Ablynx

ALX0061-C204

A Phase II Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-range Finding Study to Evaluate the Safety and Efficacy of ALX-0061 Administered Subcutaneously in Subjects with Moderate to Severe Active Systemic Lupus Erythematosus

28FEB2018

Statistical Analysis Plan

Final Version 1.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

aCL	anti-cardiolipin
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of Special Interest
AIC	Akaike Information Criterion
ALT	Alanine Aminotransferase
ANA	Anti-nuclear Antibodies
ANCOVA	Analysis of Covariance
AQL	Above Quantification Limit
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
β_2-GPI	anti-β_2-glycoprotein I
BICLA	BILAG-based composite lupus assessment
BILAG	British Isles Lupus Assessment Group
BQL	Below Quantification Limit
BST	BILAG-2004 systems tally
CI	Confidence interval
CLASI	Cutaneous lupus erythematosus disease area and severity index
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CRF	Case Report Form
CRP	C-reactive protein
CV	Coefficient of variation
DM	Data Management
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ	Equivocal
GGT	Gamma Glutamyltransferase
HEENT	Head, Ears, Eyes, Nose, Throat
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IL-6	Interleukin-6
INR	International Normalized Ratio
IWRS	Interactive Web Response System

LA	Lupus anti-coagulant
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiac Events
mADA	modified anti-drug antibodies
mBICLA	modified BILAG-based composite lupus assessment
MCP-Mod	Multiple Comparison Procedure – Modelling
MRD	Minimal Required Dilution
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mSFI	mSLEDAI-2K Flare Index
mSLEDAI-2K	modified systemic lupus erythematosus disease activity index 2000
mSRI	modified systemic lupus erythematosus responder index
NAb	Neutralizing antibody
NA	Not Analyzed
NC	Not Calculable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRI	Non-response imputation
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamics
PGA	Physician's global assessment
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred term
q2w	Every 2 weeks
q4w	Every 4 weeks
QTcB	QT corrected Bazett Interval
QTcF	QT corrected Fridericia Interval
RA	Rheumatoid arthritis
s.c.	Subcutaneous(ly)
SAE	Serious adverse event
SAP	Statistical analysis plan
sBST	Simplified BILAG-2004 systems tally
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SF-36	Short Form (36) Health Survey
SI	International Standard Unit

sIL-6R	Soluble interleukin-6 receptor
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic lupus erythematosus disease activity index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SMQs	Standardized MedDRA Queries
SOC	System Organ Class
SRI	Systemic lupus erythematosus responder index
TB	Tuberculosis
TE	Treatment Emergent
TEAE	Treatment-emergent adverse events
TTP	Thrombotic Thrombocytopenic Purpura
uMCP-1	Monocyte Chemotactic Protein-1 in urine
uCr	urine creatinine
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

Systemic lupus erythematosus (SLE) is a clinically heterogeneous disease that affects multiple organs, with the most common manifestations ranging from rash, fatigue and mucocutaneous and musculoskeletal conditions, to more severe renal and neurological manifestations. SLE is characterized by periods of active disease, alternated with temporary remission and relapses.

ALX-0061 has been developed by Ablynx as a new compound neutralizing pro-inflammatory activity in the Interleukin-6 (IL-6) pathway. Based on its mode of action, ALX-0061 is currently in development for the treatment of autoimmune diseases such as SLE and rheumatoid arthritis (RA).

This study is intended to evaluate the efficacy and safety of different dose regimens of ALX-0061 administered subcutaneously (s.c.) on top of standard of care to subjects with moderate to severe active, seropositive SLE. The selection of the doses used in this study was based on the results of study ALX0061-C102 in healthy volunteers (for pharmacokinetics [PK], safety and tolerability), study ALX-0061-1.1/10 in RA patients (for efficacy and pharmacological activity), and the exposure levels measured in preclinical toxicology studies (for safety margin calculation).

As this is an add-on therapy study, all subjects (including subjects in the placebo group) will receive standard of care treatment for SLE in line with their severity of disease and according the Investigator's clinical practice. Analysis of the placebo group will be of value in the assessment of whether or not any abnormalities observed were due to ALX-0061 or to study procedures, and will allow statistical comparison of efficacy between ALX-0061 and placebo.

This statistical analysis plan (SAP) has been created based on study Protocol version 3.0 dated 03-May-2016 and following the International Council for Harmonisation (ICH) guidelines.

2 Objectives

2.1 Primary objective

To assess the efficacy and safety of different dose regimens of ALX-0061 administered s.c. to subjects with moderate to severe active, seropositive SLE compared to placebo.

2.2 Secondary objectives

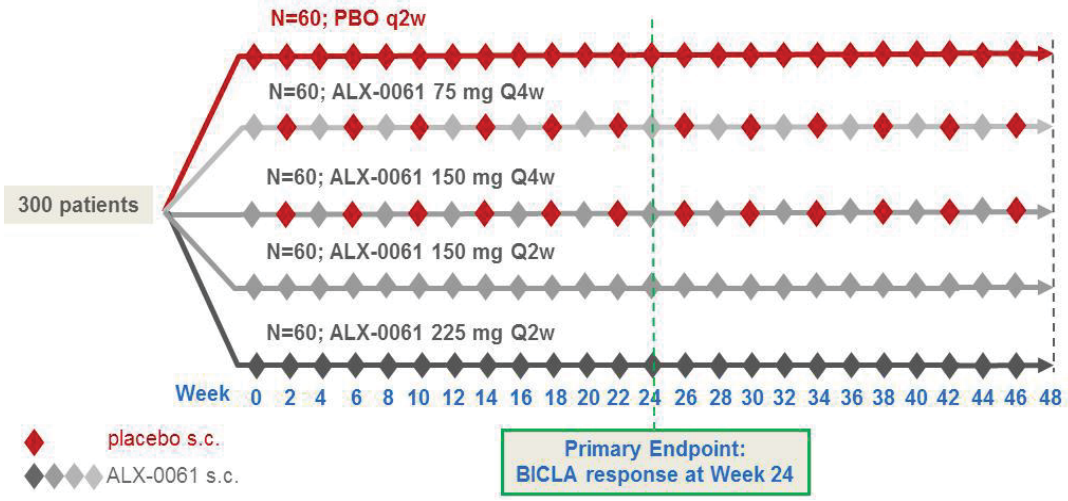
To assess the PK, pharmacodynamics (PD), immunogenicity, flare rate, steroid reduction and health-related quality of life, with different dose regimens of ALX-0061.

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, dose-range finding Phase II study of ALX-0061 administered s.c. on top of standard of care, in subjects with moderate to severe active, seropositive SLE. Approximately 300 subjects will be randomized into 5 treatment groups in a 1:1:1:1:1 ratio (Placebo, ALX-0061 75 mg every 4 weeks [q4w], 150 mg q4w, 150 mg every 2 weeks [q2w] and 225 mg q2w). An overview of the study design is included in Figure 3-1.

Figure 3-1: Overview of the design of Study ALX0061-C204



At the Screening Visit, informed consent will be obtained from all subjects who are deemed potentially eligible for the study according to the protocol-specified inclusion and exclusion criteria, for enrolment in the study.

After obtaining oral and written informed consent, subjects will be screened according to the inclusion and exclusion criteria and will receive a unique subject identification number, assigned by Interactive Web Response System (IWRS).

After receipt of the approval by the eligibility review committee (see Protocol Section 3.4.1.1), subjects can be randomized.

At randomization, subjects will be reassessed and, if they meet the specified entry criteria, subjects will be allocated in a randomization to 1 of 5 treatment groups in a 1:1:1:1:1 ratio, and will receive a randomization number just prior to dosing according

to the randomization scheme. Randomization will be stratified by geographic region (North America, Latin America, Europe and Asia-Pacific).

Subjects will receive one of the following treatments:

- Placebo,
- ALX-0061 75 mg q4w,
- ALX-0061 150 mg q4w,
- ALX-0061 150 mg q2w,
- ALX-0061 225 mg q2w.

ALX-0061 s.c. or placebo s.c. injections, as applicable, will be administered via single-use pre-filled syringe by an appropriately licensed and authorized health professional.

At each administration, the subject will receive 2 s.c. injections in succession at a different quadrant in the abdominal region. As injections are to be performed q2w, the injections can be performed in an abdominal quadrant of choice. The dosing combinations are shown in Section 17.2.

Subjects and investigational staff will be blinded for treatment and dose. Subjects will be followed for efficacy through Week 48 and for safety through Week 58. Visits are planned every 2 weeks from randomization to Week 48 and then at follow-up at Week 58 [12 weeks after the last dose; last dose is at Week 46].

The schedule of assessment is included in Section 17.1.

3.1.1 Sample Size

Up to approximately 300 subjects will be randomized over 5 treatment arms in a 1:1:1:1:1 ratio. Randomization will be stratified by geographic region.

Simulations were performed to evaluate the power of detecting a significant dose-response relationship, i.e., whether changes in ALX-0061 dose regimen lead to significant changes in mBICLA response rate at Week 24 by using the MCP-Mod methodology [1]. A set of 5 plausible candidate models containing both monotonous and non-monotonous exposure-response shapes was defined. For these models an estimated placebo response rate of 25%, and a difference in response rate between the ALX-0061 dose regimen with the largest response rate and placebo of 25% was assumed, taking into account a discontinuation rate of 15% (homogeneous over treatment arms). With this methodology a sample size of 60 subjects per arm will provide at least 85% power at a family-wise 5% significance level.

3.1.2 Blinding and Unblinding

3.1.2.1 Study Drug Administration Blinding

Since the 225 mg dose of ALX-0061 exceeds the volume that can be administered in a single injection, the placebo and ALX-0061 groups will have 2 different combinations of injections to ensure the double-blinded design. All subjects are to receive 2 injections in succession (syringe A containing 1 mL and syringe B containing 0.5 mL) at each dosing day, every 2 weeks. Syringes containing ALX-0061 or placebo are a visual match. When containing the active product, syringes A and B contain 150 mg and 75 mg of ALX-0061, respectively.

Therefore, there will be a total of 5 dosing combinations in the study, with 4 possible active dose regimens. These dosing combinations are shown in Section 17.2.

In order to protect the integrity of the data, ALX-0061 treatment assignment will be kept blinded for investigative sites, site monitors, subjects, vendors and PPD/Sponsor until the final database lock (including the Follow-up Visit 12 weeks after the last dosing).

Identification of Sponsor and vendor personnel who will have access to the unblinded data before final database lock, will be documented prior to their unblinding. The number of Sponsor personnel having access to the unblinded data will be limited.

3.1.2.2 Blinding of Potentially Unblinding Parameters

Given the pronounced effect of an anti-IL-6 compound on the acute phase reactants, the results of CRP and fibrinogen tests performed by the central laboratory will not be communicated to the investigational sites and PPD/Sponsor until after database lock and unblinding (unless in case of an alert). If an investigational site requests these data, it will be provided after the end of the study.

If the clinical condition of the subject warrants knowledge of the values of CRP or fibrinogen in order to provide appropriate medical care, the Investigator can request these assessments to be performed locally.

PK concentrations will be determined within Ablynx by dedicated personnel and will not be communicated to the investigational sites, PPD and Sponsor personnel (except for dedicated study personnel) until after the database lock and unblinding. The dedicated study personnel performing the analysis will be documented in the bioanalytical plan and unblinding forms according to Sponsor procedures. PK concentrations will be transferred to the immunogenicity study personnel to allow correct immunogenicity subject classification. The dedicated study personnel will also be documented in the unblinding forms according to Sponsor procedures.

sIL-6R concentrations will be determined within Eurofins and will not be communicated to the investigational sites and PPD/Sponsor until after the database lock and unblinding.

3.1.2.3 Emergency Unblinding

Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via the IWRS, which will be accessible 24 hours per day/7 days per week.

Unblinding by the Investigator should occur only in the event of an AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject.

If the Investigator must identify the treatment assignment of an individual subject, the Investigator or qualified designee is to call the IWRS. Unblinding performed by the IWRS at the request of the Investigator is to be reported to the Sponsor. When possible, the Investigator must first discuss options with the Medical Monitor.

Subjects for whom the code has been broken by the Investigator will have to discontinue treatment and all efforts must be made to conduct the Early Termination Visit and Follow-up Visit.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the percentage of subjects in the mITT population who achieved a response at Week 24 according to the modified British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (mBICLA) score, see Section 17.6. Handling of missing data is described in Section 8.1.

3.2.2 Secondary Endpoints

The following endpoints are secondary endpoints (see Section 8.2, Section 17.3 to Section 17.12 for more details):

Efficacy Endpoints:

- Composite endpoint mBICLA response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint BICLA response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint Systemic lupus erythematosus Responder Index (SRI) response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint SRI-5 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint SRI-6 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint SRI-7 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint SRI-8 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint modified SRI (mSRI) response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint mSRI-5 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint mSRI-6 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Composite endpoint mSRI-7 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.

- Composite endpoint mSRI-8 response rate at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Actual and change from Baseline values in Systemic Lupus Erythematosus Disease activity index 2000 (SLEDAI-2K) score at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Actual and change from Baseline values in modified SLEDAI-2K (mSLEDAI-2K) score at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Number and percent of subjects with BILAG-2004 improvement (normal and enhanced) from Baseline at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Actual and change from Baseline values in BILAG-2004 Total Score at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Normal improvement in individual organ systems of the BILAG-2004 at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Number of BILAG-2004 systems with active/worsening disease, improving disease, or persistent minimal or no activity compared to previous visit (BILAG-2004 systems tally) at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Actual and change from Baseline values in Physician's Global Assessment (PGA) at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Actual and change from Baseline values in patient's global assessment at Week 24 and Week 48.
- Actual values and change from Baseline in efficacy laboratory parameters:
    - Proteinuria (as measured by spot urine protein to creatinine ratio) and estimated glomerular filtration rate (eGRF) at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
    - Serum creatinine at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Follow-up.
- Shift from Baseline in urine sediment (present/not present) at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Proportion of treatment failures at Week 24 and at Week 48.
- Severe flare rate at Week 24 and at Week 48 using the following indexes:
    - BILAG-2004 Flare Index
    - mSLEDAI-2K Flare Index (mSFI)
- Mild/moderate flare rate at Week 24 and at Week 48 using the following indexes:
    - BILAG-2004 Flare Index
    - mSFI

- Actual values, change from baseline and percent change from Baseline in Prednisone Equivalent Total Daily Dose at Week 12, Week 24 and Week 48.
- Percent of subjects whose prednisone equivalent dose was >7.5 mg/day at Baseline and reduced to ≤7.5 mg/day during Weeks 40–48 without experiencing a mSFI-defined or BILAG-2004-defined flare (regardless of the severity of flare) after the first prednisone equivalent dose decrease.
- Percent of subjects whose prednisone equivalent dose was >7.5 mg/day at Baseline and reduced to ≤7.5 mg/day during Weeks 40–48 without experiencing a mSFI-defined or BILAG-2004-defined severe flare after the first prednisone equivalent dose decrease.
- Percent of subjects who are able to discontinue prednisone (or equivalent) before or on Week 48 without experiencing an mSFI-defined or BILAG-2004-defined flare (regardless of the severity of flare) after the first prednisone equivalent dose decrease.
- Percent of subjects who are able to discontinue prednisone (or equivalent) before or on Week 48 without experiencing an mSFI-defined or BILAG-defined severe flare after the first prednisone equivalent dose decrease.
- Actual values and change from Baseline in the physical and mental component scores of Short Form (36) Health Survey (SF-36) at Week 24 and at Week 48.
- Actual values and change from Baseline in 28 joint count swollenness and tenderness at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48.
- Actual values and change from Baseline in Cutaneous Lupus Erythematosus disease Area and Severity Index (CLASI) at Week 12, 24 and Week 48.

Pharmacokinetic (PK) Endpoints:

- Pharmacokinetic (PK) concentration at Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48.

Pharmacodynamics Endpoints:

- Actual values and percent change from baseline in the following Pharmacodynamic (PD) markers (including total sIL-6R, C-reactive protein [CRP], fibrinogen, anti-dsDNA (FARR), C3, C4 and CH50)
    - For sIL-6R: at Week 4, Week 8, Week 12, Week 16, Week 24, Week 32, Week 40, Week 48 and Follow-up.
    - For CRP, fibrinogen, anti-dsDNA (FARR), C3, C4 and CH50: at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Follow-up.
- Shift from Baseline in Fibrinogen CTCAE grade category at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Follow-up and Worst on-treatment post-baseline visit.
- Actual values and percent change from Baseline in the following biomarkers at Week 8, Week 24 and Week 48.
    - Monocyte Chemotactic Protein-1 in urine (uMCP-1),
    - uMCP-1/urine creatinine (uCr).

Immunogenicity Endpoints:

- Overall subject classification based on ADA/mADA assays results.
- Overall subject classification based on NAb assay results.

Safety Endpoints:

- Number of events as well as number and percent of subjects with Adverse Events (AEs), treatment-related AEs, Serious Adverse Events (SAEs), non-Serious AEs, treatment-related SAEs, AEs leading to treatment discontinuation and Adverse Events of Special Interest (AESI) categorized by System Organ Class (SOC), Preferred Term (PT) and Maximum Severity (where applicable).
- Actual values and change from Baseline in vital signs measurements at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Follow-up.
- Actual values and change from Baseline in Electrocardiogram (ECG) values at Week 48.
- Actual values and change from Baseline in blood chemistry parameters (including liver enzymes and lipids), hematology parameters (including neutrophils and platelets) and coagulation parameters at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Follow-up and worst on-treatment.
- Number and percent of subjects with abnormal laboratory parameters of special interest at time post-Baseline.
- Shift from Baseline in laboratory parameters categorized with normal ranges or CTC grades at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Follow-up and worst on-treatment post-Baseline.
- Number and percent of subjects for each pattern of anti-nuclear antibodies (ANA) at Screening and Week 24.
- Actual titres of ANA at Screening and Week 24.
- Actual values and change from Baseline in β2-glycoprotein I IgG, β2-glycoprotein I IgM, anti-cardiolipin IgA, anti-cardiolipin IgG, anti-cardiolipin IgM and anti-lupus at Week 24.

4 General Statistical Considerations

Statistical analysis will be performed using SAS® Version 9.3 or higher on the Windows 7 platform. The Multiple Comparison Procedure – Modelling (MCP-Mod) procedure will be implemented using R version 3.1.0 (or higher) with the DoseFinding package version 0.9.15 (or higher) on the Windows 7 platform. SF-36 domains and components score will be derived by SF-36 v2 Scoring software.

Standardized and validated SAS macros from PPD will be used to set up table, listing, figure (TLF) formats (headers/footers and tabulation format) and tabulate the summaries (with the exception of the tables and figures programmed in R). All tables and listings will be independently validated using double programming; all figures will be independently validated manually.

Treatment Labels

The following treatment labels will be used in the Tables, Figures and Listings. Placebo will be presented first and then active treatment in increasing dosing received. An all active treatments combined group will be presented as an additional column for disposition, demographic and baseline characteristics, prior/concomitant medication, immunogenicity and safety outputs. Where applicable, in the listing, subjects who are randomized but not treated will be presented in a "Not Treated" column, which will be presented prior to the Placebo column.

Table 4-1: Treatment Labels

Treatment group	Treatment Label
Placebo	Placebo
ALX-0061 75 mg q4w	ALX-0061 75 mg q4w
ALX-0061 150 mg q4w	ALX-0061 150 mg q4w
ALX-0061 150 mg q2w	ALX-0061 150 mg q2w
ALX-0061 225 mg q2w	ALX-0061 225 mg q2w
All ALX-0061	All ALX-0061

Visit Naming Conventions

For immunogenicity, Screening and Baseline assessments will be reported separately. The CRF visit label will be used to classify the assessments. All other assessments (including post Baseline immunogenicity) will be windowed (see Section 17.16).

The TLF shell Section 2.2.3 presents the visits labels convention that will be used in the Tables, Figures and Listings. For the Tables and Figures only scheduled post-Baseline visits will be displayed as per the schedule of events (see Section 17.1) in addition to the Baseline results, unless otherwise specified.

Visit Windows

The visit windows as defined in Section 17.16 will be applied to all parameters. For immunogenicity, both Screening and Baseline visits will be summarized separately and the CRF visit label will be used to classify the assessments.

Display of Data Summary and Analysis

Continuous variables will be summarized using descriptive statistics, including the following: mean, standard deviation (SD) for demographics and Baseline disease characteristics summaries as well as for PK summaries, standard error (SE) for all PD and other summaries, median, minimum and maximum value; additional descriptive statistics will be provided for the summary of drug concentration, PD and ANA endpoints (see Section 9.2.6, Section 10 and Section 11). All minimum and maximum values will be displayed to the level of precision as the raw data, the quartiles (if applicable), mean and median will be displayed to one level of precision greater, and the SD and SE will be displayed to two additional levels of precision. For the safety and efficacy laboratory data, PD and immunogenicity data; the precision level of the raw data can be found in Section 17.14. Pharmacokinetic concentrations and descriptive statistics will be reported to 3 significant digits for values up to, but not including 1000. Values equal to and above 1000 will be reported as the value without decimal place.

95% confidence intervals (CIs) will be two-sided and displayed to the same level of precision as the statistic they relate to. If an estimate or a CI is not estimable, it will be

presented as 'NE'. If neither an estimate, nor its CI are estimable, it will be presented as simply 'NE', not displaying 'NE' twice.

The p-values will be two-sided and will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as '<0.001.' If a p-value is greater than 0.999 it will be reported as '>0.999.'

Categorical variables will be summarized using frequency counts and percentages. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted 'Missing' will be included in count tabulations for demographics, Baseline characteristics and compliance to account for missing values. No percentages will be displayed on the 'Missing' rows and the percentages will be based on the number of non-missing observations. Unless otherwise specified, the denominator for all other percentages will be the number of subjects in that treatment within the specific analysis set of interest. Percentages will be displayed using one decimal place.

Figures display

The TLF shell Section 2.2.7 presents the display that will be used in the Figures.

Listing display/contents

See Section 17.19 for details on listings contents and display.

Baseline, study day and duration derivations

Baseline will be defined as the last non-missing assessment prior to the first dose. If there are multiple non-missing assessments collected on Day 1 where the time is not available, the assessment linked with the Baseline CRF Visit will be considered the baseline value. Where applicable, time will also be used to determine the pre/post Baseline assessment. Thus, the Baseline assessments for different variables may be collected at different times or on different days.

For post-Baseline visits, all visits including unscheduled visits are used to determine the analysis visit. For BILAG-2004, the visit mapping will be based on the date of assessments. If there are multiple results within the same visit windows, the non-missing assessment/sample closest to the planned study day will be selected for analysis. In case of ties, the first non-missing assessment after the target day will be selected for analysis. In case of ties on the same day with time not available, the assessment linked with the CRF visit will be selected for analysis.

For immunogenicity, Screening and Baseline assessments will be reported separately. The CRF visit label will be used to classify the assessments.

Calculations using dates (e.g. subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days on or after the start day of study drug will be calculated as the difference between the date of interest (TARGET DATE) and the first date of dosing of study drug (DSTART) plus 1 day. The generalized calculation algorithm for relative day is the following:
    - If TARGET DATE ≥ DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
    - Else use STUDY DAY = TARGET DATE – DSTART.

Note that Study Day 1 is the first day of treatment of study drug. Study days on or before Day 1 are reflective of observations obtained during the Baseline/Screening period.

- Intervals that are presented in weeks will be transformed from days to weeks by using (without rounding) the following conversion formula:

  WEEKS = DAYS /7

- Intervals that are presented in months will be transformed from days to months by using (without rounding) the following conversion formula:

  MONTHS = DAYS /30.4375

4.1 Analysis Populations

4.1.1 All Screened Population

The all Screened population includes every subject who has signed informed consent.

The all Screened population will be used for summaries of disposition and associated listing. Listing of Informed Consent and Protocol Version will also use the all Screened population.

4.1.2 All Randomized Population

The all Randomized population includes all subjects who have been randomized.

The all Randomized population will be used for listing of the subjects excluded from analysis populations as well as summarizing the number of subjects randomized in each country. Subjects will be summarized and listed based on the treatment they have been randomized to.

4.1.3 Modified Intent-to-Treat (mITT) Population

The mITT population comprises all randomized subjects who received at least 1 administration of study drug. All subjects will be analyzed based on the treatment group they were randomized to regardless of the dosing regimen (dose and/or frequency for ALX-0061) received.

The mITT population will be used for summaries and analysis of demographics and Baseline characteristics, treatments and medications, secondary efficacy endpoints and will be the primary population for the analysis of the primary endpoint.

4.1.4 Per Protocol (PP) Population

The PP population consists of a subset of the mITT population, and excludes those subjects who have had a major protocol violation or deviation which might potentially impact the primary endpoint. All violations and deviations will be reviewed in a blinded fashion prior to database lock and classified as major or minor.

The Protocol Deviation Plan will contain all the information regarding the definitions of deviations, the frequency of meetings to be held by the study team to discuss any deviation related data, and the deviations to be used, which are also in the below categories. Protocol deviations will be reviewed on an ongoing basis throughout the trial.

Major protocol deviations are generally those which affect the general well-being and safety of the subject or have an impact on the scientific integrity of the study and will include the following violations (not an exhaustive list):

- Missing primary endpoint at Week 24:

  - BILAG-2004 missing at Baseline and/or at Week 24.
  - SLEDAI-2K missing at Baseline and/or at Week 24.
  - PGA missing at Baseline and/or at Week 24.
- Failure to meet eligibility criteria.
- Incorrect treatment received:
  - Incorrect dose received.
  - Incorrect dosing regimen received.
- Criteria for study drug discontinuation met but the subject was not withdrawn from treatment.
- Intake of prohibited concomitant medications:
  - Investigational or biological drug.
  - Live, attenuated vaccine during the study or within 6 months after dosing.
  - Intravenous immunoglobulins, cyclophosphamide or tacrolimus.
  - Therapy blocking the IL-6 pathway, such as but not limited to ALX-0061, sirukumab, tocilizumab, sarilumab, clazakizumab, olokizumab, or JAK inhibitors.

Based on the Protocol Deviation Plan, the following deviations reported into the CTMS and imported in the DV domain will lead to excluding the subject from the PP Population.

Deviation Category	DVDECOD	DVTERM
Missing primary endpoint at Week 24	Efficacy Assessment Deviation	Physician Global assessment not completed by the Investigator at baseline
		Physician Global assessment not completed by the Investigator at Week 24
		(BILAG-2004 not completed at screening **or** BILAG-2004 2 not fully completed at screening: <specify body system and/or items number missing>) **and** (BILAG-2004 not completed at baseline **or** BILAG-2004 not fully completed at baseline: <specify body system and/or items number missing>)
		BILAG-2004 not completed at Week 24
		BILAG-2004 not fully completed at Week 24: <specify body system and/or items number missing>.

Deviation Category	DVDECOD	DVTERM
Missing primary endpoint at Week 24	Efficacy Assessment Deviation	(SLEDAI not completed at screening **or** SLEDAI not fully completed at screening. Descriptor item <specify item(s)> missing) **and** (SLEDAI not completed at baseline **or** SLEDAI not fully completed at baseline. Descriptor item <specify item(s)> missing.
		SLEDAI not completed at week 24
		SLEDAI not fully completed at Week 24. Descriptor item <specify item(s)> missing.
	Other	The subject missed visit week 24
		Visit out of window: Week 24 was done <specify days before/after> the planned visit date. Where <specify days before/after> is greater or equals to 14.
Failure to meet eligibility criteria.	Selection Criteria not met	Any
Incorrect treatment received	Treatment non-compliance	Any deviation recorded under "Kit number of study drug dispensed to subject at <specify visit> was not the same as kit number assigned by IRT.", where <specify visit> is Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 20 or Week 22. **and** for which (after unblinding) the dispensed kit number correspond to the incorrect treatment (e.g. kit number should correspond to Placebo but correspond to ALX0061)
Criteria for study drug discontinuation met but the subject was not withdrawn from treatment	Subject Not Withdrawn as per Protocol	Any deviations with a text started by "Before or at week 24"
Intake of prohibited concomitant medications	Prohibited concomitant medication	Any deviations with a text started by "Before or at week 24"

Deviation Category	DVDECOD	DVTERM
Undeclared/rejected IMP received	Treatment non-compliance	Any deviation recorded under "DOSING WITH UNDECLARED/REJECTED IP: DEVIATIONS TO THE STUDY DRUG CONDITIONS WHEN ADMINISTERED TO THE SUBJECT AT <specify visit>." Where • for subjects randomized to ALX0061 75 or 150 mg q4w: visit is Baseline, Week 4, Week 8, Week 12, Week 16 or Week 20. • for subjects randomized to ALX0061 150 or 225 mg q2w: visit is Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 20 or Week 22

In addition, the following criteria will be programmed and subjects meeting this criterion will be excluded from the PP Population.

- For subjects randomized in the ALX-0061 75 mg q4w or ALX-0061 150 mg q4w: if ≥ 1 active dose has been missed between Baseline and Week 20 visit.
- For subjects randomized in the ALX-0061 150 mg q2w or ALX-0061 225 mg q2w: if ≥ 2 active doses missing between Baseline and Week 22 visit.

Subjects included in the PP population will be analyzed according to the randomized treatment. The PP population will be used as a supportive population for summaries and analyses of the primary endpoint.

4.1.5 Safety Population

The Safety population consists of all subjects who received at least 1 administration of study drug. All subjects will be classified based on the actual treatment group. This is the treatment group they were randomized to, except if the subject received a different dose regimen during the whole treatment period. In that case, the subject will be summarized based on the first treatment received. For subjects who received 150 mg as first dose, the dose administered at the following planned dosing visit (e.g. Week 2 if the first dose was administered at Baseline) will be considered as described in Table 4-2. For the subjects for which no dose was received at the planned dosing visit following the first dose (e.g. the subject discontinued, the visit was missed and no drug administered), the actual treatment group should be derived as follows:

- If the subject was randomized to 150 mg q2w or 150 mg q4w, the actual treatment will be set to be equal to the planned treatment
- If the subject was randomized to placebo, 75 mg q4w or 225 mg q2w, the actual treatment will be set to be 150 mg q4w.

Table 4-2: Actual Treatment Group

First Dose Received (ALX-0061)[a]	Second Dose Received (ALX-0061)[a]	Actual Treatment Group
0 mg	Any	Placebo
75 mg	Any	ALX-0061 75 mg q4w
150 mg	150 mg or 225 mg	ALX-0061 150 mg q2w
150 mg	0 mg or 75 mg	ALX-0061 150 mg q4w
225 mg	Any	ALX-0061 225 mg q2w

[a] first dose received should be at Baseline and second dose at Week 2.

The Safety population will be used for the summaries and analyses of the safety data as well as for the PK concentrations summaries and immunogenicity summaries.

5 Subject Disposition

5.1 Disposition

Subject disposition will be summarized and listed for the all Screened population for each treatment group, "All ALX-0061" group and overall. A disposition of subjects includes the number of subjects who were screened, number of subjects who were randomized, number and percentage of subjects who were treated, number and percentage of subjects who completed the study, number and percentage of subjects who discontinued from study during treatment period (i.e. have discontinued from the study and did not perform their Week 48 visit) and number and percentage of subjects who discontinued from the study during the follow-up period (i.e. have discontinued from the study but attended Week 48 visit). Percentages will be based on the number of subjects randomized. The reasons for discontinuation will also be summarized in this table. Percentages will be based on the number of subjects randomized.

The number of subjects randomized per country will be summarized for the all Randomized population.

A listing of screen failures will be provided.

5.2 Analysis Populations

A summary of the analysis sets including the number and percentage of subjects for the following categories: subjects in the Safety population, subjects in the mITT population, and subjects in the PP population will be presented by treatment group, "All ALX-0061" group and overall. Percentage of subjects in the PP population will be based on the number of subjects in the mITT population.

A listing of subjects excluded from analysis populations will be provided.

5.3 Protocol Deviations

The Protocol Deviation Plan document will contain all the information regarding the definitions of deviations, and the frequency of meetings to be held by the study team to discuss any deviation related data. All information held in that document will be updated as needed. General examples for major protocol deviations are provided in the PP population description, in Section 4.1.4 of this document. All major protocol deviations will be identified, and therefore the list of subjects excluded from the PP population will be finalized before database lock and unblinding.

A summary table of subjects per major protocol deviation category will be presented by treatment group, "All ALX-0061" group and overall and will be based on the mITT population.

Listing of protocol major deviations will be provided.

6 Demographics and Baseline Characteristics

Summaries for this section will be presented by treatment group, "All ALX-0061" group and overall using the mITT population.

6.1 Demographics

The demographic characteristics consist of age (years), sex, race, and ethnicity. The Baseline characteristics consist of Baseline height (cm), Baseline weight (kg), Baseline body mass index (BMI) (kg/m^2) and geographic region. BMI is calculated as (body weight in kilograms) / (height in meters)^2.

The following characteristics will be summarized using descriptive statistics.

- Age (years),
- Baseline height (cm),
- Baseline weight (kg),
- Baseline BMI (kg/m^2),

The number and percentage of subjects will be calculated for the following characteristics. Percentages will be based on the number of subjects in the mITT population and relevant treatment group with non-missing data.

- Age (18 to <45 years, 45 to <65 years),
- Sex (Male, Female),
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- BMI (≤25 kg/m², > 25 kg/m²),
- Geographic region (North America, Latin America, Europe and Asia-Pacific),

Listings of demographics and Baseline characteristics will be provided. All CRF scheduled study visits dates will be displayed in a listing. In addition, the first subject first visit date and last subject last visit date will be provided in a listing.

6.2 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized using descriptive statistics.

- Baseline SLEDAI-2K score,
- Baseline BILAG-2004 total score,
- Baseline PGA score,
- Baseline CLASI activity score,
- Baseline CLASI damage score,
- Baseline SF-36 physical component score,
- Baseline SF-36 mental component score,
- Baseline 28-joint count total score – Swollenness,
- Baseline 28-joint count total score – Tenderness,
- Baseline Prednisone Equivalent Dose intake,
- Disease duration (months),
- Baseline SLICC damage score.

The number and percentage of subjects for the following baseline disease characteristics will also be reported. Percentages will be based on the number of subjects in the mITT population and the relevant treatment group with non-missing data.

- Baseline SLEDAI-2K score (< 10, ≥ 10),
- At least one organ system with BILAG-2004 score A at Baseline (yes, no),
- At least two organ systems with BILAG-2004 score B at Baseline (yes, no),
- At least one BILAG-2004 score A or B at Baseline by organ system (yes, no),
- Baseline immunosuppressants intake (yes, no),
- Baseline corticosteroids intake (yes, no),
- Baseline Prednisone Equivalent Dose intake > 7.5 mg/day (yes, no),
- Baseline anti-dsDNA (FARR) ≥ 8 IU/mL (yes, no),
- Baseline SLEDAI-2K low complement item (yes, no),

- Baseline anti-malarial intake (yes, no).
- SLICC/ACR disease classification (None, SLICC, ACR, SLICC and ACR).
- Disease duration (< 6 months, 6 months to <1 year, 1 year to < 5 years and ≥ 5 years).

Disease duration (months) is derived as the date of informed consent minus the date of diagnosis divided by 30.4375.

If the date of diagnosis is partial:

- If only the day is missing, the date will be imputed by the 15th;
- If only the day and month are missing, the date will be imputed by the 1st of July if the year of diagnosis is smaller than year of informed consent. If the year of diagnosis is the same as the year of informed consent then the day and month will not be imputed.

The SLICC damage score will be derived as described in Section 17.13. Individual responses to questions will be listed.

6.3 Tobacco Usage

Past and present tobacco usage will not be summarized but will be listed only.

6.4 Medical History

The number and percentage of subjects with any medical history will be summarized overall and for each predefined body system. Applicable body system codes include Dermatologic; Head, Eyes, Ears, Nose, Throat (HEENT); Respiratory; Cardiovascular; Gastrointestinal; Endocrine/Metabolic; Genitourinary; Neurologic; Blood/Lymphatic; Musculoskeletal; Hepatic; Allergy/Drug Sensitivity; Psychological/Psychiatric and Other. Percentages will be calculated based on number of subjects in the mITT population. Body system codes will be sorted in descending order of frequency based on the total of all treatment groups.

A listing of medical history will be provided.

6.5 Additional Screening/Baseline Assessments

Screening test results for Hepatitis B, Hepatitis C and human immunodeficiency virus (HIV) will be provided in data listing.

7 Treatments and Medications

7.1 Prior and Concomitant Medications

Summaries for this section will be presented by treatment group, "All ALX-0061" group and overall using the mITT population.

All medications (including SLE medications) used within a year of the date of informed consent through the end of the study (follow-up visit) will be collected on the CRF. SLE medications are recorded on the "SLE Medication" CRF page, while the other medications are recorded on the "Concomitant Medications" CRF page. All medications will be coded according to the latest World Health Organization Drug Dictionary (WHO-DD).

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Section 17.15.

SLE Prior/Concomitant Medications and Other Prior/Concomitant medications will be summarized and listed.

7.1.1 Prior Medications

A prior medication is defined as any medication that is taken prior to the first dose of study drug.

SLE Prior Medications

The number and percentage of subjects with at least one prior SLE medication will be summarized by treatment group. The number and percentage of all prior SLE medications will be summarized by treatment group and listed by ATC level 4 and PT. Medications will be sorted in descending order of frequency of ATC 4 category based on the total of all treatment groups. Within each ATC 4 category, PTs will be sorted in descending order of frequency based on the total of all treatment groups.

Other Prior Medications

Other prior medications will be summarized similarly as prior SLE medications.

7.1.2 Concomitant Medications

A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug.

Concomitant SLE Medications

The number and percentage of subjects with at least one concomitant SLE medication will be summarized by treatment group. The number and percentage of all concomitant SLE medications will be summarized by treatment group and listed by ATC level 4 and PT. Medications will be sorted in descending order of frequency of ATC 4 category based on the total of all treatment groups. Within each ATC 4 category, PTs will be sorted in descending order of frequency based on the total of all treatment groups.

Other Concomitant Medications

Other concomitant medications will be summarized similarly as concomitant SLE medications.

7.2 Study Treatments

Extent of exposure and compliance will be summarized using descriptive statistics and frequency count by treatment group, and listed based on the Safety population.

Duration of Exposure (weeks):

The duration of exposure is the number of weeks elapsed between the first and last dose (i.e. Date of last dose - date of first dose + 1 day, divided by 7).

The duration of exposure will be summarized by treatment group using descriptive statistics.

Actual Cumulative Dose (mg):

The actual cumulative dose is the sum of all doses received (from syringes A and B); if a dose was administered but not complete, it will be assumed that 50% of the syringe content was administered. The actual cumulative dose (mg) will be summarized using descriptive statistics.

Compliance to Injections (%)

Compliance to injections is the number of injections received regardless of the syringe type received (complete and incomplete) divided by the expected number of injections x 100. The expected number of injections is the expected number of injections up to the last available visit. For prematurely discontinued subjects, it corresponds to the expected number of injections up to last available assessment visit before discontinuation. The compliance to injections will be summarized by descriptive statistics; in addition the number and percentage of subjects with compliance to injections < 90%, between 90% and 110% and > 110% will be provided.

8 Efficacy Analysis

The statistical inference will be 2-sided and performed at the 5% significance level, thereby providing 95% (2-sided) CIs. The MCP-Mod will be employed to address any multiplicity arising from the analysis of the primary endpoint using different models. Analyses will be performed on the secondary efficacy endpoints (see Section 8.2 for details) using 2-sided tests at 5% significance level. No adjustment for multiplicity for the secondary endpoints analysis will be performed as those analyses will be exploratory in nature. Statistical interpretation of the results will not be done on a single endpoint but will be based on the patterns of results.

Change from Baseline will be calculated as follows: post-Baseline value – Baseline value. Percent change from baseline will be (change from Baseline divided by Baseline value) x 100. For the changes from Baseline, only subjects with a value at both the Baseline visit and the specific post-Baseline visit will be included. Note that the post-Baseline visit value may be imputed, as described in Section 8.1 below.

All endpoints will be summarized by treatment group using descriptive statistics or frequency count and percentages.

For all secondary efficacy endpoints (excluding BILAG-2004 Systems Tally), the following inferential statistics will be provided:

- LSMeans, SE of the LSMeans and 95% CI of the change from Baseline for continuous endpoints from an analysis of covariance (ANCOVA) model or the Clopper Pearson 95% CI of the response rate/incidence will be provided by treatment group,
- LSMeans and 95% CI (from the ANCOVA) of the difference between each of the active treatment group versus the placebo group for continuous endpoints and difference and 95% CI (from the stratified CHM test) of the difference between each of the active treatment group versus the placebo group for binary endpoints.

In addition, p-values from the Cochran-Mantel-Haenszel (CMH) test stratified by geographic region [15] will be provided for the comparison of each active treatment group versus placebo group for the following endpoints and both Week 24 and Week 48 time points. Details for deriving the stratified CMH 95% CI and p-value can be found in Section 17.22.

- mBICLA response rate,
- mSRI response rate,
- Mild/moderate and severe mSFI-defined flare incidence rate (overall and split by intensity),
- Mild/moderate and severe BILAG-2004-defined flare incidence rate (overall and split by intensity),
- Treatment Failure incidence rate.

Unless otherwise specified, the mITT population will be the basis for all efficacy analyses. The PP population will be used for supportive summary and analysis of the primary endpoint. In addition, subgroup summary (see Section 8.1.4) will be performed for the primary endpoint based on the mITT population.

8.1 Primary Efficacy Endpoint

The primary endpoint is the mBICLA response rate at Week 24. The derivation of this endpoint is described in Section 17.6.

For the purpose of calculating the mBICLA response rate for the primary endpoint at Week 24, if mSLEDAI-2K is done but there are a few missing items in mSLEDAI-2K, the following imputation rule will be applied. If no more than 25% (including 25%) of the mSLEDAI-2K items are missing at Week 24 then the value will be imputed with the previous recorded value of the same item (last observation carried forward [LOCF] imputation). Baseline items (i.e. any records that occurred prior or on the first dose of study drug) will not be used to impute missing on-treatment items. If more than 25% of the items are missing then imputations rules will not be applied and mSLEDAI-2K score may be missing. Missing BILAG-2004 items will be imputed according to the specific rules described in Section 17.3.5.1.

Subjects will have mBICLA missing if any of the following is missing after the LOCF imputation for mSLEDAI-2K or after the imputation rules described in Section 17.3.5.1 have been applied for BILAG-2004 system organs scores:

- Missing BILAG-2004 at baseline or/and missing at Week 24, or
- Missing mSLEDAI-2K at baseline or/and missing at Week 24, or
- Missing PGA at baseline or/and missing at Week 24.

Subjects with missing mBICLA response at Week 24 including subjects who discontinued prior to Week 24 or who are confirmed treatment failures by a medical review (as described in Section 17.5) will be imputed as non-responders (i.e. non-response imputation approach [NRI]).

8.1.1 Primary Analysis

mBICLA response rates at Week 24 will be analyzed for dose-response using the MCP-Mod methodology [1, 11]. As the subjects are assigned to different dose schedules, the nominal doses included in the dose-response modelling will be as follows:

- Subjects randomized to Placebo will be assigned a dose of 0 mg,
- Subjects randomized to ALX-0061 75 mg q4w will be assigned a dose of 37.5 mg,
- Subjects randomized to ALX-0061 150 mg q4w will be assigned a dose of 75 mg,
- Subjects randomized to ALX-0061 150 mg q2w will be assigned a dose of 150 mg,
- Subjects randomized to ALX-0061 225 mg q2w will be assigned a dose of 225 mg.

The MCP-Mod method entails a unified strategy to the analysis of data from dose-response studies which combines multiple comparison and modelling techniques. The existence of several candidate parametric models is assumed and multiple comparison techniques are used to choose the model(s) most likely to represent the true underlying dose-response curve, while preserving the family-wise error rate. The selected model may further be used to guide the choice of adequate doses.

The MCP-Mod consists of the 2 major steps [11]: a multiple comparison step and a modelling step. The focus for the primary analysis will be on the MCP step. This step aims to establish evidence of a drug effect by testing for a statistically significant dose-response signal for the clinical endpoint and patient population investigated in the study. This step will be performed using a multiple contrast test, adjusting for the fact that multiple candidate dose-response models are being considered.

The adjusted p-values for all models will be reported, with the primary objective being met if at least one of the values < 0.05.

Candidate models will be selected amongst the following types of parametric models. In these models, the following notation is used:

- d is the treatment dose,
- $E(d)$ is the probability of a response at dose d,
- E_0 represents the probability of a response for the placebo treatment group,
- $E_0 + E_{max}$ is the maximum possible response probability,
- ED_{50} is the dose that evokes a response of $E_0 + E_{max}/2$,
- δ, δ_1, δ_2, ε, θ and scal are model-specific parameters.

Linear model $$E(d) = E_0 + \delta d$$

Emax model $$E(d) = E_0 + E_{max}\frac{d}{ED_{50} + d}$$

Logistic $$E(d) = E_0 + \frac{E_{max}}{\left(1 + e^{\frac{ED_{50}-d}{\delta}}\right)}$$

Beta model

$$E(d) = E_0 + E_{max}B(\delta_1, \delta_2) \times \left(\frac{d}{scal}\right)^{\delta_1} \times \left(1 - \frac{d}{scal}\right)^{\delta_2}$$

where

$$B(\delta_1, \delta_2) = \frac{(\delta_1 + \delta_2)^{\delta_1+\delta_2}}{\delta_1^{\delta_1} \times \delta_2^{\delta_2}}$$

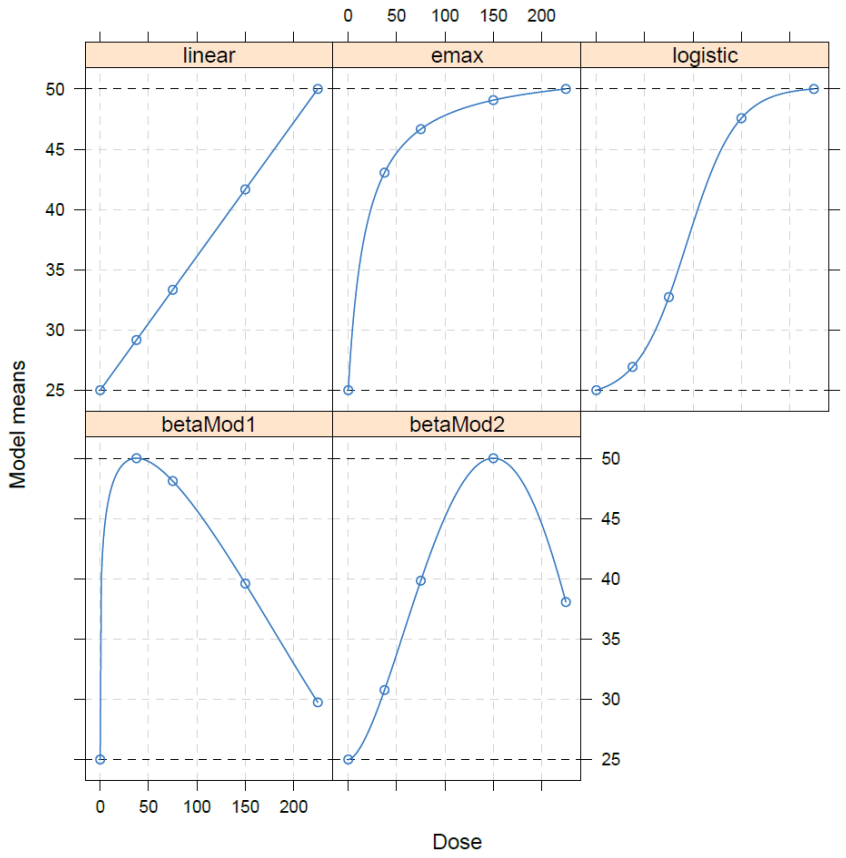
scal is a fixed parameter.

The following parametrization will be used for the Emax, logistic and Beta models; plot of the models are included in Figure 8-1.

- **Emax model** with 80% of the maximum effect at 75 mg.
- **Logistic model** with 10% of the maximum effect at 37.5 mg and 90% effect at 150 mg.
- **1st Beta model** with 90% of the maximum effect at 75 mg and 70% of maximum effect at 150 mg, the maximum effect is reached at 37.5 mg dose and the maximal dose is 225 mg. The scale effect is 270 (1.2 times the maximal dose).
- **2nd Beta model** with 40% of the maximum effect at 37.5 mg and 70% of maximum effect at 75 mg, the maximum effect is reached at 150 mg dose and the maximal dose is 225 mg. The scale effect is 270 (1.2 times the maximal dose).

For all models E_0 will be set to 25% and E_{max} will be set to 25%.

Figure 8-1: Graphical Representation of the Candidate models



The following steps [11] are used to determine the best dose response model and optimal dose using the DoseFinding package available in R. An example R code is provided in Section 17.17.

- Define the doses used in the study.
- Estimate the model parameters for each candidate model using the **guesst** function.
- Create the class object containing all the candidate models using the **Mods** function.
- Obtain asymptotic covariance matrix $\hat{S}$, which is required to perform the multiple contrast test, by using the **glm** function to apply a logistic regression (with response rate as response, dose level as factor, and no intercept). Note that the logistic regression is used here only to obtain $\hat{S}$ from the design matrix which depends on nuisance parameters in the model when applied to non-normal data. Since the logistic regression model will be used, the candidate models are formulated on the logit scale.
- Perform the multiple contrast test using optimal trend contrasts (obtained from the **optContr** function). The optimal contrasts for non-normal data are calculated using the asymptotic covariance matrix obtained from the logistic regression model in the previous step. The optimal contrasts and asymptotic covariance matrices will be re-calculated for NRI per-protocol and observed case mITT analyses but will not be reported. A seed of 61204 will be defined to generate the results.

- If there are two or more significant models,
  - Model the data using the candidate model(s) for which the contrast test is significant with the **MCPMod** function.
  - Obtain fitted values as a weighted average of the response estimates from models identified as significant in the previous step. The weights are based on the Akaike Information Criterion (AIC) criterion and are calculated as follows: $w_i = exp(-0.5AIC_i) / \sum_i (exp(-0.5AIC_i))$ where i=1,..,number of significant models [12].
  - The weighted average is calculated as

$$\bar{x}_k = \frac{\sum_{i=1}^{n} w_i \hat{x}_{i,k}}{\sum_{i=1}^{n} w_i}$$

    where $\bar{x}_k$ is the weighted average of the fitted value for the logit transformed responder rate for dose k and $\hat{x}_{i,k}$ is the fitted value for the transformed responder rate for model i at dose k.
  - A confidence interval will be calculated for $\bar{x}_k$ as $\bar{x}_k \pm Z_{\alpha/2} \times sd(\bar{x}_k)$. A conservative estimate of the standard deviation of $\bar{x}_k$ will be used to calculate the confidence interval where

$$sd\left(\bar{x}_k\right) = \sum_k w_i \sqrt{var(\hat{x}_{i,k})}$$

    is the upper bound for $sd(\bar{x}_k)$, $Z_{\alpha/2}$ is the quantile from the normal distribution for confidence level $1-\alpha$, and $var(\hat{x}_{i,k})$ is obtained by squaring the standard error of $\hat{x}_{i,k}$ [12].

- If none of the models are significant, then no dose-response has been shown and no further steps will be undertaken.

The parameter estimates from the candidate models will be provided in a table (the **guesst** function will be applied to each candidate model to estimate the required model parameters, then the **Mods** function will be applied to combine all model parameters into a "matrix" and provide the parametrization described earlier, i.e. E_0, E_{max},ED_{50}, δ etc.).

The following tables representing each step of the procedure will be provided; the analysis will be based on the mITT population. The multiple contrast test results will also be provided for the PP population.

- The asymptotic covariance matrix $\hat{S}$ using the **glm** function.
- The optimal contrast for each model using the **optContr** function.
- The multiple contrast test (t-statistics and adjusted p-values) as well as the critical value (obtained from the **MCPMod** function), the AIC value for each model, and the corresponding weight.
- The estimated model parameters (for example E_0, E_{max} and ED_{50} for the Emax model) on the logit scale for each model that is significant (obtained from the **MCPMod** function).
- The fitted values and confidence interval obtained as a weighted average of predicted values from the significant model(s) at each dose of interest.

For each model, the observed mean and associated CI of the response rate on the logit scale will be plotted alongside the candidate model and its confidence curve (logit scale)

against dose. The observed mean and associated CI of the response rate on the logit scale will also be plotted alongside the predicted values and corresponding confidence curves (logit scale) obtained from weighted averaging of the significant models, against dose.

The mBICLA response rates at Week 24 will be summarized by treatment group and presented for both the mITT and PP populations in the same table. Percentages will be derived based on the number of subjects in the analysis population and corresponding treatment group.

The tables will be programmed in SAS, and the figures will be produced using R (rtf package version 0.4-11). The SAS dataset (export format) containing the response rates will be imported into R using theSASxport package (version 1.5.3). The results from the MCP-Mod analyses will be exported from R in CSV format using the foreign package (version 0.8-67) and the CSV files will be imported into SAS using code generated by the foreign package.

The trial will be considered to have met its primary endpoint if at least one of the adjusted p-values is < 0.05.

8.1.2 Assumption Testing

No assumption testing of the dose-response model will be performed.

8.1.3 Sensitivity Analysis

The sensitivity of results to missing data will be assessed with the use of observed case analysis, i.e. without applying the imputation rules for mSLEDAI-2K described in Section 8.1. The observed mBICLA response rates at Week 24 will be summarized by treatment group and presented for the mITT population. Percentages will be derived based on the number of subjects in the analysis population evaluated at Week 24 and corresponding treatment group.

In addition, to further evaluate the impact of the imputation of missing values, the multiple contrast test results from the primary endpoint analysis (MCP-Mod) will be provided as well using observed mBICLA responses on the mITT population, and the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be also presented. 95% CI for the difference between each active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, the associated p-value will be provided.

8.1.4 Subgroup Analysis

The primary endpoint will be summarized using frequency count and percentages by treatment groups on the mITT population for the following subgroups. Imputation rules from Section 8.1 will be applied to the data for subgroup analysis at Week 24.

- Age (18 to <45 years, 45 to <65 years),
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other),
- Geographic Region (Europe, Latin America, North America and Asia-Pacific),
- Baseline SLICC damage score (= 0 , > 0),
- Baseline BMI (≤ 25 kg/m², > 25 kg/m²),
- Baseline immunosuppressants intake (yes, no),
- Baseline corticosteroids intake (yes, no),
- Baseline SLEDAI-2K score ≥ 10 (yes, no),
- Baseline mSLEDAI-2K score ≥ 10 (yes, no),
- System Mucocutaneous with BILAG-2004 score A at Baseline (yes, no),
- System Musculoskeletal with BILAG-2004 score A at Baseline (yes, no),
- Baseline Prednisone Equivalent Dose intake > 7.5 mg/day (yes, no),
- Baseline anti-dsDNA (FARR) ≥ 8 IU/mL (yes, no),
- Baseline SLEDAI-2K low complement item (yes, no).

8.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints (see Section 3.2.2) will be summarized and analyzed by planned treatment group, using the observed data (i.e. without applying the imputation rules for mSLEDAI-2K described in Section 8.1) in the mITT population. For continuous secondary efficacy endpoints, summary statistics include mean, SE, median, minimum and maximum, while for categorical secondary efficacy endpoints frequencies and proportions are provided. Definitions of endpoints are included in Section 17.3 to Section 17.13.

8.2.1 mBICLA

The number and percentage of subjects who are mBICLA responders will be presented for each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of subjects evaluated at that visit. The mBICLA responder rate will be presented as percentage and derived based on the number of subjects who are evaluable at the visit.

Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be also presented. 95% CI for the difference between each active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, at Week 24 and at Week 48, the associated p-value will be provided.

In addition, a line plot of the mBICLA response rate with the associated 95% CI will be provided by treatment group and visit.

The subgroup analysis from Section 8.1.4 will be repeated for mBICLA at Week 48. No imputation rules will be applied.

8.2.2 BICLA

The number and percentage of subjects who are BICLA responders will be presented for each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of

subjects evaluated at that visit. The BICLA responder rate will be presented as percentage and derived based on the number of subjects who are evaluable at the visit. Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region.

In addition, a line plot of the BICLA response rate with the associated 95% CI will be provided by treatment group and visit.

8.2.3 SRI

The number and percentage of subjects who are SRI (see Section 17.7 for details) responders will be presented for each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of subjects evaluated at that visit. The SRI responder rate will be presented as percentage and derived based on the number of subjects who are evaluable at the visit.

Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region.

In addition, a line plot of the SRI response rate with the associated 95% CI will be provided by treatment group and visit.

Similar summaries and analyses will be presented for SRI-5, SRI-6, SRI-7 and SRI-8. For each cut-off, the number of assessable subjects will be displayed in these summaries; the number of assessable subjects is the number of subjects with Baseline SLEDAI-2K score greater than or equal to the cut-off point considered. For example, the cut-off for SRI is 4 and assessable subjects are subjects with Baseline SLEDAI_2K score ≥ 4, the cut-off for SRI-5 is 5 and assessable subjects are subjects with Baseline SLEDAI-2K score ≥ 5 etc. The SRI responder rate will be presented as percentage and derived based on the number of assessable subjects who are evaluable at the visit.

8.2.4 mSRI

The number and percentage of subjects who are mSRI (see Section 17.7 for details) responders will be presented for each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of subjects evaluated at that visit. The mSRI responder rate will be presented as percentage and derived based on the number of subjects who are evaluable at the visit.

Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, at Week 24 and at Week 48, the associated p-value will be provided.

In addition, a line plot of the mSRI response rate with the associated 95% CI will be provided by treatment group and visit.

Similar summaries and analyses will be presented for mSRI-5, mSRI-6, mSRI-7 and mSRI-8. For each cut-off, the number of assessable subjects will be displayed in these summaries; the number of assessable subjects is the number of subjects with Baseline

mSLEDAI-2K score greater or equal to the cut-off point considered. The mSRI responder rate will be presented as percentage and derived based on the number of assessable subjects who are evaluable at the visit.

The same subgroups as for the primary endpoint (see Section 8.1.4) will also be used to summarize mSRI responders at Week 24 and 48 using frequency count and percentages by treatment group.

8.2.5 SLEDAI-2K

The SLEDAI-2K score (see Section 17.4 for details) will be summarized at each visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48).

In addition, at each post-Baseline visit, the change from Baseline will be modelled using an analysis of covariance (ANCOVA) model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

8.2.6 mSLEDAI-2K

The mSLEDAI-2K score (see Section 17.4 for details) will be summarized at each visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48).

In addition, at each post-Baseline visit, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

8.2.7 BILAG-2004 Improvement

Normal Improvement:

The number and percentage of subjects with normal improvement (see Section 17.3 for details) will be presented for each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of subjects evaluated at that visit. The percentage of subjects with normal improvement will be presented and derived based on the number of subjects who are evaluable at the visit.

Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region.

Enhanced Improvement:

The number and percentage of subjects with enhanced improvement (see Section 17.3 for details) will be presented for each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of subjects evaluated at that visit. The percentage of subjects with enhanced improvement will be presented and derived based on the number of subjects who are evaluable at the visit.

Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region.

Subjects who meet the requirements for enhanced improvement also by definition meet the requirements for normal improvement and will therefore be counted as "responders" in both sets of presentations.

8.2.8 BILAG-2004 Total Score

The BILAG-2004 total score (see Section 17.3 for details) will be summarized at each visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48).

In addition, at each post-Baseline visit, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

8.2.9 BILAG-2004 Improvement by Individual Organ System

For each organ system (with at least 5 subjects in each treatment group with A or B score at Baseline), the number and percentage of subjects with normal improvement (see Section 17.3 for details) will be presented at each post-Baseline visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48) alongside the number of subjects evaluated at that visit. The percentage of subjects with normal improvement will be presented and derived based on the number of subjects who are evaluable at the visit.

Furthermore, at each post-Baseline visit, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be also presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region.

8.2.10 BILAG-2004 Systems Tally

Each organ system will be classified under active/worsening disease, improving disease, or persistent minimal or no activity (see Section 17.3 for details). For each subject the number of organ systems will be tallied within each category. Within the categories active/worsening disease and improving disease, the number and percentage of subjects with 1, 2, 3 and > 3 organ systems included will be summarized at each visit (Week 4, Week 8, week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48). For the persistent minimal or no activity category, the number and percentage of subjects with ≤6, 7, 8 and 9 organ systems included will be summarized at each visit (Week 4, Week 8, week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48). Percentages will be

calculated based on the total number of subjects at the considered visit. Only subjects with non-missing assessments at Baseline and post-Baseline will be included in the summary.

8.2.11 PGA

The physician will make a mark between 0 ("very good") and 100 mm ("very bad") on the visual analogue scale (VAS) to indicate disease activity (independent of the subject's self-assessment).

The PGA score will be summarized at each visit (Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48).

In addition, at each post-Baseline visit, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment groups and placebo will be presented with the associated 95% CI.

8.2.12 Patient's Global Assessment

The subject will make a mark between 0 ("very good") and 100 mm ("very bad") on the VAS to indicate disease activity.

The patient's global assessment of disease activity will be summarized at each visit (Week 24 and Week 48).

In addition, at each post-Baseline visit, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment groups and placebo will be presented with the associated 95% CI.

8.2.13 Laboratory Efficacy Assessment

Summary tables presenting observed numeric values and changes from Baseline at each visit (Week 2 [blood chemistry parameters only], Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Follow-up [blood chemistry parameters only]), will be provided for the following parameters (see Section 17.14 for the tests to be reported and units).

- Blood chemistry: Serum creatinine, eGFR
- Urinalysis: Proteinuria (urinary protein) as measured by spot urine protein to creatinine ratio.

In addition, at each post-Baseline visit, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

Active urine sediment (yes versus no) from the BILAG Renal CRF page will be summarized at each visit by way of shift table (i.e. summarizing the number of subjects who have [yes] or don't have [no] active urine sediment at Baseline and their shift at post-Baseline visit). The percentages will be based on the number of subjects with non-missing values at the Baseline and at the considered visit.

For urine protein/creatinine ratio, shift from Baseline at each post-Baseline visit and worst on-treatment using grade criteria below (Grade 0, Grade 1, Grade 2 and Grade 3) will be presented by treatment group.

- Grade 0: ≤ 17.0 g/mol (i.e. ≤0.15 g/g),
- Grade 1: > 17.0 g/mol to < 113.1 g/mol (i.e. > 0.15 g/g to < 1 g/g),
- Grade 2: ≥ 113.1 g/mol to ≤ 384.6 g/mol (i.e. ≥1.0 g/g to ≤3.4 g/g),
- Grade 3: > 384.6 g/mol (i.e. > 3.4 g/g).

8.2.14 Treatment Failure

The number and percentage of subjects with treatment failure (see derivation details in Section 17.5) will be presented at Week 24 and at Week 48. The percentage of treatment failures will be also presented and derived based on the number of subjects in the mITT population.

Furthermore, at Week 24 and Week 48, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, the associated p-value will be provided.

8.2.15 BILAG-2004 Flare

The number of subjects with BILAG-2004 flare between Baseline and Week 24, and between Baseline and Week 48 (see Section 17.3 for details) will be presented by category (mild/moderate and severe). The percentage of subjects with BILAG-2004 flares will be presented and derived based on the number of subjects in the mITT population.

Furthermore, at Week 24 and Week 48, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be also presented for each flare category. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, the associated p-value will be provided.

8.2.16 mSLEDAI-2K Flare (mSFI)

The number of subjects with mSLEDAI-2K flare between Baseline and Week 24, and between Baseline and Week 48 (see Section 17.4 for details) will be presented by category (mild/moderate and severe). The percentage of subjects with mSLEDAI-2K flares will be presented and derived based on the number of subjects in the mITT population.

Furthermore, at Week 24 and Week 48, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be also presented for each flare category. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, the associated p-value will be provided.

8.2.17 Prednisone Equivalent Total Daily Dose

The prednisone equivalent total daily dose at Week 12, Week 24 and Week 48 will be presented. The total daily dose at Baseline will be the sum of the Prednisone equivalent dose of steroids taken on the date the first dose of study drug was administered. The total daily dose will be derived as described in Section 17.9.

In addition, at each post-Baseline visit, the change from baseline and percent change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment groups and placebo will be presented with the associated 95% CI.

8.2.18 Reduction Rate in Steroids Intake Without Severe Flare

The number and percentage of subjects whose prednisone equivalent dose was >7.5 mg/day at Baseline and ≤7.5 mg/day between Week 40 to 48 without experiencing a severe mSFI-defined or severe BILAG-2004flare after the first decrease in prednisone equivalent dose and up to and including Week 48 cut-off date will be summarized. Percentages will be based on subjects in the mITT population whose prednisone equivalent dose was >7.5 mg/day at Baseline. The duration of flare assessment time which is starting from the date of first decrease in prednisone equivalent dose up to and including Week 48 cut-off date will be summarized.

Furthermore, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, the associated p-value will be provided.

8.2.19 Discontinuation Rate in Steroids Intake without Severe Flare

The number and percentage of subjects who are able to permanently discontinue prednisone (or equivalent) before or on Week 48 without experiencing a severe mSFI-defined or severe BILAG-2004-defined flare after the first decrease in prednisone equivalent dose and up to and including Week 48 cut-off date (see Section 17.5.1). Percentages will be based on subjects in the mITT population who took steroids at Baseline. The duration of flare assessment time which is starting from the date of first decrease in prednisone equivalent dose up to and including Week 48 cut-off date will be summarized.

Furthermore, the Clopper Pearson 95% CI of the incidence rate (expressed in percentage) and the 95% CI of the difference in incidence rate between each active treatment group and placebo (i.e. active treatment – placebo) will be also presented. 95% CI for the difference between active treatment and placebo will be based on the CMH test stratified by geographic region. In addition, the associated p-value will be provided.

Details of the derivation of prednisone equivalent dose can be found in Section 17.9.

8.2.20 SF-36 Physical and Mental Component

SF-36 physical and mental component scores (see Section 17.10 for details) at Week 24 and at Week 48 will be summarized.

In addition, at each post-Baseline visit and for each component separately, the change from Baseline will be modelled using an ANCOVA model with Baseline and geographic region as covariates and treatment as factors. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

8.2.21 28-Joint Count

The 28-Joint count swollenness and tenderness (see Section 17.11 for details) at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 will be summarized.

In addition, at each post-Baseline visit and for 28-Joint count swollenness, tenderness separately, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

8.2.22 CLASI

The CLASI will be performed in interested sites having experience in this assessment. The CLASI activity and damage scores (see Section 17.12 for details) at Week 12, 24 and Week 48 will be summarized.

In addition, at each post-Baseline visit and for CLASI activity and damage scores separately, the change from Baseline will be modelled using an ANCOVA model with treatment as factor and Baseline and geographic region as covariates. The LSMeans and SE of the LSMeans will be presented at each visit alongside the 95% CI. The difference in LSMeans between each of the active treatment group and placebo will be presented with the associated 95% CI.

9 Safety Analysis

All safety summaries will be based on the Safety population and presented by treatment group and for the "All ALX-0061" group.

For laboratory parameters, vital signs and ECG, visits will be mapped to analysis visits using the rules defined in Section 17.16. Summaries will be based on those analysis visits.

Any abnormal laboratory test results, vital signs and/or ECG, including those that worsen from Baseline, believed to be clinically significant in the medical and scientific judgment of the investigator are recorded and analyzed along with other collected AEs or SAEs.

9.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject enrolled into the study, regardless of its causal relationship to study drug. A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- begins on or after the first dose of study drug;
- begins before the first dose of study drug and worsens in severity on or after the first dose of study drug;
- begins on the first dose date of study drug and onset time is missing;
- onset date and end date are completely missing;
- onset date is completely missing and the end date is on or after the date of the first dose of study drug.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as described in Section 17.15.

All AEs will be classified by System Organ Class (SOC) and PT according to the MedDRA version that is current at the time of the database lock.

An overview summary of the number of events, the subjects and percentage of subjects within the following categories will be provided by treatment group.

- Any TEAE,
- Any Severe TEAE
- Any study drug-related TEAE,
- Any TEAE leading to treatment discontinuation,
- Any serious TEAE,
- Any study drug-related serious TEAE,
- Any serious TEAE leading to treatment discontinuation,
- Any injection-site related TEAE,
- Any study drug-related injection-site related TEAE,
- Any serious injection-site related TEAE,
- Any study drug-related serious injection-site related TEAE,
- Any TEAE of special interest,
- Any study drug-related TEAE of special interest,
- Any serious TEAE of special interest,
- Any study drug-related serious TEAE of special interest,
- Any TEAE leading to death.

A TEAE will be categorized as study drug-related if the relationship to the study drug is reported to be 'Possibly Related', or 'Related' as collected on the Adverse Events CRF page, or missing.

Tabulated listings for the following category will be provided:

- AE leading to death,
- SAE,
- AE leading to treatment discontinuation

In addition to the listing of all AEs, a listing for adverse events of interest will be provided.

TEAEs will be presented by SOC and PT and will be sorted in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in the same manner as the SOC, i.e. in descending order from the PT with the highest total incidence.

9.1.1 Incidence of Adverse Events

Summaries of the number of TEAEs and the number and percentage of subjects with any TEAE will be provided by treatment group. The TEAEs will be presented by SOC and PT.

Similar summaries for subjects with any non-serious TEAE and for subjects with any serious TEAE will be provided.

At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the relevant treatment group.

9.1.2 Relationship of Adverse Events to Study Drug

Summaries of the number of study drug-related TEAEs and the number and percentage of subjects with any study drug-related TEAE will be provided by treatment group. The study drug-related TEAEs will be presented by SOC and PT.

At each level of subject summarization, a subject is counted once if the subject reported one or more events. TEAEs with missing relationship will be included in the summary of study drug-related TEAE and will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of subjects in the relevant treatment group.

9.1.3 Severity of Adverse Event

Summaries of number and percentage of subjects with any TEAE will be provided by treatment group and by severity (Mild, Moderate and Severe). The TEAEs will be presented by SOC, PT and severity.

At each level of subject summarization, a subject is counted once if the subject reported one or more events. If a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. TEAEs with missing severity will be presented in tables under 'Missing' row and in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the relevant treatment group.

9.1.4 Serious Adverse Events

Summaries of the number of serious TEAEs and the number and percentage of subjects with any serious TEAE will be provided by treatment group. These TEAEs will be presented by SOC and PT.

Summaries of the number of study drug-related serious TEAEs and the number and percentage of subjects with any study drug-related serious TEAE will be provided by treatment group. The study drug-related serious TEAEs will be presented by SOC and PT.

Summaries of number and percentage of subjects with any serious TEAE will be provided by treatment group and by severity (Mild, Moderate and Severe). The serious TEAEs will be presented by SOC, PT and severity.

9.1.5 Adverse Events Leading to Treatment Discontinuation

Summaries of the number of TEAEs leading to treatment discontinuation and the number and percentage of subjects with any TEAE leading to treatment discontinuation will be provided by treatment group. These TEAEs will be presented by SOC and PT. An AE leading to treatment discontinuation is an AE for which the action with regards to study drug was recorded as 'Drug withdrawn' on the CRF.

9.1.6 Adverse Event of Special Interest (AESI)

Injection-site reaction

An injection-site reaction is an AE that occurred at the location of the study drug administration. Using the start date and the location of the injection-site reaction (for TEAE recorded as injection-site reaction in the CRF and related to study drug administration), each injection-site reaction will be associated to the material injected at the site of the injection-site reaction (Placebo or ALX-0061) immediately prior to start of the AE.

Within each treatment group, study drug-related injection-site reactions will be summarized according to the material injected at the site of the ISR (i.e. ALX-0061 or

placebo). Summaries of the number of study drug-related injection-site reactions and the number and percentage of subjects with any study drug-related injection-site reaction will be provided by treatment group. These TEAEs will be presented by PT and will be sorted in descending order.

Hypersensitivity

Summaries of the number and percentage of subjects with any hypersensitivity will be provided by treatment group and by severity (Mild, Moderate and Severe). These TEAEs will be presented by SOC and PT.

In addition, summary of treatment-emergent adverse event of hypersensitivity leading to treatment discontinuation will be provided and will present the number of treatment-emergent events of hypersensitivity leading to treatment discontinuation and the number and percentage of subjects with any treatment-emergent event of hypersensitivity leading to treatment discontinuation by treatment group. These TEAEs will be presented by SOC and PT.

Note: Hypersensitivity, Anaphylactic reaction and Angioedema Standardized MedDRA Queries (SMQs) with a narrow search will be used to determine hypersensitivity reactions (see Section 17.18).

Samples collected upon occurrence of serious and/or severe hypersensitivity reactions will be analyzed in the ADA and/or mADA assay (see Section 12) and optionally for the biomarkers tryptase and CH50. A listing of these serious and/or severe hypersensitivity adverse events will be presented, including ADA/mADA $\log_{10}$(titer) and tryptase and CH50 test results.

Other AESI:

The Other Adverse Events of Special Interest are:

- Infections
- Serious Infections
- Opportunistic infections (excluding Tuberculosis [TB])
- Active TB
- Latent TB
- Herpes zoster infection
- Malignancies
- Lymphoma
- Gastrointestinal (GI) perforation
- Demyelinating disorder
- Major adverse cardiac events (MACE)

The number of treatment-emergent AESI and the number and percentage of subjects with any treatment-emergent AESI will be provided by treatment group for each of the AESI above.

Note: Search criteria for AESI are included in Section 17.18.

9.1.7 Death

Summaries of the number of TEAEs leading to death and the number and percentage of subjects with any TEAE leading to death will be provided by treatment group. These TEAEs will be presented by SOC and PT and will be sorted in descending order for SOC

and PT. An AE leading to death is an AE for which the outcome was recorded as 'Death Related to Adverse Event' on the CRF.

9.2 Clinical Laboratory Evaluations

International Normalized Ratio (INR) (collected for subjects taking vitamin K antagonist) and Coombs' test (collected for all subjects) will be performed by local laboratories; other laboratory assessments will be performed by a central laboratory. All summaries will be based on the international system of units (SI) units provided by the central laboratory, no conversion will be done (see Section 17.14 for the tests to be reported and units).

Unless otherwise specified, if a laboratory value is reported using a non-numeric qualifier (e.g., less than [<] a certain value, or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

9.2.1 Haematology, Blood Chemistry, Lipid Profile and Coagulation

The following parameters will be summarized and displayed at the scheduled time points (see Section 17.1). For lipid profile parameters only fasting values will be summarized (i.e. if the sample was not marked as fasting, the associated results will not be used in the summary)

- Haematology: Leukocytes, Erythrocytes, Haemoglobin, Haematocrit, Platelets (recorded as Thrombocytes), Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils, Absolute Neutrophils, Mean Corpuscular Volume, Mean Corpuscular Haemoglobin and Mean Corpuscular Haemoglobin Concentration,
- Blood Chemistry: Total Bilirubin, Alkaline Phosphatase, Gamma Glutamyltransferase (GGT), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lactate Dehydrogenase, Creatine Phosphokinase, Urea, Total Protein, Albumin, Glucose, Inorganic Phosphate, Sodium, Potassium, Calcium and Chloride,
- Lipid Profile (fasting): Total Cholesterol, HDL-cholesterol, LDL-cholesterol, LDL/HDL-cholesterol ratio and Triglycerides
- Coagulation: activated Partial Prothrombin Time and Prothrombin Time.

Summary tables presenting observed numeric values and changes from Baseline (where applicable) will be provided for clinical laboratory tests with numeric values by treatment group for subjects in the Safety population.

Box plots of the change from Baseline at each post-Baseline visit will be presented for all central laboratory parameters by treatment group.

All relevant clinical laboratory tests will be classified as Low, Normal, and High according to the normal ranges; for selected lab parameters (see Section 17.20), directional National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events CTCAE grades) will be presented instead. These categorical data will be summarized in shift tables comparing the results (Low, Normal, High and for selected tests, Grade 0, Grade 1, Grade 2, Grade 3, Grade 4) at each post-Baseline visit with those at the Baseline visit. In addition, worst on-treatment post-Baseline excluding those taken more than 25 days after last dose of treatment will also be presented. Missing laboratory values will not be analysed in shift tables.

Note: Only patients consented under protocol version 3.0 (dated 16-May-2016) or subsequent protocol amendments have results for Creatine Phosphokinase test. This parameter will not be summarized separately.

9.2.2 Urinalysis

Proteinuria as measured by spot urine protein/creatinine ratio and urine sediment will be summarized as part of the efficacy endpoints.

9.2.3 Laboratory Parameters of Special Interest

The incidence rate of the following events will be provided by treatment group based on the Safety population. A subject will be counted in a category if he/she experienced the event at any time after the first dose of study drug up to 25 days after the last dose date. The percentage will be derived based on the number of subjects with at least one non-missing post-Baseline value for the considered parameter. If the criterion is based on change from Baseline, only subjects with non-missing Baseline results for the considered parameters will be considered in the table.

- Increase from Baseline in LDL Cholesterol ≥ 20 %,
- ALT > 3 x ULN and/or AST > 3 x ULN,
- Thrombocytopenia (platelets <100 $x10^9$/L),
- Neutropenia (absolute neutrophils count <0.500 $x10^9$/L),
- Neutropenia (absolute neutrophils count 0.5-1.0 $x10^9$/L),
- Neutropenia (absolute neutrophils count 1.0-1.5 $x10^9$/L),
- Complement deficiency (C3, C4 or CH50 < LLN),
- Increase from Baseline in proteinuria (protein / creatinine ratio) ≥ 20 %,
- Increase from Baseline in serum creatinine ≥ 26.52 µmol/L or ≥ 50 %,
- Urinary cast scored '4' from SLEDAI,
- Decrease from Baseline in eGFR ≥ 20 %,
- Hy's law: AST or ALT >3x ULN and total bilirubin > 2x ULN and alkaline phosphatase <2x ULN.

9.2.4 Coombs' test

Coombs' test results (positive and negative) will be summarized at the scheduled time points (see Section 17.1) by way of frequency count and percentages. Percentages will be based on the number of subjects who have no missing results.

9.2.5 INR

INR test is locally performed for subjects taking Vitamin K antagonist at the scheduled time points (see Section 17.1). Subjects taking or not taking vitamin K antagonist at each visit is collected on the "Local Laboratory" CRF page.

INR will be classified as Low, Normal, and High according to the normal ranges. These categorical data will be summarized at Baseline and each post-Baseline visit. In addition worst on-treatment post-Baseline excluding those taken more than 25 days after last dose of treatment will also be presented (see Section 17.21 for definition of worst on-treatment). Percentages will be calculated based on the number of subjects for which the INR test was performed at the corresponding visit.

9.2.6 Antibodies

Anti-nuclear Antibodies (ANA)

At Baseline, frequency count and percentage of subjects with positive and negative results for ANA will be presented by treatment groups. For the subjects with positive ANA test results, the following summaries will be provided:

- Frequency count and percentages of subjects with each possible pattern of antibodies (atypical speckled, speckled, nucleolar, centromere and homogeneous, etc.); percentages will be based on the number of subjects with positive ANA results.
- Frequency count and percentages of subjects with titer below and above quantification limit; percentages will be based on the number of subjects with positive ANA results.
- Descriptive statistics (n, mean, median, SD, minimum, maximum, coefficient of variation [CV%], geometric mean, geometric SD, 5% and 95% percentiles). The descriptive statistics will only be provided if ≥ 20% of the subjects in the treatment group have positive ANA results.

The CV% is calculated as follows: $\mathrm{CV\%} = \frac{\mathrm{SD}}{\mathrm{mean}} \times 100.$

Geometric CV% is calculated as follows: $Geometric\ \mathrm{CV\%} = 100 \times \sqrt{(\exp(\sigma^2) - 1)}$, where σ^2 denotes the variance of the log-transformed values.

Geometric mean is calculated as follows: $\mu_g = \exp\left(\frac{\sum_{i=1}^{n} \ln x_i}{n}\right)$ where x_i is the individual titer at current visit.

The Geometric SD is calculated as follows: $\exp\sqrt{\frac{\sum_{i=1}^{n}(\ln x_i - \ln \mu_g)^2}{n}}$

For the descriptive statistics, the following rules will be used:

- Titres recorded as <1:80 or negative will be imputed as 40,
- Titres recorded as >1:1280 will be imputed as 1280,
- Titres recorded as 1:X where X is the dilution factor, will be converted to X (i.e. just the dilution factor).

Other Antibodies:

The following antibody parameters will be summarized and displayed: β2-glycoprotein 1 IgG, β2-glycoprotein 1 IgM, anti-cardiolipin IgA, anti-cardiolipin IgG, anti-cardiolipin IgM and anti-lupus antibodies at Baseline and Week 24.

Summary tables presenting observed numeric values and changes from Baseline will be presented as well as the percentages of subjects below and above quantification limit (percentages will be based on the number of subjects with no missing data at the considered visit) for subjects in the Safety population.

9.3 Vital Sign Measurements

Summary tables presenting observed values at Baseline, each post-Baseline visit as well as changes from Baseline will be presented for all vital signs parameters (systolic blood pressure, diastolic blood pressure, temperature [converted to Celsius], pulse and weight [converted to kilogram]), by treatment group for subjects in the Safety population.

Box plots of the change from Baseline at each post-Baseline visit will be presented for all vital signs parameters (systolic blood pressure, diastolic blood pressure, temperature, pulse and weight), by treatment group.

Temperature in degrees Fahrenheit will be converted to Celsius using the following formula:

Temperature (°C) = (Temperature (°F) - 32) × 5/9.

Weight in pounds will be converted to kilograms using the following formula:

Weight (kg) = Weight (lbs) × 0.4536.

9.4 Physical Examination

Abnormal findings in physical examinations will be listed. No summaries will be provided.

9.5 Electrocardiogram

A summary table presenting observed values at Baseline and at Week 48 and changes from Baseline will be provided for all ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, QT corrected Bazett (QTcB) and QT corrected Fridericia (QTcF)), by treatment group for subjects in the Safety population.

QT corrected Bazett and QT corrected Fridericia will be derived using the following formulae:

$$\text{QTcB} = \frac{QT}{\sqrt{RR}}$$

$$\text{QTcF} = \frac{QT}{\sqrt[3]{RR}}$$

9.6 Other Safety Data

9.6.1 Tuberculosis Assessment

TB assessments will be listed and not summarized.

9.6.2 Pregnancy test

Pregnancy tests for females of childbearing potential will be listed.

10 Pharmacokinetics (PK)

PK analysis will be performed on the Safety population.

Drug concentrations will be summarized by treatment group using descriptive statistics (n, mean, median, SD, minimum, maximum, CV%, geometric mean, geometric SD, 5% and 95% percentiles). In general, geometric mean and the geometric SD will be derived from non-zero concentration values. These results will be tabulated by treatment group and visit (Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48).

The CV% is calculated as follows: $\text{CV\%} = \frac{\text{SD}}{\text{mean}} \times 100$.

Geometric mean is calculated as follows: $\mu_g = \exp\left(\frac{\sum_{i=1}^{n} \ln x_i}{n}\right)$ where x_i is the individual drug concentration at current visit.

The Geometric SD is calculated as follows: $\exp\sqrt{\frac{\sum_{i=1}^{n}(\ln x_i - \ln \mu_g)^2}{n}}$.

Individual pharmacokinetic concentrations will be reported and listed in µg/mL (i.e. the concentrations reported as ng/mL will be converted to µg/mL by dividing the concentrations by 1000).

Individual pharmacokinetic concentrations below the limit of detection or below the quantification limit (BQL) will be reported as BQL. To compute descriptive statistics (i.e. mean [or median or geometric mean], SD, CV%, geometric SD, minimum, maximum, 5% and 95% percentiles), all BQL values will be treated as missing. When the total number of BQL values exceeds 1/3 of the total number of values at that time point, descriptive statistics will not be calculated. Descriptive statistics not calculated for the above reasons will be reported as not calculated (NC) in the associated table. In case the actual sampling time deviates more than allowed per study protocol from the nominal time (i.e. the sample should be prior to the dosing on that visit and within ±5 days if the scheduled visit date, see Section 17.16), these samples will not be included in the calculation of descriptive statistics on pharmacokinetic concentrations and associated plots.

The following figures will be provided by treatment groups (linear and semi-logarithmic plots will be displayed on the same page):

- Spaghetti plot of Individual subjects concentration (linear scale) over time;
- Spaghetti plot of Individual subjects concentration (semi-logarithmic scale) over time;
- Mean and ± SE of concentration (linear scale) over time plot;
- Mean of concentration (semi-logarithmic scale) over time plot.
- Geometric mean ± geometric SD of concentration (linear scale) over time plot;
- Geometric mean of concentration (semi-logarithmic scale) over time plot.

For individual spaghetti plots, nominal sampling times are used, unless the actual time deviates more than allowed per study protocol. In that case the actual time is used.

A listing of the actual sampling times will be presented. Actual sample time that deviated from the protocol allowed window will not be assigned an analysis visit in the listing.

11 Pharmacodynamics (PD)

Evaluations of PD

The biomarkers results and percent change from Baseline will be summarized over time by treatment groups based on the Safety population using descriptive statistics (n, mean, median, SE, minimum, maximum, CV%, geometric mean, geometric SD, 5% and 95% percentiles [see Section 10 for details on CV%, geometric mean and geometric SD derivation]). To compute descriptive statistics (i.e. mean [or median or geometric mean], SD, CV%, geometric SD, minimum, maximum, 5% and 95% percentiles), all BQL values will be treated as missing. For percent change from baseline, CV%, geometric mean and geometric SD will not be provided. The biomarkers evaluated are:

- sIL-6R: at Week 4, Week 8, Week 12, Week 16, Week 24, Week 32, Week 40, Week 48 and Follow-up.
- CRP, Fibrinogen, anti-dsDNA (FARR), C3, C4 and CH50: at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Follow-up.
- uMCP-1 and uMCP-1/uCr: at Week 8, Week 24 and Week 48.

Finally, Fibrinogen will be classified according to NCI CTCAE. This categorical data will be summarized in shift tables comparing the results (Grade 0, Grade 1, Grade 2, Grade 3, Grade 4) at each post-Baseline visit (included worst on-treatment) with those at the Baseline visit. Worst on-treatment post-Baseline results exclude the samples taken more than 25 days after last dose of treatment (see Section 17.21 for definition of worst-on-treatment).

Note: during the study, the testing of anti-dsDNA was switched from ELISA assay to an FARR assay, therefore FARR assay will be used in the summaries, the ELISA assay results will only be listed. If results are recorded as '<' or '>', the same handling rules as the safety laboratory data will be used (see Section 9.2).

In addition, for each biomarker the following graphical representation will be provided by treatment group:

- Mean and ± SE of biomarkers results (linear scale) over time plot (all treatments on the same page);
- Mean of biomarkers results (semi-logarithmic scale) over time plot, (all treatments on the same page);

Exposure-response Model(s)

Exposure-response modelling will be described in a separate Data Analysis Plan, and will be performed under the responsibility of Ablynx NV. Results of this analysis will be provided in a separate Modelling and Simulation report. Pooled data from other studies might be included as well.

12 Immunogenicity

Samples for immunogenicity are collected for all subjects during the study.

The ADA assay will detect treatment emergent (TE) ADA as well as pre-existing antibodies (pre-Ab). However, using the ADA assay, sensitive detection of TE ADA might be defied in subjects presenting pre-Ab. Therefore, the mADA characterization assay will be implemented for subjects classified as equivocal ([EQ], TE ADA status remains uncertain due to presence of pre-Ab; no significant titer increase upon dosing) to enable

detection of TE ADA in presence of pre-Ab and will be implemented as additional tier after the conventional ADA assay.

The immunogenicity samples are evaluated to determine if they are positive or negative in the ADA assay (tiered analysis in screening and confirmatory assay); only samples confirmed as positive in the ADA assay are titrated and they are reported as $\log_{10}$(titer). Samples scoring negative in the ADA assay are not titrated and the respective titer is reported as < $\log_{10}$(MRD) with Minimal Required Dilution (MRD) = 100, i.e. $\log_{10}$(titer) <2.00.

Only subjects which are classified as "pre-Ab positive – equivocal" in the ADA assay will have their samples analyzed in the mADA assay; similarly to the ADA assay, only positive samples in the mADA assay (i.e. confirmed as positive) are titrated and are reported as $\log_{10}$(titer).

In addition, subjects presenting positive ADA samples, will have their samples (positive ADA samples) analyzed in the qualitative NAb assay (reported as the normalized assay result [i.e. ratio sample assay result/negative control assay result]). A subset of the available pre-dose samples will be analyzed in the NAb assay to evaluate the study-specific cut-point for the NAb assay. Subjects scoring negative in the NAb assay will be reported as 'neg' result.

- Subjects will be classified based on ADA assay results and mADA assay results (if applicable), separately, and will receive an overall subject classification as specified in the Table 12-1. No mADA subject classification will be attributed in case the subject was not analyzed in the mADA assay.
- Subjects will be classified based on their NAb pre-dose status and status on treatment as specified in the Table 12-2. Subjects with no positive ADA samples post-dose will be classified as 'Negative on treatment' by default.

No records will be reported for samples not evaluated in the mADA assay. Also, for samples not evaluated in the NAb assay (i.e., ADA negative samples), no records will be reported. These unavailable NAb records, for which the corresponding ADA record is negative, should be considered NAb negative in all further incidence calculations. Patients from which all time points are ADA negative should be classified per default as "Pre-dose neg – neg on treatment" in the NAb assay.

Table 12-1: ADA, mADA and Overall Subject Classification

ADA Assay Classification	mADA Assay Classification	Overall Subject Classification
MISSING		MISSING
PRE-AB NEG - TE NEG		PRE-AB NEG - TE NEG
PRE-AB NEG - TE POS		PRE-AB NEG - TE POS
PRE-AB NEG - TE INCONCLUSIVE		PRE-AB NEG - TE INCONCLUSIVE
PRE-AB POS - TE NEG		PRE-AB POS - TE NEG
PRE-AB POS - TE POS		PRE-AB POS - TE POS
PRE-AB POS - TE INCONCLUSIVE		PRE-AB POS - TE INCONCLUSIVE
PRE-AB POS – EQ	PRE-AB NEG - TE POS	PRE-AB POS - TE POS
	PRE-AB POS - TE POS	PRE-AB POS - TE POS
	PRE-AB NEG – TE NEG	PRE-AB POS – EQ
	PRE-AB POS – EQ	PRE-AB POS – EQ
	PRE-AB POS - TE NEG	PRE-AB POS – EQ
	PRE-AB NEG - TE INCONCLUSIVE	PRE-AB POS - TE INCONCLUSIVE

ADA Assay Classification	mADA Assay Classification	Overall Subject Classification
	PRE-AB POS - TE INCONCLUSIVE	PRE-AB POS - TE INCONCLUSIVE

Table 12-2: NAb Assay Classification

NAb assay classification
Pre-dose Neg, Neg on treatment
Pre-dose Neg, Pos on treatment
Pre-dose Pos, Neg on treatment
Pre-dose Pos, Pos on treatment

12.1 Available data

The following parameters will be summarized by treatment group:

- ADA subject classification
- mADA subject classification (based on subset of subjects)
- Overall subject classification per subject (based on ADA and/or mADA analysis)
- NAb subject classification (based on subset of subjects)

Note that, for immunogenicity, screening and baseline visits are derived based on the CRF visit label.

12.1.1 ADA and mADA

The following 2 populations will be defined and used where specified in the summary statistics:

- **Pre-Ab negative population**: includes all the subjects who had all their available pre-dose titers (Screening and/or Baseline) reported as <2.00.
- **Pre-Ab positive population**: includes all the subjects with at least one pre-dose $\log_{10}$(titer) reported as a numeric value equal to or above 2.00.

ADA Subject Classification:

The incidence rate (number and percentage of subjects) of pre-Ab status (negative, positive and total) versus treatment-emergent ADA status (TE negative, TE positive, TE inconclusive and equivocal) will be presented by treatment group and by all ALX-0061 treated subjects. The percentages will be based on the number of subjects within each treatment group, excluding the subjects who are classified as missing.

In addition, the incidence rate of pre-Ab status (negative, positive and total) versus treatment-emergent ADA/mADA positive status (TE negative, TE positive, TE inconclusive and equivocal) will be presented for both the pre-Ab negative and positive populations. The percentages will be based on the number of subjects within each treatment group in the subpopulations (i.e., pre-Ab negative and pre-Ab positive), excluding the subjects who are classified as missing.

The following subject categories will be used in the table:

- Pre-Ab Negative – TE Negative
- Pre-Ab Negative – TE Positive

- Pre-Ab Negative – TE inconclusive,
- Pre-Ab Positive – TE Negative,
- Pre-Ab Positive – TE Positive,
- Pre-Ab Positive – Equivocal,
- Pre-Ab Positive – TE inconclusive,
- Total Pre-Ab Negative ("Pre-Ab Negative – TE Negative", "Pre-Ab Negative – TE Positive" and "Pre-Ab Negative – TE inconclusive"),
- Total Pre-Ab Positive ("Pre-Ab Positive – TE Negative", "Pre-Ab Positive – TE Positive", "Pre-Ab Positive – Equivocal" and "Pre-Ab Positive – TE inconclusive"),
- Total TE Negative ("Pre-Ab Negative – TE Negative" and "Pre-Ab Positive – TE Negative"),
- Total TE Positive ("Pre-Ab Negative – TE Positive" and "Pre-Ab Positive – TE Positive"),
- Total TE inconclusive ("Pre-Ab Negative – TE Inconclusive" and "Pre-Ab Positive – TE Inconclusive"),
- Missing
- TE Positive within Pre-Ab Negative population
- TE Positive within Pre-Ab Positive population

mADA Subject Classification:

Similar summary (as for the ADA subject classification) will be provided for the mADA subject classification with exception that subjects will not be classified as missing.

ADA/mADA Overall Subject Classification:

Similar summary (as for the ADA subject classification) will be provided for the overall subject classification.

12.1.2NAb

The incidence rate of pre-dose status (negative, positive) versus NAb status on treatment (negative on treatment, positive on treatment) will be presented by treatment group. The percentages will be based on the number of subjects within each treatment group. For the pre-dose negative and pre-dose positive population, the percentages are based on the number of subjects within each treatment group in the subpopulation.

The following NAb subject categories will be used:

- Pre-dose negative – negative on treatment
- Pre-dose negative – positive on treatment
- Pre-dose positive – negative on treatment
- Pre-dose positive – positive on treatment
- Total Pre-dose Negative
- Total Pre-dose Positive

- Total negative on treatment
- Total positive on treatment
- Positive on treatment within Pre-dose negative population
- Positive on treatment within Pre-dose positive population

12.2 Subgroup analyses

The incidence rate of pre-Ab status (negative, positive and total) versus treatment-emergent ADA/mADA status (TE negative, TE positive, TE inconclusive and equivocal) will be presented by treatment group for the following subgroups. The percentages will be based on the number of subjects within each treatment group and subgroup, excluding the subjects who are classified as missing.

In addition, for the following subgroups, the incidence rate of pre-Ab status (negative, positive and total) versus treatment-emergent ADA/mADA positive status (TE positive) will be presented for both the pre-Ab negative and positive populations. The same classifications will be used as the ones outlined above (see ADA subject classifications).

- Injection-site reaction
    - No injection-site reaction
    - At least 1 injection-site reaction
- Hypersensitivity reaction
    - No hypersensitivity reaction
    - At least 1 hypersensitivity reaction

13 Interim Analysis

No interim analysis is planned for the study.

14 Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) is an independent committee. None of the members are participating in the study. The major function of this committee is to monitor the safety of the subjects participating in the ALX-0061 clinical program by periodically reviewing unblinded safety data. They advise concerning continuation, modification or termination of study. The DSMB meets every 6 months to review the study data. PPD provides the blinded SDTM datasets to the company responsible to organize the DSMB.

The DSMB charter and DSMB SAP define and document the content of the safety summaries, the DSMB's role and responsibilities, and the general procedures (including communications).

15 Changes in the Planned Analysis

The following points are changes in analysis from the protocol.

- Primary endpoint: sensitivity analysis was added using the observed case data.
- SRI definition was updated by adding that a subject will be deemed to be non-responder at any time point after treatment failure (including the premature discontinuation from study treatment) has been determined.

- Treatment failure definition was harmonized to exclude early discontinuation as the protocol was including early discontinuation in some of the references of treatment failure but not all, therefore early discontinuation was added to the following endpoints definitions:
    - BICLA and mBICLA
    - SRI and mSRI
- Subgroup analyses for secondary endpoints (except mSRI at Week 24 and 48) and safety endpoints were not included.
- Subgroup summaries for mBICLA at Week 48 were added.
- Inferential statistics were added for all secondary endpoints.
- PK population was removed and Safety population was used instead.
- QTcB and QTcF were added in the list of ECG endpoints.
- Percent Change from Baseline in Daily Prednisone or Equivalent now includes Week 12 (in addition to Week 24 and Week 48).
- Change from Baseline in Daily Prednisone or Equivalent to Week 12, 24 and 48 was added.
- SE was used instead of SD for secondary endpoints (excluding PK and ANA data) and safety endpoints summaries.
- Shift tables from Baseline in NCI CTCAE or Ablynx defined grades for selected laboratory parameters (AST, ALT, serum Creatinine, eGFR, GGT, Total Cholesterol, Leukocytes, Absolute Lymphocytes, Absolute Neutrophils, Platelets, Fibrinogen and Proteinuria as measured by spot urine protein to creatinine ratio) were included.
- The following laboratory parameters have been added to the list of endpoints (and will be derived):
    - Fasting LDL/HDL-cholesterol ratio
    - UCr
- The following parameters will not be summarized:
    - Plasma cells
    - T-helper 17
    - T regulatory cells

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17 Appendices

17.1 Schedule of Study Procedures[a]

Study Period	Screening	Base-line (Day)	Treatment and Assessment Period (Week ± 5 days)																							Early Termination Visit	Follow-up (± 2 weeks)
Study Visit	**Within 28 days prior to baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**Within 3 weeks after last dosing**	**12 weeks after last dosing**
Written informed consent	x																										
Demographics, medical history	x																										
Physical examination	x	x						x						x						x						x	x	x
Vital signs [b]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x	x	x
12-lead ECG [c]	x																									x	x	
Screening Hep B, Hep C, HIV [d]	x																											
IGRA test	x																											
Chest radiograph [e]	x																											
TB evaluation [f]		→																										→
Review of entry criteria	x	x																										
Prior medication	x																											
Concomitant medication		→																										→
Randomization		x																										
ANA, LA, aCL, β_2-GPI [g]	x													x														
Study drug allocation and administration		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
SLEDAI-2K	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
BILAG-2004	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
Physician's Global Assessment		x		x		x		x		x		x		x		x		x		x		x		x		x	x	
Patient's Global Assessment		x												x												x	x	
SF-36		x												x												x	x	
28 joint count	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
CLASI [h]		x						x						x												x	x	

Study Period	Screening	Base-line (Day)	Treatment and Assessment Period (Week ± 5 days)																								Early Termination Visit	Follow-up (± 2 weeks)
Study Visit	**Within 28 days prior to baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**Within 3 weeks after last dosing**	**12 weeks after last dosing**
SLICC/ ACR damage score		x																										
Adverse events[i]	←																											→
Clinical laboratory analyses[j]	x	x	x	x		x		x		x		x		x		x		x		x		x		x		x	x	x
Urinalysis	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
Pregnancy test (serum at screening/urine at other visits)	x	x						x						x												x	x	x
PK [k]		x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x	x	
PD biomarker (sIL-6R) [k,]		x		x		x		x		x				x				x				x				x	x	x
PD biomarker (others) [k,l]	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	x
Exploratory biomarkers[m]		x				x								x												x	x	
Immunogenicity [k,i]	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	x
Local lab analyses (Direct Coombs) [n]	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	

[a] If assessments are planned at the same time, following guidance should be followed: 1) ECG and vital signs should be assessed prior to blood sampling, 2) Patient assessments (patient's global assessment and SF-36) should occur prior to physician's assessments, 3) Study drug should be dosed after all other assessments have been performed.

[b] Vital signs (assessment after 5 min in supine position): including height, weight, blood pressure, pulse and temperature. Height measurement is only required at the screening visit.

[c] To be performed after 5 min in supine position.

[d] Lab tests for hepatitis B will be done according to the guidelines [2].

[e] If a chest radiograph has not been performed within 12 weeks prior to screening as part of standard of care, a chest radiograph must be performed during the screening period. In case local regulations do not allow radiographs during the study, a radiograph as part of standard of care should be available prior to screening.

[f] If TB is suspected at any time during the study, chest radiography and IGRA or a comparable local practice test should be performed.

[g] Lupus anti-coagulant (LA), anticardiolipin (aCL) and anti-β_2-glycoprotein I (β_2-GPI) antibodies will be evaluated at screening and Week 24. Anti-nuclear antibodies (ANA) will be evaluated at screening only.

[h] The CLASI will be performed in interested sites having experience in this assessment.

[i] In case of acute or delayed severe/serious hypersensitivity reactions, an additional blood sample should be collected as soon as possible after the start of the event.

[j] On dosing days, blood sampling will be performed pre-dose. Subjects will be fasted for at least 10h at baseline and Weeks 4, 8, 12, 24, 36 and 48 and/or the Early Termination Visit for assessment of fasting serum lipids. Samples will be assessed by a central laboratory.

[k] On dosing days, PK, PD biomarker and immunogenicity samples will be taken predose.

[l] CRP, fibrinogen, anti-dsDNA, C3, C4, CH50.

[m] Urine samples for uMCP-1 will be collected in all subjects. Blood samples for immunophenotyping will be collected in a subset of subjects (at selected sites based on qualification).

[n] Parameters to be assessed by the local laboratory include Direct Coombs and INR (INR for subjects on vitamin K antagonist only). INR will be performed at Weeks 0, 2, 4, 8, and 12, and every 4 weeks (or more frequent if considered necessary by Investigator) thereafter up to Week 48 (or Early Termination Visit), and Follow-Up Visit.

17.2 Dosing Schedule

Placebo (Group 1)

Syringe A with placebo (1 mL) q2w starting at Week 0 (Day 1), up to and including Week 46.

Syringe B with placebo (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 17-1: Dosing schedule for Group 1

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Placebo 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 1 mL																								
ALX 0.5 mL																								

75 mg q4w (Group 2)

Syringe A with placebo (1 mL) q2w starting at Week 0, up to and including Week 46.

Syringe B with ALX-0061 (0.5 mL) q4w at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44, and syringe B with placebo (0.5 mL) q4w at Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42 and 46.

Table 17-2: Dosing schedule for Group 2

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Placebo 0.5 mL		X		X		X		X		X		X		X		X		X		X		X		X
ALX 1 mL																								
ALX 0.5 mL	X		X		X		X		X		X		X		X		X		X		X		X	

150 mg q4w (Group 3)

Syringe A with ALX-0061 (1 mL) q4w at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44, and syringe A with placebo (1 mL) q4w at Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42 and 46.

Syringe B with placebo (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 17-3: Dosing schedule for Group 3

	Visit (Weeks)																								
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL		X		X		X		X		X		X		X		X		X		X		X		X
Placebo 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 1 mL	X		X		X		X		X		X		X		X		X		X		X		X	
ALX 0.5 mL																								

150 mg q2w (Group 4)

Syringe A with ALX-0061 (1 mL) q2w starting at Week 0, up to and including Week 46.
Syringe B with placebo (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 17-4: Dosing schedule for Group 4

	Visit (Weeks)																								
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL																								
Placebo 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 0.5 mL																								

225 mg q2w (Group 5)

Syringe A with ALX-0061 (1 mL) q2w starting, at Week 0, up to and including Week 46.
Syringe B with ALX-0061 (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 17-5: Dosing schedule for Group 5

	Visit (Weeks)																								
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL																								
Placebo 0.5 mL																								
ALX 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

17.3 BILAG-2004

The BILAG-2004 [2-4] is a comprehensive composite clinical index that has been developed based on the principle of a physician's intention to treat using a nominal consensus approach. In the index, the nine systems (not organs) considered are: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, renal, ophthalmic and haematological. Disease activity in each of the nine systems is categorized into five levels (Grades A-E). For the assessment of the BILAG-2004 scores, Coombs' test from local laboratory assessments will be used and all other laboratory parameters will be from the central laboratory. The BILAG-2004 version dated 2009 (latest validated version) will be used.

17.3.1 BILAG-2004 Improvement (overall and individual):

BILAG-2004 improvement will be evaluated as normal and enhanced improvement and as improvement by individual organ system score.

- ***Normal improvement***: all A scores at Baseline improved to B/C/D, and all B scores improved to C or D.
- ***Enhanced improvement***: all A scores at Baseline improved to B/C/D, and all B scores improved to C or D and no worsening between consecutive visits from Baseline up to considered visit. For enhanced improvement if no more than one consecutive score is missing in visit(s) between the Baseline and the visit of interest for a considered organ system and no worsening is observed at the prior and subsequent visits it is assumed that the missing score is the same as the one at the prior visit.
- ***Improvement by individual organ system score***: For each organ system, an improvement is defined as an A score at Baseline improved to B/C/D or a B score improved to C or D.

17.3.2 BILAG-2004 Total Score:

BILAG total score is derived by assigning the following value to each grade [3] and summing the scores over all organ systems:

- A = 12,
- B = 8,
- C = 1,
- D/E = 0.

17.3.3 BILAG-2004 Systems Tally:

BILAG-2004 system tally (BST) [14] is derived by classifying changes in the BILAG-2004 index system scores, using counts of systems with specified transitions in scores. It records the number of systems in which activity increased, decreased or remained the same between two consecutive visits and expresses this as a tally. It has the following six components:

- ***Major deterioration***: change from grade B/C/D/E to A or grade D/E to B
- ***Minor deterioration***: change from grade C to B
- ***Persistent significant activity***: no change from grade A or B
- ***Major improvement***: change from grade A to C/D or grade B to D
- ***Minor improvement***: change from grade A to B or grade B to C

- ***Persistent minimal or no activity***: change from grade C/D/E to C/D/E

BST was further simplified into three components (simplified BILAG-2004 systems tally, sBST) by grouping major deterioration, minor deterioration and persistent activity into a single group, and major improvement with minor improvement into a separate group. The simplified version of the BST will be used in the study.

- ***Active/worsening disease***: systems with major deterioration, minor deterioration or persistent significant activity
- ***Improving disease***: systems with major improvement or minor improvement
- ***Persistent minimal or no activity***.

17.3.4 BILAG-2004 Flare Index:

Using the BILAG-2004 score, severe and mild/moderate flares are defined as follows:

- Severe flare defined as a new A score in any system of the BILAG-2004 index following a B, C, D or E score at the previous assessment.
- Mild/moderate flare defined as a new B score following a C, D or E score at the previous assessment.

Flares will be evaluated from Baseline up to Week 24 and from Baseline up to Week 48.

17.3.5 BILAG-2004 Scoring System:

The BILAG-2004 scoring system is based on the physician's intention to treat.

Grade	Definition
A	Severe disease activity requiring any of the following treatment: 1. Systemic high dose oral corticosteroids (equivalent to Prednisolone > 20 mg/day) 2. Intravenous pulse corticosteroids (equivalent to pulse methylprednisolone ≥ 500 mg) 3. Systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis) 4. Therapeutic high dose anticoagulation in the presence of high dose corticosteroids or immunomodulators (e.g. warfarin with target INR 3 - 4)
B	Moderate disease activity requiring any of the following treatment: 1. Systemic low dose oral corticosteroids (equivalent to prednisolone ≤ 20 mg/day) 2. Intramuscular or intra-articular or soft tissue corticosteroids injection (equivalent to methylprednisolone < 500 mg) 3. Topical corticosteroids 4. Topical immunomodulators 5. Antimalarials or thalidomide or prasterone or acitretin 6. Symptomatic therapy (e.g. NSAIDs for inflammatory arthritis)
C	Mild disease
D	Inactive disease but previously affected
E	System never involved

The following 9 systems are evaluated as follow: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, renal, ophthalmic and haematology.

If the answer to the question "Has the subject ever had any previous involvement of this system (prior to the past 4 weeks)" is answered as No, then

the organ system is graded at E. If the answer is missing then the organ system is graded at D.

The following imputation for missing items will be used prior to determining the score for each system.

17.3.5.1 Imputation of missing items

For the **Constitutional, Cardiorespiratory, Gastrointestinal, Mucocutaneous, Musculoskeletal, Ophthalmic and Neuropsychiatric** system organs, the following algorithm will be used for missing items:

- Step 1: If the current involvement is "NO", the missing items will be imputed as "NOT PRESENT".
- Step2:
  - For assessments performed prior or on the first dose of study drug, the missing items will be imputed by the previous last non-missing items (therefore the baseline score will be derived using the last non-missing items across all assessments performed prior or on the first dose of study drug).
  - For post-baseline assessments, if the current involvement is "YES", the missing items will be imputed if the previous and next values are as described in Table 17-6 as well as the rules for Week 48 described further below.

Table 17-6: Constitutional, Cardiorespiratory, Gastrointestinal, Mucocutaneous, Musculoskeletal, Ophthalmic and Neuropsychiatric system organs - Imputed values for $Visit_x$

$Visit_{x-1}$	$Visit_x$	$Visit_{x+1}$
Not present	Not present	Not present
Not present	New	Same, Improving or Worse
Not present	Not present	New
New, Same, Improving or Worse	Improving	Not present
New, Same, Improving or Worse	Same	Same, Improving or Worse
New, Same or Worse		New
Improving	Not present	New

For the **Hematology and Renal** system organs, the following algorithm will be used for missing items:

- For characters items (TTP, evidence of active hemolysis, Coombs' test positive, accelerated hypertension, nephrotic syndrome, active urinary sediment and active nephritis) items:
  - Step 1: If the current involvement is "NO", TTP will be imputed as "NOT PRESENT" and the other items will be imputed as "NO".
  - Step 2:
    - For assessments performed prior or on the first dose of study drug, the missing items will be imputed by the previous last non-missing items (therefore the baseline score will be derived using the last non-missing items across all assessments performed prior or on the first dose of study drug).
    - For post-baseline assessments, if the current involvement is "YES", the missing items will be imputed if the previous and next values are as

described in Table 17-6 for TTP items and Table 17-7 for the other items as well as the rules for Week 48 described further below.

Table 17-7: Hematological and Renal system organs (excluding TTP) - Imputed values for $Visit_x$

$Visit_{x-1}$	$Visit_x$	$Visit_{x+1}$
Yes	Yes	Yes or No
No	Yes	Yes
No	No	No

- For numeric items (hemoglobin (g/dL), total white cell count (x 10^9/L), neutrophils (x 10^9/L), lymphocytes (x 10^9/L), platelets (x 10^9/L), systolic blood pressure, diastolic blood pressure, urine protein-creatinine ratio (mg/mmol), creatinine (plasma/serum) (umol/L) and GFR (calculated) (mL/min/1.73 m^2)), LOCF will be used. Post-baseline results will not be imputed with baseline (or pre-baseline values). If week 4 have missing results those will not be imputed if there are no unscheduled results available on the BILAG page that have been assessed after the 1st dose of study drug.

At Week 48 (or the last visit performed), the values at Week 44 (or the visit prior to the last visit performed) will be used to impute the missing values as follow:

- If the previous value is "NEW" then the missing value will be imputed with "SAME".
- If the previous value is "IMPROVING", "SAME", "WORSE" or "NOT PRESENT", the missing value will be imputed with the value from the previous visit (i.e. "SAME" if the previous visit has a value of "SAME").
- If the previous visit value is missing, no imputation will be performed.

17.3.5.2 Constitutional

Category A:

Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Weight loss
- Lymphadenopathy/splenomegaly
- Anorexia

Category B:

Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Weight loss
- Lymphadenopathy/splenomegaly
- Anorexia

BUT do not fulfil criteria for Category A

Category C

Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

- Weight loss
- Lymphadenopathy/Splenomegaly
- Anorexia

BUT does not fulfil criteria for category A or B

Category D

Previous involvement

Category E

No previous involvement

17.3.5.3 Mucocutaneous

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Skin eruption - severe
- Angio-oedema - severe
- Mucosal ulceration - severe
- Panniculitis/Bullous lupus - severe
- Major cutaneous vasculitis/thrombosis

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - mild

Panniculitis/Bullous lupus - mild

Digital infarcts or nodular vasculitis

Alopecia - severe

Category C

Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild

Mucosal ulceration - mild

Alopecia - mild

Periungual erythema/chilblains

Splinter haemorrhages

Category D

Previous involvement

Category E

No previous involvement

17.3.5.4 Neuropsychatric

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Aseptic meningitis

Cerebral vasculitis

Demyelinating syndrome

Myelopathy

Acute confusional state

Psychosis

Acute inflammatory demyelinating polyradiculoneuropathy

Mononeuropathy (single/multiplex)

Cranial neuropathy

Plexopathy

Polyneuropathy

Status epilepticus

Cerebellar ataxia

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Seizure disorder
- Cerebrovascular disease (not due to vasculitis)
- Cognitive dysfunction
- Movement disorder
- Autonomic disorder
- Lupus headache - severe unremitting
- Headache due to raised intracranial hypertension

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

17.3.5.5 Musculoskeletal

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Severe Myositis
- Severe Arthritis

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Mild Myositis
- Moderate Arthritis/Tendonitis/Tenosynovitis

Category C

Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

- Mild Arthritis/Arthralgia/Myalgia

Category D

Previous involvement

Category E

No previous involvement

17.3.5.6 Cardiorespiratory

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Myocarditis/Endocarditis + Cardiac failure
- Arrhythmia
- New valvular dysfunction
- Cardiac tamponade
- Pleural effusion with dyspnoea
- Pulmonary haemorrhage/vasculitis
- Interstitial alveolitis/pneumonitis
- Shrinking lung syndrome
- Aortitis
- Coronary vasculitis

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Pleurisy/Pericarditis
- Myocarditis - mild

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

17.3.5.7 Gastrointestinal

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Peritonitis
- Lupus enteritis/colitis
- Intestinal pseudo-obstruction
- Acute lupus cholecystitis
- Acute lupus pancreatitis

Category B

Any Category A feature recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Abdominal serositis and/or ascites
- Malabsorption
- Protein losing enteropathy
- Lupus hepatitis

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

17.3.5.8 Ophthalmic

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

- Orbital inflammation/myositis/proptosis
- Keratitis - severe
- Posterior uveitis/retinal vasculitis - severe
- Scleritis - severe
- Retinal/choroidal vaso-occlusive disease
- Optic neuritis
- Anterior ischaemic optic neuropathy

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Keratitis - mild

Anterior uveitis

Posterior uveitis/retinal vasculitis - mild

Scleritis - mild

Category C

Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Episcleritis

Isolated cotton-wool spots (cytoid bodies)

Category D

Previous involvement

Category E

No previous involvement

17.3.5.9 Renal

For Proteinuria, only urine protein-creatinine ratio will be used in calculation of the grades. Abnormal laboratory values will be used for scoring only if they are due to SLE.

Category A

Two or more of the following **providing 1, 4 or 5 is included**:

1. Deteriorating proteinuria (severe) defined as
   (a) urine protein-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥ 25%;
2. Accelerated hypertension
3. Deteriorating renal function (severe) defined as
   (a) plasma creatinine > 130 µmol/L and having risen to > 130% of previous value; **or**
   (b) eGFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value; **or**
   (c) eGFR < 50 ml/min per 1.73 m^2, and last time was > 50 ml/min per 1.73 m^2 or was not measured.
4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

Category B

One of the following:

1. One of the Category A feature
2. Proteinuria (that has not fulfilled Category A criteria)
   (a) urine protein-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%; **or**
3. Plasma creatinine > 130 µmol/L and having risen to ≥ 115% but ≤ 130% of previous value

Category C

One of the following:

1. Mild/Stable proteinuria defined as
   (a) urine protein-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B;
2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as
   (a) systolic rise of ≥ 30 mm Hg; **and**
   (b) diastolic rise of ≥ 15mm Hg

Category D

Previous involvement

Category E

No previous involvement

17.3.5.10 Hematological

Abnormal laboratory values will be used for scoring only if they are due to SLE.

Category A

Thrombotic Thrombocytopenic Purpura (TTP) recorded as 2 (same), 3 (worse) or 4 (new)
OR

Any of the following:

Haemoglobin < 8 g/dL

White cell count < 1.0 x 10^9/L

Neutrophil count < 0.5 x 10^9/L

Platelet count < 25 x 10^9/L

Category B

TTP recorded as 1 (improving) **OR**

Any of the following:

- Haemoglobin 8 - 8.9 g/dL
- White cell count 1 - 1.9 x 10^9/L
- Neutrophil count 0.5 - 0.9 x 10^9/L
- Platelet count 25 - 49 x 10^9/L
- Evidence of active haemolysis

Category C

Any of the following:

- Haemoglobin 9 - 10.9 g/dL
- White cell count 2 - 3.9 x 10^9/L
- Neutrophil count 1 - 1.9 x 10^9/L
- Lymphocyte count < 1.0 x 10^9/L
- Platelet count 50 - 149 x 10^9/L
- Isolated Coombs' test positive

Category D

Previous involvement

Category E

No previous involvement

17.4 SLEDAI-2K Scoring System

The SLEDAI-2K [5] is a one-page weighted scale for 24 items (seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, haematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, leukopenia). The manifestations felt to be most commonly contributing to disease activity are included and scored based on the presence or absence within 30 days prior to the evaluation. The score can range from 0-105 and reflects all aspects of disease activity. Results from central laboratory will be used in the SLEDAI-2K scoring by the investigator.

SLEDAI-2K weighted scoring sheet can be found below.

Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the **preceding 30 days**.

SLEDAI 2K Weight	SLEDAI 2K SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	$\geq$ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).

SLEDAI 2K Weight	SCORE		Descriptor	Definition
4	_____		Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____		Urinary casts	Heme-granular or red blood cell casts.
4	_____		Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____		Proteinuria	>0.5 gram/24 hours
4	_____		Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____		Rash	Inflammatory type rash.
2	_____		Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____		Mucosal ulcers	Oral or nasal ulcerations.
2	_____		Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	P	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____		Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____		Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____		Fever	>38° C. Exclude infectious cause.
1	_____		Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____		Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.

TOTAL SCORE: _____

Imputation of missing data for Baseline Score:

For assessments performed prior or on the first dose of study drug, the missing items will be imputed by the previous last non-missing items (therefore the baseline score will be derived using the last non-missing items across all assessments performed prior or on the first dose of study drug).

Modified SLEDAI-2K (mSLEDAI-2K):

An mSLEDAI-2K index [6] will be derived from the standard index by omitting 1 of the standard items (low complement). An anti-IL-6R compound strongly decreases production of acute phase reactants, including complement [7, 8]. Therefore, the complement (C3/C4) values (parameters of the low complement item in the SLEDAI-2K index) may be decreased due to decreased production while effect on complement consumption (relevant for disease activity evaluation) cannot be assessed.

mSLEDAI-2K Flare Index (mSFI):

Using the mSLEDAI-2K score [10], severe and mild/moderate flares are defined as follows. The flares will be assessed at Week 24 (i.e. from Baseline to the end of Week 24 visit window as defined in Section 17.16) and at Week 48 (i.e. from Baseline to the end of Week 48 visit window as defined in Section 17.16).

- Severe flare defined as:
  - Change from Baseline in mSLEDAI-2K > 12, or
  - New/worse central nervous system (CNS) SLE, vasculitis (captured in SLEDAI-2K), nephritis, myositis (captured in SLEDAI-2K), Platelets < 60 000, haemolytic anaemia with Haemoglobin < 7 mg/dL, requiring doubling (compared to baseline) or an increase to a dose > 0.5 mg/kg/day prednisone, or
  - Hospitalization for SLE, or
  - Increase of Prednisone equivalent dose to a dose > 0.5 mg/kg/day, or
  - New or increased immunosuppressive, or
  - Increase of PGA from Baseline and PGA > 83.3 (using a 100 VAS).
- Mild/moderate flare defined as:
  - Change from Baseline in mSLEDAI-2K ≥ 3, or
  - New/worse skin, stomatitis, serositis, arthritis, fever, or
  - Increase in prednisone equivalent dose to a dose ≤ 0.5 mg/kg/day, or
  - Added non-steroidal anti-inflammatory drug (NSAID)/Plaquenil, or
  - Increase from Baseline in PGA of ≥ 33.3 (using a 100 VAS).

The following items of the mSFI will be derived programmatically:

- Change from Baseline in mSLEDAI-2K ≥ 3
- Change from Baseline in mSLEDAI-2K > 12,
- Prednisone Equivalent Dose > 0.5 mg/kg/day (weight will be derived from the weight assessed at the visit prior to or on the medication start date; if the weight is missing, LOCF principle will be applied; see Section 17.9 for details on how Prednisone Equivalent Dose is derived at Week 24 and Week 48),
- Increase in Prednisone Equivalent Dose to a dose ≤ 0.5 mg/kg/day,
- Added non-steroidal anti-inflammatory drug (NSAID)/Plaquenil (anti-malarial),
- Increase of PGA from Baseline and PGA > 83.3 (using a 100 VAS),
- Increase from Baseline in PGA of ≥ 33.3 (using a 100 VAS),
- New/worse skin is defined as any items (except "mucosal ulceration") recorded as 3 (worse) or 4 (new) in system "mucocutaneous" of BILAG-2004 index or new score >0 recorded or increase of score from Baseline in "rash" and "alopecia" items of SLEDAI-2K index,
- New/worse stomatitis is defined as any "Mucosal ulceration – severe" or "Mucosal ulceration – Mild" items recorded as 3 (worse) or 4 (new) in system "mucocutaneous" of BILAG-2004 index or new score > 0 recorded or increase of score from Baseline in "mucosal ulcers" items of SLEDAI-2K index,
- New/worse serositis is defined as any "Pleurisy/pericarditis", "Cardiac tamponade" or "Pleural effusion with dyspnoea" items recorded as 3 (worse) or 4 (new) in system 'Cardiorespiratory" of BILAG-2004 or new score > 0 recorded or increase of score from Baseline in "Pleurisy" and "Pericarditis" items of SLEDAI-2K index,

- New/worse arthritis is defined as any "Arthritis (severe)", "Arthritis (moderate)/ Tendonitis/ Tenosynovitis" or "Arthritis (mild)/ Arthralgia/ Myalgia" items recorded as 3 (worse) or 4 (new) in system "Musculoskeletal" of BILAG-2004 or new score > 0 recorded or increase of score from Baseline in "Arthritis" item of SLEDAI-2K index,
- New/worse fever is defined as any "Pyrexia – documented > 37.5 °C" item recorded as 3 (worse) or 4 (new) in system "constitutional" of BILAG-2004 index or new score > 0 recorded or increase of score from Baseline in "Fever" item of SLEDAI-2K index.

The following items will be medically reviewed to determine if they meet the criteria of severe mSFI flare.

- New/worse central nervous system (CNS) SLE, vasculitis (captured in SLEDAI-2K), nephritis, myositis (captured in SLEDAI-2K), Platelets < 60 000, haemolytic anaemia with Haemoglobin < 7 mg/dL, requiring doubling (compared to baseline) or > 0.5 mg/kg/day prednisone, and
- New or increased immunosuppressive, and
- Hospitalization for SLE.

PPD Programming and Biostatistics will provide medical monitor with a listing of study drugs (restricted to immunosuppressives, anti-malarials and systemic corticosteroids with prednisone equivalent dose and changes post-Baseline) for their review (data fields will be agreed and documented in the Data Validation Manual and/or the Medical Manual). The listing will be programmed based on the analysis datasets and approved SAP. The medical monitor team will review the listings on an agreed frequency for sufficiently clean subjects. The outcome of the review will be included in subsequent delivery of the listings by PPD Programming and Biostatistics and will be used to derive flare in the analysis datasets. Prior to database lock (during soft lock process), a medical review on the final listing will be performed to confirm the subjects who experience severe flare based on the 3 criteria listed under medical review.

17.5 Treatment Failure Derivation Algorithm

A subject is deemed a treatment failure prior to a certain analysis visit (for example prior to week 24) if any of the following criteria are met and the corresponding date of the event is prior to the cut-off date (see Section 17.5.1).

- New or increased immunosuppressives or anti-malarials (see Section 17.5.3 and Section 17.5.4)
- Non-protocol allowed increased oral, intravenous or intramuscular corticosteroids (see Section 17.9 for selection of the corticosteroids drugs);

During blinded targeted medical review prior to database lock, the criteria above will be evaluated. The medication and corresponding start date will be identified. PPD Programming and Biostatistics will provide medical monitor with a listing of prior and concomitant medications recorded on the SLE medication page (restricted to immunosuppressives, anti-malarials and systemic corticosteroids with prednisone equivalent dose and changes post-Baseline) for their review (data fields will be agreed and documented in the Data Validation Manual and/or the Medical Manual). The listing will be programmed based on the analysis datasets and approved SAP. The medical monitor team will review the listings on an agreed frequency for clean subjects. The outcome of the review will be included in subsequent delivery of the listings by PPD Programming and Biostatistics and will be used to derive treatment failure in the analysis datasets. Prior to database lock (during soft lock process), a medical review on the final listing will be performed to confirm the subjects who are treatment failure.

17.5.1 Cut-off date

The cut-off date is defined as the latest of the following assessment/sample dates for the analysis visit considered. For subjects who discontinue from the study before the analysis visit considered, the cut-off date is defined as the latest of the following assessment/sample dates prior to the analysis visit considered (for example, for a subject who discontinued at Week 16 (last assessment=Week 16), the treatment failure should still be evaluated from baseline up to Week 16). In case no assessment is available and subject is still on treatment for the analysis visit considered, the cut-off date is defined as the upper bound of visit window for that visit (see Section 17.16). In case of partial start date for medications, the start date is imputed as per Section 17.15.

- BILAG-2004 assessment date for constitutional system
- BILAG-2004 assessment date for mucocutaneous system
- BILAG-2004 assessment date for neuropsychiatric system
- BILAG-2004 assessment date for musculoskeletal system
- BILAG-2004 assessment date for cardiorespiratory system
- BILAG-2004 assessment date for gastro intestinal system
- BILAG-2004 assessment date for ophthalmic system
- BILAG-2004 assessment date for renal system
- BILAG-2004 assessment date for hematological system
- SLEDAI-2K assessment date
- PGA assessment date

17.5.2 New / Increased dose Determination

New/increase intake of steroids, immunosuppressive or anti-malarial drugs are defined as new records in the concomitant SLE medication page with either a new PT in the

same category or the same PT but with a total daily dose (i.e. dose times frequency) higher than the previous record of the same drug.

If an immunosuppressive, steroid or anti-malarial drug is interrupted or decreased due to an AE and re-started at the same dose as before the interruption, then it should not be considered as a treatment failure during the medical review.

17.5.3 Selection of Immunosuppressive Drugs:

The following ATC codes will be used to select immunosuppressive drugs from the CRF.

- L04AX
- L04AD
- L01AA
- L04AA
- L04AB
- L01XX
- L01XC
- M01CX

17.5.4 Selection of anti-malarials Drugs

The following ATC codes will be used to select anti-malarial drugs (including Plaquil) from the CRF.

- P01BA

17.6 BILAG based Composite Lupus Assessment (BICLA)

BICLA responders are defined as subjects who meet all of the following criteria:

1. BILAG-2004 normal improvement: all A scores at Baseline improved to B, C or D, and all B scores improved to C or D.
2. No worsening in disease activity: no new BILAG-2004 A scores and ≤ 1 new increase to B.
3. No worsening of total SLEDAI-2K score from Baseline.
4. No significant deterioration (< 10 % worsening from Baseline) in PGA.
5. No treatment failure (including the premature discontinuation from study treatment).

A subject will be deemed to be non-responder at any time point after treatment failure has been determined.

The date associated with premature discontinuation from treatment will be the date of last dose of treatment + 1 day, i.e. if criteria 1, 2, 3 and 4 are met prior to or on the date of last dose of treatment and there is no treatment failure prior to or on the date of last dose of treatment, the subject will be BICLA responder.

Modified BICLA:

A modified BICLA (mBICLA) will be derived from BICLA by using the mSLEDAI-2K instead of SLEDAI-2K.

mBICLA responders are defined as subjects who meet all of the following criteria:

1. BILAG-2004 normal improvement: all A scores at Baseline improved to B, C or D, and all B scores improved to C or D.
2. No worsening in disease activity: no new BILAG-2004 A scores and ≤ 1 new increase to B.
3. No worsening of total mSLEDAI-2K score from Baseline.
4. No significant deterioration (< 10 % worsening from Baseline) in PGA.
5. No treatment failure (including the premature discontinuation from study treatment).

A subject will be deemed to be non-responder at any time point after treatment failure has been determined.

The date associated with premature discontinuation from treatment will be the date of last dose of treatment + 1 day, i.e. if criteria 1, 2, 3 and 4 are met prior to or on the date of last dose of treatment and there is no treatment failure prior to or on the date of last dose of treatment, the subject will be mBICLA responder.

17.7 SLE Responder Index (SRI)

The composite index SRI enables quantification of decrease and increase in disease activity in a broad spectrum of manifestations thereby offering a comprehensive assessment of SLE disease status [9].

SRI combines advantages from three validated measurement tools:

- SLEDAI covers global disease improvement,
- BILAG covers organ specific disease worsening or improvement, and
- PGA is used as a validity and safety net for items that were not addressed by the other two indices.

The composite SRI criteria for response are:

- SLEDAI-2K: ≥ 4 point reduction.
- BILAG-2004: no new A domain score and no more than 1 new increase to B.
- PGA: no worsening (<10% increase from Baseline).

When all 3 criteria are met, the subject is a responder according to the SRI at that time point, i.e., a clinically meaningful improvement of disease is detected.

A subject will be deemed to be a non-responder at any time point after treatment failure (including the premature discontinuation from study treatment) has been determined. This criterion is also applicable for SRI-5, SRI-6, SRI-7, SRI-8 and their modified version.

SRI-5:

The composite SRI-5 criteria for response are:

- SLEDAI-2K: ≥ 5 point reduction.
- BILAG-2004: no new A domain score and no more than 1 new increase to B domain score.
- PGA: no worsening (<10% increase from Baseline).

Only subjects with Baseline SLEDAI-2K ≥ 5 will be considered for the derivation of that endpoint.

SRI-6:

The composite SRI-6 criteria for response are:

- SLEDAI-2K: ≥ 6 point reduction.
- BILAG-2004: no new A domain score and no more than 1 new increase to B domain score.
- PGA: no worsening (<10% increase from Baseline).

Only subjects with Baseline SLEDAI-2K ≥ 6 will be considered for the derivation of that endpoint.

SRI-7:

The composite SRI-7 criteria for response are:

- SLEDAI-2K: ≥ 7 point reduction.
- BILAG-2004: no new A domain score and no more than 1 new increase to B domain score.

- PGA: no worsening (<10% increase from Baseline).

Only subjects with Baseline SLEDAI-2K ≥ 7 will be considered for the derivation of that endpoint.

SRI-8:

The composite SRI-8 criteria for response are:

- SLEDAI-2K: ≥ 8 point reduction.
- BILAG-2004: no new A domain score and no more than 1 new increase to B domain score.
- PGA: no worsening (<10% increase from Baseline).

Only subjects with Baseline SLEDAI-2K ≥ 8 will be considered for the derivation of that endpoint.

Modified SRI (mSRI):

The mSRI will be assessed using the modified (excluding the low component item) version of the SLEDAI-2K as a criterion.

mSRI-5:

The mSRI-5 will be assessed using the modified (excluding the low component item) version of the SLEDAI-2K as a criterion. Only subjects with Baseline mSLEDAI-2K ≥ 5 will be considered for the derivation of that endpoint.

mSRI-6:

The mSRI-6 will be assessed using the modified (excluding the low component item) version of the SLEDAI-2K as a criterion. Only subjects with Baseline mSLEDAI-2K ≥ 6 will be considered for the derivation of that endpoint.

mSRI-7:

The mSRI-7 will be assessed using the modified (excluding the low component item) version of the SLEDAI-2K as a criterion. Only subjects with Baseline mSLEDAI-2K ≥ 7 will be considered for the derivation of that endpoint.

mSRI-8:

The mSRI-8 will be assessed using the modified (excluding the low component item) version of the SLEDAI-2K as a criterion. Only subjects with Baseline mSLEDAI-2K ≥ 8 will be considered for the derivation of that endpoint.

17.8 Selection of NSAIDS

The following ATC codes will be used to select NSAIDs from the SLE medication CRF page.

- M01AB
- M01AE
- M01AH
- M01AC

17.9 Selection of Steroids drugs and Drug Equivalence

The following ATC codes will be used to select steroids drugs from the CRF. Only systemic corticosteroids will be considered for the assessment of treatment failure. Systemic corticosteroids are corticosteroids with a route of administration of oral, intramuscular and intravenous.

- H02AB

Total daily dose will be derived using the frequency and the corresponding dose recorded in CRF (i.e. if a subject takes a dose of 5 mg at a frequency of twice a day, their total daily dose will be 10 mg) and will be converted to Prednisone equivalent using the equivalence Table 17-8 below.

Table 17-8: Prednisone Equivalence Table

Glucocorticoid	Approximate equivalent dose (mg)	Conversion factor
Cortisone	25	0.20
Hydrocortisone	20	0.25
Methylprednisolone, Methylprednisolone Sodium Succinate, Methylprednisolone Acetate	4	1.25
Prednisolone	5	1.00
Prednisone	5	1.00
Triamcinolone Triamcinolone Acetonide	4	1.25
Betamethasone DIPROSPAN /00582101/	0.70	7.15
Dexamethasone	0.75	6.67
Deflazacort	6	0.83
Meprednisone	4	1.25

- Dixon JS. Second-line Agents in the Treatment of Rheumatic Diseases. Informa Health Care, 1991. (456).
- Meikle AW and Tyler FH. Potency and duration of action of glucocorticoids. Am J of Med 1977;63;200.
- Webb R, Singer M. Oxford Handbook of Critical Care. Oxford ; New York : Oxford University Press, 2005.
- Nayak S, Acharjya B. Deflazacort versus other glucocorticoids: A comparison. Indian J Dermatol 2008;53:167-70

The total daily dose of steroids is the sum of all Prednisone equivalent doses taken by the subject on the date of the visit of interest. For example, if the subject takes steroid every other day, it will be assumed that the steroid was taken every day and the dose recorded on the CRF will be halved.

- **Week 12:** total daily dose is the sum of the Prednisone equivalent doses for all steroids that have a start date (included imputed date) prior to or on the latest assessment date for Week 12 for assessments defined in Section 17.5.1 and have a stop date on or after the same cut-off date.
- **Week 24**: total daily dose is the sum of the Prednisone equivalent doses for all steroids that have a start date (included imputed date) prior to or on the cut-off date for treatment failure at Week 24 and have a stop date on or after the same cut-off date.
- **Week 48**: total daily dose is the sum of the Prednisone equivalent doses for all steroids that have a start date (included imputed date) prior to or on the cut-off date for treatment failure at Week 48 and have a stop date on or after the same cut-off date.
- **Week 40 to Week 48**: total daily dose is the average of Prednisone equivalent doses adjusted by their duration within the period of interest (Week 40 to Week 48) for all steroids that meet one of the following conditions. The start of the Week-40-to-Week-48 period is defined as the earliest of the dates of the BILAG-2004, SLEDAI-2K and PGA assessments that fall within the Week 40 visit window. The end of theWeek-40-to-Week-48 period is defined as the cut-off date for treatment failure at Week 48 (Section 17.5.1).
    - A start date (included imputed date) prior to or on the start of the Week-40-to-Week-48 period and have a stop date on or after the end of the Week-40-to-48-period; or
    - A start date (included imputed date) between the start of the Week-40-to-Week-48 period and the end of the Week-40-to-Week-48 period; or
    - A stop date (included imputed date) between the start of the Week-40–to-Week-48 period and the end of the Week-40-to-Week-48 period.

  For each steroid the daily dose (expressed as Prednisone equivalent dose) will be multiplied by the number of days within the period (week 40-48) that the subject was treated with steroid (end date of interest – start date of interest + 1) and divided by the number of days within the period (the end of the Week 40 to Week 48 period to the start of the Week 40 to Week 48 period + 1 day). The average daily doses by steroid will then be summed to get the total daily dose for each subject.

17.10 Medical Outcome Survey Short Form 36 (SF-36)

The SF-36 consists of 36 items that can be summarized into 8 domains: physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. Two summary measures, the physical component summary and the mental component summary, can be derived based on these domain scores.

The domain scores for the SF-36 questionnaire will be derived based on the responses collected for the 36 questions directly in the CRF. In order to derive SF-36 domain scores based on the questionnaire, the SF-36 v2 Scoring software will be used (the handling of missing data with regards to the derivation of the domain and component score will be performed by the software). The handling and the implementation of the derived scores into the datasets will be described in the Datasets Specification document.

The following options will be selected in the software to derive the domains scores.

Survey: SF-26 v2
Recall period: 4 weeks
T-Scores: 2009 US T-Scores
Benchmarks: None
Missing data Estimation (MDE) Method: Maximum data recovery
Additional Component Scores Using Alternative Method: No

17.11 28-Joint Count

Twenty-eight joints will be assessed separately for tenderness and swollenness (a score of 1 for a joint denotes a presence of tenderness or swollenness). The sum will be derived to create a total score (ranging from 0 to 28; where the highest score indicate all 28 joints are swollen/tender, respectively). If any joint assessment is missing, the LOCF imputation will be performed at a joint level.

17.12 CLASI Questionnaire

The CLASI will be performed in interested sites having experience in this assessment.

The CLASI consists of two scores, i.e., one for damage and one for activity:

- Activity is scored based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and nonscarring alopecia.
- Damage is score based on dyspigmentation and scarring, including scarring alopecia.

Subjects are asked whether dyspigmentation due to SLE lesions usually remains visible for more than 12 months, which is considered to be permanent and resulting in doubling of the dyspigmentation score. The scores are calculated by addition of the different sub-scores for clinical symptoms.

The CLASI is designed as a table where the rows represent anatomical areas and the columns represent major clinical symptoms. The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas taking into account the worst affected lesion within that area for each symptom.

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

Extent

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient)	
0- dyspigmentation usually lasts less than 12 months 1- dyspigmentation usually lasts at least 12 months	

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score		Total Damage Score	
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy,		(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation,	

17.13 SLICC Score

The SLICC damage score is derived by summing the individual score for each symptom/event present as described in the below scoring sheet.

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change *or* optic atrophy	1
Neuropsychiatric	
Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) *or* major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 if >1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria ≥3.5 gm/24 hours	1
or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina *or* coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur >3/6)	1
Pericarditis for 6 months, *or* pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if >1 site)	1 (2)
Venous thrombosis with swelling, ulceration, *or* venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if >1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture *or* upper gastrointestinal tract surgery ever	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if >1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1 (2)

17.14 Laboratory Parameters Precision Levels

Table 17-9 described the precision level to be applied to the laboratory parameters in the summary statistics. Only the laboratory tests to be summarized are included in the table.

Table 17-9: Laboratory Precision Levels

Laboratory Parameter	SI Unit	Precision (raw)	LLOQ	ULOQ
BIOCHEMISTRY				
Total Bilirubin	umol/mL	2	2.5	
Alkaline Phosphatase	U/L	0		
GGT	U/L	0		
AST	U/L	0		
ALT	U/L	0		
Lactate Dehydrogenase	U/L	0		
Creatine Phosphokinase	U/L	0		
Urea	mmol/L	2		
Total Protein	g/L	1		
Albumin	g/L	1		
Glucose	mmol/L	2		
Inorganic Phosphate	mmol/L	2		
Sodium	mmol/L	0		
Potassium	mmol/L	1		
Calcium	mmol/L	2		
Chloride	mmol/L	0		
LIPID PROFILE				
Total Cholesterol	mmol/L	2		
HDL-cholesterol	mmol/L	2		
LDL-cholesterol	mmol/L	2		
LDL/HDL-cholesterol ratio[d]	1	2		
Triglycerides	mmol/L	2		
HAEMATOLOGY				
Leukocytes (White Blood Cells)	10^9/L	1		
Erythrocytes (Red Blood Cells)	10^{12}/L	2		
Haemoglobin	g/L	0		
Haematocrit	%	1		
Thrombocytes (Platelets)	10^9/L	0		
Absolute Lymphocytes	10^9/L	1		
Absolute Monocytes	10^9/L	1		
Absolute Eosinophils	10^9/L	1		
Absolute Basophils	10^9/L	1		
Absolute Neutrophils	10^9/L	1		
Mean Corpuscular Volume (MCV)	fL	1		
Mean Corpuscular Haemoglobin (MCH)	pg	1		
Mean Corpuscular Haemoglobin Concentration (MCHC)	g/dL	1		
COAGULATION				
activated Partial Prothrombin Time (aPTT)	sec	1		
Prothrombin Time (PT)	sec	1		
INR [b]		2		
SEROLOGY				
ANA Titer	TITER	0	80	1280
β_2 Glycoprotein IgG	SGU U/mL	0	9	150
β_2 Glycoprotein IgM	SMU U/mL	0	9	150
aCL IgA	APL U/mL	0	9	150
aCL IgG	GPL U/mL	0	9	150
aCL IgM	MPL U/mL	0	9	150
LA [c]	sec	1		300

Laboratory Parameter	SI Unit	Precision (raw)	LLOQ	ULOQ
EFFICACY PARAMETERS				
Serum Creatinine	µmol/L	1		
eGFR [a]	mL/min/1.73 m²	1		
Proteinuria	g/mol	1		
EXPLORATORY BIOMARKERS				
uMCP-1	pg/mL	1	29.8	
uCr	pg/mol	1		
PD BIOMARKERS				
sIL-6R	mg/mL	2		
CRP	mg/L	1		
Fibrinogen	mg/dL	0		
anti-dsDNA [FARR]	IU/mL	1	1	
C3	mg/dL	0		
C4	mg/dL	0	6	
CH50	U	0		

[a] eGFR is derived based on the modification of the diet in renal disease (MDRD) formula, i.e. eGFR = 175 x (Serum creatinine [mg/dL])$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American).
[b] For subjects on vitamin K antagonist only.
[c] DRVVT: Dilute Russell Viper Venom Time.
[d] Derived from LDL and HDL-cholesterol.

17.15 Date Imputation (medications and AEs)

17.15.1 Adverse Events

Incomplete Start Date

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE if end date of AE is after the first dose date or the end date is also missing.

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Incomplete Stop Date

Missing day and month

- The missing day and month will be imputed as the 31st of December.

Missing day only

- The missing day will be assigned as the last day of the month.

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Partially missing AE start and end dates will be imputed in the derived dataset for AEs and will only be used to derived treatment emergent flag.

17.15.2 Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the derived dataset for prior/concomitant medications/procedures.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

If the start date is completely missing and end date is not prior to the first dose, then the medication will be classified as both prior and concomitant. If the start date is completely missing and the end date is prior to the first dose of study drug, then the medication will be classified as prior. Medications for which the start and end dates are missing will be classified as both prior and concomitant.

For the purpose of determining treatment failure, flare and deriving Prednisone Equivalent Doses the following additional imputation rules will be implemented in the following order before the above rules are derived. Those imputation rules are only for the medications recorded on the SLE medications eCRF page.

- If the start date and the stop date of a medication are identical and only month/year are known, the start date will be imputed as the first of the month and the stop date will be imputed as the last day of the month.

If, for a patient, the stop date of a medication is partial (only month and year known) and in the same month there is a partial start date for a different medication (or dose) coded to the same preferred term, the stop date is imputed as the 14th of the month and the start date is imputed to the 15th of the month (so the medications do not overlap).

17.16 Analysis Visit / Visit Window

Table 17-10 provides the study day ranges to be applied to the assessment/sample collection date to derive the analysis visits. The following considerations are to be followed when deriving the analysis visits.

- All visits including unscheduled visits are used to determine the analysis visits.
- For BILAG-2004, the visit mapping will be based on the date of assessments.
- For immunogenicity, Screening and Baseline assessments will be reported separately. The CRF visit label will be used to classify the assessments.
- If there are multiple results within the same visit windows, the non-missing assessment/sample closest to the planned study day will be selected for analysis. In case of ties on the same day with time not available, the assessment linked with the CRF visit will be selected for analysis.

Table 17-10:Visit Windows (Post-Baseline)

Analysis Visit	Planned Day	Efficacy	Systolic/Diastolic Blood Pressure, Temperature	PK	Central laboratory	Direct Coombs, Urinalysis, Immunogenicity, PD	Other Safety Parameters
Week 2	15		[8; 22]	[10;20]	[8; 22]		[8; 22]
Week 4	29	[16; 43]	[23; 36]	[24;34]	[23; 43]	[16; 43]	[23; 36]
Week 6	43		[37; 50]	[38; 48]			[37; 50]
Week 8	57	[44; 71]	[51; 64]	[52; 62]	[44; 71]	[44; 71]	[51; 64]
Week 10	71		[65; 78]	[66; 76]			[65; 78]
Week 12	85	[72; 99]	[79; 99]	[80; 90]	[72; 99]	[72; 99]	[79; 99]
Week 16	113	[100; 127]	[100; 127]	[108; 118]	[100; 127]	[100; 127]	[100; 127]
Week 20	141	[128; 155]	[128; 155]	[136; 146]	[128; 155]	[128; 155]	[128; 155]
Week 24	169	[156; 183]	[156; 183]	[164; 174]	[156; 183]	[156; 183]	[156; 183]
Week 28	197	[184; 211]	[184; 211]	[192; 202]	[184; 211]	[184; 211]	[184; 211]
Week 32	225	[212; 239]	[212; 239]	[220; 230]	[212; 239]	[212; 239]	[212; 239]
Week 36	253	[240; 267]	[240; 267]	[248; 258]	[240; 267]	[240; 267]	[240; 267]
Week 40	281	[268; 295]	[268; 295]	[276; 286]	[268; 295]	[268; 295]	[268; 295]
Week 44	309	[296; 323]	[296; 323]	[304; 314]	[296; 323]	[296; 323]	[296; 323]
Week 48	337	[324; 351]	[324; 351]	[332; 342]	[324; 351]	[324; 351]	[324; 351]
Follow-up	85*		[26; 106]		[26; 106]	[26; 106]	[26; 106]

Notes:

- For Week 2 to Week 48, Study day is calculated from the day of the first dose of study drug administration (Day 1 is the day of first administration). For Week 2 to Week 48, if the assessment /sample date is less than or equal to 25 days after the last dose of treatment, the assessment will be mapped to the corresponding analysis visit.
  For Week 2 to Week 48, if the assessment/sample date is more than 25 days after the last dose of treatment, the assessment will be mapped to Follow-up visit.
- Early Termination visit will be flagged in listings, by adding a symbol after the Visit Name in the Analysis Visit column and associated footnote will be added.
- * For Follow-up, the study day is based on the date of last dose (Day 1 is the day after last administration).
- For PK sampling, the samples need to be taken prior to the study drug injection.

17.17 Example of R code (MCP-Mod):

```
# load add-on package DoseFinding for MCP-Mod functionalities
library(DoseFinding)
# define doses to be used in models
doses <- c(0, 37.5, 75, 150, 225)

# calculate guesstimates for model parameters of set of 5 candidate models
nmodels <- 5
ndoses <- length(doses)
betascaling <- 1.2
emax1 <- guesst(d=75,p=0.8,model="emax")
logistic1 <- guesst(d=c(37.5,150),p=c(0.1,0.9),model="logistic")
beta1 <- guesst(d=c(75,150), p=c(0.9,0.7), scal=betascaling*225, dMax=37.5,
Maxd=225, model="betaMod")
beta2 <- guesst(d=c(37.5,75), p=c(0.4,0.7), scal=betascaling*225, dMax=150,
Maxd=225, model="betaMod")

# create "Mods" class object of the set of candidate models
models <- Mods(linear=NULL, emax=emax1, logistic=logistic1,
betaMod=rbind(beta1,beta2), addArgs=list(scal=betascaling*doses[ndoses]),
doses=doses, placEff=25, maxEff=25, direction="increasing")

# plot the models
plot(models)

# example mBICLA response proportion for different groups
rrObs <- c(0.2,0.316667,0.55,0.433333,0.3833333)
# logistic regression (on logit scale) without intercept to obtain covariance matrix
logfit <- glm(rrObs~as.factor(doses)-1, family=binomial, weights=rep(60,5))
# optimum contrast
contMat <- optContr(models, w=1)
muHat <- coef(logfit)
S <- vcov(logfit)

# multiple contrast test from the optimal trend contrasts
mcpModTest <- MCTtest(doses, rrObs, S=S, models=models, type="general")

# t-statistics with adjusted p-values
mcpModTest$tStat

# Calculate the functions for the candidate models using pre-specified parameters
gfit <- MCPMod(doses, rrObs, S=S, models=models, type = "general", Delta = 0.2,
selModel = “aveAIC”)

# create a sequence of dose values used to predict the response for a range of dose
values
sq <- seq(0,max(doses),length=11)

# get predicted values for this sequence of doses
pred <- predict(gfit, doseSeq=sq, predType="ls-means")
```

```
# pull out weights from model object
modWeights <- gfit$selMod

# model averaged predictions - this is just matrix multiplication of predicted values
from each significant candidate model multiplied by weights
pred <- do.call("cbind", pred)%*%modWeights
```

17.18 Search criteria for adverse events of special interest

Search criteria for AESIs are either MedDRA PT clusters or SMQs. The SMQs and the individual PTs for the PT clusters are provided below.

Infections

Abdominal abscess
Abdominal hernia gangrenous
Abdominal infection
Abdominal lymphadenopathy
Abdominal sepsis
Abdominal wall abscess
Abdominal wall infection
Abortion infected
Abscess
Abscess bacterial
Abscess fungal
Abscess intestinal
Abscess jaw
Abscess limb
Abscess neck
Abscess of external auditory meatus
Abscess of eyelid
Abscess of salivary gland
Abscess oral
Abscess rupture
Abscess soft tissue
Abscess sweat gland
Acanthamoeba infection
Acanthamoeba keratitis
Acariasis
Acarodermatitis
Acid fast bacilli infection
Acinetobacter bacteraemia
Acinetobacter infection
Acinetobacter test positive
Acne pustular
Acquired immunodeficiency syndrome
Acrodermatitis chronica atrophicans
Actinomyces test positive
Actinomycosis
Actinomycotic abdominal infection
Actinomycotic pulmonary infection
Actinomycotic skin infection
Acute endocarditis
Acute focal bacterial nephritis
Acute haemorrhagic conjunctivitis
Acute hepatitis B
Acute hepatitis C
Acute HIV infection
Acute pulmonary histoplasmosis
Acute sinusitis
Acute tonsillitis
Adenoiditis
Adenopathy syphilitic
Adenoviral conjunctivitis
Adenoviral haemorrhagic cystitis
Adenoviral hepatitis
Adenoviral upper respiratory infection
Adenovirus infection
Adenovirus test
Adenovirus test positive
Adiponectin increased
Administration site abscess
Administration site cellulitis
Administration site infection
Adrenal gland abscess
Adrenal gland tuberculosis
Adrenalitis
Aeromona infection
Aeromonas test positive
African trypanosomiasis
AIDS cholangiopathy
AIDS dementia complex
AIDS related complex
AIDS related complication
AIDS retinopathy
Air-borne transmission
Alcaligenes infection
Allescheriosis
Alopecia syphilitic
Alpha haemolytic streptococcal infection
Alphaviral infection
Alphavirus test
Alphavirus test positive
Alternaria infection
Alveolar osteitis
American trypanosomiasis
Amniotic cavity infection
Amniotic infection syndrome of Blane
Amoeba test
Amoeba test positive
Amoebiasis
Amoebic brain abscess
Amoebic colitis
Amoebic dysentery
Amoebic lung abscess
Amoebic skin ulcer
Anal abscess
Anal candidiasis
Anal chlamydia infection
Anal fistula infection

Anal fungal infection
Anal infection
Anal tinea
Angina gangrenous
Angiostrongylus infection
Anicteric leptospirosis
Anisakiasis
Anogenital warts
Anorectal cellulitis
Anorectal human papilloma virus infection
Anorectal infection
Anorectal infection bacterial
Anthrax
Anthrax sepsis
Antifungal treatment
Antimicrobial susceptibility test
Antimicrobial susceptibility test intermediate
Antimicrobial susceptibility test resistant
Antimicrobial susceptibility test sensitive
Aortic aneurysm syphilitic
Aortitis salmonella
Aortitis syphilitic
Aphthovirus test positive
Apical granuloma
Appendiceal abscess
Appendicitis
Appendicitis perforated
Application site abscess
Application site cellulitis
Application site folliculitis
Application site infection
Application site pustules
Arachnoiditis
Arboviral infection
Arbovirus test positive
Arenaviral haemorrhagic fever
Arenavirus test positive
Argentine haemorrhagic fever
Arteriosclerotic gangrene
Arteriovenous fistula site infection
Arteriovenous graft site abscess
Arteriovenous graft site infection
Arteritis infective
Arthritis bacterial
Arthritis fungal
Arthritis gonococcal
Arthritis helminthic
Arthritis infective
Arthritis reactive
Arthritis rubella
Arthritis salmonella
Arthritis viral
Arthropod infestation
Arthropod-borne disease
Ascariasis
Aspergilloma
Aspergillosis oral
Aspergillus infection
Aspergillus test
Aspergillus test positive
Astrovirus test positive
Asymptomatic bacteriuria
Asymptomatic HIV infection
Asymptomatic viral hepatitis
Atypical mycobacterial infection
Atypical mycobacterial lower respiratory tract infection
Atypical mycobacterial lymphadenitis
Atypical mycobacterial pneumonia
Atypical mycobacterium pericarditis
Atypical mycobacterium test positive
Atypical pneumonia
Avian influenza
Babesiosis
Bacillary angiomatosis
Bacillus bacteraemia
Bacillus infection
Bacillus test positive
Bacteraemia
Bacterascites
Bacterial abscess central nervous system
Bacterial allergy
Bacterial dacryocystitis
Bacterial diarrhoea
Bacterial disease carrier
Bacterial food poisoning
Bacterial infection
Bacterial iritis
Bacterial labyrinthitis
Bacterial pericarditis
Bacterial prostatitis
Bacterial pyelonephritis
Bacterial rhinitis
Bacterial sepsis
Bacterial test
Bacterial test positive
Bacterial toxaemia
Bacterial tracheitis
Bacterial translocation
Bacterial vaginosis
Bacteriuria
Bacteriuria in pregnancy
Bacteroides bacteraemia
Bacteroides infection
Bacteroides test positive
Balamuthia infection
Balanitis candida
Balanoposthitis
Balanoposthitis infective
Balantidiasis
Bartholin's abscess
Bartonella test positive
Bartonellosis

Bed bug infestation
Beta haemolytic streptococcal infection
Bifidobacterium infection
Bifidobacterium test positive
Bile culture
Bile culture positive
Biliary abscess
Biliary sepsis
Biliary tract infection
Biliary tract infection bacterial
Biliary tract infection cryptosporidial
Biliary tract infection fungal
Biliary tract infection helminthic
Biliary tract infection viral
BK virus infection
Black piedra
Bladder candidiasis
Bladder diverticulitis
Blastocystis infection
Blastomycosis
Blebitis
Blepharitis
Blister infected
Blood bactericidal activity
Blood beta-D-glucan abnormal
Blood beta-D-glucan decreased
Blood beta-D-glucan increased
Blood culture
Blood culture positive
Blood HIV RNA
Blood HIV RNA below assay limit
Blood HIV RNA decreased
Blood HIV RNA increased
Body tinea
Bolivian haemorrhagic fever
Bone abscess
Bone tuberculosis
Borderline leprosy
Bordetella infection
Bordetella test
Bordetella test positive
Borrelia infection
Borrelia test
Borrelia test positive
Botryomycosis
Botulism
Boutonneuse fever
Bovine pustular stomatitis virus infection
Bovine tuberculosis
Brain abscess
Brain empyema
Breast abscess
Breast cellulitis
Breast discharge infected
Bronchiectasis
Bronchiolitis
Bronchitis
Bronchitis bacterial
Bronchitis fungal
Bronchitis haemophilus
Bronchitis moraxella
Bronchitis pneumococcal
Bronchitis viral
Bronchoalveolar lavage abnormal
Bronchopneumonia
Bronchopulmonary aspergillosis
Bronchopulmonary aspergillosis allergic
Bronchoscopy abnormal
Brucella sepsis
Brucella test
Brucella test positive
Brucellosis
Bubonic plague
Bulbar poliomyelitis
Bullous impetigo
Burkholderia cepacia complex infection
Burkholderia cepacia complex sepsis
Burkholderia gladioli infection
Burkholderia infection
Burkholderia mallei infection
Burkholderia pseudomallei infection
Burkholderia test positive
Burn infection
Bursitis infective
Bursitis infective staphylococcal
Calicivirus test positive
Campylobacter gastroenteritis
Campylobacter infection
Campylobacter sepsis
Campylobacter test positive
Candida cervicitis
Candida endophthalmitis
Candida infection
Candida nappy rash
Candida osteomyelitis
Candida pneumonia
Candida retinitis
Candida sepsis
Candida test
Candida test positive
Candiduria
Capillariasis
Capillaritis
Capnocytophaga infection
Capnocytophaga test positive
Carbuncle
Cardiac granuloma
Cardiac infection
Cardiac valve abscess
Cardiac valve vegetation
Cardiovascular syphilis
Carditis
Cat scratch disease
Catheter culture
Catheter culture positive
Catheter site abscess

Catheter site cellulitis
Catheter site infection
Catheter site pustule
Catheter site warmth
Cavernous sinus thrombosis
Cellulitis
Cellulitis enterococcal
Cellulitis gangrenous
Cellulitis laryngeal
Cellulitis of male external genital organ
Cellulitis orbital
Cellulitis pasteurella
Cellulitis pharyngeal
Cellulitis staphylococcal
Cellulitis streptococcal
Central nervous system abscess
Central nervous system enteroviral infection
Central nervous system fungal infection
Central nervous system infection
Central nervous system inflammation
Central nervous system viral infection
Cerebral aneurysm ruptured syphilitic
Cerebral aspergillosis
Cerebral fungal infection
Cerebral malaria
Cerebral sarcoidosis
Cerebral septic infarct
Cerebral toxoplasmosis
Cervicitis
Cervicitis gonococcal
Cervicitis human papilloma virus
Cervicitis mycoplasmal
Cervicitis streptococcal
Cervicitis trichomonal
Cervix warts
Cestode infection
Chancroid
Chest wall abscess
Chikungunya virus infection
Chlamydia test
Chlamydia test positive
Chlamydial cervicitis
Chlamydial infection
Chlamydial pelvic inflammatory disease
Cholangitis infective
Cholecystitis infective
Cholera
Cholesteatoma
Cholesterol granuloma
Choriomeningitis lymphocytic
Chorioretinitis
Choroid tubercles
Choroiditis
Chromoblastomycosis
Chronic gastritis
Chronic hepatitis
Chronic hepatitis B
Chronic hepatitis C
Chronic pulmonary histoplasmosis
Chronic recurrent multifocal osteomyelitis
Chronic sinusitis
Chronic tonsillitis
Citrobacter infection
Citrobacter sepsis
Citrobacter test positive
Clitoris abscess
Clonorchiasis
Clostridial infection
Clostridium bacteraemia
Clostridium colitis
Clostridium difficile colitis
Clostridium difficile infection
Clostridium difficile sepsis
Clostridium test
Clostridium test positive
CNS ventriculitis
Coccidioides encephalitis
Coccidioidomycosis
Colitis herpes
Colon gangrene
Colonic abscess
Colorado tick fever
Colorado tick fever virus test positive
Colostomy infection
Community acquired infection
Condyloma latum
Congenital condyloma
Congenital cytomegalovirus infection
Congenital hepatitis B infection
Congenital herpes simplex infection
Congenital HIV infection
Congenital infection
Congenital malaria
Congenital pneumonia
Congenital rubella infection
Congenital syphilis
Congenital syphilitic encephalitis
Congenital syphilitic meningitis
Congenital syphilitic osteochondritis
Congenital toxoplasmosis
Congenital tuberculosis
Congenital varicella infection
Congo-Crimean haemorrhagic fever
Conjunctivitis
Conjunctivitis bacterial
Conjunctivitis chlamydial
Conjunctivitis gonococcal neonatal
Conjunctivitis tuberculous
Conjunctivitis viral
Corneal abscess
Corneal endotheliitis
Corneal infection
Corona virus infection
Coronavirus test positive

Corynebacterium infection
Corynebacterium sepsis
Corynebacterium test
Corynebacterium test positive
Cow pox
Coxiella infection
Coxiella test positive
Coxsackie carditis
Coxsackie endocarditis
Coxsackie myocarditis
Coxsackie pericarditis
Coxsackie viral disease of the newborn
Coxsackie viral infection
Coxsackie virus test
Coxsackie virus test positive
Cranial nerve infection
Creutzfeldt-Jakob disease
Cronobacter bacteraemia
Cronobacter infection
Cronobacter necrotising enterocolitis
Cronobacter test positive
Cross infection
Croup infectious
Cryptococcal cutaneous infection
Cryptococcal fungaemia
Cryptococcosis
Cryptococcus test
Cryptococcus test positive
Cryptosporidiosis infection
CSF culture
CSF culture positive
CSF immunoglobulin G index
CSF leukocyte/erythrocyte ratio
CSF leukocyte/erythrocyte ratio increased
CSF measles antibody positive
CSF virus identified
CSF virus no organisms observed
Culture
Culture cervix
Culture cervix positive
Culture positive
Culture stool
Culture stool positive
Culture throat
Culture throat positive
Culture tissue specimen
Culture tissue specimen positive
Culture urine
Culture urine positive
Culture wound
Culture wound positive
Cutaneous anthrax
Cutaneous coccidioidomycosis
Cutaneous larva migrans
Cutaneous leishmaniasis
Cutaneous sporotrichosis
Cutaneous tuberculosis
Cyclitis
Cyclosporidium infection
Cystitis
Cystitis bacterial
Cystitis erosive
Cystitis escherichia
Cystitis glandularis
Cystitis gonococcal
Cystitis haemorrhagic
Cystitis helminthic
Cystitis interstitial
Cystitis klebsiella
Cystitis noninfective
Cystitis pseudomonal
Cystitis radiation
Cystitis ulcerative
Cystitis viral
Cytomegalovirus chorioretinitis
Cytomegalovirus colitis
Cytomegalovirus duodenitis
Cytomegalovirus enteritis
Cytomegalovirus enterocolitis
Cytomegalovirus gastritis
Cytomegalovirus gastroenteritis
Cytomegalovirus gastrointestinal infection
Cytomegalovirus hepatitis
Cytomegalovirus infection
Cytomegalovirus mononucleosis
Cytomegalovirus mucocutaneous ulcer
Cytomegalovirus myelomeningoradiculitis
Cytomegalovirus myocarditis
Cytomegalovirus oesophagitis
Cytomegalovirus pancreatitis
Cytomegalovirus pericarditis
Cytomegalovirus syndrome
Cytomegalovirus test
Cytomegalovirus test positive
Cytomegalovirus urinary tract infection
Cytomegalovirus viraemia
Dacryoadenitis acquired
Dacryocanaliculitis
Dacryocystitis
Deltaretrovirus test positive
Demodicidosis
Dengue fever
Dental caries
Dental fistula
Dental gangrene

Dermatitis infected
Dermatomyositis
Dermatophytosis
Dermo-hypodermitis
Device related infection
Device related sepsis
Diabetic foot infection
Diabetic gangrene
Diaphragmatic hernia gangrenous
Diarrhoea infectious
Diarrhoea infectious neonatal
Diphtheria
Diphtheria carrier
Diphyllobothriasis
Direct infection transmission
Disseminated cryptococcosis
Disseminated cytomegaloviral infection
Disseminated tuberculosis
Diverticulitis
Douglas' abscess
Dracunculiasis
Dural abscess
Dysentery
Ear infection
Ear infection bacterial
Ear infection fungal
Ear infection staphylococcal
Ear infection viral
Ear lobe infection
Ear tuberculosis
Ebola disease
Ebola Reston virus infection
Ebola virus test positive
Echinococciasis
Echo virus infection
Echovirus test
Echovirus test positive
Ecthyma
Eczema herpeticum
Eczema impetiginous
Eczema infected
Eczema vaccinatum
Ehrlichia test
Ehrlichia test positive
Elephantiasis nostras verrucosa
Embolic pneumonia
Empedobacter brevis infection
Empedobacter test positive
Emphysematous cholecystitis
Emphysematous cystitis
Emphysematous pyelonephritis
Empyema
Encephalitis
Encephalitis allergic
Encephalitis australia
Encephalitis brain stem
Encephalitis california
Encephalitis cytomegalovirus
Encephalitis eastern equine
Encephalitis enteroviral
Encephalitis fungal
Encephalitis haemorrhagic
Encephalitis influenzal
Encephalitis Japanese B
Encephalitis lethargica
Encephalitis meningococcal
Encephalitis mumps
Encephalitis post immunisation
Encephalitis post measles
Encephalitis post varicella
Encephalitis protozoal
Encephalitis rickettsial
Encephalitis toxic
Encephalitis venezuelan equine
Encephalitis viral
Encephalitis western equine
Encephalomyelitis
Encephalomyelitis rubella
End stage AIDS
Endemic syphilis
Endocarditis
Endocarditis bacterial
Endocarditis candida
Endocarditis enterococcal
Endocarditis gonococcal
Endocarditis haemophilus
Endocarditis helminthic
Endocarditis histoplasma
Endocarditis meningococcal
Endocarditis pseudomonal
Endocarditis Q fever
Endocarditis rheumatic
Endocarditis staphylococcal
Endocarditis syphilitic
Endocarditis viral
Endometritis
Endometritis bacterial
Endometritis decidual
Endometritis gonococcal
Endophthalmitis
Endotoxaemia
Endotoxic shock
Enteritis infectious
Enteritis necroticans
Enterobacter bacteraemia
Enterobacter infection
Enterobacter pneumonia
Enterobacter sepsis
Enterobacter test positive
Enterobacter tracheobronchitis
Enterobiasis
Enterococcal bacteraemia
Enterococcal infection
Enterococcal sepsis
Enterococcus test positive
Enterocolitis AIDS
Enterocolitis bacterial
Enterocolitis fungal

Enterocolitis helminthic
Enterocolitis infectious
Enterocolitis viral
Enterovirus infection
Enterovirus test
Enterovirus test positive
Eosinophilia myalgia syndrome
Eosinophilic cystitis
Ependymitis
Epidemic pleurodynia
Epidemic polyarthritis
Epidemic typhus
Epidermodysplasia verruciformis
Epididymitis
Epididymitis blastomyces
Epididymitis mumps
Epididymitis tuberculous
Epididymitis ureaplasmal
Epididymo-orchitis gonococcal
Epiglottitis
Epiglottitis haemophilus
Epiglottitis obstructive
Epstein-Barr viraemia
Epstein-Barr virus antibody
Epstein-Barr virus antibody positive
Epstein-Barr virus antigen positive
Epstein-Barr virus associated lymphoma
Epstein-Barr virus associated lymphoproliferative disorder
Epstein-Barr virus infection
Epstein-Barr virus test
Epstein-Barr virus test positive
Erosive balanitis
Eruptive pseudoangiomatosis
Erysipelas
Erysipeloid
Erysipelothrix infection
Erysipelothrix test positive
Erythema induratum
Erythema infectiosum
Erythema migrans
Erythrasma
Escherichia bacteraemia
Escherichia infection
Escherichia pyelonephritis
Escherichia sepsis
Escherichia test positive
Escherichia urinary tract infection
Escherichia vaginitis
Eubacterium infection
Exanthema subitum
Exserohilum infection
External ear cellulitis
Extradural abscess
Extrapulmonary tuberculosis
Eye abscess
Eye infection
Eye infection bacterial
Eye infection chlamydial
Eye infection fungal
Eye infection gonococcal
Eye infection helminthic
Eye infection intraocular
Eye infection staphylococcal
Eye infection syphilitic
Eye infection toxoplasmal
Eye infection viral
Eyelid boil
Eyelid folliculitis
Eyelid infection
Faecal-oral transmission of infection
Fallopian tube abscess
Fascial infection
Fascioliasis
Fasciolopsiasis
Febrile infection
Female genital tract tuberculosis
Femoral hernia
gangrenous
Filariasis
Filariasis lymphatic
Filovirus infection
Filovirus test positive
Flavivirus infection
Flavivirus test positive
Flavobacterium infection
Flavobacterium test positive
Flea infestation
Folliculitis
Foot and mouth disease
Francisella test positive
Fungaemia
Fungal abscess central nervous system
Fungal cystitis
Fungal endocarditis
Fungal infection
Fungal labyrinthitis
Fungal oesophagitis
Fungal paronychia
Fungal peritonitis
Fungal retinitis
Fungal rhinitis
Fungal sepsis
Fungal skin infection
Fungal test
Fungal test positive
Fungal tracheitis
Fungating wound
Funisitis
Furuncle
Fusarium infection
Fusobacterium infection
Fusobacterium test positive
Gallbladder abscess
Gallbladder empyema
Gangrene
Gangrene neonatal
Gangrenous balanitis
Gardnerella infection
Gardnerella test positive

Gas gangrene
Gastric infection
Gastric ulcer helicobacter
Gastritis bacterial
Gastritis fungal
Gastritis helminthic
Gastritis herpes
Gastritis viral
Gastroenteritis
Gastroenteritis adenovirus
Gastroenteritis aerobacter
Gastroenteritis aeromonas
Gastroenteritis astroviral
Gastroenteritis bacillus
Gastroenteritis bacterial
Gastroenteritis caliciviral
Gastroenteritis clostridial
Gastroenteritis cryptococcal
Gastroenteritis cryptosporidial
Gastroenteritis enteroviral
Gastroenteritis Escherichia coli
Gastroenteritis norovirus
Gastroenteritis paracolon bacillus
Gastroenteritis proteus
Gastroenteritis pseudomonas
Gastroenteritis rotavirus
Gastroenteritis salmonella
Gastroenteritis sapovirus
Gastroenteritis shigella
Gastroenteritis staphylococcal
Gastroenteritis vibrio
Gastroenteritis viral
Gastroenteritis yersinia
Gastrointestinal anthrax
Gastrointestinal bacterial infection
Gastrointestinal candidiasis
Gastrointestinal fungal infection
Gastrointestinal gangrene
Gastrointestinal infection
Gastrointestinal mucosal necrosis
Gastrointestinal necrosis
Gastrointestinal protozoal infection
Gastrointestinal viral infection
Generalised vaccinia
Genital abscess
Genital candidiasis
Genital herpes
Genital herpes simplex
Genital herpes zoster
Genital infection
Genital infection bacterial
Genital infection female
Genital infection fungal
Genital infection helminthic
Genital infection male
Genital infection viral
Genital tract inflammation
Genitourinary chlamydia infection
Genitourinary tract gonococcal infection
Genitourinary tract infection
Genotype drug resistance test
Genotype drug resistance test abnormal
Genotype drug resistance test positive
Geotrichum infection
Gerstmann Straussler Scheinker syndrome
Gianotti-Crosti syndrome
Giardia test
Giardia test positive
Giardiasis
Gingival abscess
Gingivitis
Gliosis
Gnathostomiasis
Gonococcal pelvic inflammatory disease
Gonorrhoea
Gradenigo's syndrome
Graft infection
Gram stain
Gram stain positive
Granuloma inguinale
Granulomatous dermatitis
Granulomatous liver disease
Granulomatous pneumonitis
Groin abscess
Groin infection
Group B streptococcus neonatal sepsis
Guillain-Barre syndrome
Gynaecological chlamydia infection
H1N1 influenza
Haematoma infection
Haemophilus bacteraemia
Haemophilus infection
Haemophilus sepsis
Haemophilus test positive
Haemorrhagic fever
Haemorrhagic fever with renal syndrome
Haemorrhoid infection
Hand-foot-and-mouth disease
Hantaviral infection
Hantavirus pulmonary infection
Hantavirus test positive

HBV-DNA polymerase increased
Helicobacter gastritis
Helicobacter infection
Helicobacter sepsis
Helicobacter test
Helicobacter test positive
Helminthic infection
Henipavirus test positive
Hepatic amoebiasis
Hepatic candidiasis
Hepatic cyst infection
Hepatic echinococciasis
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatic infiltration eosinophilic
Hepatic necrosis
Hepatitis
Hepatitis A
Hepatitis A antibody
Hepatitis A antibody abnormal
Hepatitis A antibody positive
Hepatitis A antigen positive
Hepatitis A virus test
Hepatitis A virus test positive
Hepatitis acute
Hepatitis B
Hepatitis B antibody
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B antigen
Hepatitis B antigen positive
Hepatitis B core antibody
Hepatitis B core antibody positive
Hepatitis B core antigen
Hepatitis B core antigen positive
Hepatitis B DNA assay
Hepatitis B DNA assay positive
Hepatitis B DNA decreased
Hepatitis B DNA increased
Hepatitis B e antibody
Hepatitis B e antibody positive
Hepatitis B e antigen
Hepatitis B e antigen positive
Hepatitis B surface antibody
Hepatitis B surface antibody positive
Hepatitis B surface antigen
Hepatitis B surface antigen positive
Hepatitis B virus test
Hepatitis B virus test positive
Hepatitis C
Hepatitis C antibody
Hepatitis C antibody positive
Hepatitis C RNA
Hepatitis C RNA decreased
Hepatitis C RNA fluctuation
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C virus test
Hepatitis C virus test positive
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis D
Hepatitis D antibody
Hepatitis D antibody positive
Hepatitis D antigen
Hepatitis D antigen positive
Hepatitis D RNA
Hepatitis D RNA positive
Hepatitis D virus test
Hepatitis D virus test positive
Hepatitis E
Hepatitis E antibody
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen
Hepatitis E antigen positive
Hepatitis E virus test positive
Hepatitis F
Hepatitis fulminant
Hepatitis G
Hepatitis H
Hepatitis infectious
Hepatitis infectious mononucleosis
Hepatitis mumps
Hepatitis neonatal
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis post transfusion
Hepatitis syphilitic
Hepatitis toxoplasmal
Hepatitis viral
Hepatitis viral test
Hepatitis viral test positive
Hepatitis virus-associated nephropathy
Hepatobiliary infection
Hepatosplenic candidiasis
Hernia gangrenous
Herpangina
Herpes dermatitis
Herpes oesophagitis
Herpes ophthalmic
Herpes pharyngitis
Herpes sepsis
Herpes simplex
Herpes simplex colitis

Herpes simplex DNA test positive
Herpes simplex encephalitis
Herpes simplex gastritis
Herpes simplex hepatitis
Herpes simplex meningitis
Herpes simplex meningoencephalitis
Herpes simplex meningomyelitis
Herpes simplex necrotising retinopathy
Herpes simplex oesophagitis
Herpes simplex otitis externa
Herpes simplex pharyngitis
Herpes simplex pneumonia
Herpes simplex sepsis
Herpes simplex serology
Herpes simplex serology positive
Herpes simplex virus conjunctivitis neonatal
Herpes simplex visceral
Herpes virus infection
Herpes zoster
Herpes zoster cutaneous disseminated
Herpes zoster disseminated
Herpes zoster infection neurological
Herpes zoster meningitis
Herpes zoster meningoencephalitis
Herpes zoster meningomyelitis
Herpes zoster necrotising retinopathy
Herpes zoster oticus
Herpes zoster pharyngitis
Heterophyiasis
Hirudiniasis
Histiocytic necrotising lymphadenitis
Histoplasmosis
Histoplasmosis cutaneous
Histoplasmosis disseminated
HIV antibody
HIV antibody positive
HIV antigen
HIV antigen positive
HIV associated nephropathy
HIV cardiomyopathy
HIV carrier
HIV enteropathy
HIV infection
HIV infection CDC category A
HIV infection CDC category B
HIV infection CDC category C
HIV infection CDC Group I
HIV infection CDC Group II
HIV infection CDC Group III
HIV infection CDC group IV
HIV infection CDC Group IV subgroup A
HIV infection CDC Group IV subgroup B
HIV infection CDC Group IV subgroup C1
HIV infection CDC Group IV subgroup C2
HIV infection CDC Group IV subgroup D
HIV infection CDC Group IV subgroup E
HIV infection WHO clinical stage I
HIV infection WHO clinical stage II
HIV infection WHO clinical stage III
HIV infection WHO clinical stage IV
HIV peripheral neuropathy
HIV test
HIV test positive
HIV tropism test
HIV wasting syndrome
Hookworm infection
Hordeolum
HTLV test positive
HTLV-1 carrier
HTLV-1 test positive
HTLV-2 test positive
Human anaplasmosis
Human ehrlichiosis
Human herpes virus 6 serology
Human herpes virus 6 serology positive
Human herpes virus 8 test positive
Human herpesvirus 6 infection
Human herpesvirus 7 infection
Human herpesvirus 8 infection
Human immunodeficiency virus transmission
Human papilloma virus test
Human papilloma virus test positive
Human polyomavirus infection
Human rhinovirus test positive
Human T-cell lymphocytic virus type II infection
Human T-cell lymphotropic virus infection
Human T-cell lymphotropic virus type I infection
Hydrocele male
infected
Hymenolepiasis
Hypopyon

Iatrogenic infection
Ileal gangrene
Immune reconstitution inflammatory syndrome associated tuberculosis
Impetigo
Implant site abscess
Implant site cellulitis
Implant site infection
Implant site pustules
Incision site abscess
Incision site cellulitis
Incision site infection
Incisional hernia gangrenous
Inclusion body myositis
Inclusion conjunctivitis
Inclusion conjunctivitis neonatal
Indeterminate leprosy
Indirect infection transmission
Induced abortion infection
Infantile septic granulomatosis
Infected bites
Infected bunion
Infected cyst
Infected dermal cyst
Infected fistula
Infected lymphocele
Infected naevus
Infected neoplasm
Infected seroma
Infected skin ulcer
Infected varicose vein
Infection
Infection in an immunocompromised host
Infection masked
Infection parasitic
Infection protozoal
Infection reactivation
Infection susceptibility increased
Infection transmission via personal contact
Infection via vaccinee
Infectious colitis
Infectious crystalline keratopathy
Infectious disease carrier
Infectious iridocyclitis
Infectious mononucleosis
Infectious pleural effusion
Infectious thyroiditis
Infective aneurysm
Infective aortitis
Infective chondritis
Infective corneal ulcer
Infective episcleritis
Infective exacerbation of bronchiectasis
Infective exacerbation of chronic obstructive airways disease
Infective gastroduodenitis
Infective glossitis
Infective iritis
Infective mesenteric panniculitis
Infective myositis
Infective periostitis
Infective pulmonary exacerbation of cystic fibrosis
Infective spondylitis
Infective tenosynovitis
Infective thrombosis
Infective uveitis
Infestation
Influenza
Influenza A virus test
Influenza A virus test positive
Influenza B virus test
Influenza B virus test positive
Influenza C virus test positive
Influenza virus test
Influenza virus test positive
Infusion site abscess
Infusion site cellulitis
Infusion site infection
Infusion site pustule
Inguinal hernia gangrenous
Injection site abscess
Injection site cellulitis
Injection site infection
Injection site joint infection
Injection site pustule
Instillation site abscess
Instillation site infection
Instillation site pustules
Intervertebral discitis
Intestinal fistula infection
Intestinal gangrene
Intestinal tuberculosis
Intrauterine infection
Iridocyclitis
Iritis
Isosporiasis
Japanese spotted fever
JC virus granule cell neuronopathy
JC virus infection
JC virus test
JC virus test positive
Jejunal gangrene
Joint abscess
Joint tuberculosis
Kaposi's sarcoma AIDS related
Kaposi's varicelliform eruption
Kawasaki's disease
Keratitis
Keratitis bacterial
Keratitis fungal
Keratitis interstitial
Keratitis viral
Keratoconjunctivitis measles
Keratosis gonococcal
Kerion
Kidney infection
Klebsiella bacteraemia
Klebsiella infection
Klebsiella sepsis
Klebsiella test positive
Kuru
Kyasanur Forest disease

Labyrinthitis
Lacrimal sac cellulitis
Lactobacillus infection
Lactobacillus test positive
Laryngitis
Laryngitis bacterial
Laryngitis fungal
Laryngitis viral
Laryngotracheitis obstructive
Lassa fever
Latent syphilis
Latent tuberculosis
Legionella infection
Legionella test
Legionella test positive
Leishmaniasis
Lemierre syndrome
Lentivirus test positive
Lepromatous leprosy
Leprosy
Leptospira test positive
Leptospirosis
Leptotrichia infection
Leuconostoc infection
Lice infestation
Ligneous conjunctivitis
Lineal gingival erythema
Lip infection
Listeria encephalitis
Listeria sepsis
Listeria test positive
Listeriosis
Liver abscess
Lobar pneumonia
Localised infection
Lochial infection
Louping ill
Lower respiratory tract infection
Lower respiratory tract infection bacterial
Lower respiratory tract infection fungal
Lower respiratory tract infection viral
Ludwig angina
Lung abscess
Lung infection
Lung infection pseudomonal
Lupus encephalitis
Lupus vulgaris
Lyme disease
Lymph gland infection
Lymph node abscess
Lymph node tuberculosis
Lymphadenitis bacterial
Lymphadenitis fungal
Lymphadenitis helminthic
Lymphadenitis viral
Lymphangitis
Lymphogranuloma venereum
Lyssavirus test positive
Malaria
Malaria antibody test
Malaria antibody test positive
Malarial myocarditis
Male genital tract tuberculosis
Malignant syphilis
Marburg disease
Marburg virus test positive
Mastitis
Mastitis bacterial
Mastitis fungal
Mastitis postpartum
Mastoid abscess
Mastoid empyema
Mastoiditis
Measles
Measles antibody
Measles antibody positive
Measles post vaccine
Mediastinal abscess
Mediastinitis
Meibomian gland discharge
Meibomianitis
Meningitis
Meningitis aseptic
Meningitis aspergillus
Meningitis bacterial
Meningitis borrelia
Meningitis candida
Meningitis chemical
Meningitis coccidioides
Meningitis coxsackie viral
Meningitis cronobacter
Meningitis cryptococcal
Meningitis echo viral
Meningitis enterococcal
Meningitis enteroviral
Meningitis eosinophilic
Meningitis exserohilum
Meningitis fungal
Meningitis gonococcal
Meningitis haemophilus
Meningitis herpes
Meningitis histoplasma
Meningitis leptospiral
Meningitis listeria
Meningitis meningococcal
Meningitis mumps
Meningitis neonatal
Meningitis pneumococcal
Meningitis salmonella
Meningitis staphylococcal
Meningitis streptococcal
Meningitis toxoplasmal
Meningitis trypanosomal
Meningitis tuberculous
Meningitis viral
Meningococcal bacteraemia
Meningococcal carditis
Meningococcal infection
Meningococcal sepsis
Meningoencephalitis adenoviral
Meningoencephalitis amoebic
Meningoencephalitis bacterial
Meningoencephalitis helminthic
Meningoencephalitis herpes simplex neonatal
Meningoencephalitis herpetic

Meningoencephalitis viral
Meningomyelitis herpes
Mesenteric abscess
Mesenteritis
Metagonimiasis
Metapneumovirus infection
Methylobacterium infection
Microbiology test
Microbiology test abnormal
Micrococcal sepsis
Micrococcus infection
Micrococcus test positive
Microsporidia infection
Microsporum infection
Middle ear operation
Middle East respiratory syndrome
Miliary pneumonia
Milker's nodules
Minimum inhibitory concentration
Minor cognitive motor disorder
Molluscipoxvirus test positive
Molluscum contagiosum
Monkeypox
Mononucleosis heterophile test
Mononucleosis heterophile test positive
Mononucleosis syndrome
Moraxella infection
Moraxella test positive
Morbillivirus test positive
Morganella infection
Morganella test positive
Mucocutaneous candidiasis
Mucocutaneous leishmaniasis
Mucosal infection
Mumps
Mumps antibody test
Mumps antibody test positive
Mumps deafness
Murine typhus
Murray Valley encephalitis
Muscle abscess
Muscular sarcoidosis
Mycetoma mycotic
Mycobacterial disease carrier
Mycobacterial infection
Mycobacterial peritonitis
Mycobacterium abscessus infection
Mycobacterium avium complex immune restoration disease
Mycobacterium avium complex infection
Mycobacterium chelonae infection
Mycobacterium fortuitum infection
Mycobacterium kansasii infection
Mycobacterium leprae test positive
Mycobacterium marinum infection
Mycobacterium test
Mycobacterium test positive
Mycobacterium tuberculosis complex test
Mycobacterium tuberculosis complex test positive
Mycobacterium ulcerans infection
Mycoplasma genitalium infection
Mycoplasma infection
Mycoplasma test
Mycoplasma test positive
Mycoplasmal postabortal fever
Mycoplasmal postpartum fever
Mycotic corneal ulcer
Mycotic endophthalmitis
Mycotoxicosis
Myelitis
Myelitis transverse
Myiasis
Myocardiac abscess
Myocarditis
Myocarditis bacterial
Myocarditis helminthic
Myocarditis infectious
Myocarditis meningococcal
Myocarditis mycotic
Myocarditis post infection
Myocarditis septic
Myocarditis syphilitic
Myocarditis toxoplasmal
Myometritis
Myositis
Myositis ossificans
Myositis-like syndrome
Myringitis
Myringitis bullous
Naegleria infection
Nail bed infection
Nail bed infection bacterial
Nail bed infection fungal
Nail bed infection viral
Nail candida
Nail infection
Nairovirus test positive
Nasal abscess
Nasal candidiasis
Nasal discharge discolouration
Nasal herpes
Nasal vestibulitis
Nasopharyngitis
Natural killer cell count
Natural killer cell count decreased
Natural killer cell count increased
Natural killer T cell count

Natural killer T cell count decreased
Natural killer T cell count increased
Necrobacillosis
Necrotising fasciitis
Necrotising fasciitis fungal
Necrotising fasciitis staphylococcal
Necrotising fasciitis streptococcal
Necrotising herpetic retinopathy
Necrotising myositis
Necrotising retinitis
Necrotising ulcerative gingivostomatitis
Necrotising ulcerative periodontitis
Neisseria infection
Neisseria test positive
Nematodiasis
Neonatal candida infection
Neonatal infection
Neonatal infective mastitis
Neonatal mucocutaneous herpes simplex
Neonatal pneumonia
Neuroborreliosis
Neurocryptococcosis
Neurocysticercosis
Neurological infection
Neurosyphilis
Neutropenic infection
Neutropenic sepsis
Newcastle disease
Newcastle disease virus test positive
Nipah virus infection
Nipple infection
Nipple inflammation
Nocardia sepsis
Nocardia test positive
Nocardiosis
Norovirus test positive
North Asian tick typhus
Nosocomial infection
Obstetric infection
Oculoglandular syndrome
Oesophageal candidiasis
Oesophageal infection
Oesophageal tuberculosis
Oesophagitis bacterial
Omphalitis
Omsk haemorrhagic fever
Onchocerciasis
Oncovirus test positive
Onychomycosis
Oophoritis
Ophthalmia neonatorum
Ophthalmic herpes simplex
Ophthalmic herpes zoster
Opisthorchiasis
Opportunistic infection
Optic neuritis
Optic neuritis meningococcal
Oral bacterial infection
Oral candidiasis
Oral fungal infection
Oral hairy leukoplakia
Oral helminthic infection
Oral herpes
Oral infection
Oral pustule
Oral viral infection
Orbital infection
Orbivirus infection
Orbivirus test positive
Orchitis
Orchitis mumps
Orf
Organic dust toxic syndrome
Oro-pharyngeal aspergillosis
Oropharyngeal candidiasis
Oropharyngeal gonococcal infection
Oropharyngitis fungal
Orthobunyavirus test positive
Orthopox virus infection
Orthopoxvirus test positive
Osler's nodes
Osteomyelitis
Osteomyelitis acute
Osteomyelitis bacterial
Osteomyelitis blastomyces
Osteomyelitis chronic
Osteomyelitis fungal
Osteomyelitis salmonella
Osteomyelitis viral
Otitis externa
Otitis externa bacterial
Otitis externa candida
Otitis externa fungal
Otitis externa viral
Otitis media
Otitis media acute
Otitis media bacterial
Otitis media chronic
Otitis media fungal
Otitis media haemophilus
Otitis media moraxella
Otitis media post measles
Otitis media viral
Otorrhoea
Otosalpingitis
Ovarian abscess
Ovarian bacterial infection
Overgrowth bacterial
Pachymeningitis
Pancreas infection
Pancreatic abscess
Pancreatitis bacterial
Pancreatitis fungal
Pancreatitis helminthic
Pancreatitis mumps
Pancreatitis viral
Panencephalitis
Panophthalmitis
Pantoea agglomerans infection

Pantoea agglomerans test positive
Papilloma viral infection
Paracoccidioides infection
Paragonimiasis
Parainfluenzae viral laryngotracheobronchitis
Parainfluenzae virus infection
Parametric abscess
Parametritis
Paraoesophageal abscess
Parapox virus infection
Parapoxvirus test positive
Parasite allergy
Parasite blood test
Parasite blood test positive
Parasite cervical specimen test positive
Parasite DNA test
Parasite DNA test positive
Parasite stool test
Parasite stool test positive
Parasite tissue specimen test positive
Parasite urine test positive
Parasitic encephalitis
Parasitic gastroenteritis
Parasitic oesophagitis
Parasitic test
Parasitic test positive
Paraspinal abscess
Parathyroid gland abscess
Paratyphoid fever
Paravaccinia
Paravaccinia virus test positive
Parechovirus infection
Paronychia
Parophthalmia
Parotid abscess
Parotitis
Parvovirus B19 test
Parvovirus B19 test positive
Parvovirus infection
Pasteurella infection
Pasteurella test positive
Pathogen resistance
Peliosis hepatis
Pelvic abscess
Pelvic infection
Pelvic inflammatory disease
Pelvic inflammatory disease mycoplasmal
Pelvic sepsis
Penicilliosis
Penile abscess
Penile infection
Penile wart
Peptic ulcer helicobacter
Peptostreptococcus infection
Peptostreptococcus test positive
Perianal streptococcal infection
Pericarditis amoebic
Pericarditis fungal
Pericarditis gonococcal
Pericarditis helminthic
Pericarditis histoplasma
Pericarditis infective
Pericarditis meningococcal
Pericarditis mycoplasmal
Pericarditis rheumatic
Pericarditis syphilitic
Pericarditis tuberculous
Perichondritis
Pericoronitis
Perihepatic abscess
Perihepatitis
Perihepatitis gonococcal
Perinatal HBV infection
Perinatal HIV infection
Perineal abscess
Perineal infection
Perinephric abscess
Periodontal destruction
Periodontal inflammation
Periodontitis
Periorbital abscess
Periorbital cellulitis
Periorbital infection
Peripheral nerve infection
Periporitis staphylogenes
Perirectal abscess
Peritoneal abscess
Peritoneal candidiasis
Peritoneal chlamydia infection
Peritoneal tuberculosis
Peritonitis
Peritonitis bacterial
Peritonitis gonococcal
Peritonitis helminthic
Peritonitis pneumococcal
Peritonitis syphilitic
Peritonitis viral
Peritonsillar abscess
Peritonsillitis
Periumbilical abscess
Persistent generalised lymphadenopathy
Pertussis
Petrositis
Phaehyphomycosis
Pharyngeal abscess
Pharyngeal chlamydia infection
Pharyngitis
Pharyngitis bacterial
Pharyngitis mycoplasmal
Pharyngitis streptococcal
Pharyngoconjunctival fever of children
Pharyngolaryngeal abscess
Pharyngotonsillitis
Phlebitis infective
Phlebotomus fever
Phlebovirus test positive
Pilonidal cyst

Pilonidal cyst congenital
Pingueculitis
Pinta
Pitted keratolysis
Plague
Plague sepsis
Plasma cell mastitis
Plasmodium falciparum infection
Plasmodium malariae infection
Plasmodium ovale infection
Plasmodium vivax infection
Pleural fluid analysis
Pleural infection
Pleural infection bacterial
Pleurisy viral
Pneumococcal bacteraemia
Pneumococcal infection
Pneumococcal sepsis
Pneumocystis jirovecii infection
Pneumocystis jirovecii pneumonia
Pneumocystis test positive
Pneumonia
Pneumonia adenoviral
Pneumonia anthrax
Pneumonia bacterial
Pneumonia blastomyces
Pneumonia bordetella
Pneumonia chlamydial
Pneumonia cryptococcal
Pneumonia cytomegaloviral
Pneumonia escherichia
Pneumonia fungal
Pneumonia haemophilus
Pneumonia helminthic
Pneumonia herpes viral
Pneumonia influenzal
Pneumonia klebsiella
Pneumonia legionella
Pneumonia measles
Pneumonia moraxella
Pneumonia mycoplasmal
Pneumonia necrotising
Pneumonia parainfluenzae viral
Pneumonia pneumococcal
Pneumonia pseudomonal
Pneumonia respiratory syncytial viral
Pneumonia salmonella
Pneumonia staphylococcal
Pneumonia streptococcal
Pneumonia toxoplasmal
Pneumonia tularaemia
Pneumonia viral
Pneumonic plague
Pneumovirus test positive
Pogosta disease
Polioencephalitis
Poliomyelitis
Poliomyelitis post vaccine
Poliovirus test
Poliovirus test positive
Polymerase chain reaction
Polymyositis
Polyneuropathy mumps
Polyomavirus test positive
Polyomavirus-associated nephropathy
Pontiac fever
Porphyromonas infection
Porphyromonas test positive
Portal pyaemia
Portal tract inflammation
Post abortion infection
Post herpetic neuralgia
Post polio syndrome
Post procedural cellulitis
Post procedural infection
Post procedural pneumonia
Post procedural sepsis
Post streptococcal glomerulonephritis
Post vaccination autoinoculation
Post viral fatigue syndrome
Postoperative abscess
Postoperative wound infection
Postpartum sepsis
Potassium hydroxide preparation
Potassium hydroxide preparation positive
Presumed ocular histoplasmosis syndrome
Primary syphilis
Primary transmission
Prion agent test positive
Proctitis bacterial
Proctitis chlamydial
Proctitis fungal
Proctitis gonococcal
Proctitis herpes
Proctitis infectious
Proctitis monilial
Proctitis mycoplasmal
Progressive massive fibrosis
Progressive multifocal leukoencephalopathy
Progressive vaccinia
Propionibacterium infection
Propionibacterium test positive
Prostate infection
Prostatic abscess
Prostatitis
Prostatitis Escherichia coli
Prostatitis gonococcal
Prostatitis trichomonal
Prostatitis tuberculous
Prostatovesiculitis

Proteus infection
Proteus test positive
Protozoal corneal ulcer
Pseudallescheria infection
Pseudallescheria sepsis
Pseudocroup
Pseudofolliculitis barbae
Pseudomembranous colitis
Pseudomonal bacteraemia
Pseudomonal sepsis
Pseudomonas aeruginosa meningitis
Pseudomonas bronchitis
Pseudomonas infection
Pseudomonas test positive
Psittacosis
Psoas abscess
Psorospermiasis
Puerperal infection
Puerperal pyrexia
Pulmonary echinococciasis
Pulmonary mycosis
Pulmonary sepsis
Pulmonary syphilis
Pulmonary trichosporonosis
Pulmonary tuberculoma
Pulmonary tuberculosis
Pulpitis dental
Punctate keratitis
Puncture site abscess
Puncture site discharge
Puncture site infection
Puncture site oedema
Purulence
Purulent discharge
Purulent pericarditis
Purulent synovitis
Pyelocystitis
Pyelonephritis
Pyelonephritis acute
Pyelonephritis chronic
Pyelonephritis fungal
Pyelonephritis mycoplasmal
Pyelonephritis viral
Pyloric abscess
Pyoderma
Pyoderma streptococcal
Pyometra
Pyomyositis
Pyonephrosis
Pyopneumothorax
Pyospermia
Pythium insidiosum infection
Pyuria
Q fever
Queensland tick typhus
Rabies
Raoultella ornithinolytica infection
Raoultella test positive
Rash pustular
Recrudescent typhus
Rectal abscess
Rectovaginal septum abscess
Reiter's syndrome
Relapsing fever
Renal abscess
Renal cyst infection
Renal syphilis
Renal tuberculosis
Respiratory moniliasis
Respiratory papilloma
Respiratory syncytial virus bronchiolitis
Respiratory syncytial virus bronchitis
Respiratory syncytial virus infection
Respiratory syncytial virus test
Respiratory syncytial virus test positive
Respiratory tract infection
Respiratory tract infection bacterial
Respiratory tract infection fungal
Respiratory tract infection viral
Respirovirus test positive
Retinitis
Retinitis histoplasma
Retinitis viral
Retroperitoneal abscess
Retroperitoneal infection
Retroviral infection
Retroviral rebound syndrome
Reye's syndrome
Rheumatic fever
Rheumatic heart disease
Rhinitis
Rhinolaryngitis
Rhinoscleroma
Rhinosporidiosis
Rhinotracheitis
Rhinovirus infection
Rhodococcus infection
Rhodococcus test positive
Rickettsialpox
Rickettsioses not tick borne
Rickettsiosis
Rift Valley fever
Rocky mountain spotted fever
Root canal infection
Roseola
Roseolovirus test positive
Rotavirus infection
Rotavirus test
Rotavirus test positive
Rubella
Rubella antibody positive
Rubella antibody test
Rubella immunity confirmed
Rubella in pregnancy
Rubella infection neurological
Rubivirus test positive
Rubulavirus test positive
Salmonella bacteraemia
Salmonella sepsis
Salmonella test positive
Salmonellosis

Salpingitis
Salpingitis gonococcal
Salpingitis tuberculous
Salpingo-oophoritis
Sapovirus test positive
Sarcocystis infection
Scarlet fever
Scedosporium infection
Schistosoma test
Schistosoma test positive
Schistosomiasis
Schistosomiasis bladder
Schistosomiasis cutaneous
Schistosomiasis liver
Scrotal abscess
Scrotal gangrene
Scrotal infection
Scrub typhus
Sebaceous gland infection
Secondary syphilis
Secondary transmission
Seminal vesicular infection
Seminal vesiculitis
Seminal vesiculitis gonococcal
Sepsis
Sepsis neonatal
Sepsis pasteurella
Sepsis syndrome
Septic arthritis haemophilus
Septic arthritis neisserial
Septic arthritis staphylococcal
Septic arthritis streptobacillus
Septic arthritis streptococcal
Septic embolus
Septic encephalopathy
Septic necrosis
Septic phlebitis
Septic rash
Septic shock
Septic vasculitis
Seroconversion test
Seroconversion test positive
Serology abnormal
Serology positive
Serology test
Serratia bacteraemia
Serratia infection
Serratia sepsis
Serratia test positive
Severe acute respiratory syndrome
Severe invasive streptococcal infection
Sexual transmission of infection
Sexually transmitted disease
Sexually transmitted disease carrier
Shigella infection
Shigella sepsis
Shigella test positive
Shunt infection
Sialoadenitis
Silicotuberculosis
Simplex virus test positive
Sinobronchitis
Sinusitis
Sinusitis aspergillus
Sinusitis bacterial
Sinusitis fungal
Skin bacterial infection
Skin candida
Skin graft infection
Skin infection
Skin infection helminthic
Slit-lamp tests abnormal
Slow virus infection
Small intestinal bacterial overgrowth
Small intestine gangrene
Smallpox
Snowshoe hare virus infection
Soft tissue infection
Spermatic cord funiculitis
Spermatic cord inflammation
Sphingomonas paucimobilis infection
Spinal cord abscess
Spinal cord infection
Spirillary fever
Spirillum test positive
Spirochaetal infection
Spleen tuberculosis
Splenic abscess
Splenic candidiasis
Splenic infection
Splenic infection bacterial
Splenic infection fungal
Splenic infection helminthic
Splenic infection viral
Sporotrichosis
Spotted fever rickettsia test positive
Sputum culture
Sputum culture positive
Sputum purulent
St. Louis encephalitis
Staphylococcal abscess
Staphylococcal bacteraemia
Staphylococcal impetigo
Staphylococcal infection
Staphylococcal mediastinitis
Staphylococcal osteomyelitis
Staphylococcal parotitis
Staphylococcal pharyngitis
Staphylococcal scalded skin syndrome
Staphylococcal sepsis
Staphylococcal skin infection
Staphylococcal toxaemia
Staphylococcus test
Staphylococcus test positive
Stenotrophomonas infection

Stenotrophomonas sepsis
Stenotrophomonas test positive
Sternitis
Stitch abscess
Stoma site abscess
Stoma site candida
Stoma site cellulitis
Stoma site infection
Stomach granuloma
Stomatococcal infection
Stomatococcus test positive
Strawberry tongue
Streptobacillary fever
Streptobacillus infection
Streptobacillus test positive
Streptococcal abscess
Streptococcal bacteraemia
Streptococcal endocarditis
Streptococcal impetigo
Streptococcal infection
Streptococcal sepsis
Streptococcal urinary tract infection
Streptococcus test
Streptococcus test positive
Strongyloidiasis
Subacute endocarditis
Subacute sclerosing panencephalitis
Subarachnoid abscess
Subcutaneous abscess
Subdiaphragmatic abscess
Subperiosteal abscess
Superinfection
Superinfection bacterial
Superinfection fungal
Superinfection mycobacterial
Superinfection viral
Suspected transmission of an infectious agent via product
Sweat gland infection
Sweating fever
Sycosis barbae
Syphilis
Syphilis anal
Syphilis genital
Syphilis musculoskeletal
Syphilitic endocarditis of heart valve
Systemic candida
Systemic mycosis
Taeniasis
Tertiary syphilis
Testicular abscess
Tetanus
Tetanus neonatorum
Thornwaldt disease
Thrombophlebitis septic
Thymus abscess
Thyroglossal cyst infection
Thyroid echinococciasis
Thyroid gland abscess
Thyroid tuberculosis
Thyroiditis subacute
Tick-borne fever
Tick-borne viral encephalitis
Tinea barbae
Tinea blanca
Tinea capitis
Tinea cruris
Tinea faciei
Tinea imbricata
Tinea infection
Tinea manuum
Tinea nigra
Tinea pedis
Tinea versicolour
Tongue abscess
Tonsillitis
Tonsillitis bacterial
Tonsillitis fungal
Tonsillitis streptococcal
Tooth abscess
Tooth infection
Torulopsis infection
Toxic shock syndrome
Toxic shock syndrome staphylococcal
Toxic shock syndrome streptococcal
Toxocariasis
Toxoplasma serology
Toxoplasma serology positive
Toxoplasmosis
Tracheitis
Tracheitis obstructive
Tracheobronchitis
Tracheobronchitis mycoplasmal
Tracheobronchitis viral
Tracheostomy infection
Trachoma
Transmission of an infectious agent via product
Transplant abscess
Trematode infection
Trench fever
Treponema test
Treponema test false positive
Treponema test positive
Trichiniasis
Trichomoniasis
Trichomoniasis intestinal
Trichophytic granuloma
Trichophytosis
Trichosporon infection
Trichostrongyliasis
Trichuriasis
Trigonitis
Tropical eosinophilia
Tropical infectious disease
Tropical spastic paresis
Tropical ulcer
Trypanosoma serology positive
Trypanosomiasis
Tuberculin test
Tuberculin test positive
Tuberculoid leprosy
Tuberculoma of central nervous system
Tuberculosis
Tuberculosis bladder
Tuberculosis gastrointestinal
Tuberculosis liver

Tuberculosis of central nervous system
Tuberculosis of eye
Tuberculosis of genitourinary system
Tuberculosis of intrathoracic lymph nodes
Tuberculosis of peripheral lymph nodes
Tuberculosis ureter
Tuberculous abscess central nervous system
Tuberculous endometritis
Tuberculous laryngitis
Tuberculous pleurisy
Tuberculous tenosynovitis
Tubo-ovarian abscess
Tularaemia
Type 1 lepra reaction
Type 2 lepra reaction
Typhoid carrier
Typhoid fever
Typhus
Typhus rickettsia test
Typhus rickettsia test positive
Ulcerative keratitis
Umbilical hernia gangrenous
Umbilical sepsis
Upper aerodigestive tract infection
Upper respiratory fungal infection
Upper respiratory tract infection
Upper respiratory tract infection bacterial
Upper respiratory tract infection helminthic
Urachal abscess
Ureaplasma infection
Ureaplasma test positive
Ureter abscess
Ureteritis
Urethral abscess
Urethral carbuncle
Urethral stricture post infection
Urethritis
Urethritis chlamydial
Urethritis gonococcal
Urethritis mycoplasmal
Urethritis trichomonal
Urethritis ureaplasmal
Urinary bladder abscess
Urinary tract abscess
Urinary tract infection
Urinary tract infection bacterial
Urinary tract infection enterococcal
Urinary tract infection fungal
Urinary tract infection neonatal
Urinary tract infection pseudomonal
Urinary tract infection staphylococcal
Urinary tract infection viral
Urinary tract inflammation
Urogenital infection bacterial
Urogenital infection fungal
Urogenital trichomoniasis
Urosepsis
Uterine abscess
Uterine infection
Uveitis
Vaccination site abscess
Vaccination site cellulitis
Vaccination site discharge
Vaccination site infection
Vaccination site pallor
Vaccination site pustule
Vaccine breakthrough infection
Vaccine virus shedding
Vaccinia test positive
Vaccinia virus infection
Vaginal abscess
Vaginal cellulitis
Vaginal infection
Vaginitis bacterial
Vaginitis chlamydial
Vaginitis gardnerella
Vaginitis viral
Variant Creutzfeldt-Jakob disease
Varicella
Varicella post vaccine
Varicella virus test
Varicella virus test positive
Varicella zoster gastritis
Varicella zoster oesophagitis
Varicella zoster pneumonia
Vector-borne transmission of infection
Veillonella infection
Veillonella test positive
Vertical infection transmission
Vessel puncture site infection
Vestibular neuronitis
Vestibulitis
Vibrio test positive
Viraemia
Viral cardiomyopathy
Viral corneal ulcer
Viral diarrhoea
Viral epiglottitis
Viral haemorrhagic cystitis
Viral hepatitis carrier
Viral infection
Viral labyrinthitis
Viral load
Viral load decreased
Viral load increased
Viral mastitis
Viral mutation identified
Viral myelitis
Viral myocarditis
Viral myositis

Viral oesophagitis
Viral parotitis
Viral pericarditis
Viral pharyngitis
Viral rash
Viral rhinitis
Viral sepsis
Viral sinusitis
Viral skin infection
Viral test
Viral test positive
Viral titre
Viral titre decreased
Viral titre increased
Viral tonsillitis
Viral tracheitis
Viral upper respiratory tract infection
Viral uveitis
Viral vasculitis
Virologic failure
Visceral larva migrans
Visceral leishmaniasis
Vitreous abscess
Vitritis
Vorticella infection
Vulval abscess
Vulval cellulitis
Vulvitis
Vulvovaginal candidiasis
Vulvovaginal human papilloma virus infection
Vulvovaginal mycotic infection
Vulvovaginal warts
Vulvovaginitis
Vulvovaginitis chlamydial
Vulvovaginitis gonococcal
Vulvovaginitis helminthic
Vulvovaginitis streptococcal
Vulvovaginitis trichomonal
Waterhouse-Friderichsen syndrome
Weil's disease
West Nile viral infection
Whipple's disease
Withdrawal hepatitis
Wound abscess
Wound contamination
Wound infection
Wound infection bacterial
Wound infection fungal
Wound infection helminthic
Wound infection pseudomonas
Wound infection staphylococcal
Wound infection viral
Wound sepsis
Yaws
Yaws of bone
Yaws of skin
Yellow fever
Yellow fever vaccine-associated neurotropic disease
Yellow fever vaccine-associated viscerotropic disease
Yersinia bacteraemia
Yersinia infection
Yersinia sepsis
Yersinia test
Yersinia test positive
Young's syndrome
Zoonosis
Zoonotic bacterial infection
Zygomycosis

Serious infections

Infections as defined above, assessed as serious

Opportunistic infections (excluding TB)

Aeromona infection
Aeromonas test positive
Allescheriosis
Alternaria infection
Aspergilloma
Aspergillosis oral
Aspergillus infection
Aspergillus test
Aspergillus test positive
Atypical mycobacterial lower respiratory tract infection
Atypical mycobacterial pneumonia
Atypical mycobacterium pericarditis
Bacillary angiomatosis
BK virus infection
Bronchopulmonary aspergillosis
Burkholderia cepacia complex infection
Burkholderia cepacia complex sepsis
Burkholderia gladioli infection
Burkholderia infection
Burkholderia test positive
Candida endophthalmitis
Candida osteomyelitis
Candida pneumonia
Candida retinitis
Candida sepsis
Capnocytophaga infection
Capnocytophaga test positive
Cerebral aspergillosis
Cerebral fungal infection

Cerebral toxoplasmosis
Chronic pulmonary histoplasmosis
Coccidioides encephalitis
Coccidioidomycosis
Colitis herpes
Cryptococcal cutaneous infection
Cryptococcal fungaemia
Cryptococcosis
Cryptococcus test
Cryptococcus test positive
Cutaneous coccidioidomycosis
Cytomegalovirus chorioretinitis
Cytomegalovirus colitis
Cytomegalovirus duodenitis
Cytomegalovirus enteritis
Cytomegalovirus enterocolitis
Cytomegalovirus gastritis
Cytomegalovirus gastroenteritis
Cytomegalovirus gastrointestinal infection
Cytomegalovirus gastrointestinal ulcer
Cytomegalovirus hepatitis
Cytomegalovirus infection
Cytomegalovirus mucocutaneous ulcer
Cytomegalovirus myelomeningoradiculitis
Cytomegalovirus myocarditis
Cytomegalovirus oesophagitis
Cytomegalovirus pancreatitis
Cytomegalovirus pericarditis
Cytomegalovirus syndrome
Cytomegalovirus test
Cytomegalovirus test positive
Cytomegalovirus urinary tract infection
Cytomegalovirus viraemia
Disseminated cryptococcosis
Disseminated cytomegaloviral infection
Encephalitis cytomegalovirus
Encephalitis fungal
Endocarditis histoplasma
Enterocolitis fungal
Exserohilum infection
Exserohilum test
Exserohilum test positive
Eye infection toxoplasmal
Fungaemia
Fungal abscess central nervous system
Fungal oesophagitis
Fungal retinitis
Fungal sepsis
Fungal tracheitis
Fusarium infection
Gastritis fungal
Gastritis herpes
Gastroenteritis cryptococcal
Hepatic candidiasis
Hepatic infection fungal
Hepatitis toxoplasmal
Hepatosplenic candidiasis
Herpes oesophagitis
Herpes sepsis
Herpes simplex colitis
Herpes simplex encephalitis
Herpes simplex gastritis
Herpes simplex hepatitis
Herpes simplex meningitis
Herpes simplex meningoencephalitis
Herpes simplex meningomyelitis
Herpes simplex necrotising retinopathy
Herpes simplex oesophagitis
Herpes simplex pneumonia
Herpes simplex sepsis
Herpes simplex visceral
Herpes zoster cutaneous disseminated
Herpes zoster disseminated
Herpes zoster meningitis
Herpes zoster meningoencephalitis
Herpes zoster meningomyelitis
Herpes zoster necrotising retinopathy
Herpes zoster pharyngitis
Histoplasmosis cutaneous
Histoplasmosis disseminated
Infection in an immunocompromised host
JC virus granule cell neuronopathy
JC virus infection
JC virus test
JC virus test positive
Kaposi's sarcoma AIDS related
Kaposi's varicelliform eruption
Listeria encephalitis
Listeria sepsis
Listeria test positive
Lymphadenitis fungal
Meningitis aspergillus
Meningitis candida
Meningitis coccidioides

Meningitis cryptococcal
Meningitis exserohilum
Meningitis fungal
Meningitis histoplasma
Meningitis listeria
Meningitis toxoplasmal
Meningomyelitis herpes
Methylobacterium infection
Miliary pneumonia
Mucocutaneous candidiasis
Mycobacterium avium complex immune restoration disease
Mycobacterium avium complex infection
Mycobacterium chelonae infection
Mycobacterium fortuitum infection
Mycobacterium kansasii infection
Myocarditis toxoplasmal
Necrotising herpetic retinopathy
Neurocryptococcosis
Neutropenic infection
Neutropenic sepsis
Nocardia sepsis
Nocardia test positive
Nocardiosis
Oesophageal candidiasis
Opportunistic infection
Oral candidiasis
Oral fungal infection
Oral hairy leukoplakia
Oro-pharyngeal aspergillosis
Oropharyngeal candidiasis
Oropharyngitis fungal
Otitis media fungal
Pancreatitis fungal
Penicilliosis
Pericarditis fungal
Pericarditis histoplasma
Phaehyphomycosis
Pneumocystis jirovecii infection
Pneumocystis jirovecii pneumonia
Pneumocystis test positive
Pneumonia cryptococcal
Pneumonia cytomegaloviral
Pneumonia herpes viral
Pneumonia toxoplasmal
Polyomavirus-associated nephropathy
Presumed ocular histoplasmosis syndrome
Progressive multifocal leukoencephalopathy
Progressive vaccinia
Pseudallescheria infection
Pseudallescheria sepsis
Pyelonephritis fungal
Respiratory moniliasis
Retinitis histoplasma
Retinitis viral
Rhodococcus infection
Rhodococcus test positive
Scedosporium infection
Sepsis pasteurella
Sinusitis aspergillus
Sinusitis fungal
Splenic candidiasis
Splenic infection fungal
Stomatococcal infection
Stomatococcus test positive
Strongyloidiasis
Systemic candida
Systemic mycosis
Tonsillitis fungal
Upper respiratory fungal infection
Varicella zoster gastritis
Varicella zoster oesophagitis
Varicella zoster pneumonia
Viral oesophagitis
Yersinia sepsis
Zygomycosis
Varicella zoster virus infection
Meningitis herpes
Proctitis herpes
Herpes zoster oticus
Herpes zoster infection neurological
Genital herpes zoster
Ophthalmic herpes zoster

Active TB

Adrenal gland tuberculosis
Bone tuberculosis
Choroid tubercles
Congenital tuberculosis
Conjunctivitis tuberculous
Cutaneous tuberculosis
Disseminated tuberculosis
Ear tuberculosis
Epididymitis tuberculous
Erythema induratum
Exposure to communicable disease
Extrapulmonary tuberculosis
Female genital tract tuberculosis
Joint tuberculosis
Lymph node tuberculosis
Male genital tract tuberculosis
Meningitis tuberculous
Oesophageal tuberculosis
Pericarditis tuberculous
Peritoneal tuberculosis
Prostatitis tuberculous
Pulmonary tuberculoma

Pulmonary tuberculosis
Renal tuberculosis
Salpingitis tuberculous
Silicotuberculosis
Spleen tuberculosis
Thyroid tuberculosis
Tuberculoma of central nervous system
Tuberculosis
Tuberculosis bladder
Tuberculosis gastrointestinal
Tuberculosis liver
Tuberculosis of central nervous system
Tuberculosis of eye
Tuberculosis of genitourinary system
Tuberculosis of intrathoracic lymph nodes
Tuberculosis of peripheral lymph nodes
Tuberculosis ureter
Tuberculous abscess central nervous system
Tuberculous endometritis
Tuberculous laryngitis
Tuberculous pleurisy
Tuberculous tenosynovitis

Latent TB

Latent tuberculosis
Mycobacterium test positive
Mycobacterium tuberculosis complex test positive
Tuberculin test false negative
Tuberculin test positive

Herpes zoster infection

Herpes zoster
Colitis herpes
Gastritis herpes
Herpes oesophagitis
Herpes sepsis
Herpes virus infection
Herpes ophthalmic
Herpes pharyngitis
Herpes zoster cutaneous disseminated
Herpes zoster disseminated
Herpes zoster meningitis
Herpes zoster meningoencephalitis
Herpes zoster meningomyelitis
Herpes zoster necrotising retinopathy
Herpes zoster pharyngitis
Meningomyelitis herpes
Pneumonia herpes viral
Varicella zoster gastritis
Varicella zoster oesophagitis
Varicella zoster pneumonia
Varicella zoster virus infection
Meningitis herpes
Proctitis herpes
Herpes zoster oticus
Herpes zoster infection neurological
Genital herpes zoster
Ophthalmic herpes zoster

Malignancies

Malignancies (SMQ) (Narrow)

Lymphoma

Malignant Lymphomas (SMQ) (Narrow)

Hypersensitivity reactions (including anaphylaxis and angioedema)

- Hypersensitivity (SMQ) (Narrow)
- Anaphylactic reaction (SMQ) (Narrow)
- Angioedema (SMQ) (Narrow)

Gastrointestinal (GI) perforation

Gastrointestinal perforation (SMQ) (Narrow)

Demyelinating disorders

Demyelination (SMQ) (Narrow)

Major adverse cardiac events (MACE)

- Ischaemic heart disease (SMQ) (Narrow)
- Central nervous system vascular disorders (SMQ) (Narrow)
- Cardiac failure (SMQ) (Narrow)

17.19 Listing display/contents

All data recorded in the CRF and mapped to Study Data Tabulation Model (SDTM) except for individual scores of SF-36 and CLASI, and individual items of 28-joint Count will be displayed in data listings unless it is recorded as not done; where applicable analysis visit (i.e. visit used in the analysis) will be included in the listings. Data used in the analysis (where there are multiple results for the same analysis visit) will be flagged.

Derived parameters (for example index scores, composites endpoints, change from Baseline, etc.) used in summaries and/or analyses as well as study day will be displayed in data listings. In addition, data imputations where performed for the efficacy endpoints and Baseline records will be displayed and/or flagged in the corresponding listings.

Listings will be sorted by subject identification number, test/parameter (if applicable), date of assessment and analysis visits (if applicable) and grouped by treatment arm.

Missing/partial dates for medications and AEs will be imputed as per imputations rules described in Section 17.15 for the purpose of determining prior, concomitant, treatment failure as well as treatment emergent flags but the imputed dates will not be displayed in data listings.

Dates will be displayed as DDMMMYYYY format in the data listings. In the event of partial date, partial dates where the day only is missing will be displayed as --MMMYYYY and partial dates where the day and month are missing will be displayed as -----YYYY (i.e. dashes will replace the missing elements).

17.20 CTCAE Grades

The rules defined in Table 17-11 will be used to derive the CTCAE grades (the rules are based on the laboratory results and the numeric portion of the definition of AEs per the NCI CTCAE v4.03 guidance).

Table 17-11:NCI CTCAE Grades

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Blood Chemistry	Alanine Aminotransferase (Serum)	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood Chemistry	Aspartate Aminotransferase (Serum)	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood Chemistry	Creatinine (Serum)	Creatinine increased	>1 - 1.5 x Baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x Baseline; >1.5 - 3.0 x ULN	>3.0 Baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Blood Chemistry	eGFR	Chronic kidney disease	eGFR <LLN – 60 ml/min/1.73 m^2	eGFR 59 – 30 ml/min/1.73 m^2	eGFR 29 - 15 ml/min/1.73 m^2	eGFR <15 ml/min/1.73 m^2
Blood Chemistry	GGT	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Lipid Profile	Cholesterol (Serum)	Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 -12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Hematology	Leukocytes (Blood)	Leukocytosis	-	-	>100,000/mm3	-
		White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10^9/L	<3000 - 2000/mm3; <3.0 - 2.0 x 10^9/L	<2000 - 1000/mm3; <2.0 - 1.0 x 10^9 /L	<1000/mm3; <1.0 x 10^9/L
Hematology	Lymphocytes (Blood)	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10^9/L	<800 - 500/mm3; <0.8 - 0.5 x 10^9/L	<500 - 200/mm3; <0.5 - 0.2 x 10^9/L	<200/mm3; <0.2 x 10^9/L
		Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 10^9/L	>20,000/mm3; >20 10^9/L	-
Hematology	Neutrophils, Segmented (Blood)	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10^9 /L	<500/mm3; <0.5 x 10^9 /L
Hematology	Platelets (Blood)	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L
PD	Fibrinogen	Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from Baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from Baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from Baseline	<0.25 x LLN or 75% decrease from Baseline or absolute value <50 mg/dL

17.21 Worst on-treatment definition

Table 17-12 display how the worst on-treatment is defined for each laboratory parameter. If a laboratory test is not listed below, no worst on–treatment summary will be provided.

Table 17-12: Worst on-treatment

Category	Analyte Name	Worst on-treatment
Blood Chemistry	Alanine Aminotransferase (Serum)	Maximum value
Blood Chemistry	Aspartate Aminotransferase (Serum)	Maximum value
Blood Chemistry	Creatinine (Serum)	Maximum value
Blood Chemistry	GGT	Maximum value
Blood Chemistry	Albumin (Serum)	Minimum value
Blood Chemistry	Alkaline Phosphatase (Serum)	Maximum value
Blood Chemistry	Bilirubin (Serum)	Maximum value
Blood Chemistry	Calcium (Serum)	Minimum value; Maximum value
Blood Chemistry	Creatine Kinase (Serum)	Maximum value
Blood Chemistry	Glucose (Serum Fasting)	Minimum value; Maximum value
Blood Chemistry	Potassium (Serum)	Minimum value; Maximum value
Blood Chemistry	Sodium (Serum)	Minimum value; Maximum value
Blood Chemistry	Lactate Dehydrogenase	Maximum value
Blood Chemistry	Urea	Maximum value
Blood Chemistry	Total Protein	Minimum value
Blood Chemistry	Chloride	Minimum value; Maximum value
Coagulation	Prothrombin Time	Maximum value
Coagulation	Activated Partial Thromboplastin Time (Plasma)	Maximum value
Coagulation	INR	Maximum value
Lipid Profile	Triglycerides (Serum)	Maximum value
Lipid Profile	Cholesterol (Serum)	Maximum value
Lipid Profile	LDL-Cholesterol	Maximum value
Lipid Profile	HDL- Cholesterol	Minimum value
Hematology	Leukocytes (Blood)	Minimum value
Hematology	Lymphocytes (Blood)	Minimum value
Hematology	Neutrophils, Segmented (Blood)	Minimum value
Hematology	Platelets (recorded as Thrombocytes) (Blood)	Minimum value
Hematology	Hemoglobin (Blood)	Minimum value; Maximum value
Hematology	Erythrocytes	Minimum value
Hematology	Haematocrit	Minimum value
Hematology	Absolute Monocytes	Minimum value
Hematology	Absolute Eosinophils	Minimum value
Hematology	Absolute Basophils,	Minimum value
Hematology	Mean Corpuscular Volume,	Minimum value; Maximum value
Hematology	Mean Corpuscular Haemoglobin	Minimum value
Hematology	Mean Corpuscular Haemoglobin Concentration	Minimum value
Efficacy	eGFR	Minimum value
Efficacy	Urine protein / creatinine ratio	Maximum value
PD	Fibrinogen	Minimum value
PD	C3	Minimum value
PD	C4	Minimum value
PD	CH50	Minimum value

17.22 Stratified CMH 95%CI and p-value

The following formula will be used to derived the stratified CHM [15].

Using standard notation, let n_{ij} be the number of patients that enter stratum i ($i=1, \ldots, s$) and are randomized to treatment j ($j= 0, 1$), let $N_j = \sum_{i=1}^{s} n_{ij}$ denote the total number of patients on treatment j, and let $\hat{p}_{ij}$ denote the observed success rate among patients in stratum i on treatment j.
The point estimate of the difference in success rate between the treatments, denoted as δ, take the form $\delta = \sum_{i=1}^{s} w_i \, \delta_i$ where w_i is the weight assigned to the stratum i,

$$w_i = \frac{(n_{i0} n_{i1})/(n_{i0}+n_{i1})}{\sum_{k=1}^{s}(n_{k0} n_{k1})/(n_{k0}+n_{k1})}$$

and

$$\delta_i = \hat{p}_{i1} - \hat{p}_{i0}$$

The statistic for testing H_0: $\delta = 0$ is

$$Z_w = \frac{|\hat{\delta}_w|}{\sqrt{\{\sum_{i=1}^{s} w_i^2 \, \hat{V}_0(\hat{\delta}_i)\}}}$$

Where

$$\hat{V}_0(\hat{\delta}_i) = \bar{p}_i(1-\bar{p}_i)\left(\frac{1}{n_{i0}} + \frac{1}{n_{i1}}\right) \text{ and } \bar{p}_i = \frac{n_{i0}\hat{p}_{i0} + n_{i1}\hat{p}_{i1}}{n_{i0}+n_{i1}}$$

The confidence interval is:

$$\hat{\delta}_w \pm Z_{\alpha/2} \sqrt{\left\{\sum_{i=1}^{s} w_i^2 \, \hat{V}(\delta_i)\right\}}$$

[redacted]

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Ablynx**
Protocol Number:	**ALX0061-C204**
Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase II Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-range Finding Study to Evaluate the Safety and Efficacy of ALX-0061 Administered Subcutaneously in Subjects with Moderate to Severe Active Systemic Lupus Erythematosus
SAP Version Number:	Final version 1.0
Effective Date:	28-FEB-2018

Author(s):

[redacted]

Approved by:

[redacted]

[redacted]

[redacted]

Statistical Analysis Plan (SAP) Client Approval Form

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[redacted]

[redacted]

PROTOCOL NUMBER: ALX0061-C204

Errata	
Date	Description
09/Mar/2018	Site 361001 - For subject 2040196, a major Protocol Deviation is missing in the DV dataset (and final PD log on CTMS). "Kit number of study drug dispensed to subject at W36 was not the same as kit number assigned by IRT". It has been evaluated if this issue warrants a reopening of the database and after discussion with the internal and external statistical team, it was concluded no reopening is needed but documentation on the errata list is sufficient. The conclusion was as follows: In the SAP the below is mentioned concerning deviations leading to subjects to be excluded from the PP analysis: "Any deviation recorded under "Kit number of study drug dispensed to subject at <specify visit> was not the same as kit number assigned by IRT.", where <specify visit> is Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 20, Week 22 or Week 24 AND for which (after unblinding) the dispensed kit number corresponds to the incorrect treatment (e.g. kit number should correspond to Placebo but corresponds to ALX0061)." These missing deviations will not have an impact on the PP population as it relates to visits after Week 24.
09/Mar/2018	Site 001025 - For subject 2040226, a major Protocol Deviation is missing in the DV dataset (and final PD log on CTMS). "Kit number of study drug dispensed to subject at W34 was not the same as kit number assigned by IRT". It has been evaluated if this issue warrants a reopening of the database and after discussion with the internal and external statistical team, it was concluded no reopening is needed but documentation on the errata list is sufficient. The conclusion was as follows: In the SAP the below is mentioned concerning deviations leading to subjects to be excluded from the PP analysis: "Any deviation recorded under "Kit number of study drug dispensed to subject at <specify visit> was not the same as kit number assigned by IRT.", where <specify visit> is Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 20, Week 22 or Week 24 AND for which (after unblinding) the dispensed kit number corresponds to the incorrect treatment (e.g. kit number should correspond to Placebo but corresponds to ALX0061)."

<table>
<tr><td></td><td>These missing deviations will not have an impact on the PP population as it relates to visits after Week 24.</td></tr>
<tr><td>13/Mar/2018</td><td>Site 420001- For subject 2040485, for Adverse Events 4, 5, 6, 7 and 8 the question 'Was the AE related to study drug injection?' was answered as 'Other, please specify: the exact location not known, no reaction was observed during the visit, patient informed us about mild local reaction at the next study visit, she did not remember the exact site'.

This is present in SUPPAE as QVAL. However, as the specification is 201 characters long, QVAL has been truncated in these cases to "OTHER, PLEASE SPECIFY THE EXACT LOCATION NOT KNOWN, NO REACTION WAS OBSERVED DURING THE VISIT, PATIENT INFORMED US ABOUT MILD LOCAL REACTION AT THE NEXT STUDY VISIT, SHE DID NOT REMEMBER THE EXACT SIT" where the final "E" is missing.
It has been evaluated if this issue warrants a reopening of the database and after internal discussion, it was concluded no reopening is needed but documentation on the errata list is sufficient. After all the specification is still readable.</td></tr>
<tr><td>20/Sep/2018</td><td>Site 052003 – For subject 2040444, Neutralizing antibody results (ISTEST='NAB0061') for two samples (Week 44 and Week 48) were erroneously reported as negative (ISORRES='NEG').

The correct values are:
<table>
<tr><th>Subject</th><th>Visit</th><th>Ref ID</th><th>ISORRES</th></tr>
<tr><td>2040444</td><td>WK44</td><td>Q3820192910</td><td>0.922</td></tr>
<tr><td>2040444</td><td>WK48</td><td>Q3820323982</td><td>0.921</td></tr>
</table>
It has been evaluated if this issue warrants a reopening of the database, it was concluded no reopening is needed but documentation on the errata list is sufficient.

Changing the NAb results for these two visits, has no impact on the NAb classification of this subject, as the subject was already classified as "PRE-DOSE NEG -POS ON TREATMENT" based on positive samples at other visits. As such, there is no impact on resulting incidence tables and no need to reopen the database.</td></tr>
</table>

Name: [redacted]

Function

Date: