients with Lupus.* Autoimmune Diseases, 2015. **2015**: p. 943490.
30. Demirkaya, E., et al., *New Horizons in the Genetic Etiology of Systemic Lupus Erythematosus and Lupus-Like Disease: Monogenic Lupus and Beyond.* Journal of Clinical Medicine, 2020. **9**(3): p. 712.
31. Dennis, G.J., *Belimumab: a BLyS-specific inhibitor for the treatment of systemic lupus erythematosus.* Clinical Pharmacology and Therapeutics, 2012. **91**(1): p. 143-149.
32. Dörner, T. and R. Furie, *Novel paradigms in systemic lupus erythematosus.* The Lancet, 2019. **393**(10188): p. 2344-2358.
33. EMA, *Benlysta.* European Medicines Agency, 2018.
34. EMA. *The ENcePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies*. 2018; Available from: https://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct.pdf.
35. EMA, *The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 5).* 2010(EMA/95098/2010).
36. EMA. *Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products*. 2017; Available from:

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf.
37. EMA, *Guidelines for good pharmacoepidemiology practice (GPP).* Pharmacoepidemiol Drug Saf, 2016. **25**(1): p. 2-10.
38. EMA, *Saphnelo.* European Medicines Agency, 2021.
39. Erazo-Martínez, V., et al., *Systemic erythematosus lupus and pregnancy outcomes in a Colombian cohort.* Lupus, 2021. **30**(14): p. 2310-2317.
40. Euro-Peristat Scientific, C., *European Perinatal Health Report 2015 - Euro-Peristat.* 2015.
41. Eurocat, *EUROCAT Guide 1.5: Instruction for the registration of congenital anomalies.* 2022.
42. Eurostat. *Population change - Demographic balance and crude rates at national level.* 2022 18/11/2022]; Available from: https://ec.europa.eu/eurostat/cache/metadata/en/demo_r_gind3_esms.htm.
43. Fanouriakis, A., et al., *2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.* Annals of the Rheumatic Diseases, 2019. **78**(6): p. 736-745.
44. Feldkamp, M.L., L.D. Botto, and J.C. Carey, *Reflections on the etiology of structural birth defects: Established teratogens and risk factors.* Birth Defects Res A Clin Mol Teratol, 2015. **103**(8): p. 652-5.
45. Fischer-Betz, *Pregnancy course and outcome in SLE patients compared to patients with other connective tissue and inflammatory rheumatic diseases – Real World data from a prospective Pregnancy Register.* ACR, San Diego, 03-08, 2017.
46. Flenady, V., et al., *Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis.* Lancet (London, England), 2011. **377**(9774): p. 1331-1340.
47. Furie, R., et al., *Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus.* Arthritis & Rheumatology, 2017. **69**(2): p. 376-386.
48. Furie, R.A., et al., *Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial.* The Lancet Rheumatology, 2019. **1**(4): p. e208-e219.
49. Garrido, M.M., et al., *Methods for Constructing and Assessing Propensity Scores.* Health Services Research, 2014. **49**(5): p. 1701-1720.
50. Garris, C., et al., *Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan.* Journal of Medical Economics, 2013. **16**(5): p. 667-677.
51. Gladman, D.D., et al., *The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications.* J Rheumatol, 2010. **37**(4): p. 754-8.
52. Goldenberg, R.L., et al., *Epidemiology and causes of preterm birth.* Lancet (London, England), 2008. **371**(9606): p. 75-84.
53. González, L.A. and G.S. Alarcón, *The evolving concept of SLE comorbidities.* Expert Rev Clin Immunol, 2017. **13**(8): p. 753-768.
54. Goobie, G.C., et al., *Malignancies in systemic lupus erythematosus: a 2015 update.* Curr Opin Rheumatol, 2015. **27**(5): p. 454-60.

55. Gordon, C., et al., *The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults.* Rheumatology, 2017. **57**(1): p. e1-e45.
56. Hallare, J. and V. Gerriets, *Half Life*. 2022, StatPearls Publishing: Treasure Island (FL).
57. Harris, B.S., et al., *Risk Factors for Birth Defects.* Obstetrical & Gynecological Survey, 2017. **72**(2): p. 123-135.
58. He, H., et al., *Association of Maternal Autoimmune Diseases With Risk of Mental Disorders in Offspring in Denmark.* JAMA Netw Open, 2022. **5**(4): p. e227503.
59. Honein, M.A. and L.J. Paulozzi, *Birth defects surveillance: assessing the "gold standard".* Am J Public Health, 1999. **89**(8): p. 1238-40.
60. HSS, *A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTATM (belimumab).* 2012.
61. Jamal-Allial, A.H., X. Avula, R. Dinh, J. Lanes, S, *Developing Methodology To Estimate Gestational Age Using Administrative Claims" ICPE All Access conference abstracts #4957*, in *Pharmacoepidemiol Drug Saf*. 2020. p. 552.
62. Jentink, J., et al., *Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations.* New England Journal of Medicine, 2010. **362**(23): p. 2185-2193.
63. Jiang, M., et al., *High-risk factors for adverse pregnancy outcomes in systemic lupus erythaematosus: a retrospective study of a Chinese population.* BMJ Open, 2021. **11**(11): p. e049807.
64. Kowaleski, J., *State definitions and reporting requirements for live births, fetal deaths, and induced terminations of pregnancy* 1997, Natinal Center for Health Statistics: Hyattsville, Maryland.
65. Kuss, O., M. Blettner, and J. Börgermann, *Propensity Score: an Alternative Method of Analyzing Treatment Effects.* Dtsch Arztebl Int, 2016. **113**(35-36): p. 597-603.
66. Langham, J., et al., *Disease severity, flares and treatment patterns in adults with systemic lupus erythematosus in the UK: a real-world observational retrospective cohort analysis.* Rheumatology Advances in Practice, 2021. **5**(3): p. rkab061.
67. Larosa, M., et al., *Evaluation of lupus anticoagulant, damage, and remission as predictors of pregnancy complications in systemic lupus erythematosus: the French GR2 study.* Rheumatology (Oxford), 2022. **61**(9): p. 3657-3666.
68. Lash, T.L., et al., *Quantitative Bias Analysis in Regulatory Settings.* Am J Public Health, 2016. **106**(7): p. 1227-30.
69. Lichtman, E.I., S.M. Helfgott, and M.A. Kriegel, *Emerging therapies for systemic lupus erythematosus--focus on targeting interferon-alpha.* Clin Immunol, 2012. **143**(3): p. 210-21.
70. Linnakaari, R., et al., *Trends in the incidence, rate and treatment of miscarriage-nationwide register-study in Finland, 1998-2016.* Hum Reprod, 2019. **34**(11): p. 2120-2128.
71. Liossis, S.N. and C. Staveri, *What's New in the Treatment of Systemic Lupus Erythematosus.* Frontiers in Medicine, 2021. **8**.
72. Masnoon, N., et al., *What is polypharmacy? A systematic review of definitions.* BMC Geriatrics, 2017. **17**: p. 230.

73. McNamara, K., K. O'Donoghue, and R.A. Greene, *Intrapartum fetal deaths and unexpected neonatal deaths in the Republic of Ireland: 2011 - 2014; a descriptive study.* BMC Pregnancy Childbirth, 2018. **18**(1): p. 9.
74. Meissner, Y., et al., *Pregnancy and neonatal outcomes in women with axial spondyloarthritis: pooled data analysis from the European Network of Pregnancy Registries in Rheumatology (EuNeP).* Annals of the rheumatic diseases, 2022.
75. Michel, M., et al., *Familial Lupus Erythematosus: Clinical and Immunologic Features of 125 Multiplex Families.* Medicine, 2001. **80**(3): p. 153-158.
76. Mikolajczyk, R.T., et al., *A global reference for fetal-weight and birthweight percentiles.* The Lancet, 2011. **377**(9780): p. 1855-1861.
77. Miller, F.W., et al., *Epidemiology of environmental exposures and human autoimmune diseases: Findings from a National Institute of Environmental Health Sciences Expert Panel Workshop.* Journal of Autoimmunity, 2012. **39**(4): p. 259-271.
78. Mohangoo, A.D., et al., *Gestational age patterns of fetal and neonatal mortality in Europe: results from the Euro-Peristat project.* PloS One, 2011. **6**(11): p. e24727.
79. Morand, E.F., et al., *Trial of Anifrolumab in Active Systemic Lupus Erythematosus.* New England Journal of Medicine, 2020. **382**(3): p. 211-221.
80. Nikolopoulos, D.S., et al., *Transition to severe phenotype in systemic lupus erythematosus initially presenting with non-severe disease: implications for the management of early disease.* Lupus Sci Med, 2020. **7**(1).
81. Ntali, S., et al., *Remission or low disease activity at pregnancy onset are linked to improved foetal outcomes in women with systemic lupus erythematosus: results from a prospective observational study.* Clin Exp Rheumatol, 2022. **40**(9): p. 1769-1778.
82. Nybo Andersen, A.M., et al., *Maternal age and fetal loss: population based register linkage study.* Bmj, 2000. **320**(7251): p. 1708-12.
83. Osterman, M., et al., *Births: Final Data for 2020.* Natl Vital Stat Rep, 2021. **70**(17): p. 1-50.
84. Perrotta, K., et al., *Pregnancy outcomes following maternal treatment with rituximab prior to or during pregnancy: a case series.* Rheumatol Adv Pract, 2021. **5**(1): p. rkaa074.
85. Petri, M., *Long-term outcomes in lupus.* The American Journal of Managed Care, 2001. **7**(16 Suppl): p. S480-485.
86. Petri, M., et al., *Belimumab use during pregnancy: a summary of birth defects and pregnancy loss from belimumab clinical trials, a pregnancy registry and postmarketing reports.* Ann Rheum Dis, 2022.
87. Petri, M., et al., *Predictors of organ damage in systemic lupus erythematosus: The Hopkins Lupus Cohort.* Arthritis & Rheumatism, 2012. **64**(12): p. 4021-4028.
88. Polifka, J.E. and J.M. Friedman, *Medical genetics: 1. Clinical teratology in the age of genomics.* Cmaj, 2002. **167**(3): p. 265-73.
89. Pons-Estel, G.J., et al., *Understanding the Epidemiology and Progression of Systemic Lupus Erythematosus.* Seminars in Arthritis and Rheumatism, 2010. **39**(4): p. 257-268.
90. Pons-Estel, G.J., M.F. Ugarte-Gil, and G.S. Alarcón, *Epidemiology of systemic lupus erythematosus.* Expert Review of Clinical Immunology, 2017. **13**(8): p. 799-814.
91. Ramsey-goldman, R. and S. Manzi, *55 - Systemic Lupus Erythematosus.* Women and Health, 2000: p. 704-723.

92. Rees, F., et al., *The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012.* Annals of the Rheumatic Diseases, 2016. **75**(1): p. 136-141.
93. Rossen, L.M., K.A. Ahrens, and A.M. Branum, *Trends in Risk of Pregnancy Loss Among US Women, 1990-2011.* Paediatr Perinat Epidemiol, 2018. **32**(1): p. 19-29.
94. Rossides, M., et al., *Asthma in Children of Mothers With Systemic Lupus Erythematosus and the Role of Preterm Birth.* Arthritis Care Res (Hoboken), 2018. **70**(8): p. 1269-1274.
95. Ruiz-Arruza, I., et al., *Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus.* Rheumatology (Oxford), 2014. **53**(8): p. 1470-6.
96. Sawah, S.A., et al., *Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus—the Hopkins Lupus Cohort.* Lupus Science & Medicine, 2015. **2**(1): p. e000066.
97. Schwarzer, G., *meta: An R package for meta-analysis.* R news, 2007. **7**(3): p. 40-45.
98. Semih Demirtaş, M., *The Pathogenesis of Congenital Anomalies: Roles of Teratogens and Infections*, in *Congenital Anomalies in Newborn Infants - Clinical and Etiopathological Perspectives*. 2021, IntechOpen.
99. Singh, N., et al., *Birth outcomes and re-hospitalizations among pregnant women with rheumatoid arthritis and systemic lupus erythematosus and their offspring.* Arthritis Care Res (Hoboken), 2023.
100. Sinicato, N.A., P.A. da Silva Cardoso, and S. Appenzeller, *Risk factors in cardiovascular disease in systemic lupus erythematosus.* Curr Cardiol Rev, 2013. **9**(1): p. 15-9.
101. Smolen, J.S., et al., *New therapies for treatment of rheumatoid arthritis.* Lancet (London, England), 2007. **370**(9602): p. 1861-1874.
102. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update.* Ann Rheum Dis, 2023. **82**(1): p. 3-18.
103. Smyth, A., et al., *A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis.* Clinical journal of the American Society of Nephrology: CJASN, 2010. **5**(11): p. 2060-2068.
104. SNDS. *National Health Data System*. 09 January 2023]; Available from: https://www.snds.gouv.fr/SNDS/Composantes-du-SNDS.
105. Soltanifar, S. and R. Russell, *The National Institute for Health and Clinical Excellence (NICE) guidelines for caesarean section, 2011 update: implications for the anaesthetist.* International Journal of Obstetric Anesthesia, 2012. **21**(3): p. 264-272.
106. Speyer, C.B., et al., *Comparison of an administrative algorithm for SLE disease severity to clinical SLE Disease Activity Index scores.* Rheumatol Int, 2020. **40**(2): p. 257-261.
107. Stürmer, T., et al., *Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs.* Journal of Internal Medicine, 2014. **275**(6): p. 570-580.
108. Suissa, S., *Immortal time bias in pharmaco-epidemiology*. American Journal of Epidemiology, 2008. **167**(4): p. 492-499.
109. TERRIS. *The Teratogen Information System*. 2021 [cited 2022 February 21, 2022]; Available from: https://deohs.washington.edu/teris/.

110. Thamer, M., et al., *Prednisone, Lupus Activity, and Permanent Organ Damage.* The Journal of Rheumatology, 2009. **36**(3): p. 560-564.
111. Thunbo, M.O., et al., *Polypharmacy in polymorbid pregnancies and the risk of congenital malformations-A systematic review.* Basic Clin Pharmacol Toxicol, 2022. **130**(3): p. 394-414.
112. VanderWeele, T.J. and P. Ding, *Sensitivity Analysis in Observational Research: Introducing the E-Value.* Ann Intern Med, 2017. **167**(4): p. 268-274.
113. Vinet, E., et al., *A population-based assessment of live births in women with systemic lupus erythematosus.* Ann Rheum Dis, 2012. **71**(4): p. 557-9.
114. Vinet, E., et al., *Major congenital anomalies in children born to women with systemic lupus erythematosus.* Arthritis Research & Therapy, 2012. **14**(3): p. A11.
115. Vinet, É., et al., *Increased congenital heart defects in children born to women with systemic lupus erythematosus: results from the offspring of Systemic Lupus Erythematosus Mothers Registry Study.* Circulation, 2015. **131**(2): p. 149-156.
116. Wagner, S.J., et al., *Maternal and foetal outcomes in pregnant patients with active lupus nephritis.* Lupus, 2009. **18**(4): p. 342-347.
117. Wallenius, M., et al., *Systemic lupus erythematosus and outcomes in first and subsequent births based on data from a national birth registry.* Arthritis Care & Research, 2014. **66**(11): p. 1718-1724.
118. Wang, Y., et al., *Update on prevalence of diagnosed systemic lupus erythematosus (SLE) by major health insurance types in the US in 2016.* BMC Research Notes, 2022. **15**(1): p. 5.
119. WHO, *WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development.* 2006.
120. Wu, J., et al., *Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study.* BMJ Open, 2018. **8**(4): p. e020909.
121. Zhu, L., et al., *Maternal and Live-birth Outcomes of Pregnancies following Assisted Reproductive Technology: A Retrospective Cohort Study.* Sci Rep, 2016. **6**: p. 35141.
122. Zomerdijk, I.M., et al., *Dispensing of potentially teratogenic drugs before conception and during pregnancy: a population-based study.* Bjog, 2015. **122**(8): p. 1119-29.

Appendix A. List of stand-alone documents

None

Appendix B. ENCePP checklist for study protocols

Study title: A Non-interventional Multi-database Post-Authorisation Study to Assess Pregnancy-related Safety Data from Women with SLE Exposed to Anifrolumab

EU PAS Register® number: Study not yet registered **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[18]	☒	☐	☐	6
1.1.2 End of data collection[19]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.4, 7.5
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1
2.1.3 The target population? (i.e. population or sub-group to whom the study results are intended to be generalised)	☒	☐	☐	8.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8.1, 9.5
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[18] 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.

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

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)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
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))	☒	☐	☐	8.1, 9.5, 9.7
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1, 9.2, 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2, 9.4
	4.2.4 Disease/indication	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

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)	☒	☐	☐	9.3.1 Appendix D
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7.5 Appendix D
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.7.5
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

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?	☒	☐	☐	9.3.2 Appendix D
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2 Appendix D
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)	☒	☐	☐	9.3.2, 9.7.5 Appendix D
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)	☒	☐	☐	9.7.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.3.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.5

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.1, 9.3.1, 9.3.3, 9.7.5

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)	☒	☐	☐	9.4 Appendix C
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4 Appendix C
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4 Appendix C
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4 Appendix C
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4 Appendix C
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4 Appendix C
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4 Appendix C
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4 Appendix C
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4 Appendix C
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Separate subsections for each country.

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4	Are stratified analyses included?	☐	☒	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.1
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.5
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
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).	☒	☐	☐	9.9
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)	☒	☐	☐	9.3.1, 9.5, 9.9

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?	☒	☐	☐	10, 11.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6, 10

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?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.4

Comments:

Name of the primary investigator: Ana Cristina Santos

Date: 28/August/2023

Signature: _____

Appendix C. Description of data sources and data availability

Table 14: Data sources included in the feasibility assessment

Country	Data source	Assessed in feasibility assessment	Selected for this study	Rationale for decision / Considerations
USA	Carelon Research	Yes	Yes	Ability to capture anifrolumab exposure and primary outcomes Number of pregnancies captured
	DAPI	Yes	Yes	Ability to capture anifrolumab exposure and primary outcomes Number of pregnancies captured
	CVS Aetna	Yes	No	Stillbirth not available Larger USA data sources are available
	OM1 SLE Registry	Yes	No	Does not capture pregnancy outcomes
Denmark	National Registers	Yes	Yes	Ability to capture anifrolumab exposure and primary outcomes
Finland	National Registers	Yes	Yes	Ability to capture anifrolumab exposure and primary outcomes
Sweden	National Registers	Yes	No	Anifrolumab exposure is not captured without linkage to additional data sources
UK	CPRD-HES (GOLD)	Yes	No	Anifrolumab exposure is not captured May change in later years therefore keep as back up option
France	SNDS	Yes	Yes	Stillbirth not available Ability to capture anifrolumab exposure (if included in the list of

Country	Data source	Assessed in feasibility assessment	Selected for this study	Rationale for decision / Considerations
				expensive drugs) and primary outcome
Spain	SIDIAP	Yes	No	Ability to capture anifrolumab exposure and primary outcomes but limited sample size
	RELESSER	Yes	No	Dates for diagnosis, hospitalisation and exposure not available. Information on outcomes is limited
Germany	SHI	Yes	No	Ability to capture anifrolumab exposure and primary outcomes Impossible to assess the overlap between SHI and RHEKISS
	RHEKISS	Yes	Yes	RHEKISS has a larger number of pregnancies captured compared to SHI Limited hospital drug capture, only if treatment is prescribed in retail hospital setting or out-patient prescription that is reimbursed and not part of a diagnosis related group
International	The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)	Yes	No	The SLICC data base stopped actively collecting data in July 2022, therefore exposure data for the study period (2022-2032) will be unavailable

Abbreviations used in the table: DAPI, Dynamic Assessment of Pregnancies and Infants; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; SNDS, National Health Data System; SIDIAP, System for the Development of Primary Care Research Database; RELESSER, Spanish Society of Rheumatology Systemic Lupus Erythematosus Registry; SHI, Statutory Health Insurance; RHEKISS, Rheuma-Kindwunsch und Schwangerschaft

Table 15: Data source description

Data source	Datasets	Type of data and brief description
Finnish national health and socioeconomic registries	Population Information System	Source of data for basic information on civil status, employment status and educational level and immigration/emigration data since 1969 (from 1971 in electronic format). The Population Information System includes basic information about Finnish citizens and foreign citizens residing permanently in Finland and has virtually 100% coverage.
	Care Register for Health Care (HILMO)	Care Register for Health Care established in 1994 containing data on patients discharged from inpatient care, count of patients in inpatient care in health centres and hospitals on 31 December; day surgeries and specialised outpatient care in Finland. The ICD-10 coding system has been used for the duration of our study period.
	Register of Primary Health Care Visits (AvoHILMO)	All outpatient primary health care delivered in Finland including type of visit, diagnoses, procedures and intervention is available since 2011. The ICPC-2 coding system has been used for the duration of our study period.
	Finnish Prescription Registry	Source of all reimbursed outpatient dispensations of prescription. Recorded information includes ATC code, package size, strength, number of packages and number of DDD since 1994 in Finland.
	Medical Birth Register (MBR)	Source of information on date of birth, LMP, gestational age, vital status, head circumference, weight at birth, 1 and 5-minute Apgar score, smoking during pregnancy, date of infant's diagnoses by the age of 7 days. Data available since 1987.
	Register of Congenital malformations	Register of Congenital Malformations is managed by THL and has data since 1963. The register contains data on children who have been diagnoses with at least one major congenital chromosomal or structural anomalies. There is also data on other congenital anomalies such us congenital hypothyroidism and teratomas, detected or suspected in stillborn and live-born infants and foetuses. Anomalies are recorded in accordance with the EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) guidance. The congenital anomalies are recorded during the first year of the child.
	Statistics Finland	Source of data for demographic as well as socioeconomic (including education) data of the Finnish population.
Danish national health and socioeconomic registries	Danish Civil Registration System	Source of data for basic information on personal identifiers, vital status, migration status and marital status.
	National Health Insurance Service Register (NHISR)	Source of data on the services supported by public health insurance and provided by general practitioners and specialists in private practice outside the secondary setting at hospitals. Information on the description of services and 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 is available from 1990 and onwards.

Data source	Datasets	Type of data and brief description
	National Patient Registry	Source of data for all diagnosis outcomes of interest at public and private hospitals (somatic and psychiatric wards). The registry tracks primary and secondary diagnoses with dates and information about procedures and treatment. The ICD-10 coding system has been used for the duration of our study period (since 1994). Diagnoses at general practitioners, psychiatrists (and other specialists) who have their own private practice are not registered in the NPR.
	Register of Medicinal Product Statistics (RMPS)	Source of data for all dispensations of prescription medications at community pharmacies at individual patient-level. Recorded information includes data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 1995.
	Medical Birth Registry (MBR)	Source of data on gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, congenital malformations, smoking during pregnancy, BMI, LMP and date of conception (estimated from gestational age and date of birth). Data available since 1973, with a data break in 1996-1997 due to improvement of register.
	Statistics Denmark	Source of data for demographic as well as socioeconomic (including education, special needs education) data of the Danish population.
Système national des données de santé (SNDS)	Système national d'information inter régimes de l'assurance maladie (SNIIRAM)	Source of information about patients' demographics, presence of long-term diseases (« *affection de longue durée* », with a total of 3448 ICD-10 codes available), dispensed medication in ATC code, type of medical and paramedical (except psychologists) specialty, lab tests without results and duration of hospital admissions in France. Data available since 2008.
	Programme de médicalisation des systèmes d'information (PMSI)	Source of data on diagnoses (main and associated) in ICD-10 and medical procedures in Common Classification System of Medical Acts in public and private hospitals in France. Maternity data including maternal age at delivery, LMP, gestational week, date of birth, gender, vital status of the baby and neonatal level of care is also available. Data available since 2006.
The German inflammatory rheumatic disease and pregnancy register	Rheuma-Kindwunch und Schwangershaft (RHEKISS)	At baseline, socio-demographics, prior pregnancies, comorbidities, treatment, disease activity and severity as well as antibody status are reported. During pregnancy, rheumatologists and patients report drug treatments, course of the maternal disease, development of foetus and complications once per trimester. After delivery, the pregnancy outcome and child development during the first two years of life are collected.
The USA administrative, medical and pharmacy	Carelon Research	Data from health plan members. Source of information about patient health plan enrolment data, inpatient and outpatient medical care, outpatient prescription drug use, outpatient laboratory test results, and health care utilisation. Diagnoses and procedures are captured by ICD-

Data source	Datasets	Type of data and brief description
billing or claims data, electronic health records		10, Current Procedural Terminology, and Healthcare Common Procedure Coding System. Drug dispensing claims are captured by National Drug Codes. For women with a recorded delivery, linked infants can be identified. Data available since 2006.
	The Optum Dynamic Assessment of Pregnancies and Infants (DAPI)	Information on medical and pharmacy claims, outpatient clinical laboratory results, socioeconomic measures, and patient enrolment data from members of a USA health insurer. Information on pregnancies and link between health care data of mothers with that of their infants. Diagnoses, procedures, and medication exposures captured in the ICD-10 coding system Current Procedural Terminology; Healthcare Common Procedure Coding System; and National Drug Codes. Data available since 1994.

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision; ICPC-2, International classification of primary care, version 2; ATC, Anatomical therapeutic chemical classification system; DDD, Defined daily dose; LMP, Last menstrual period; THL, Finnish Institute for Health and Welfare; NPR, National patient registry; BMI, Body mass index; USA, United States of America

Table 16: Availability of the study outcomes

	USA		Denmark	Finland	France	Germany
Outcome	**Carelon Research**	**DAPI**	**National Registers**	**National Registers**	**SNDS**	**RHEKISS**
MCM	Yes	Yes	Yes	Yes	Yes	Yes
mCM	Yes	Yes	Yes	Yes	Yes	Yes
Spontaneous abortions	Yes	Yes	Yes	Yes	Partial[1]	Yes
Ectopic pregnancy	Yes	Yes	Yes	Yes	Yes	Yes
Elective termination	Yes	Yes	Yes	Yes	Yes	Yes
Infections requiring hospitalisation during pregnancy	Yes	Yes	Yes	Partial[2]	Yes	Yes
Stillbirth	Yes	Yes	Yes	Yes	Yes	Yes
Caesarean section	Yes	Yes	Yes	Yes	Yes	Yes
Preterm birth	Yes	Yes	Yes	Yes	Yes	Yes
Small for gestational age	Yes	Yes	Yes	Yes	Yes	Yes
Growth and development up to 1 year of age	Yes	Partial[3]	Partial[4]	Partial[5]	Partial[6]	Yes

Abbreviations used in the table: USA, United States of America; DAPI, Dynamic Assessment of Pregnancies and Infants; SNDS, National Health Data System; RHEKISS, Rheuma-Kindwunsch und Schwangerschaft; MCM, Major congenital malformations; mCM, Minor congenital malformations

[1] Spontaneous abortions not managed in inpatient setting or not notified by mothers are not included.
[2] There is no direct variable to determine hospitalisations due to infection. If an ICD-10 code for infection was used as the primary reason for health care visit, then it is captured in the national registers.
[3] May be extracted from medical records for a subset of patients.
[4] High completeness for weight and length/height (with dates) in the Children's Database, but number and frequency of measurements are unknown.
[5] Hospital visits with a linked ICD-10 code are available. Height and weight might be available from HILMO and AvoHILMO.
[6] The database is used for planning and funding purposes and is subject to coding quality control.

Table 17: Availability of maternal characteristics, other baseline characteristics and covariates

Databases/Countries	USA		Denmark	Finland	France	Germany
	Carelon Research	DAPI	National Registers	National Registers	SNDS	RHEKISS
Date at first SLE diagnosis	Partial[1]	Yes	Yes	Yes	Yes	Yes (year)
Age at conception (LMP2)	No[2]	Yes	Yes	Partial[3]	Yes	Yes
Socioeconomic status at conception	No	Not provided	Yes	No	Yes (via proxy)	No
Ethnicity	No	Yes	No	No	No	No
Pre-pregnancy BMI	Partial[1,4]	Yes	Yes[5]	Yes[5]	No	Yes
Smoking (during pregnancy)	Yes	Yes	Yes	Yes	No	Yes
Alcohol and Substance abuse (during pregnancy)	Yes	Yes	Yes	Yes	No	Yes
Pre-pregnancy diabetes	Yes	Yes	Yes	Yes	Yes	Yes
Gestational diabetes	Yes	Yes	Yes	Yes	Yes	Yes
Pre-eclampsia	Partial[1]	Not provided	Yes	Partial[6]	Yes	Yes
Previous spontaneous abortions	Partial[1]	Not provided	Partial[7]	Partial[8]	Partial [9]	Yes
Previous stillbirths	Partial	Not provided	Yes	Yes[8]	Yes	Yes
Previous elective terminations of pregnancies	Partial[1]	Not provided	Yes	Yes	Partial[9]	Yes
Previous preterm births	Partial[1]	Not provided	Yes	Yes	Yes	Yes
Previous small for gestational age births	Partial[1]	Not provided	Yes	Yes	Yes	Yes
Laboratory results and date of testing[10]	Partial	Not provided	Yes	Yes	No	Yes
Number of healthcare visits six months before LMP2 and during pregnancy[11]	Yes	Yes	Yes	Yes[12]	Yes	Partial[13]

Abbreviations used in the table: LMP2, Last menstrual period plus 2 weeks; SLE, Systemic lupus erythematosus; UK, United Kingdom; USA, United States of America

[1] These data are available through medical claims but may be incomplete if diagnosis occurred prior to entry into an Anthem health plan.

[2] Not captured by claims but will be calculated using an algorithm for gestational age which prioritizes the week of gestation using Z3A% codes-ICD-10CM (primary approach). Single Z3A ± 3 days of the estimated delivery date is preferred, followed by at least two Z3A codes within a lookup period that represent a distinct pregnancy in a monotonically decreasing order. If Z3A codes are not available, other codes with a range of gestational age (GA) are used, with codes indicating a specific GA or longer GA being given priority. An approximate midpoint of GA +4 days is applied for codes with the GA range. If no codes indicating GA are found, a fixed GA is assigned based on trimester or term status (61).

[3] The potential age at conception can be calculated based on the delivery and mother's birth date.

[4] Code Z68 is introduced in the ICD-10 version of medical claims, so it is possible to obtain it from the claims for 2015 and onwards.

[5] Can be derived from weight and height, but completeness is unknown.

[6] Available if hospital visits with ICD-10 code as main reason.

[7] Previous spontaneous abortion is only captured (in NPR) if the patient is in contact with a hospital regarding this. This information is not available if only a GP or a specialist in private practice (e.g., gynaecologist) is contacted regarding this because diagnoses are not available. For that reason, many early spontaneous abortions will not be captured.
[8] Available (amount available in Medical Birth Register, Register of Congenital Malformations and Register of Induces Abortions. Available in HILMO and AvoHILMO if ICD-10 code was the main reason for health care visit).
[9] No information was provided by the data source.
[10] Testing for antinuclear antibodies, anti-dsDNA antibodies, anti-Smith antibodies, complement proteins (C3, C4, CH50) or blood panel including kidney function tests.
[11] Available, if ICD-10 code was the main reason for health care visit.
[12] Available if coded during visits but it is unknown to the level of completeness or availability.
[13] Only partially available since women are either enrolled when they want to conceive or when they are already pregnant.

Appendix D. Exemplar Codelists

Codelists included in this appendix are still under development and will be finalised in the SAP.

Table 18: Inclusion and exclusion criteria for the overall study population, EXEMPLARY codelist

Inclusion criteria for the overall source population	ICD-10
Systemic lupus erythematosus	
Systemic lupus erythematosus with organ or system involvement	M32.1
Other forms of systemic lupus erythematosus	M32.8
Systemic lupus erythematosus, unspecified	M32.9
Exclusion criteria for the overall source population	**ICD-10**
Multifetal pregnancies	
Multiple gestation	O30
IVF	
In vitro fertilisation	Z31.2

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision; IVF, In vitro fertilisation

Table 19: Drug classes and active substances used in SLE SOC [1]

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

Drug/Procedure	ATC codes
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

Abbreviations used in the table: ATC, Anatomical therapeutic chemical classification system

[1] drugs that have been investigated in failed SLE clinical trials have not been included in the list of SLE SOC drugs. The list does not consider emerging therapeutic agents (in phase II/III development), of which the efficacy in the management of SLE has not been established.
[2] As Mycophenolate Mofetil.

Table 20: Confirmed teratogenic drugs

This list has been developed and will be continually updated based on the data available in the TERIS database of teratogenic agents and recent publications (44, 88, 109, 122)

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
Androgen	Methyltestosterone	G03BA02 G03EK01 G03EA01	2.5 to 3.5 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters
	Testosterone (unmodified)	G03BA03 G03EA02	10 to 100 min	1 day prior to LMP2	1st, 2nd, and 3rd trimesters
	Testosterone cypionate	G03BA03	8 days	40 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Testosterone enanthate	G03BA03	4.5 days	23 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Mesterolone	G03BB01	12 to 13 h	3 days prior to LMP2	Not in TERIS
	Nandrolone	A14AB01	144 to 288 h	2 months prior to LMP2	Not in TERIS
	Oxandrolone	A14AA08	13.3 h	3 days prior to LMP2	Not in TERIS

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Prasterone	A14AA07 G03XX01 G03EA03	216 h	45 days prior to LMP2	Not in TERIS
Angiotensin II receptor antagonist	Candesartan	C09CA06 C10BX19 C09DB07 C09DA06 C09DX06	9 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Eprosartan	C09CA02 C09DA02	5 to 9 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Irbesartan	C09CA04 C09DB05 C09DA04 C09DX07	11 to 15 h	4 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Losartan	C09CA01 C09DB06 C09DA01	2 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters
	Olmesartan	C09CA08 C09DB02 C09DA08 C09DX03	13 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Tasosartan	C09CA05	Not available, but half-life of ARBs range from 1 to 3 days	15 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Telmisartan	C09CA07 C09DB04 C09DA07 C09DX08	24 h	5 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Valsartan	C09CA03 C10BX10	6 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
		C09DX02 C09DB01 C09DA03 C09DB08 C09DX05 C09DX04 C09DX01			
Angiotensin-converting enzyme inhibitors	Benazepril	C09AA07 C09BB13 C09BA07	10 to 11 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Captopril	C09AA01 C09BA01	2 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters
	Cilazapril	C09AA08 C09BA08	9 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Enalapril	C09AA02 C09BA02 C09BB02 C09BB06	11 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Fosinopril	C09AA09 C09BA09	11.5 to 14 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Lisinopril	C09AA03 C09BB03 C09BA03 C10BX07	12.6 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Moexipril	C09AA13 C09BA13	2 to 9 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Perindopril	C09AA04 C10BX15 C10BX12 C10BX11	0.8 to 1 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
		C09BB04 C09BX02 C09BA04 C09BX01 C09BX04 C10BX14 C10BX13			
	Quinapril	C09AA06 C09BA06	3 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters
	Ramipril	C09AA05 C10BX06 C10BX18 C09BB07 C09BX05 C09BA05 C09BB05 C09BX03 C10BX17 C10BX04	13 to 17 h	4 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Trandolapril	C09AA10 C09BB10	6 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
Antiarrhythmic	Amiodarone	C01BD01	61 days	10 months prior to LMP2	1st, 2nd, and 3rd trimesters
Antibiotic	Sulfamethoxazole/ Trimethoprim	J01EE01 J04AM08	8 to 10 h	3 months prior to LMP2	3 months prior to conception and 1st trimester for MCM and 2nd trimester for preterm birth and LBW
Anticoagulant	Acenocoumarol	B01AA07	8 to 11 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Dicoumarol	B01AA01	5 to 28 h	6 days prior to LMP2	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Phenprocoumon	B01AA04	4 to 6 days	1 month prior to LMP2	1st, 2nd, and 3rd trimesters
	Warfarin	B01AA03	40 h	9 days prior to LMP2	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Phenprocoumon	B01AA04	0.75 h	1 day prior to LMP2	1st trimester
Anticonvulsant	Lamotrigine	N03AX09	Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy)	15 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Trimethadione/Paramethadione	N03AC02 N03AC01	Paramethadione —12 to 24 hours Trimethadione —11 to 16 hours	5 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Valproic Acid / Valproate	N03AG01	4 to 16 h	4 days prior to LMP2	Primarily 1st trimester, but MCM have been associated with 2nd and 3rd trimester exposures.
	Carbamazepine	N03AF01	18 to 65 h	2 weeks prior to LMP2	1st, 2nd, and 3rd trimesters
	Ethotoin	N03AB01	3 to 9 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Phenytoin/Fosphenytoin	N03AB02 N03AB05 N03AB52	15 min	1 day prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Primidone	N03AA03	10 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Topiramate	N03AX11 A08AA51	21 h	5 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Ethosuximide	N03AD01 N03AD51	17 to 56 h	12 days prior to LMP2	Unknown
	Oxcarbazepine	N03AF02	Oxcarbazepine: immediate-release formulations, about 2 hours; extended-release tablet, 7 to 11 hours Active metabolite, 10–monohydroxy: 9 to 11 hours	3 days prior to LMP2	Unknown
	Sultiame	N03AX03	24 h	5 days prior to LMP2	Not in TERIS
	Vigabatrin	N03AG04	10.5 h	3 days prior to LMP2	Unknown
	Phenobarbital	N03AA02	70 to 140 h	1 month prior to LMP2	1st, 2nd, and 3rd trimesters
	Methylphenobarbital	N03AA01	34 h	8 days prior to LMP2	Not in TERIS
Antifungal	Fluconazole[2]	J02AC01 J01RA07	30 h	1 week prior to LMP2	2 weeks before conception and 1st trimester
Antineoplastic	Aminopterin	NA	12 to 24 h	5 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Methotrexate[3]	L01BA01 L04AX03	55 h	6 months prior to LMP2	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cytarabine	L01BC01 L01XY01	1 to 3 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Daunorubicin	L01DB02 L01XY01	Per google: The plasma half-life of daunorubicin averages 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has as average terminal plasma half-life of 26.7 hours	6 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Mechlorethamine	L01AA05	11 hours	3 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Mercaptopurine[3]	L01BB02	47 min	1 day prior to LMP2	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Vinblastine	L01CA01	24.8 h	6 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Cyclophosphamide	L01AA01	3 to 12 h	3 days prior to LMP2	1st trimester
	Altretamine	L01XX03	4.7 to 10.2 hours	3 days prior to LMP2	Unknown
	Amsacrine	L01XX01	5 h	2 days prior to LMP2	Unknown
	Bevacizumab	L01FG01	480 h	100 days prior to LMP2	Unknown

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Bleomycin	L01DC01	2 h	1 day prior to LMP2	Unknown
	Bortezomib	L01XG01	40 to 193 h	40 days prior to LMP2	Unknown
	Busulfan	L01AB01	2.3 to 3.4 h	1 day prior to LMP2	Not in TERIS
	Capecitabine	L01BC06	0.75 h	1 day prior to LMP2	Unknown
	Carboplatin	L01XA02	24 h	5 days prior to LMP2	Not in TERIS
	Carmustine	L01AD01	IV, 22 min, 1.4 min (1st phase), 17.8 min (2nd phase)	1 day prior to LMP2	Unknown
	Cetuximab	L01FE01	112 h	24 days prior to LMP2	Unknown
	Chlorambucil	L01AA02	1.5 h	1 day prior to LMP2	Not in TERIS
	Cisplatin	L01XA01	120 h	25 days prior to LMP2	Not in TERIS
	Cladribine	L01BB04 L04AA40	5.4 h	2 days prior to LMP2	Not in TERIS
	Clofarabine	L01BB06	5.2 h	2 days prior to LMP2	Unknown
	Dacarbazine	L01AX04	5 h	2 days prior to LMP2	Unknown
	Dactinomycin	L01DA01	36 h	8 days prior to LMP2	Not in TERIS
	Dasatinib	L01EA02	3 to 5 h	2 days prior to LMP2	Unknown
	Docetaxel	L01CD02	11.1 h	3 days prior to LMP2	Unknown
	Doxorubicin	L01DB01	20 to 48 h	10 days prior to LMP2	Unknown

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Epirubicin	L01DB03	31.1 h +/- 6 h to 35.3 h +/- 9 h	10 days prior to LMP2	Not in TERIS
	Erlotinib	L01EB02	36.2 h	8 days prior to LMP2	Unknown
	Estramustine	L01XX11	10 to 20 h	5 days prior to LMP2	Not in TERIS
	Etoposide	L01CB01	4 to 11 h	3 days prior to LMP2	Unknown
	Fludarabine	L01BB05	20 h	5 days prior to LMP2	Unknown
	Fluorouracil	L01BC02 L01BC52	8 to 20 min	1 day prior to LMP2	Unknown
	Gemcitabine	L01BC05	1.7 to 19.4 h	5 days prior to LMP2	Not in TERIS
	Hydroxycarbamide	L01XX05	2 to 4.5 h	1 day prior to LMP2	Unknown
	Idarubicin	L01DB06	20 to 22 h	5 days prior to LMP2	Not in TERIS
	Ifosfamide	L01AA06	15 h	4 days prior to LMP2	Unknown
	Imatinib	L01EA01	18 h	4 days prior to LMP2	Unknown
	Irinotecan	L01CE02	6 to 12 h	3 days prior to LMP2	Unknown
	Lapatinib	L01EH01	24 h	5 days prior to LMP2	Unknown
	Lomustine	L01AD02	16 to 48 h	10 days prior to LMP2	Unknown
	Melphalan	L01AA03	10 to 75 min	1 day prior to LMP2	Unknown
	Mitomycin	L01DC03	46 min	1 day prior to LMP2	Not in TERIS
	Mitoxantrone	L01DB07	23 to 215 h	45 days prior to LMP2	Not in TERIS

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Nelarabine	L01BB07	Adults: prodrug: 30 min; ara-G: 3 h	1 day prior to LMP2	Unknown
	Oxaliplatin	L01XA03	392 h	3 months prior to LMP2	Unknown
	Paclitaxel	L01CD01 L01CD51	13 to 52 h	11 days prior to LMP2	Not in TERIS
	Pemetrexed	L01BA04	3.5 h	1 day prior to LMP2	Unknown
	Pentostatin	L01XX08	5.7 h	2 days prior to LMP2	Not in TERIS
	Procarbazine	L01XB01	(IV), approximately 10 min	1 day prior to LMP2	Not in TERIS
	Raltitrexed	L01BA03	260 h	2 months prior to LMP2	Not in TERIS
	Sorafenib	L01EX02	25 to 48 h	10 days prior to LMP2	Unknown
	Streptozocin	L01AD04	Systemic: 35 min unchanged drug; 40 h metabolites	9 days prior to LMP2	Not in TERIS
	Sunitinib	L01EX01	40 to 60 h	13 days prior to LMP2	Unknown
	Tegafur	L01BC03 L01BC53	6.7 to 11.3 hours	3 days prior to LMP2	Not in TERIS
	Temozolomide	L01AX03	1.8 h	1 day prior to LMP2	Unknown
	Teniposide	L01CB02	5 h	2 days prior to LMP2	Not in TERIS
	Tioguanine	L01BB03	80 min	1 day prior to LMP2	Not in TERIS
	Thiotepa	L01AC01	1.4 to 3.7 hours	1 day prior to LMP2	Not in TERIS

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Topotecan	L01CE01	2 to 3 h	1 day prior to LMP2	Unknown
	Vincristine	L01CA02	85 h	18 days prior to LMP2	Unknown
	Vindesine	L01CA03	2.9 h	1 day prior to LMP2	Not in TERIS
	Vinorelbine	L01CA04	27.7 to 43.6 h	10 days prior to LMP2	Not in TERIS
	Lenalidomide	L04AX04	3 h	1 day prior to LMP2	Not in TERIS
Antithyroid	Propylthiouracil	H03BA02	1 to 2 h	1 day prior to LMP2	1st and 2nd trimesters
	Methiamazole	H03BB02 H03BB52	4.9 to 5.7 h	2 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Radioiodine	V10XA01 V09FX03	192 h	40 days prior to LMP2	Unknown
Antiviral	Ribavirin	J05AP01	120 to 170 hours	36 days prior to LMP2	1st, 2nd, and 3rd trimesters
Estrogen	Diethylstilbestrol	G03CB02 G03CC05 L02AA01	Per google: Once in the human body, DES reaches peak concentration within 20–40 min, having a primary half-life of 3–6 hr. It has a terminal half-life of 2–3 days due to entero-hepatic circulation, and is primarily excreted in urine	15 days prior to LMP2	1st, 2nd, and 3rd trimesters
Immunomodulatory agent	Mycophenolate mofetil	L04AA06	16 h	4 days prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Thalidomide	L04AX02	5 to 7 h	1 month prior to LMP2	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Penicillamine	M01CC01	2 to 4 h	1 day prior to LMP2	1st, 2nd, and 3rd trimesters
	Azathioprine[3]	L04AX01	5 h	2 days prior to LMP2	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Leflunomide	L04AA13	432 to 456 h	3 months prior to LMP2	Unknown
	Mycophenolic acid	L04AA06	8 to 16 h	4 days prior to LMP2	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
Mood stabilizer	Lithium	N05AN01 D11AX04	24 h	5 days prior to LMP2	1st, 2nd, and 3rd trimesters
Prostaglandins analogue	Misoprostol	A02BB01 G02AD06 M01AE56	20 to 40 min	1 day prior to LMP2	1 month prior to conception and 1st, 2nd, and 3rd trimesters
Retinoid	Alitretinoin	D11AH04 L01XF02	1 to 3 h	1 day prior to LMP2	Unknown
	Tretinoin	D10AD01 L01XF01 D10AD51	0.5 to 2 h	1 day prior to LMP2	Unknown
	Vitamin A	A11CA01 A11CA02	TERIS only notes "long half-	12 months prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
		A11CB	life"; 75 days per google search		
	Acitretin	D05BB02	50 to 60 h	2 years prior to LMP2	2 years prior to stopping treatment and throughout pregnancy, especially 1st trimester.
	Etretinate	D05BB01	120 days to 3 years	10 years prior to LMP2	10 years prior to stopping treatment and throughout pregnancy, especially 1st trimester.
	Isotretinoin	D10AD04 D10BA01 D10AD54	10 to 12 h	1 month prior to LMP2	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tazotarotene	D05AX05 D05AX55	18 h	4 days prior to LMP2	Unknown
	Retinol	A11CA01 D10AD02 R01AX02 S01XA02	2 to 9 h	12 months prior to LMP2	12 months prior to conception and 1st trimester
Steroid	Danazol	G03XA01	9.7 to 23.7 h	5 days prior to LMP2	1st, 2nd, and 3rd trimesters
Tetracycline antibiotic	Demeclocycline	D06AA01 J01AA01	10 to 17 h	4 days prior to LMP2	1st, 2nd, and 3rd trimesters
	Oxytetracycline	A01AB25 D06AA03 G01AA07 J01AA06 J01AA56	6 to 11 h	3 days prior to LMP2	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	ATC code	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
		S01AA04			
	Tetracycline	A01AB13 A02BD02 A02BD08 D06AA04 J01AA07 J01AA20 J01RA08 S01AA09 S02AA08 S03AA02	6 to 11 h	3 days prior to LMP2	2nd and 3rd trimesters; limited data for 1st trimester exp
	Chlortetracycline	A01AB21 D06AA02 J01AA03 S01AA02	5.6 h	2 days prior to LMP2	Unknown
	Doxycycline	A01AB22 J01AA02	18 to 22 h	5 days prior to LMP2	Unknown
	Methacycline	J01AA05	14 to 22 h	5 days prior to LMP2	Unknown
	Minocycline	A01AB23 D10AF07 J01AA08	11 to 24.31 h	5 days prior to LMP2	Unknown
	Tigecycline	J01AA12	42.4 h	9 days prior to LMP2	Unknown

Abbreviations used in the table: ATC, Anatomical therapeutic chemical classification system; ara-G, Guanine nucleoside analogue; ARB, Angiotensin receptor blocker; DES, Diethylstilbesterol; LMP2, Last menstrual period + 2 weeks; IV, Intravenous; MCM, Major congenital malformation; TERIS, Teratogen Information System; NA, Not Assigned

[1] A participant will be considered exposed during the 1st trimester, if a dose is taken during this pre-conception exposure window.

[2] Only applies to ≥2 doses during pregnancy.

[3] Teratogenic risk is low; however, exposure during pregnancy may be associated with other adverse outcomes, including preterm birth and intrauterine growth restriction.

Table 21: Literature references for the choices of variables

Variable	Authors	Title	Journal	Code list
Congenital malformations				
MCM	Vinet É, Pineau CA, Scott S, Clarke AE, Platt RW, Bernatsky S.	Increased congenital heart defects in children born to women with systemic lupus erythematosus: results from the offspring of Systemic Lupus Erythematosus Mothers Registry Study.	Circulation. 2015 Jan 13;131(2):149-56. doi: 10.1161/CIRCULATIONAHA.114.010027.	Table 22
	Bundhun PK, Soogund MZ, Huang F.	Impact of systemic lupus erythematosus on maternal and foetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016.	J Autoimmun. 2017 May;79:17-27. doi: 10.1016/j.jaut.2017.02.009	
	Jakobsen IM, Helmig RB, Stengaard-Pedersen K.	Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990-2010.	Scand J Rheumatol. 2015;44(5):377-84. doi: 10.3109/03009742.2015.1013982.	
mCM	Vinet É, Pineau CA, Scott S, Clarke AE, Platt RW, Bernatsky S.	Increased congenital heart defects in children born to women with systemic lupus erythematosus: results from the offspring of Systemic Lupus Erythematosus Mothers Registry Study.	Circulation. 2015 Jan 13;131(2):149-56. doi: 10.1161/CIRCULATIONAHA.114.010027.	Table 23
	Bundhun PK, Soogund MZ, Huang F.	Impact of systemic lupus erythematosus on maternal and foetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016.	J Autoimmun. 2017 May;79:17-27. doi: 10.1016/j.jaut.2017.02.009	
Adverse pregnancy outcomes				
Ectopic pregnancy	Molokhia M, Maconochie N, Patrick AL, Doyle P.	Cross-sectional analysis of adverse outcomes in 1,029 pregnancies of Afro-Caribbean women in Trinidad with and without systemic lupus erythematosus.	Arthritis Res Ther. 2007;9(6):R124. doi: 10.1186/ar2332.	Table 24

Variable	Authors	Title	Journal	Code list
Spontaneous abortion	Bundhun PK, Soogund MZ, Huang F.	Impact of systemic lupus erythematosus on maternal and foetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016.	J Autoimmun. 2017 May;79:17-27. doi: 10.1016/j.jaut.2017.02.009	Table 24
	Braga A, Barros T, Faria R, Marinho A, Rocha G, Farinha F, Neves E, Vasconcelos C, Braga J.	Systemic Lupus Erythematosus and Pregnancy: a Portuguese Case-Control Study.	Clin Rev Allergy Immunol. 2022 Apr;62(2):324-332. doi: 10.1007/s12016-021-08893-y.	
	Wu J, Ma J, Bao C, Di W, Zhang WH.	Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study.	BMJ Open. 2018 Apr 13;8(4):e020909. doi: 10.1136/bmjopen-2017-020909.	
	Ling N, Lawson E, von Scheven E.	Adverse pregnancy outcomes in adolescents and young women with systemic lupus erythematosus: a national estimate.	Pediatr Rheumatol Online J. 2018 Apr 16;16(1):26. doi: 10.1186/s12969-018-0242-0.	
Elective termination of pregnancy	Ling N, Lawson E, von Scheven E.	Adverse pregnancy outcomes in adolescents and young women with systemic lupus erythematosus: a national estimate.	Pediatr Rheumatol Online J. 2018 Apr 16;16(1):26. doi: 10.1186/s12969-018-0242-0.	Table 24
Stillbirth	Vinet É, Genest G, Scott S, Pineau CA, Clarke AE, Platt RW, Bernatsky S.	Brief Report: Causes of Stillbirths in Women With Systemic Lupus Erythematosus.	Arthritis Rheumatol. 2016 Oct;68(10):2487-91. doi: 10.1002/art.39742.	Table 24
	Wu J, Ma J, Bao C, Di W, Zhang WH.	Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study.	BMJ Open. 2018 Apr 13;8(4):e020909. doi: 10.1136/bmjopen-2017-020909.	
	Molokhia M, Maconochie N, Patrick AL, Doyle P.	Cross-sectional analysis of adverse outcomes in 1,029 pregnancies of Afro-Caribbean women in Trinidad with and without systemic lupus erythematosus.	Arthritis Res Ther. 2007;9(6):R124. doi: 10.1186/ar2332.	
	Kim JW, Jung JY, Kim HA, Yang JI, Kwak DW, Suh CH.	Lupus Low Disease Activity State Achievement Is Important for Reducing Adverse Outcomes in Pregnant Patients With	J Rheumatol. 2021 May;48(5):707-716. doi: 10.3899/jrheum.200802.	

Variable	Authors	Title	Journal	Code list
		Systemic Lupus Erythematosus.		
Infections requiring hospitalisation during pregnancy	Clowse ME, Jamison M, Myers E, James AH.	A national study of the complications of lupus in pregnancy.	Am J Obstet Gynecol. 2008 Aug;199(2):127.e1-6. doi: 10.1016/j.ajog.2008.03.012.	Table 24
	Chan MY, Smith MA.	Infections in Pregnancy.	Comprehensive Toxicology. 2018:232–49. doi: 10.1016/B978-0-12-801238-3.64293-9.	
	Centers for Disease Control and Prevention.	Birth Defects Surveillance Toolkit. Congenital Infectious Syndromes.	Available from: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-5/chapter5.html [accessed 17 Jun 2022].	
Emergency caesarean section	Kim JW, Jung JY, Kim HA, Yang JI, Kwak DW, Suh CH.	Lupus Low Disease Activity State Achievement Is Important for Reducing Adverse Outcomes in Pregnant Patients With Systemic Lupus Erythematosus.	J Rheumatol. 2021 May;48(5):707-716. doi: 10.3899/jrheum.200802.	Table 24
Adverse birth outcomes				
Preterm birth	Erazo-Martínez V, Nieto-Aristizábal I, Ojeda I, González M, Aragon CC, Zambrano MA, Tobón GJ, Arango J, Echeverri A, Aguirre-Valencia D.	Systemic erythematosus lupus and pregnancy outcomes in a Colombian cohort.	Lupus. 2021 Dec;30(14):2310-2317. doi: 10.1177/0961203321061478.	Table 25
	Wu J, Ma J, Bao C, Di W, Zhang WH.	Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study.	BMJ Open. 2018 Apr 13;8(4):e020909. doi: 10.1136/bmjopen-2017-020909.	
	Molokhia M, Maconochie N, Patrick AL, Doyle P.	Cross-sectional analysis of adverse outcomes in 1,029 pregnancies of Afro-Caribbean women in Trinidad with and without systemic lupus erythematosus.	Arthritis Res Ther. 2007;9(6):R124. doi: 10.1186/ar2332.	

Variable	Authors	Title	Journal	Code list
Small for gestational age	Bundhun PK, Soogund MZ, Huang F.	Impact of systemic lupus erythematosus on maternal and foetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016.	J Autoimmun. 2017 May;79:17-27. doi: 10.1016/j.jaut.2017.02.009	Table 25
	Wu J, Ma J, Bao C, Di W, Zhang WH.	Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study.	BMJ Open. 2018 Apr 13;8(4):e020909. doi: 10.1136/bmjopen-2017-020909.	
Exposure				
Anifrolumab	Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, Bae SC, Brohawn PZ, Pineda L, Berglind A, Tummala R; TULIP-2 Trial Investigators.	Trial of Anifrolumab in Active Systemic Lupus Erythematosus.	N Engl J Med. 2020 Jan 16;382(3):211-221. doi: 10.1056/NEJMoa1912196.	Table 19
	Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, Ford TL, Gupta R, Hiepe PF, Santiago M, Brohawn PZ, Berglind A, Tummala R, on behalf of the TULIP-1 study investigators.	Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial.	*The Lancet Rheumatology* 2019;**1**:e208–19. doi:10.1016/S2665-9913(19)30076-1	
	Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S; CD1013 Study Investigators.	Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus.	Arthritis Rheumatol. 2017 Feb;69(2):376-386. doi: 10.1002/art.39962.	
	Tummala R, Abreu G, Pineda L, Michaels MA, Kalyani RN, Furie RA, Morand EF.	Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials.	Lupus Sci Med. 2021 Feb;8(1):e000464. doi: 10.1136/lupus-2020-000464.	
SLE SOC	Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, Cervera R, Doria A, Gordon C, Govoni M, Houssiau F, Jayne D, Kouloumas M,	2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.	Ann Rheum Dis. 2019 Jun;78(6):736-745. doi: 10.1136/annrheumdis-2019-215089.	Table 19

Variable	Authors	Title	Journal	Code list
	Kuhn A, Larsen JL, Lerstrøm K, Moroni G, Mosca M, Schneider M, Smolen JS, Svenungsson E, Tesar V, Tincani A, Troldborg A, van Vollenhoven R, Wenzel J, Bertsias G, Boumpas DT.			
	Gordon C, Amissah-Arthur MB, Gayed M, Brown S, Bruce IN, D'Cruz D, Empson B, Griffiths B, Jayne D, Khamashta M, Lightstone L, Norton P, Norton Y, Schreiber K, Isenberg D; British Society for Rheumatology Standards, Audit and Guidelines Working Group.	The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults.	Rheumatology (Oxford). 2018 Jan 1;57(1):e1-e45. doi: 10.1093/rheumatology/kex286.	
Maternal variables				
Age at conception (before or at start of exposure)	Lean SC, Derricott H, Jones RL, Heazell AEP.	Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis.	PLoS One. 2017 Oct 17;12(10):e0186287. doi: 10.1371/journal.pone.0186287.	no clinical code list
	Frederiksen LE, Ernst A, Brix N, Braskhøj Lauridsen LL, Roos L, Ramlau-Hansen CH, Ekelund CK.	Risk of Adverse Pregnancy Outcomes at Advanced Maternal Age.	Obstet Gynecol. 2018 Mar;131(3):457-463. doi: 10.1097/AOG.0000000000002504.	
	Frick AP.	Advanced maternal age and adverse pregnancy outcomes.	Best Pract Res Clin Obstet Gynaecol. 2021 Jan;70:92-100. doi: 10.1016/j.bpobgyn.2020.07.005.	
	Bermas BL, Sammaritano LR.	Fertility and pregnancy in rheumatoid arthritis and systemic lupus erythematosus.	Fertil Res Pract. 2015 Aug 27;1:13. doi: 10.1186/s40738-015-0004-3.	
	Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, Doria	EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and	Ann Rheum Dis. 2017 Mar;76(3):476-485. doi:	

Variable	Authors	Title	Journal	Code list
	A, Fischer-Betz R, Forger F, Moraes-Fontes MF, Khamashta M, King J, Lojacono A, Marchiori F, Meroni PL, Mosca M, Motta M, Ostensen M, Pamfil C, Raio L, Schneider M, Svenungsson E, Tektonidou M, Yavuz S, Boumpas D, Tincani A.	menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome.	10.1136/annrheumdis-2016-209770.	
Socioeconomic status (before or at start of exposure)	Thomson K, Moffat M, Arisa O, Jesurasa A, Richmond C, Odeniyi A, Bambra C, Rankin J, Brown H, Bishop J, Wing S, McNaughton A, Heslehurst N.	Socioeconomic inequalities and adverse pregnancy outcomes in the UK and Republic of Ireland: a systematic review and meta-analysis.	BMJ Open. 2021 Mar 15;11(3):e042753. doi: 10.1136/bmjopen-2020-042753.	no clinical code list
	Jardine J, Walker K, Gurol-Urganci I, Webster K, Muller P, Hawdon J, Khalil A, Harris T, van der Meulen J; National Maternity and Perinatal Audit Project Team.	Adverse pregnancy outcomes attributable to socioeconomic and ethnic inequalities in England: a national cohort study.	Lancet. 2021 Nov 20;398(10314):1905-1912. doi: 10.1016/S0140-6736(21)01595-6.	
	DeQuattro K, Yelin E.	Socioeconomic Status, Health Care, and Outcomes in Systemic Lupus Erythematosus.	Rheum Dis Clin North Am. 2020 Nov;46(4):639-649. doi: 10.1016/j.rdc.2020.07.004.	
	Sagy I, Cohen Y, Nahum Y, Pokroy-Shapira E, Abu-Shakra M, Molad Y.	Lower socioeconomic status worsens outcome of patients with systemic lupus erythematosus independently of access to healthcare.	Lupus. 2022 Apr;31(5):532-540. doi: 10.1177/0961203322 1084518.	
	Hahn BH.	Market for Systemic Lupus Erythematosus	N Engl J Med 2013;368:1528-35. DOI: 10.1056/NEJMct120 7259	
Health care utilisation	Macejova Z, Madarasova Geckova A, Husarova D,	Living with Systemic Lupus Erythematosus: A Profile of Young Female Patients.	International Journal of Environmental Research and Public Health. 2020;	

Variable	Authors	Title	Journal	Code list
(before or at LMP2)	Zarikova M, Kotradyova Z.		17(4):1315. https://doi.org/10.3390/ijerph17041315	
	Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S; CD1013 Study Investigators.	Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus.	Arthritis Rheumatol. 2017 Feb;69(2):376-386. doi: 10.1002/art.39962.	
SLE-related comorbid conditions (before or at start of exposure)	Saavedra MA, Cruz-Reyes C, Vera-Lastra O, Romero GT, Cruz-Cruz P, Arias-Flores R, Jara LJ.	Impact of previous lupus nephritis on maternal and foetal outcomes during pregnancy.	Clin Rheumatol. 2012 May;31(5):813-9. doi: 10.1007/s10067-012-1941-4.	Table 26
	Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S; CD1013 Study Investigators.	Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus.	Arthritis Rheumatol. 2017 Feb;69(2):376-386. doi: 10.1002/art.39962.	
SLE SOC (before or at start of exposure)	Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, Doria A, Fischer-Betz R, Forger F, Moraes-Fontes MF, Khamashta M, King J, Lojacono A, Marchiori F, Meroni PL, Mosca M, Motta M, Ostensen M, Pamfil C, Raio L, Schneider M, Svenungsson E, Tektonidou M, Yavuz S, Boumpas D, Tincani A.	EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome.	Ann Rheum Dis. 2017 Mar;76(3):476-485. doi: 10.1136/annrheumdis-2016-209770.	Table 19
	Dao KH, Bermas BL.	Systemic Lupus Erythematosus Management in Pregnancy.	Int J Womens Health. 2022 Feb 15;14:199-211. doi: 10.2147/IJWH.S282604.	
SLE activity algorithm (before or at start of exposure)	Kim JW, Jung JY, Kim HA, Yang JI, Kwak DW, Suh CH.	Lupus Low Disease Activity State Achievement Is Important for Reducing Adverse Outcomes in Pregnant Patients With	J Rheumatol. 2021 May;48(5):707-716. doi: 10.3899/jrheum.200802.	

Variable	Authors	Title	Journal	Code list
		Systemic Lupus Erythematosus.		
	Yang MJ, Chen CY, Chang WH, Tseng JY, Yeh CC.	Pregnancy outcome of systemic lupus erythematosus in relation to lupus activity before and during pregnancy.	J Chin Med Assoc. 2015 Apr;78(4):235-40. doi: 10.1016/j.jcma.2014.11.008.	
	Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S; CD1013 Study Investigators.	Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus.	Arthritis Rheumatol. 2017 Feb;69(2):376-386. doi: 10.1002/art.39962.	
Autoimmune conditions (before or at start of exposure)	Bandoli G, Singh N, Strouse J, Baer RJ, Donovan BM, Feuer SK, Nidey N, Ryckman KK, Jelliffe-Pawlowski LL, Chambers CD.	Mediation of Adverse Pregnancy Outcomes in Autoimmune Conditions by Pregnancy Complications: A Mediation Analysis of Autoimmune Conditions and Adverse Pregnancy Outcomes.	Arthritis Care Res (Hoboken). 2020 Feb;72(2):256-264. doi: 10.1002/acr.24037.	
	Stagnaro-Green A, Akhter E, Yim C, Davies TF, Magder L, Petri M.	Thyroid disease in pregnant women with systemic lupus erythematosus: increased preterm delivery.	Lupus. 2011 Jun;20(7):690-9. doi: 10.1177/0961203310394894.	
	Abbassi-Ghanavati M.	Thyroid autoantibodies and pregnancy outcomes.	Clin Obstet Gynecol. 2011 Sep;54(3):499-505. doi: 10.1097/GRF.0b013e31822730b9.	
Co-medications (non-SLE SOC) (before or at start of exposure)	Sarayani A, Albogami Y, Thai TN, Smolinski NE, Patel P, Wang Y, Nduaguba S, Rasmussen SA, Winterstein AG.	Prenatal exposure to teratogenic medications in the era of Risk Evaluation and Mitigation Strategies.	Am J Obstet Gynecol. 2022 Jan 12:S0002-9378(22)00008-4. doi: 10.1016/j.ajog.2022.01.004.	Table 27
	van Gelder MM, de Jong-van den Berg LT, Roeleveld N.	Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks.	Hum Reprod. 2014 Jan;29(1):168-83. doi: 10.1093/humrep/det370.	
Smoking (before or at LMP2)	Pineles BL, Hsu S, Park E, Samet JM.	Systematic Review and Meta-Analyses of Perinatal Death and Maternal Exposure to Tobacco Smoke During Pregnancy.	Am J Epidemiol. 2016 Jul 15;184(2):87-97. doi: 10.1093/aje/kwv301.	
	Räisänen S, Sankilampi U, Gissler M, Kramer	Smoking cessation in the first trimester reduces most obstetric risks, but not the	J Epidemiol Community Health. 2014 Feb;68(2):159-	

Variable	Authors	Title	Journal	Code list
	MR, Hakulinen-Viitanen T, Saari J, Heinonen S.	risks of major congenital anomalies and admission to neonatal care: a population-based cohort study of 1,164,953 singleton pregnancies in Finland.	64. doi: 10.1136/jech-2013-202991.	
Alcohol abuse (before or at LMP2)	Viteri OA, Soto EE, Bahado-Singh RO, Christensen CW, Chauhan SP, Sibai BM.	Foetal anomalies and long-term effects associated with substance abuse in pregnancy: a literature review.	Am J Perinatol. 2015 Apr;32(5):405-16. doi: 10.1055/s-0034-1393932.	Table 29
	Harris BS, Bishop KC, Kemeny HR, Walker JS, Rhee E, Kuller JA.	Risk Factors for Birth Defects.	Obstet Gynecol Surv. 2017 Feb;72(2):123-135. doi: 10.1097/OGX.0000000000000405.	
Substance abuse (before or at LMP2)	Viteri OA, Soto EE, Bahado-Singh RO, Christensen CW, Chauhan SP, Sibai BM.	Foetal anomalies and long-term effects associated with substance abuse in pregnancy: a literature review.	Am J Perinatol. 2015 Apr;32(5):405-16. doi: 10.1055/s-0034-1393932.	Table 28
	Viteri OA, Mendez-Figueroa H, Pedroza C, Leon MG, Sibai BM, Chauhan SP.	Relationship between Self-Reported Maternal Substance Abuse and Adverse Outcomes in the Premature Newborn.	Am J Perinatol. 2016 Jan;33(2):165-71. doi: 10.1055/s-0035-1563549.	
	Harris BS, Bishop KC, Kemeny HR, Walker JS, Rhee E, Kuller JA.	Risk Factors for Birth Defects.	Obstet Gynecol Surv. 2017 Feb;72(2):123-135. doi: 10.1097/OGX.0000000000000405.	
Gestational diabetes (before or at LMP2)	Wu Y, Liu B, Sun Y, Du Y, Santillan MK, Santillan DA, Snetselaar LG, Bao W.	Association of Maternal Prepregnancy Diabetes and Gestational Diabetes Mellitus With Congenital Anomalies of the Newborn.	Diabetes Care. 2020 Dec;43(12):2983-2990. doi: 10.2337/dc20-0261.	Table 30
	Ye W, Luo C, Huang J, Li C, Liu Z, Liu F.	Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis.	BMJ. 2022 May 25;377:e067946. doi: 10.1136/bmj-2021-067946.	
	Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C, Jacquemyn Y, Mekahli F, De Clippel K, Van Den	Characteristics and pregnancy outcomes across gestational diabetes mellitus subtypes based on insulin resistance.	Diabetologia. 2019 Nov;62(11):2118-2128. doi: 10.1007/s00125-019-4961-7.	

Variable	Authors	Title	Journal	Code list
	Bruel A, Loccufier A, Laenen A, Minschart C, Devlieger R, Mathieu C.			
Pre-pregnancy obesity (before or at LMP2)	Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, Gillman MW.	Preconceptional and maternal obesity: epidemiology and health consequences.	Lancet Diabetes EnLMP2rinol. 2016 Dec;4(12):1025-1036. doi: 10.1016/S2213-8587(16)30217-0.	
	Bjorklund J, Wiberg-Itzel E, Wallstrom T.	Is there an increased risk of cesarean section in obese women after induction of labor? A retrospective cohort study.	PLoS One. 2022 Feb 25;17(2):e0263685. doi: 10.1371/journal.pone.0263685.	
	Vats H, Saxena R, Sachdeva MP, Walia GK, Gupta V.	Impact of maternal pre-pregnancy body mass index on maternal, foetal and neonatal adverse outcomes in the worldwide populations: A systematic review and meta-analysis.	Obes Res Clin Pract. 2021 Nov-Dec;15(6):536-545. doi: 10.1016/j.orcp.2021.10.005.	
History of pre-eclampsia (before or at LMP2)	Bramham K, Briley AL, Seed P, Poston L, Shennan AH, Chappell LC.	Adverse maternal and perinatal outcomes in women with previous preeclampsia: a prospective study.	Am J Obstet Gynecol. 2011 Jun;204(6):512.e1-9. doi: 10.1016/j.ajog.2011.02.014.	
	Nelson DB, Chalak LF, McIntire DD, Leveno KJ.	Is preeclampsia associated with foetal malformation? A review and report of original research.	J Matern Foetal Neonatal Med. 2015;28(18):2135-40. doi: 10.3109/14767058.2014.980808.	
Pre-pregnancy hypertension (before or at LMP2)	Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC.	Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis.	BMJ. 2014 Apr 15;348:g2301. doi: 10.1136/bmj.g2301.	
	Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD.	A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis.	Clin J Am Soc Nephrol. 2010 Nov;5(11):2060-8. doi: 10.2215/CJN.00240110.	
Pre-pregnancy diabetes (before or at LMP2)	Tinker SC, Gilboa SM, Moore CA, Waller DK, Simeone RM, Kim SY, Jamieson DJ, Botto LD, Reefhuis J; National Birth	Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997-2011.	Am J Obstet Gynecol. 2020 Feb;222(2):176.e1-176.e11. doi: 10.1016/j.ajog.2019.08.028.	Table 30

Variable	Authors	Title	Journal	Code list
	Defects Prevention Study.			
	Wei Y, Xu Q, Yang H, Yang Y, Wang L, Chen H, Anderson C, Liu X, Song G, Li Q, Wang Q, Shen H, Zhang Y, Yan D, Peng Z, He Y, Wang Y, Zhang Y, Zhang H, Ma X.	Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women: A population-based cohort study in China.	PLoS Med. 2019 Oct 1;16(10):e1002926. doi: 10.1371/journal.pmed.1002926.	
	Murphy HR, Howgate C, O'Keefe J, Myers J, Morgan M, Coleman MA, Jolly M, Valabhji J, Scott EM, Knighton P, Young B, Lewis-Barned N; National Pregnancy in Diabetes (NPID) advisory group.	Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study.	Lancet Diabetes EnLMP2rinol. 2021 Mar;9(3):153-164. doi: 10.1016/S2213-8587(20)30406-X.	
Previous spontaneous abortions (at before or at LMP2)	Makhlouf MA, Clifton RG, Roberts JM, Myatt L, Hauth JC, Leveno KJ, Varner MW, Thorp JM Jr, Mercer BM, Peaceman AM, Ramin SM, Iams JD, Sciscione A, Tolosa JE, Sorokin Y; Eunice Kennedy Shriver National Institute of Child Health Human Development Maternal-Foetal Medicine Units Network.	Adverse pregnancy outcomes among women with prior spontaneous or induced abortions.	Am J Perinatol. 2014 Oct;31(9):765-72. doi: 10.1055/s-0033-1358771.	Table 24
	Ji H, Liang H, Yu Y, Wang Z, Yuan W, Qian X, Mikkelsen EM, Laursen ASD, Fang G, Huang G, Miao M, Li J.	Association of Maternal History of Spontaneous Abortion and Stillbirth With Risk of Congenital Heart Disease in Offspring of Women With vs Without Type 2 Diabetes.	JAMA Netw Open. 2021;4(11):e2133805. doi:10.1001/jamanetworkopen.2021.33805.	
	Campaña H, Rittler M, Gili JA, Poletta FA, Pawluk MS, Gimenez LG, Cosentino VR,	Association between a Maternal History of Miscarriages and Birth Defects.	Birth Defects Res. 2017 Mar 1;109(4):254-261. doi: 10.1002/bdra.23563.	

Variable	Authors	Title	Journal	Code list
	Castilla EE, Camelo JS.			
Previous stillbirth (before or at LMP2)	Ji H, Liang H, Yu Y, Wang Z, Yuan W, Qian X, Mikkelsen EM, Laursen ASD, Fang G, Huang G, Miao M, Li J.	Association of Maternal History of Spontaneous Abortion and Stillbirth With Risk of Congenital Heart Disease in Offspring of Women With vs Without Type 2 Diabetes.	JAMA Netw Open. 2021;4(11):e2133805. doi:10.1001/jamanetworkopen.2021.33805.	Table 24
	Paz JE, Otaño L, Gadow EC, Castilla EE.	Previous miscarriage and stillbirth as risk factors for other unfavourable outcomes in the next pregnancy.	Br J Obstet Gynaecol. 1992 Oct;99(10):808-12. doi: 10.1111/j.1471-0528.1992.tb14411.x.	
Previous preterm birth (before or at LMP2)	Yang J, Baer RJ, Berghella V, Chambers C, Chung P, Coker T, Currier RJ, Druzin ML, Kuppermann M, Muglia LJ, Norton ME, Rand L, Ryckman K, Shaw GM, Stevenson D, Jelliffe-Pawlowski LL.	Recurrence of Preterm Birth and Early Term Birth.	Obstet Gynecol. 2016 Aug;128(2):364-372. doi: 10.1097/AOG.0000000000001506.	Table 25
Previous small for gestational age (before or at LMP2)	Voskamp BJ, Kazemier BM, Ravelli AC, Schaaf J, Mol BW, Pajkrt E.	Recurrence of small-for-gestational-age pregnancy: analysis of first and subsequent singleton pregnancies in The Netherlands.	Am J Obstet Gynecol. 2013 May;208(5):374.e1-6. doi: 10.1016/j.ajog.2013.01.045.	Table 25

Table 22a: Major congenital malformations by subgroups of target body organ (EUROCAT classification), EXEMPLARY codelist

Subgroups	ICD 10-major	ICD-10 -minor (EXCLUDE)
Nervous System anomalies	Q00 Q01 Q02 Q03 Q04 Q05 Q06 Q07 Q8703	Q0780 Q0782 Q0461
Eye anomalies	Q10 Q11 Q12 Q13 Q14 Q15	Q101 Q102 Q103 Q105 Q135
Ear, face and neck anomalies	Q16 Q17 Q18	Q170 Q171 Q172 Q173 Q174 Q175 Q179 Q180 Q181 Q182 Q184 Q185 Q186 Q187 Q1880 Q189
Congenital Heart Defects	Q20 Q21 Q22 Q23 Q24 Q25 Q26	Q2111 Q246 Q250 if GA <37 weeks Q2541 Q256 if GA <37 weeks Q261
Respiratory anomalies	Q300 Q32 Q33 Q34	Q320 Q322 Q3300 Q331

Subgroups	ICD 10-major	ICD-10 -minor (EXCLUDE)
Oro-facial clefts	Q35 Q36 Q37	Q357
Gastro-intestinal anomalies	Q38 Q39 Q40 Q41 Q42 Q43 Q44 Q45 Q790	Q381 Q382 Q3850 Q400 Q401 Q4021 Q430 Q4320 Q4381 Q4382 Q444 Q4583
Abdominal wall defects	Q792 Q793 Q795	No code
Congenital anomalies of kidney and urinary tract (CAKUT)	Q60 Q61 Q62 Q63 Q64 Q794	Q610 Q627 Q633
Genital anomalies	Q50 Q51 Q52 Q54 Q55 Q56	Q523 Q525 Q527 Q5520 Q5521 Q501 Q502 Q505 Q544
Limb anomalies	Q65 Q66 Q67 Q68 Q69 Q70 Q71 Q72 Q73	Q653 Q654 Q655 Q656 Q658 Q659 Q662 Q663 Q664

Subgroups	ICD 10-major	ICD-10 -minor (EXCLUDE)
	Q74	Q665 Q666 Q667 Q668 Q669 Q670 Q671 Q672 Q673 Q674 Q675 Q676 Q677 Q678 Q680 Q6810 Q6821 Q683 Q684 Q685 Q7400 Q661
Other anomalies/syndromes	Q0435 Q044 Q206 Q240 Q3381 Q411 Q412 Q418 Q710 Q712 Q7180 Q720 Q722 Q7280 Q730 Q750 Q793 Q7980 Q7982 Q86	No code

Subgroups	ICD 10-major	ICD-10 -minor (EXCLUDE)
	Q8680 Q8706 Q8708 Q8724 Q8726 Q890 Q893 Q894 Q8980 P350 P351 P354 P358 P371	
Genetic disorders	D821 Q4471 Q6190 Q7402 Q7484 Q751 Q754 Q7581 Q77 Q780 Q781 Q782 Q783 Q784 Q785 Q786 Q788 Q789 Q796 Q800 Q801 Q802 Q803 Q804 Q808 Q809 Q810 Q811	No code

Subgroups	ICD 10-major	ICD-10 -minor (EXCLUDE)
	Q812 Q818 Q819 Q820 Q821 Q822 Q823 Q824 Q8282 Q8283 Q850 Q851 Q8581 Q87 Q8934 Q90 Q91 Q92 Q93 Q96 Q97 Q98 Q99	

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision; GA, Gestational age

Table 22b: MACDP 6-Digit Code Defect List [XLS – 114 KB] (CDC BPA Code)

Table 23: Minor Congenital Malformations, EXEMPLARY codelist

Subgroups	ICD-10
Nervous System anomalies	Q0780 Q0782 Q0461
Eye anomalies	Q101 Q102 Q103 Q105 Q135 Q752 H046 H052
Ear, face and neck anomalies	Q170 Q171 Q172 Q173 Q174 Q175 Q179 Q180 Q181 Q182 Q184 Q185 Q186 Q187 Q1880 Q189 Q6741
Congenital Heart Defects	Q2111 Q246 Q250 if GA <37 weeks Q2541 Q256 if GA <37 weeks Q261 Q270 R011 I517 I429
Respiratory anomalies	Q314 Q3140 Q315 Q320 Q322

Subgroups	ICD-10
	Q3300 Q3310 Q331
Oro-facial clefts	Q357
Gastro-intestinal anomalies	Q381 Q382 Q3850 Q400 Q401 Q4021 Q430 Q4320 Q4381 Q4382 Q444 Q4583 Q8911 K409 R160 R161
Congenital anomalies of kidney and urinary tract (CAKUT)	Q610 Q627 Q633
Genital anomalies	Q523 Q525 Q527 Q5520 Q5521 Q501 Q5010 Q5011 Q502 Q505 Q53 Q530 Q544 E250 N44 N47 P835
Limb anomalies	Q653 Q654 Q655 Q656

Subgroups	ICD-10
	Q658 Q659 Q662 Q663 Q664 Q665 Q666 Q667 Q668 Q6680 Q669 Q670 Q671 Q672 Q673 Q674 Q675 Q676 Q677 Q678 Q680 Q6810 Q6821 Q683 Q684 Q685 Q7400 Q661 Q8280 Q845 Q846
Other anomalies/syndromes	Q6740 Q753 Q833 Q8281 Q8252 Q8250 Q825 Q8251 Q7660 Q7662 Q765 Q7643 Q760

Subgroups	ICD-10
	Q7671 Q899
Genetic disorders	Q95 Q952

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision; GA, Gestational age

Table 24: Adverse pregnancy outcomes, EXEMPLARY codelist

Adverse outcomes	Description	ICD-10
Ectopic pregnancy	Ectopic pregnancy	O00
Spontaneous abortion	Spontaneous abortion	O03
Elective termination of pregnancy	Medical abortion	O04
	Other abortion	O05
	Unspecified abortion	O06
Stillbirth	Foetal death of unspecified cause	P95
	Single stillbirth	Z37.1
	Maternal care for hydrops foetalis	O36.2
	Maternal care for intrauterine death	O36.4
Infections requiring hospitalisation during pregnancy	Cholera	A00
	Typhoid and paratyphoid fevers	A01
	Other salmonella infections	A02
	Shigellosis	A03
	Other bacterial intestinal infections	A04
	Other bacterial foodborne intoxications, not elsewhere classified	A05
	Amoebiasis	A06
	Other protozoal intestinal diseases	A07
	Viral and other specified intestinal infections	A08
	Other gastroenteritis and colitis of infectious and unspecified origin	A09
	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
	Plague	A20
	Tularaemia	A21
	Anthrax	A22
	Brucellosis	A23
	Glanders and melioidosis	A24
	Rat-bite fevers	A25
	Erysipeloid	A26
	Leptospirosis	A27
	Other zoonotic bacterial diseases, not elsewhere classified	A28
	Leprosy [Hansen disease]	A30
	Infection due to other mycobacteria	A31
	Listeriosis	A32
	Tetanus neonatorum	A33

Adverse outcomes	Description	ICD-10
	Obstetrical tetanus	A34
	Other tetanus	A35
	Diphtheria	A36
	Whooping cough	A37
	Scarlet fever	A38
	Meningococcal infection	A39
	Streptococcal sepsis	A40
	Other sepsis	A41
	Actinomycosis	A42
	Nocardiosis	A43
	Bartonellosis	A44
	Erysipelas	A46
	Other bacterial diseases, not elsewhere classified	A48
	Bacterial infection of unspecified site	A49
	Congenital syphilis	A50
	Early syphilis	A51
	Late syphilis	A52
	Other and unspecified syphilis	A53
	Gonococcal infection	A54
	Chlamydial lymphogranuloma (venereum)	A55
	Other sexually transmitted chlamydial diseases	A56
	Chancroid	A57
	Granuloma inguinale	A58
	Trichomoniasis	A59
	Anogenital herpesviral [herpes simplex] infection	A60
	Other predominantly sexually transmitted diseases, not elsewhere classified	A63
	Unspecified sexually transmitted disease	A64
	Nonvenereal syphilis	A65
	Yaws	A66
	Pinta [carate]	A67
	Relapsing fevers	A68
	Other spirochaetal infections	A69
	Chlamydia psittaci infection	A70
	Trachoma	A71
	Other diseases caused by chlamydiae	A74
	Typhus fever	A75
	Spotted fever [tick-borne rickettsioses]	A77
	Q fever	A78
	Other rickettsioses	A79
	Acute poliomyelitis	A80
	Atypical virus infections of central nervous system	A81

Adverse outcomes	Description	ICD-10
	Rabies	A82
	Mosquito-borne viral encephalitis	A83
	Tick-borne viral encephalitis	A84
	Other viral encephalitis, not elsewhere classified	A85
	Unspecified viral encephalitis	A86
	Viral meningitis	A87
	Other viral infections of central nervous system, not elsewhere classified	A88
	Unspecified viral infection of central nervous system	A89
	Other mosquito-borne viral fevers	A92
	Other arthropod-borne viral fevers, not elsewhere classified	A93
	Unspecified arthropod-borne viral fever	A94
	Yellow fever	A95
	Arenaviral haemorrhagic fever	A96
	Dengue	A97
	Other viral haemorrhagic fevers, not elsewhere classified	A98
	Unspecified viral haemorrhagic fever	A99
	Herpesviral [herpes simplex] infections	B00
	Varicella [chickenpox]	B01
	Zoster [herpes zoster]	B02
	Smallpox	B03
	Monkeypox	B04
	Measles	B05
	Rubella [German measles]	B06
	Viral warts	B07
	Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified	B08
	Unspecified viral infection characterized by skin and mucous membrane lesions	B09
	Acute hepatitis A	B15
	Acute hepatitis B	B16
	Other acute viral hepatitis	B17
	Chronic viral hepatitis	B18
	Unspecified viral hepatitis	B19
	Cytomegaloviral disease	B25
	Mumps	B26
	Infectious mononucleosis	B27
	Viral conjunctivitis	B30
	Other viral diseases, not elsewhere classified	B33
	Viral infection of unspecified site	B34
	Dermatophytosis	B35
	Other superficial mycoses	B36

Adverse outcomes	Description	ICD-10
	Candidiasis	B37
	Coccidioidomycosis	B38
	Histoplasmosis	B39
	Blastomycosis	B40
	Paracoccidioidomycosis	B41
	Sporotrichosis	B42
	Chromomycosis and phaeomycotic abscess	B43
	Aspergillosis	B44
	Cryptococcosis	B45
	Zygomycosis	B46
	Mycetoma	B47
	Other mycoses, not elsewhere classified	B48
	Unspecified mycosis	B49
	Plasmodium falciparum malaria	B50
	Plasmodium vivax malaria	B51
	Plasmodium malariae malaria	B52
	Other parasitologically confirmed malaria	B53
	Unspecified malaria	B54
	Leishmaniasis	B55
	African trypanosomiasis	B56
	Chagas disease	B57
	Toxoplasmosis	B58
	Other protozoal diseases, not elsewhere classified	B60
	Unspecified protozoal disease	B64
	Schistosomiasis [bilharziasis]	B65
	Other fluke infections	B66
	Echinococcosis	B67
	Taeniasis	B68
	Cysticercosis	B69
	Diphyllobothriasis and sparganosis	B70
	Other cestode infections	B71
	Dracunculiasis	B72
	Onchocerciasis	B73
	Filariasis	B74
	Trichinellosis	B75
	Hookworm diseases	B76
	Ascariasis	B77
	Strongyloidiasis	B78
	Trichuriasis	B79
	Enterobiasis	B80
	Other intestinal helminthiases, not elsewhere classified	B81
	Unspecified intestinal parasitism	B82

Adverse outcomes	Description	ICD-10
	Other helminthiases	B83
	Pediculosis and phthiriasis	B85
	Scabies	B86
	Myiasis	B87
	Other infestations	B88
	Unspecified parasitic disease	B89
	Sequelae of tuberculosis	B90
	Sequelae of poliomyelitis	B91
	Sequelae of leprosy	B92
	Sequelae of other and unspecified infectious and parasitic diseases	B94
	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95
	Other specified bacterial agents as the cause of diseases classified to other chapters	B96
	Viral agents as the cause of diseases classified to other chapters	B97
	Other specified infectious agents as the cause of diseases classified to other chapters	B98
	Other and unspecified infectious diseases	B99
	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
	Influenza due to identified zoonotic or pandemic influenza virus	J09
	Influenza due to identified seasonal influenza virus	J10
	Influenza, virus not identified	J11
	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 due to other infectious organisms, not elsewhere classified	J16
	Pneumonia in diseases classified elsewhere	J17
	Pneumonia, organism unspecified	J18
	Acute bronchitis	J20
	Cellulitis	L03
	Glomerular disorders in infectious and parasitic diseases classified elsewhere	N08.0
	Acute tubulo-interstitial nephritis [exclude pyelonephritis]	N10

Adverse outcomes	Description	ICD-10
	Tubulo-interstitial nephritis, not specified as acute or chronic	N12
	Pyonephrosis	N13.6
	Renal and perinephric abscess	N15.1
	Renal tubulo-interstitial disorders in diseases classified elsewhere	N16
	Calculus of urinary tract in diseases classified elsewhere	N22
	Late syphilis of kidney	N29.0
	Other disorders of kidney and ureter in infectious and parasitic diseases classified elsewhere	N29.1
	Acute cystitis	N30.0
	Bladder disorders in diseases classified elsewhere	N33
	Urethritis and urethral syndrome	N34
	Urinary tract infection, site not specified	N39.0
	Inflammatory diseases of prostate	N41
	Infected hydrocele	N43.1
	Orchitis and epididymitis	N45
	Infections of genitourinary tract in pregnancy	O23
	Other infection during labour	O75.3
	Puerperal sepsis	O85
	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
Emergency caesarean section	Delivery by emergency caesarean section	O82.1

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision

Table 25: Adverse birth outcomes, EXEMPLARY codelist

Adverse outcomes	Description	ICD-10
Preterm birth	Preterm spontaneous labour with preterm delivery	O60.1
	Preterm delivery without spontaneous labour	O60.3
	Extreme immaturity	P07.2
	Other preterm infants	P07.3
Small for gestational age	Small for gestational age	P05.1

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision

Table 26: SLE-related comorbidities - for the SLE severity and activity algorithms, EXEMPLARY Code list

Condition severity	Group	Description	ICD-10
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
		Pseudotumour cerebri	G93.2
		Seizure	R56.8
	Ocular	Chorioretinitis	H30.9
		Episcleritis/scleritis	H15
	Renal	Nephritis	N10, N11
		Renal impairment (other than nephritis or end-stage renal disease)	S37.0, N18 (excl N18.5)
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
	Ocular	Optic neuritis	H46
		End-stage renal disease	N18.5
		Renal failure	N17, N19
Additional conditions to be considered to <u>define moderate and severe flares (SLE activity algorithm only)</u>	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 used in the table: ICD-10, international statistical classification of diseases tenth revision.

Table 27: Co-medication (polypharmacy index), EXEMPLARY Code list

Description	ATC
Non-steroidal anti-inflammatory drugs	M01A
Drugs used in diabetes	A10
Anabolic agents for systemic use	A14
Antithrombotic agents	B01, A01AD05, N02BA01
Antihypertensives	C02
Diuretics	C03
Beta blocking agents	C07
Calcium channel blockers	C08
Agents acting in the renin-angiotensin system	C09
Lipid modifying agents	C10
Intrauterine and intravaginal hormonal contraceptives	G02BB, G02BA03
Sex hormones and modulators of the genital system	G03
Antiemetic medications	R06AE03, R06AA09, R06AA59, R06AE05, A03FA01, A04AA01, N05AB04, R06AD02
Antibacterials and antiinfectives	J01, D06, S01A, S01C, S02A, S03C, G01
Antimycotics and antifungals	J02, D01
Antimycobacterials	J04
Antivirals	J05, D06BB, S01AD
Immune sera and immunoglobulins	J06
Immunostimulants	L03
Immunosuppressive agents except SLE-related	L04A (excludes L04AC03, L04AA32, L04AX01, L04AA28, L04AD01, L04AA13, L04AX03, L04AA06, L04AA10, L04AD02, L04AX02, L04AA29, L04AD03, L04AA51, L04AA26)
Antiepileptics	N03
Hypnotics and sedatives, Anxiolytics	N05C, N05B
Antiprotozoals	P01
Anthelmintics	P02

Abbreviations used in the table: ATC, anatomical therapeutic chemical

Table 28: Substance abuse, EXEMPLARY codelist

Description	ICD-10
Opioid related disorders	F11
Cannabis related disorders	F12
Sedative, hypnotic, or anxiolytic related disorders	F13
Cocaine related disorders	F14
Other stimulant related disorders	F15
Hallucinogen related disorders	F16
Inhalant related disorders	F18
Drug abuse counselling and surveillance	Z71.5
Foetus and new-born affected by maternal use of drugs of addiction	P04.4
Neonatal withdrawal symptoms from maternal use of drugs of addiction	P96.1

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision

Table 29: Alcohol Abuse, EXEMPLARY codelist

Description	ICD-10
Alcohol psychosis	F103-F108
Alcohol abuse	F101
Alcohol dependence syndrome	F102
Alcohol use, unspecified	F109
Alcoholic gastritis	K292
Alcoholic liver disease	K70
Alcoholic fatty liver	K700
Alcoholic hepatitis	K701
Alcoholic hepatitis without ascites	K7010
Alcoholic hepatitis with ascites	K7011
Alcoholic fibrosis and sclerosis of liver	K702
Alcoholic cirrhosis of liver	K703
Alcoholic hepatic failure	K704
Alcoholic liver disease, unspecified	K709
Alcohol abuse counseling and surveillance	Z714
Alcoholic cardiomyopathy	I426
Alcoholic poluneuropathy	G621
Alcoholic myopathy	G722
Degeneration of nervous system due to alcohol	G312

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision

Table 30: Diabetes, EXEMPLARY codelist

Description	ICD-10
Type 1 diabetes mellitus	E10
Type 2 diabetes mellitus	E11
Diabetes mellitus due to underlying condition	E08
Drug or chemical induced diabetes mellitus	E09
Unspecified diabetes mellitus	E14
Other specified diabetes mellitus	E13
Diabetes mellitus in pregnancy, childbirth, and the puerperium	O24
Syndrome of infant of mother with gestational diabetes	P700
Syndrome of infant of a diabetic mother	P701

Abbreviations used in the table: ICD-10, International statistical classification of diseases tenth revision

Appendix E. Additional information

14. PROTOCOL SIGNATURE FORM

Title: A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab

EU PAS Register number:

Date and Version No: 28 August 2023, Version 3.0

Approved by: [redacted]

[redacted]

Institution: AstraZeneca AB

[redacted]

[redacted]

Institution: AstraZeneca AB

[redacted]

[redacted]

Institution: AstraZeneca AB

Principal Investigator: Ana Cristina Santos
Senior Epidemiologist
IQVIA
Anacristina.Santos@iqvia.com

Principal Investigator Signature:

SAPHNELO™ (anifrolumab) is a trademark of the AstraZeneca group of companies.