AstraZeneca

Statistical Analysis Plan

Study Code	D3461C00008
Edition Number	2
Date	27/02/2018

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Characterizing the Pharmacokinetics, Pharmacodynamics, and Safety of Anifrolumab following subcutaneous administration in Adult Systemic Lupus Erythematosus Subjects with Type I Interferon test high result and active skin manifestations

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Study Statistician PPD

28 Feb 2018
Date

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Global Product Statistician PPD 2018-02-28

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
DA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANA	Anti-Nuclear Antibodies
AST	Aspartate Transaminase
AUC	Area Under the Curve
C_{max}	Maximum plasma (peak) drug concentration after single dose Administration
C_{trough}	Trough concentration
CLASI	Cutaneous Lupus erythematosus disease Area and Severity Index
CNS	Central Nervous System
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	Coefficient of Variation
C3, C4, CH50	Major Complement Proteins
EDV	Early Discontinuation Visit
ESR	Erythrocyte Sedimentation Rate
DBL	Database Lock
dsDNA	Double Stranded Deoxyribonucleic Acid
ECG	Electrocardiogram
GGT	Gamma Glutamyl Transferase
ICF	Informed Consent Form
IFN	Interferon
IP	Investigational Product
IPD	Important Protocol Deviation
LLOQ	Lower Limit of Quantification
MACE	Major Adverse Cardiovascular Events
nAb	Neutralizing Antibodies
OCS	Oral Corticosteroids
PD	Pharmacodynamics

Abbreviation or special term	Explanation
PGA	Physician Global Assessment
PK	Pharmacokinetic
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	Standard of Care
T_{max}	Time when C_{max} is observed
TB	Tuberculosis
TELVC	Treatment Emergent Laboratory/Vital signs Changes
VAS	Visual Analogue Scale

AMENDMENT HISTORY

Date	Brief description of change
26 Feb 2018	An update to the pharmacodynamic variable names; • "absolute score" to "fold change" • "neutralization ratio" to "percent suppression of fold change" • An addition of a pharmacodynamic analysis set definition. • Update protocol deviation definitions have been reworded to be consistent with the study protocol deviation document. • The addition of a how to handle early discontinuation visits for appropriate outputs. • Clarified CLASI objective to remove ambiguity. • Corrected when and how many blinded delivery review meetings will occur. • Important protocol deviations will be tabulated only, not tabulated and listed. • Removed unnecessary mention of treatment emergent event. • Added the definition of acute adverse event, injection related reaction, infections, hypersensitivity. • Added herpes zoster category definitions. • Clarified event rates by including formula. • Correct last date of exposure to IP from +28 days to +14 days. • Corrected wording surrounding laboratory variables for clarity. • Added ECG "Note done" category. • Clarify which vital signs measurement will be summarized. • Clarified ≥ 50% reduction in CLASI activity responder variable. • Corrected how autoantibodies and inflammatory markers will be analyzed. • Clarified OCS AUC calculations. • Corrected the definition of bursts which will be summarized and over which time periods. • Clarified that skin tape test output would not be reported for the study reports. • Added missing summary for subject disposition "subjects not randomized including reason" • Separated out surgical and medical history. • Added reporting of prior and concomitant medications.

Date	Brief description of change
	• Added exposure scenarios for the Week 12 analysis. • Removed injection count table. • Clarified that PK post-dose will not be mapped according to Table 1 visit windows. • Clarified that prohibited medication would make a subject a non-responder for responder variables. • Treatment compliance analysis added. • Clarified the CLASI damage missing component imputation for dyspigmentation. • Added the handling of percentage change from baseline for subjects with a baseline value of zero. • Clarified how early discontinuation visits will be handled. • Clarified that, where mentioned, change from baseline refers to absolute change from baseline. • Added fold change table categorization - <2 and ≥2. • Removed PD histogram. • PK scatter plots changed from arithmetic mean to geometric mean. • Added spaghetti plots for individual C_{trough} measurements. • Serum concentrations below LLOQ will be set to a value of LLOQ/2, not zero. • Removal of the imputation of "missing" for consecutive PK serum concentrations of values below LLOQ. • Add acute AEs to the overall AE summary table. • Clarified that reported MACE events will be those according to the Cardiovascular Event Adjudication Committee. • Clarified what treatment periods AEs will be reported for. • Shift tables for physical examination have been removed. • Longitudinal plot of the proportion of responders for CLASI activity was removed. • Single line plots for each subject and their change from baseline in CLASI activity score was removed. • CLASI activity and damage histogram have been removed. • Change from baseline in PGA was changed from a table to a longitudinal plot.

Date	Brief description of change
	• Table for the frequency and percentage of subjects remaining on treatment, discontinued IP but still in the study and withdrawn from the study has been added. • All data collected up until the date of data cut-off will be used, not only up to Week 12 for each subject. • Added inflammatory marker TELVC thresholds to the appendix. • Typos corrected

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measures:
To characterize the PK and PD of 150 mg and 300 mg anifrolumab administered as SC injections Q2W as measured by anifrolumab concentrations, PK parameters, 21-gene type 1 IFN PD fold change and percent suppression of fold change Week 12.	Anifrolumab concentrations and PK parameters including maximum concentration (C_{max}) after first dose and trough concentration (C_{trough}) for subsequent dosing. 21-gene type 1 IFN PD signature fold change and percent suppression of fold change (relative to baseline).

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To characterize the safety and tolerability of anifrolumab when SC administered for a 52 Week treatment period.	Adverse events (AE); serious adverse events (SAEs); Adverse events of special interest (AESIs) including herpes zoster, influenza, opportunistic infections, non-opportunistic serious infections, tuberculosis (TB), malignancies, non-SLE related vasculitis, anaphylaxis, and major adverse cardiovascular events (MACE); laboratory variables; physical examinations; vital signs; and ECG.
To characterize the immunogenicity of anifrolumab when administered SC for a 52 Week treatment period.	Anti-drug antibodies (ADA)

1.1.3 Safety objectives

Safety Objective:	Outcome Measure:
See above.	

1.1.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To characterize the efficacy of SC administered anifrolumab on SLE skin manifestations as measured by the change in Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI) score from baseline.	Proportion of subjects achieving ≥50% improvement in CLASI activity score from baseline to Week 12. Proportion of subjects achieving ≥50% improvement in CLASI activity score from baseline to Week 52.
To explore the effects of SC administered anifrolumab on type I IFN and other pathway related gene expression in skin tissue (optional part of study).	21-gene type 1 IFN and other pathway-related gene expression in skin tissue at baseline and at Week 12.

1.2 Study design

This is a Phase 2, multicentre, double-blind, randomized, placebo-controlled study characterizing the pharmacokinetics (PK), pharmacodynamics (PD) and safety of two fixed doses of anifrolumab administered as subcutaneous (SC) injections in adult systemic lupus erythematosus (SLE) subjects with type I interferon (IFN) test-high result and active skin manifestations while on stable standard of care (SOC) treatment. The study will be double-blind until database lock (DBL) for the primary analysis performed after all subjects have completed Week 12. Thereafter, the sponsor will be unblinded whilst the investigators and subjects will remain blinded throughout the remainder of the study.

Approximately 32 subjects will be randomized to one of the four treatment groups in a 3:1:3:1 ratio receiving:

- anifrolumab at a fixed dose of 150mg as added to SOC, given every 2 weeks (Q2W) as one SC injection in a volume of 1mL (12 subjects);
- placebo as added to SOC, given Q2W as one SC injection in a volume of 1mL (4 subjects);
- anifrolumab at a fixed dose of 300mg as added to SOC, given Q2W as two SC injections in a volume of 1mL each (12 subjects) or
- placebo as added to SOC, given Q2W as two SC injections in a volume of 1mL each (4 subjects).

Subjects must be taking either one or any combination of the following: oral corticosteroids (OCS), antimalarial, or immunosuppressants at stable doses. Specific medication restrictions are contained in the eligibility criteria as described in Sections 3.1 and 3.2.2 of the clinical study protocol (CSP). OCS doses should remain stable through Week 12, unless there is a clinical, safety or ethical reason to taper in which case reduction of OCS dose may be permitted from Week 4. Starting at Week 12 a mandatory steroid tapering attempt will be required for all subjects with an OCS dose ≥10.0 mg per day of prednisone or equivalent at randomization as described in Section 7.7.2.1 of the CSP.

See Figure 1 for the outline of the study design.

This study includes:

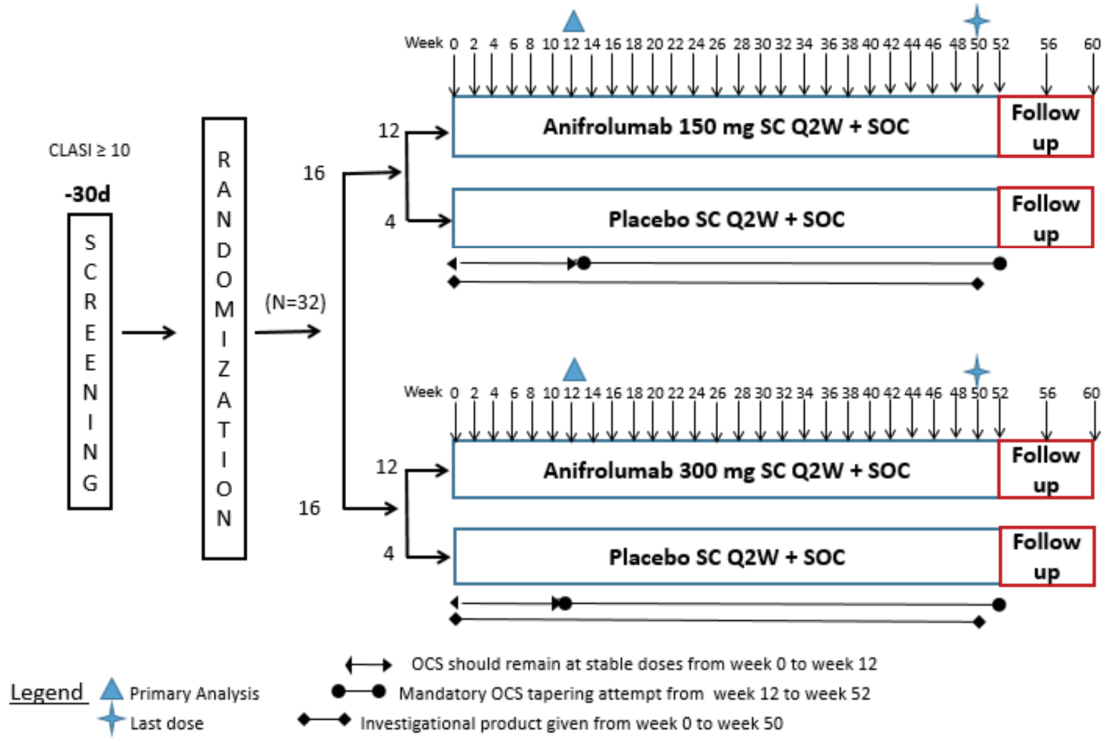
A screening period of up to 30 days;

A treatment period of 52 weeks;

A follow-up period of 8 weeks.

The investigational product (IP) will be administered at study visits for 26 doses (Week 0 to Week 50) and the last follow-up visit will be 10 weeks after the last IP dose.

Figure 1 Study flow chart



1.2.1 Steroid Tapering

Oral corticosteroid doses should remain stable through to Week 12 unless there is a clinical, safety, or ethical reason to taper earlier, in which case OCS dose reductions may be permitted from Week 4. Corticosteroid tapering must be attempted in all subjects with an OCS dose ≥10.0 mg/day (of prednisone or equivalent) at randomization and aim for a target OCS dose of ≤7.5 mg/day at Week 40 (starting at Week 12). Tapering will start at Week 12 and may continue until end of study unless at least one of the following criteria is met:

- Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) activity which is worsened compared to baseline in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever, thrombocytopenia, or haemolytic anaemia, or gastrointestinal activity).
- Newly affected organ system(s) based on the SLEDAI-2K, excluding serological abnormalities (dsDNA antibodies, hypocomplementemia).
- Persistent moderately to severely active skin manifestations as reflected by a Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI) activity score of ≥10.

- Moderate to severe arthritis disease as reflected by an active joint count of ≥8 tender and/or swollen joints.

Tapering can be started on the scheduled study visit day (e.g., Week 12, Visit 8) based on clinical manifestations and the laboratory values from the previous visit. If laboratory values or clinical evaluation of the current visit show increased or persistent SLE activity the tapering can be reversed. Steroid tapering must be started within 14 days of the visit. If steroid tapering is not attempted in an eligible subject, the AstraZeneca study physician must be contacted immediately. The recommended steroid-tapering regimen is provided in Appendix A but Investigators will have flexibility in how the OCS dose is reduced at each visit. Investigators will not be required, but may continue, to taper OCS dose beyond the target of ≤7.5 mg/day up to end of study based on disease activity. If a subject experiences increased disease activity secondary to OCS tapering, the dose may be increased up to a maximum of the baseline OCS dose for up to 2 weeks followed by a new tapering attempt.

1.2.2 Steroid Burst

Week 0 to Week 12

To allow adequate time for the investigational product to achieve significant clinical benefit, Investigators may administer one burst and taper of corticosteroids between Week 0 (Day 1) and Week 12 for increased SLE disease activity/non-SLE activity. After Week 12, additional steroid bursts may be given as per investigators judgement of clinical need.

A steroid burst is defined as one of the following:

- OCS increase up to a maximum daily dose of 40 mg/day prednisone (or equivalent) for up to a total of 14 days and that must be fully administered and tapered to less than or equal to the Day 1 dose by the end of the 14th day.; or

- Intramuscular methylprednisone (≤80 mg) or equivalent administered as a single dose between Day 1 and Week 12; or

- A maximum of 2 intra-articular/tendon sheath/bursal injections (for a total methylprednisolone ≤80 mg or equivalent) can be given.

Subjects who receive any intra-articular/tendon sheath/bursal injections should not receive OCS or intramuscular burst between Day 1 and Week 12. Subjects who receive more than one steroid burst and taper from Week 0 (Day 1) to Week 12, or who violate any of the criteria above, may continue in the study, but AZ study physician should be contacted.

From Week 12 until end of study

After Week 12 and up until end of study, additional steroid bursts, defined as above, may be given for SLE increased disease activity.

Adjustments of OCS doses above Day 1 dose for increased SLE activity may be allowed after Week 12 with the AZ study physician approval.

Intra-articular/tendon sheath/bursal injections are allowed for non-SLE related disorders from Week 12 and onwards. The injection should be administered after the completion of all assessments, including IP administration and post-injection PK blood test (if applicable).

1.3 Number of subjects

There is no formal power calculation as there will be no hypothesis testing. The data collected in this study will be used to inform further study design and development. Subjects will be randomized at a 3:1 ratio, receiving active:placebo (12 subjects on active and 4 subjects on placebo) for the two dosing levels (300 mg and 150 mg). CCI

[redacted]

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 All subjects analysis set

This analysis set will be comprised of all subjects screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

The full analysis set will be used as the primary population for reporting efficacy and safety data. This comprises of all subjects randomized into the study who receive at least one dose of IP, and will be analyzed according to randomized treatment (modified Intention-To-Treat). Any important deviations from randomized treatment will be considered when interpreting the data.

2.1.3 PK analysis set

All subjects who received anifrolumab and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

2.1.4 PD analysis set

Subjects in the full analysis set who are 21-gene IFN test high at baseline.

2.2 Violations and deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

IPDs that have a very high likelihood of affecting the interpretation of the primary and/or key secondary study results include:

- Subject did not fulfil inclusion criteria but are entered into the study.
- Subject fulfilled exclusion criteria but are entered into the study.
- Investigational product deviations, for example, subject received incorrect IP kit.
- Use of the prohibited medications listed in section 7.8 of the CSP.
- Subject met discontinuation criteria described in section 3.9 of the CSP but continued to receive IP.
- Assessment-related deviations, for example, PD and/or PK sample not collected as per protocol from Week 0 to Week 12.
- Safety reporting deviations, for example, delay in SAE/overdose/pregnancy reporting according to AZ SOP/CSP/local regulatory requirement.
- Good clinical practice violation.

In this study, all protocol deviations will be reported in IMPACT, AstraZeneca's internal protocol deviation capture system.

A list of all protocol deviations that have occurred in the study up until the last subject has completed Week 12 will be completed and documented prior to unblinding the study data and will be based on deviations as defined in the Protocol Deviation Document. Additionally, a final list of protocol deviations will be completed and documented for the end of study analysis.

During the blinded delivery review (BDR) meeting, which will take place when approximately 10 subjects have completed Week 12, protocol deviations will be classified as important or other. Only important protocol deviations will be tabulated in the study reports.

3. PRIMARY AND SECONDARY VARIABLES

The term baseline refers to the last measurement prior to randomization and dose administration on Day 1. If the Day 1 value is missing, invalid or is collected after

administration of IP, the latest assessment prior to dose administration on Day 1 will serve as baseline.

All variables and their analyses described below will be presented in the Week 12 and Week 52 study reports.

3.1 Primary variables

3.1.1 Pharmacodynamics (PD)

The two primary variables used to characterize PD are the 21-gene type 1 IFN signature fold change and percent suppression of fold change.

For the derivation of the percent suppression of fold change see Appendix F.

These variables will be characterized at every visit where the assessments are taken, with the primary time-point being at Week 12.

Missing values will not be imputed and only observed values will be used for main analyses.

3.1.2 Pharmacokinetics (PK)

The primary variables used to characterize PK are observed anifrolumab trough concentrations (predose). For the first dose, maximum concentration (post-dose [C_{max}]) and time when C_{max} is observed (T_{max}) will also be reported. Additional PK parameters will also be estimated if the data allows. Individual concentrations will be reviewed for exclusion from descriptive statistics by identifying outliers and reviewing dosing information and sample collection times. Analysis to determine if the identified concentrations should be excluded includes visual inspection of PK-time profiles and comparison of descriptive statistics with identified concentrations excluded and included. The method of data handling will be detailed in the Week 12 and Week 52 study reports.

These variables will be characterized at every visit where the assessments are taken, with the primary time-point being at Week 12.

Missing values will not be imputed and only observed values will be used for the analyses.

3.2 Secondary variables

3.2.1 Immunogenicity

Anti-drug antibodies (ADA) assessments will be conducted utilizing a tiered approach (screen, confirm, titre). The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Only ADA positive samples will be analyzed for the presence of neutralizing antibodies (nAb). Samples that are ADA negative will not be tested for (nAb). The presence or absence of neutralizing ADA will be determined using a validated bioanalytical method.

3.2.2 Safety

3.2.2.1 Adverse Events

Adverse events will be collected throughout the entire study and will be coded using the latest version of MedDRA.

Adverse event data will be categorized according to their onset date into the following study periods:

- AEs occurring during screening:
  An AE during screening is defined as an AE with a date of onset ≥ date of first screening visit and < date of the first dose of IP.
  AEs occurring during screening will only be listed.
- AEs occurring during treatment:
  An AE during treatment is defined as an AE with a date of onset ≥ day of first dose of IP and ≤ date of last dose of IP + 14 days.
- AEs occurring during follow-up:
  An AE during follow-up is defined as an AE with a date of onset > date of last dose of IP + 14 days and ≤ date of last dose of IP + 70 days.
- AEs occurring after follow-up:
  An AE after follow-up is defined as an AE with a date of onset > date of last dose of investigational product + 70 days.
  AEs occurring after follow-up will only be listed.

If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered as an AE during treatment. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an AE during treatment.

Adverse events of special interest (AESI) are marked as such in the electronic case report form (eCRF). Major acute cardiovascular events (MACE) will be determined according to the assessments of the Cardiovascular Event Adjudication Committee. The events of interest are serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, TB (including latent TB), influenza, vasculitis (non-SLE), and MACE (non-fatal myocardial infarction, non-fatal stroke, and CV death).

An AESI that meets one of the seriousness outcomes listed in Section 6.2 of the CSP will be categorised as a serious adverse event (SAE) for the purposes of follow-up responsibility and safety reporting. A non-serious AESI will be categorised as an AE. For reporting of AESIs, see Section 6.8 of the CSP.

An acute AE is defined as an AE with a time and date of onset after first administration of investigational product to +24 hours after administration of IP. If an AE has a missing time and/or date, then unless the stop date of the AE indicates otherwise, this will be considered as

an acute AE. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered acute AE.

An injection-related reaction (investigator) is defined as an AE with a related preferred term. An infection is defined as an AE within the SOC infections and infestations. Opportunistic infections are defined as given by the investigator and non-opportunistic infections are all infections not marked as opportunistic by the investigator. Hypersensitivity is defined according to the narrow MedDRA SMQ Hypersensitivity.

Herpes zoster is further classified according to the information given on the Herpes zoster log as follows:

Category	Rash [Y/N]	Episode status of HZ Event [localized/ disseminated]	Specify Disseminated [cutaneous/ systemic]	Any organ involvement [Y/N]
Cutaneous (localised) herpes zoster	Y	Localized	[no rule]	N
Cutaneous disseminated herpes zoster	Y	Disseminated	Cutaneous	[no rule]
Visceral disseminated herpes zoster	[no rule]	Disseminated	Systemic	[no rule]

Adverse events with missing intensity will be assumed severe. Events with missing relationship to study medication per the investigator will be assumed to be related. If no information about seriousness is available, the AE will be considered serious.

Adverse events will be presented by the time of first onset of the event. For this analysis, repeated events with the same preferred term will not be considered (i.e. if a subject has more than one event with the same preferred term, only the event with the earliest date of onset will be used). For partial or missing dates, the rules as described above will be used.

The event rate per 100 subject years is defined as;

$$\frac{Number\ of\ subjects\ with\ an\ event}{Sum\ of\ exposure\ time\ in\ days\ for\ all\ subjects\ in\ the\ analysis\ set} \times 36525$$

For herpes zoster (any AE with preferred name “Herpes zoster”) and other possible AESIs, an alternative event rate per 100 subject years will be derived as;

$$\frac{Number\ of\ subjects\ with\ herpes\ zoster}{Sum\ of\ exposure\ time\ at\ risk\ in\ days\ for\ all\ subjects\ in\ the\ analysis\ set} \times 36525$$

The time at risk is defined as time (including start and end date) from start of period (e.g. date of first administration of IP for events during treatment) to the date of first event, death, withdrawal of consent, or end of period, whatever comes first. This alternative event rate may also be calculated for other AESIs if suggested by data. This will be discussed during the BDR meetings and the decision will be made before unblinding the data for the end of study analysis.

The time to first onset of herpes zoster during treatment will be derived as date of first onset of herpes zoster – date of first administration of IP + 1. AEs with an onset date before the date of first administration of IP and AEs with an onset after 14 days after the date of last administration of IP will not be considered for the time to first onset of herpes zoster during treatment. If a subject has no herpes zoster during treatment, the time to first onset will be censored at the date of last administration of IP + 14 days.

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken regarding IP
- AE caused subject's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for serious adverse events (SAEs):

- Reason for being classified as an SAE

Other significant adverse events

During the characterization of the AE data, a medically qualified expert will review the list of AEs that were not reported as an SAE or AEs leading to discontinuation.

Based on the expert's judgment, significant AEs of clinical importance may, after consultation with the AstraZeneca Global Patient Safety Physician, be considered other significant AEs and reported as such in the study reports.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

3.2.2.2 Laboratory variables

The parameters haematology, clinical chemistry, urinalysis (outlined in Table 5 in Section 5.2.1 of the clinical study protocol) and of fasting lipid profile (high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) will be explored.

Laboratory data will be reported in International System of Units (SI). Changes from baseline in haematology, clinical chemistry and lipid profile variables will be calculated.

Absolute values will be compared to the reference range as given in Appendix D and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Treatment emergent laboratory/vital signs changes (TELVC) will be defined for on-treatment values according to the reference ranges given in Appendix D.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each time-point. Treatment-emergent changes will also be assessed. Treatment-emergent changes of urinalysis data are defined as

- Negative/+ at baseline to ++, +++, ++++ at any on-treatment value OR
- Increase of from baseline of at least ++ at any on-treatment value.

For the liver function tests: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT) and total bilirubin, the multiple of the upper limit of the normal (ULN) range (see Appendix D) will be calculated for each data point. Multiple = Value / ULN, ie, if the ALT value was 72 IU/L (ULN = 36) then the multiple would be 2. Subjects with AST or ALT $\geq$ 3xULN and TBL $\geq$ 2xULN at any point during the study irrespective of increase in ALP will be flagged for Hy's law (potential Hy's Law).

Additionally, to the above safety laboratory panel, coagulation tests will be performed: prothrombin time (PT) and partial thromboplastin time (PTT) will be recorded as part of the enrolment/screening tests and at various time points during the Active Treatment and Follow-up periods; please refer to Sections 4.2 and 4.3 from the CSP.

3.2.2.3 ECGs

The outcome of the 12-lead ECG measurements will be assessed by investigators as normal or abnormal. It is the investigator's judgment whether the findings/results are clinically relevant or not. The following categories are used for analysis:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

- Not done

Clinically significant abnormalities registered after screening visit should be reported as AEs.

3.2.2.4 Physical examination

Body height will be captured at screening only. Subjects will be weighed at Week 12 and Week 52. Weight (kg) will be characterized using change from baseline. Medically significant changes from the baseline physical examination / Visit 2 will be recorded as AEs unless related to SLE.

A targeted physical examination will include an assessment of the organ systems required to complete protocol-specified assessment tools (SLEDAI-2K and CLASI). Additional assessment should be done as clinically indicated. Abnormal findings will be recorded as part of AE, SAE, AESI, or SLE activity, if appropriate.

3.2.2.5 Vital signs

The following variables will be characterized:

- Pulse rate (beats per minute)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiration rate (breaths per minute)
- Body temperature (°C)

Changes from baseline will be calculated.

Where applicable, absolute values will be compared to the reference ranges given in Appendix E and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

On-treatment values will be classified as TELVC according to reference ranges given in Appendix E.

At dosing visits, only measurements before start of IP will be considered for 'by visit' presentations. In case of multiple measurements before the start of investigational product, the first measurement will be used for 'by visit' presentations but all measurements will be considered for the TELVC classification.

3.2.2.6 Colombia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an assessment tool that characterizes suicidal ideation and behaviour.

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale in an increasing order of severity from 1 to 10 to facilitate the definitions of the comparative variables.

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behaviour
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

The Suicidal Ideation or Behaviour score will be derived from the C-SSRS categories as the maximum suicidal ideation or behaviour category (1-10 on the C-SSRS) present at the assessment. The score will be derived at each assessment for each subject. Non-suicidal self-injurious behaviour will be assigned if no ideation or behaviour is present.

Composite variables based on the above re-ordered categories are defined for assessments during screening, during treatment, and during follow-up, respectively (with the same definitions for the study periods as given for AEs in Section 3.2.2.1), as follows:

- Suicidal ideation: A “yes” answer at any time in the respective study period to any one of the 5 (re-ordered) suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behaviour: A “yes” answer at any time in the respective study period, to any one of the 5 (re-ordered) suicidal behaviour questions (Categories 6-10) on the C-SSRS.
- No suicidal ideation or behaviour: No “yes” answer at any time in the respective study period to any one of the 10 (re-ordered) suicidal ideation and behaviour questions (Categories 1-10) on the C-SSRS.

3.3 Exploratory variables

3.3.1 Efficacy

Efficacy endpoints will be characterized using the following variables.

CLASI activity and damage scores

The exploratory variable used to characterize the effect of anifrolumab on skin activity is a ≥ 50% improvement in CLASI activity score from baseline, responder variable. A ≥ 50% responder in CLASI activity score from baseline is defined as having:

[CLASI activity baseline score – Post baseline CLASI activity score]*100 / [CLASI activity baseline score] ≥ 50.

Additionally, the absolute scores, as well as the change from baseline in CLASI activity and damage scores will be characterized.

These variables will be characterized at every visit where the assessments are taken, with the primary time-point being at Week 12.

Missing values will not be imputed and only observed values will be used for the main analyses.

SLEDAI-2K score and Physician Global Assessment of disease activity (PGA)

The SLE disease activity will be characterized by variables for SLEDAI-2K and physician global assessment (PGA).

SLEDAI-2K will be characterized by the absolute scores and changes from baseline in SLEDAI-2K.

PGA will be characterized using absolute scores and changes from baseline in a 3-point PGA VAS (Visual Analogue Scale), with 0 (no disease) to 3 (severe) disease activity.

These variables will be characterized at every visit where the assessments are taken, with the primary time-point being at Week 12.

Missing values will not be imputed and only observed values will be used for the main analyses.

Autoantibodies and inflammatory markers

The outcome variables for disease-related autoantibodies including anti-nuclear antibody (ANA) and anti-dsDNA will be the categorisations as negative, positive and missing. Parameters of the biological domain complements C3 and C4 will be categorised as low, normal and missing. CH50 will be categorised as normal, high and missing.

The inflammatory markers ESR, IgM, IgG and IgA, will be measured by absolute levels and change from baseline.

These variables will be characterized at every visit where the assessments are taken.

Missing values will not be imputed and only observed values will be used for the main analyses.

3.3.2 Oral corticosteroid management

The outcome variable for OCS management is the daily dose taken by subjects in the unit of mg/day.

The standardised area under the curve (AUC) of OCS dose from baseline to Week 12, baseline to Week 24 and baseline up to Week 52 will be calculated for all subjects as follows:

For each single daily dose, the duration of the single dose will be calculated as end date – start date + 1. If the start date is before Day 1, Day 1 will be used instead. If the end date is after the date of Week 12 for the primary analysis (date of Visit 8), the date of Visit 8 will be used instead. The AUC for each single dose will be derived by the daily dose (mg/day) multiplied with the duration (days). The AUC is the sum of the AUCs of the single doses. For subjects who discontinued the study before Visit 8, the AUC will be calculated up to the date of study discontinuation. The standardised AUC will be derived as AUC multiplied by 84 (12 weeks) and divided by the available days (date of Visit 8 or date of early discontinuation – date of Day 1 + 1). The same method applies for baseline to Week 24 and baseline to Week 52 analyses.

The number of steroid bursts subjects experienced between baseline and Week 12, baseline and Week 24, and baseline and Week 52, will also be characterized. For this variable, bursts are defined as any increase from baseline in daily OCS dose. Subjects can have multiple bursts if their OCS dose returns to baseline or less, before increasing above baseline again. For the baseline to Week 12 summary, bursts reported between date of first dose and date of the subject's Week 10 visit +14 days will be summarized. For the baseline to Week 24 summary, bursts reported between date of first dose and date of the subject's Week 24 visit +14 days will be summarized.

3.3.3 Skin tape test (optional)

The outcome variable for the skin tape test is the 21-gene type 1 IFN signature fold change and percent suppression of fold change will be recorded but will not be presented in the study reports.

3.4 Assessment of study population

3.4.1 Subject disposition variables

The following variables will be used to characterize subject disposition:

- Subjects enrolled
- Subjects randomized
- Subjects not randomized including reason

- Subjects who received treatment
- Subjects who completed treatment up to and including Week 10 for the primary time point analysis and Week 50 for the last dosing time-point.
- Subjects who discontinued treatment including reason for withdrawal, up to and including Week 12 for the primary time point analysis and Week 50 for the last dosing time-point.
- Subjects who completed the study up to and including Week 12 for the primary time point analysis and Week 52 for the last visit.
- Subjects withdrew from the study including reason for withdrawal, up to and including Week 12 for the primary time point analysis and Week 60 for the last visit.

A subject's country and site will be summarized.

Furthermore, the number and percentage of subjects remaining on investigational product, discontinued investigational product but remain on study and withdrawn from study will be summarized by visit up to Week 50 for the full analysis set.

3.4.2 Demographic and baseline characteristic variables

Demographic characteristics (age, age group, sex, ethnicity and race) and baseline characteristics (including height, weight, body mass index [BMI] and disease characteristics) will be summarized using the full analysis set. Disease characteristics include SLEDAI-2K, CLASI activity and damage score, OCS dose, PGA, disease duration (time from initial SLE diagnosis to randomization [months]), ANA, anti-dsDNA levels, anti-Sm antibodies, anti-RNP antibodies, complement C3, C4 and CH50 levels and 21-gene type 1 IFN score. Permitted SLE SOC treatment will also be summarized at baseline by frequency and proportion of subjects taking the SOC treatments, mentioned in section 7.7.1 of the CSP.

3.4.3 Surgical and medical history

Surgical and medical histories will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be evaluated separately for past and current conditions as given in the eCRF.

3.4.4 Prior and concomitant medications

Prior medications are reported according to the eCRF completion guidelines (ie, dependent of the relevance of the medication, the intake during the last few weeks before the first administration of IP, all medication taken during lifetime, or anything in-between will be reported). All medications will be coded using the latest version of World Health Organization Drug Dictionary (WHO-DD).

Any medications taken by the subject prior to the first dose date of investigational product will be considered prior medication. Any medication taken by the subject at any time between the date of the first dose (including the date of the first dose) of investigational product up to Week 52 (Visit 28) or discontinuation visit, inclusive, will be considered concomitant medication. Any medication started prior to the first dose of investigational product and ended after the first dose up to Week 52 (Visit 28) or discontinuation visit / was ongoing will be considered as both prior and concomitant medication.

Disease related treatments at baseline are defined as all medications with therapy reason given as "disease under study" with an intake at the date of first dose of investigational product (ie, start date on or before the date of first dose and end date on or after date of first dose or ongoing). The medications will be presented in the following categories:

- Anti-malarial
  defined as medications with an ATC code level 3 of P01B (antimalarials)
- Azathioprine
  defined as medications with preferred terms of azathioprine or azathioprine sodium
- Methotrexate
  defined as medications with preferred terms of methotrexate or methotrexate sodium
- Mycophenolate/Mycophenolic acid
  defined as medications with preferred terms of mycophenolate mofetil and mycophenolate sodium
- Mizoribine
  defined as medications with a preferred term of mizoribine
- OCS
- Other SLE medication
  defined as SLE medications not covered within the above categories

Restricted and prohibited medications are mentioned in Section 7.7 and 7.8 of the clinical study protocol.

If a medication cannot be classified as prior or concomitant due to missing or partial dates, the imputation rules as given in Appendix C will be applied.

3.4.5 Exposure of investigational product

The duration of exposure to the IP per subject is defined as the number of days between the start and the end dates of IP plus the dosing frequency time:

Duration of exposure (days) = (Last dosing date + 14 days) – first dosing date + 1.

For the Week 12 analysis there is a potential for exposure to be over or underestimated. To minimise the over or underestimation of exposure, the following rules will be applied.

- If a subject has completed the study (Week 52), the last date of exposure would be the date of last dose +14 days.
- If a subject has received their latest scheduled dose but has not completed the study, the last date of exposure would be the date of data cut-off.
- If a subject discontinues IP ≥14 days prior to the data cut, the last date of exposure would be the date of last dose +14 days.
- If a subject discontinues IP <14 days prior to the data cut, the last date of exposure would be the date of data cut-off.
- If a subject missed their latest scheduled dose but has not completed the study or discontinued IP, the last date of exposure would be the date of last dose +14 days.

For the final analysis at Week 52, the last date of exposure would be the date of last dose +14 days.

Study treatment compliance will be reported as the total number of dosing occasions divided by the total number of dosing occasions expected, multiplied by 100. If a subject discontinues IP, the number of expected dosing occasions are the number of visits up to discontinuation. For treatment compliance up to Week 12, the expected number of visits is 8 (up to Week 10) or the number of visits up to discontinuation of IP, whichever is smaller.

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Visit windows

For visit-based analyses, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows are summarized below:

Table 1 Visit windows

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline	1	Study Day ≤1
Week 2	15	2≤ Study Day ≤21
Week 4	29	22≤ Study Day ≤35
Week 6	43	36≤ Study Day ≤49
Week 8	57	50≤ Study Day ≤63
Week 10	71	64≤ Study Day ≤77
Week 12	85	78≤ Study Day ≤91

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 14	99	92≤ Study Day ≤105
Week 16	113	106≤ Study Day ≤119
Week 18	127	120≤ Study Day ≤133
Week 20	141	134≤ Study Day ≤147
Week 22	155	148≤ Study Day ≤161
Week 24	169	162≤ Study Day ≤175
Week 26	183	176≤ Study Day ≤189
Week 28	197	190≤ Study Day ≤ 203
Week 30	211	204≤ Study Day ≤ 217
Week 32	225	218≤ Study Day ≤231
Week 34	239	232≤ Study Day ≤245
Week 36	253	246≤ Study Day ≤259
Week 38	267	260≤ Study Day ≤273
Week 40	281	274≤ Study Day ≤287
Week 42	295	288≤ Study Day ≤301
Week 44	309	302≤ Study Day ≤315
Week 46	323	316≤ Study Day ≤329
Week 48	337	330≤ Study Day ≤343
Week 50	351	344≤ Study Day ≤357
Week 52	365	358≤ Study Day ≤371
Week 56	393	372≤ Study Day ≤406
Week 60	421	407≤ Study Day ≤433

The PK post-dose visit 2 measurement will not be mapped according to the windows above and will instead be mapped to baseline in all cases.

For assignment of data to time points using the visit windows, study day will be defined as,

(Date of assessment – date of first administration of IP) +1.

Using this definition, the day of first dose of IP will be baseline and the scheduled visit date of Week 2 will be study day 15 (=14+1) for example.

If multiple readings are recorded within a single visit window, the following rules will be followed.

- If there are two or more observations within the same visit window, then the non-missing one closest to the scheduled visit will be used in the analysis.
- If two observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If two observations are collected on the same day, then the non-missing one with the earlier collection time will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

For overall analyses not based on any particular study visit, all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified.

4.1.2

4.1.3 Presentation of results

All analyses will use SAS® version 9.3 or higher. A separate document will be produced containing the template table, listing, and figure shells.

Due to the small sample size, which is purposely not sized to detect a difference between treatment groups, there will be no formal comparisons made for all variables. Results will be presented by treatment, with the two placebo arms pooled for the analyses. If deemed appropriate, data from the two anifrolumab treatment arms may be pooled for the exploratory analyses regarding efficacy. Details for when the pooling takes place is specified for each analysis.

Unless otherwise noted, categorical data will be presented using counts and percentages with the denominator for percentages being the number of subjects in the analysis set by treatment group. Percentages will be rounded to 1 decimal place; except 100%, which will be displayed without any decimal places. Percentages will not be displayed for zero counts.

Unless otherwise noted, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean and median to a further decimal place and the SD to two additional decimal places. Confidence intervals may be used in some descriptive statistics when specified.

Individual subject data (including derived variables) will be presented in listings sorted by treatment group and subject number.

4.1.4 Missing Data

Subjects who discontinue IP will be asked to come to visits 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 (as applicable) (or for a minimum of 10 weeks after last dose of IP for subjects for whom IP was discontinued within 10 weeks prior to Week 52). After subjects discontinue IP, visits that they are not required to attend and do not attend will be classified as missing.

For responder variables, there are 2 criteria that correspond to a non-responder imputation for subjects who prematurely discontinue from investigational product, or who receive prohibited medications or restricted medications beyond the protocol-allowed threshold.

Missing data will not be imputed for PD, PK, or exploratory efficacy endpoints.

Missing safety data will generally not be imputed. However, safety assessment values of the form of <x (ie, below the lower limit of quantification) or >x (ie, above the upper limit of quantification) will be imputed as x in the calculation of summary statistics but displayed as <x or >x in the listings.

Details about imputation of partial or missing dates are given in Appendix C. The imputation of single missing items for the derivation of a total score is described in Appendix B.

4.2 Analysis methods

Wherever mentioned, change from baseline refers to absolute change from baseline.

4.2.1 Primary variable analysis

Unless otherwise specified, early discontinuation visits (EDV) will be mapped to the visit windows specified in Section 4.1.1 for 'at visit' based reporting.

4.2.1.1 Pharmacodynamics (PD)

The primary time-point for the 21-gene type 1 IFN PD signature fold change and percent suppression of fold change is at Week 12.

The following PD analysis will be created using the PD analysis set, by visit and with the treatment groups anifrolumab 300 mg, anifrolumab 150 mg, pooled active arms (if deemed appropriate) and pooled placebo.

A table of summary statistics will be created for fold change and percent suppression of fold change for the treatment groups.

A table will be created for the frequency and percentage of subjects by treatment group in the following percent suppression of fold change categories; < 50%, ≥ 50% and < 75%, ≥ 75%, and missing.

Additionally, a table of fold change will be categorized as < 2, ≥ 2 and missing.

Spaghetti plots of 21-gene type 1 IFN PD signature percent suppression of fold change for each treatment group will be created. After the point at which a subject discontinues IP or has received restricted medication over the protocol allowed threshold, their plotted lines will be dashed. A boxplot will also be created for Week 12, Week 24 and Week 52.

Median percent suppression of fold change for the treatment groups will also be displayed graphically using a longitudinal plot with precision bars (median absolute deviation) and the number of subjects in the analysis displayed at each time point.

4.2.1.2 Pharmacokinetics (PK)

All analyses of PK data will be performed using the PK analysis set separately for each active treatment arm.

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Serum concentrations and PK parameters of anifrolumab will be summarized by treatment (dose level of anifrolumab) using descriptive statistics. Where possible, the following descriptive statistics will be presented: n (number of non-missing values), m (number of values above LLOQ), geometric mean, geometric CV%, arithmetic mean, SD, arithmetic CV%, median, minimum and maximum. If applicable, this summary will be repeated including individual concentrations excluded from descriptive statistics.

Serum concentration-time profiles of anifrolumab will be generated as plots of arithmetic mean values (including SD) by time point in a semi-log scale and a linear scale. This will be presented for all values and additionally for values measured before administration (C_{trough}).

Scatter plots showing the individual PK parameters and geometric mean versus dose level will be presented for C_{max} and C_{trough} (select time points).

Spaghetti plots of individual C_{trough} measurements will created for both anifrolumab treatment arms.

Data from subjects excluded from the PK analysis set will be included in the data listings.

Serum concentrations below lower limit of quantification (LLOQ) prior to the first quantifiable concentration will be set to a value of LLOQ/2.

Due to the limited sampling schedule, the relationship between PK and PD may be explored on a population level (i.e. population PK/PD modelling). In addition, anifrolumab concentrations may be compared to historical data via intravenous route to understand the drug exposure after subcutaneous dosing. These analyses will be performed by MedImmune's Clinical Pharmacology and DMPK group and will not be reported in the study reports.

4.2.2 Secondary variable analysis

All analyses of the secondary outcome variables will be conducted with the full analysis set.

Unless otherwise specified, for outputs with summaries by visit, EDVs will be presented on their own row.

4.2.2.1 Immunogenicity

ADA assessments will be conducted utilising a tiered approach (screen, confirm, titre). The presence of nAb will be tested in all ADA-positive samples.

EDVs will be mapped to the visit windows specified in Section 4.1.1 for outputs which are summarised by visit for immunogenicity.

Week 12 analysis (primary analysis time-point)

A listing of all ADA positive subjects at baseline and/or post baseline will be presented for the Week 12 analysis (including available nAb, PK and PD results).

End of Study analysis

The following ADA results will be characterized by treatment group (anifrolumab 300 mg, anifrolumab 150 mg and pooled placebo) when all subjects have reached the study end. The frequency and percentage of:

- Subjects who are ADA positive at any time (including baseline).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and post baseline.
- Subjects who are ADA positive post-baseline and not positive at baseline.
- Subjects who are persistently positive are defined as having at least 2 post-baseline ADA positive measurements (with $\geq$ 16 weeks between first and last positive) or an ADA positive result at the last available post-baseline assessment.
- Subjects who are transiently positive, defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- Subjects who are ADA positive by visit.
- Subjects who are ADA positive at a post-baseline measurement for the first time by visit.

The presence of neutralising antibodies (nAb) will be tested only in samples that were previously found to contain ADA, using a ligand binding assay. The following variables will be characterized:

- Number and proportion of subjects who are nAb positive among the ADA-positive subjects (at any time).
- Number and proportion of subjects who are nAb positive for the first time by visit (with baseline nAb negative or missing) among the ADA-positive subjects (at any time).

The variables above, regarding neutralizing antibodies, will be summarized presenting the frequency and percentage.

ADA titres-time profiles (line plots for subject values by visit) will be generated separately for each treatment group (anifrolumab 300 mg, anifrolumab 150 mg and pooled placebo). Titres of positive measurements reported as ≤30 (limit of detection) will be imputed as 30.

The impact of ADA on PK will be explored by spaghetti plots of individual concentration data over time using different styles by ADA result (positive at any time/negative). This will be presented for all PK values and additionally for values measured before administration (Ctrough).

The impact of ADA on the IFN 21 gene PD signature will be explored using spaghetti plots of 21-gene type 1 IFN PD percent suppression of fold change over time using different styles by ADA result (positive at any time/negative).

Due to the small sample size, analyses regarding the impact of ADA on safety and efficacy may be explored if warranted.

If there are three or less subjects with ADA positive results, the summary tables and plots will not be created, other than those that characterize the impact of ADA on PK and PD. Instead, results will be presented in a listing similar to the Week 12 analysis.

4.2.2.2 Analysis methods for safety variables

Safety variables will be summarized by treatment group (anifrolumab 300 mg, anifrolumab 150 mg, pooled anifrolumab arms, pooled placebo) for the full analysis set.

Adverse events

If not stated otherwise, all summaries described below will be presented separately for

- AEs during treatment
- AEs during follow-up

For summaries during follow-up, only subjects with any study documentation after the date of last dose of IP + 14 days will be considered.

An overall summary of the frequency and percentage of subjects with at least one AE in the following categories will be presented:

- Any AE
- Any acute AE
- Any AE with outcome = death
- Any SAE (including events with outcome = death)
- Any AE leading to discontinuation of IP
- Any AE related to IP
- Any AE of severe intensity
- Any AESI

  - Any AESI of non-opportunistic serious infections
  - Any AESI of opportunistic infections
  - Any AESI of anaphylaxis
  - Any AESI of malignancy
  - Any AESI of herpes zoster
  - Any AESI of tuberculosis (including latent tuberculosis)
  - Any AESI of influenza
  - Any AESI of vasculitis (non SLE)
  - Any AESI of major acute cardiovascular events according to the Cardiovascular Event Adjudication Committee (CV-EAC)
- Any other significant AE may be presented if necessary

The frequency and percentage of subjects with at least one AE (ie, multiple occurrences of an AE in one subject will only be counted once) will be summarized by MedDRA System Organ Class and preferred term for the following AE categories. These summaries will also include the event rate per 100 subject years, as well as the exposure in years, unless otherwise specified. Event rates will generally not be included in summaries presented for AEs follow-up or during treatment and follow-up.

- Any AE
- Any AE above reporting threshold of 10% in the anifrolumab total treatment group
  This summary will be presented for AEs during treatment only.
- Non-serious AE above reporting threshold of 10% in the anifrolumab total treatment group
  This summary will be presented for AEs during treatment only.
- Any AE with outcome = death
  This summary will be presented for AEs during treatment and follow-up only.
- Any SAE (including events with outcome = death)
- Any AE leading to discontinuation of IP
  This summary will be presented for AEs during treatment only.
- Any AE by relationship to IP (yes, no)
  (multiple occurrences of an AE in one subject will only be counted once as related if at least one AE is related and as not related if all occurrences are not related)
  This summary will be presented for AEs during treatment only.
- Any AE by maximum intensity (mild, moderate, severe)
  (ie, multiple occurrences of an AE in 1 subjects will only be counted once with the maximum intensity in this AE)
  This summary will be presented for AEs during treatment only.
- Any AESI
  This summary will not be presented by System Organ Class but by AESI category (non-opportunistic serious infections, opportunistic infections, anaphylaxis,

malignancy, herpes zoster, tuberculosis, influenza, vasculitis, and major acute cardiovascular events).

- Any other significant AE may be summarized if necessary
  This summary will be presented for AEs during treatment only.

Cardiovascular outcome events as determined by the CV-EAC will be presented separately, summarizing the number of AEs submitted for adjudication and the outcomes of the adjudication including MACE classification. Site reported cardiovascular AEs and their corresponding adjudicated outcomes will be listed.

A table of the number and percentage of subjects with at least one anaphylaxis will be summarized for the following respective subcategories: SAE (including events with outcome of death), AE leading to discontinuation. Additionally, hypersensitivity, and injection-related reactions (investigator), will be summarized overall as well as for the following respective subcategories: SAE (including events with outcome of death), AE leading to discontinuation, and AE by maximum intensity (mild, moderate, and severe).

Infections and opportunistic infections will be summarized with the same subcategories as given above.

The time to first onset of herpes zoster during treatment will be presented as Kaplan-Meier plot including the number of subjects at risk at each visit.

Furthermore, the alternative event rates per 100 subject years for herpes zoster (and other possible AESIs) will be summarized for events during treatment and follow-up, during treatment, and during follow-up.

Key subject information for subjects with an AE with outcome of death, subjects with SAEs, subjects with an AE leading to discontinuation of IP and subjects with AESIs, respectively, will be listed.

Laboratory variables

Laboratory variables will be created using the full analysis set and will have the treatment groups of anifrolumab 150 mg, anifrolumab 300 mg, placebo 150 mg and placebo 300 mg.

Observed values and changes from baseline of laboratory data for haematology, clinical chemistry and fasting lipid profile will be summarized by visit. The summary statistics presented will be minimum, 1st quartile, median, 3rd quartile, maximum, mean, and SD.

If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at specific visits then shift plots of these data may also be produced. This will be discussed and agreed upon during the BDR meeting.

For each laboratory parameter with available criteria, the frequency and percentage of subjects with TELVC values will be summarized by visit. Additionally, the frequency and percentage of subjects with at least one TELVC value will be presented.

The frequency and percentage of subjects with laboratory values below, within or above the corresponding normal range will be presented as shift tables from baseline to maximum and minimum on-treatment value, respectively.

Urinalysis and urine protein-creatinine ratio will be summarized as shift tables from baseline to the last on-treatment value for each parameter. Furthermore, the frequency and percentage of subjects with treatment-emergent changes will be summarized by parameter.

To identify potential Hy's Law cases, a table of number and percentage of subjects with maximum post baseline total bilirubin <2xULN and ≥2xULN will be presented against maximum post baseline ALT and AST <3xULN, ≥3 and <5 ULN, and ≥5xULN.

For all subjects who meet the biochemical criteria for Hy's law (potential Hy's Law), a Subject Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these subjects. Subjects with elevated ALT or AST, and elevated total bilirubin, at any time may be explored further graphically using individual subject profile plots presenting AST, ALT, Alkaline phosphatase, GGT, and total bilirubin as multiples of ULN in a log scale.

ECGs

The frequency and percentage of subjects with normal, abnormal (not clinically significant), abnormal (clinically significant) and not done ECG results will be presented as a shift table from baseline to Week 52/early discontinuation visit (EDV).

Physical examination

Observed values and changes from baseline of body weight will be summarized.

Vital Signs

Observed values and changes from baseline of pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature, respectively, will be summarized by visit. Shift tables for each of the parameters presenting baseline values versus minimum post-baseline values and maximum post-baseline values, respectively, will be provided.

For each parameter with available criteria, the frequency and percentage of subjects with TELVC values will be summarized by visit. Additionally, the frequency and percentage of subjects with at least one TELVC value will be presented. For each parameter, the frequency and percentage of subjects with values below, within or above the corresponding normal range will be presented by visit. In addition, this information will be presented in a shift table from baseline to each post-baseline visit.

Colombia-Suicide Severity Rating Scale (C-SSRS)

The frequency and percentage of subjects with suicidal ideation (overall and by maximum category), suicidal behaviour (overall and by maximum category), and no suicidal ideation or behaviour will be given for assessments during screening, during treatment, and during follow-up, respectively, for each treatment group.

The proportion of subjects within each of the 4 suicidal behaviour categories and within each of the 5 suicidal ideation sub-categories during screening, during treatment, and during follow-up, respectively, will also be presented for each treatment group.

Furthermore, descriptive statistics on the total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be summarized for attempts during screening, during treatment and during follow-up, respectively, for each treatment group.

4.2.3 Exploratory variable analysis

Unless otherwise specified, for outputs with summaries by visit, EDVs will be presented on their own row.

4.2.3.1 Efficacy

CLASI activity and damage scores

For the following CLASI activity and damage score analysis, the treatment groups are anifrolumab 300 mg, anifrolumab 150 mg, pooled active arms (if deemed appropriate) and pooled placebo.

A table of summary statistics will be used to characterize the ≥ 50% improvement in CLASI activity score from baseline responder variable for each visit, displaying the frequency and percentage of responders with a 95% confidence interval, by treatment group. Subjects treated with restricted medication beyond protocol allowed threshold or discontinue IP are regarded as non-responders. If any of the conditions cannot be evaluated at the respective time point, the subject is regarded as a non-responder. Subjects with a CLASI activity score of zero at baseline will be excluded from this analysis.

Tables of summary statistics will be used to characterize the absolute CLASI activity and damage scores and change from baseline at each visit by treatment group and pooled treatment groups using; number of observations (n), mean, standard deviation (SD), median, minimum and maximum.

Spaghetti plots of change from baseline in CLASI activity score for each treatment group will be created with the number of subject data displayed at each time point. A boxplot will be created at Week 12, 24 and 52 for each treatment group.

Mean change from baseline in CLASI activity score for the treatment groups will be displayed graphically using a longitudinal plot with ± standard error (SE) and the number of subject data displayed at each time point.

The relationship between CLASI activity score and OCS dose will be explored using shift plots by treatment group. The following shift plots will be created:

- Baseline CLASI activity score versus Week 12, 24 and 52 CLASI activity score, split by an increase, decrease or no change in OCS dose at the respective time-points.

- Baseline OCS dose versus Week 12, 24 and 52 OCS dose, split by 50% reduction in CLASI activity response at the respective time-points.

The number of subjects for each subgroup will be displayed on the plots.

SLEDAI-2K score and Physician Global Assessment of disease activity (PGA)

The SLE disease activity will be characterized by variables for SLEDAI-2K and physician global assessment (PGA).

For the following SLEDAI-2K and PGA analysis, the treatment groups are anifrolumab 300 mg, anifrolumab 150 mg, pooled active arms (if deemed appropriate) and pooled placebo.

SLEDAI-2K will be characterized by a summary table of the absolute scores and changes from baseline at each visit; displaying number of observations (n), mean, standard deviation (SD), median, minimum and maximum.

EDV assessments performed at a visit where the SLEDAI-2K assessment was due to take place will be summarized at the visit. For EDV assessments performed at visits where the SLEDAI-2K assessment was not due to take place will not be reported in the table and will instead be reported in a listing.

Mean change from baseline in PGA will be characterized graphically by a longitudinal plot with ± standard error (SE) and the number of subject data displayed at each time point.

Autoantibodies and inflammatory markers

Tables for the total scores and change in baseline for the inflammatory markers ESR, IgM, IgG and IgA will be created by treatment group (anifrolumab 300 mg, anifrolumab 150 mg, placebo 300 mg and placebo 150 mg). These tables will display; number of observations (n), mean, standard deviation (SD), median, minimum and maximum.

Shift tables will be created for the disease related autoantibodies, anti-nuclear antibody (ANA), anti-dsDNA, parameters of the biological domain (complements C3, C4 and CH50) from baseline to Week 12 and baseline to Week 52.

4.2.3.2 OCS management analysis

For the following OCS (prednisone or equivalent) analysis, the treatment groups are anifrolumab 300 mg, anifrolumab 150 mg, pooled active arms and pooled placebo.

Tables with summary statistics showing the frequency and percentage of subjects with zero to the maximum number of observed steroid bursts will be summarized during the periods of baseline to Week 12, baseline to Week 24 and baseline to Week 52, by treatment group.

Tables with summary statistics of daily dose and change from baseline by treatment group will be produced displaying; number of observations (n), mean, standard deviation (SD), median, minimum and maximum. OCS daily dose reported for a visit will be the final dose during the last visit in a visit window.

Furthermore, the standardised AUC up to Week 12, 24 and 52 will be summarized by treatment group for all subjects.

4.2.3.3 Skin tape test (optional)

There will be no outputs for the skin tape test in the study reports.

4.2.4 Assessment methods for the study population

4.2.4.1 Subject disposition

Frequency and percentage of subject disposition variables mentioned in Section 3.4.1 will be presented by treatment group (anifrolumab 150 mg, anifrolumab 300 mg, pooled anifrolumab, placebo 150 mg, placebo 300mg and pooled placebo) and overall.

In addition, the frequency and percentage of subjects in each analysis set will be provided. Percentages will be based on all randomized subjects.

The frequency and percentage of subjects remaining on treatment, discontinued IP but still in study and withdrawn from the study will be presented by visit.

Important protocol deviations will be summarized by frequency and percentage, using the full analysis Set.

4.2.4.2 Demographic and baseline characteristics

Demographics and subject characteristics will be summarized by treatment group (anifrolumab 300 mg, anifrolumab 150 mg, pooled anifrolumab, placebo 300 mg and placebo 150 mg, placebo pooled) and overall, using frequency and percentages (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median, and maximum (for continuous variables) using the full analysis set.

Surgical history and past and current medical history will be summarized separately by MedDRA System Organ Class and preferred term by the frequency and percentage of subjects for each treatment group (anifrolumab 300 mg, anifrolumab 150 mg, pooled anifrolumab, placebo 300 mg, placebo 150 mg, pooled placebo) and overall.

The prior medications, categorized according to the WHO Drug Reference List dictionary, which employs the Anatomical Therapeutic Chemical (ATC) classification system, will be summarized by treatment group (anifrolumab 300 mg, anifrolumab 150 mg, pooled

anifrolumab, placebo 300 mg, placebo 150 mg, pooled placebo and overall) as frequency and percentage of subjects reporting usage.

The concomitant medication will be categorized according to the WHO Drug Reference List dictionary, which employs the Anatomical Therapeutic Chemical (ATC) classification system. The frequency and percentage of subjects taking concomitant medications and non-drug therapies during the treatment period will be summarized by drug class and drug name using ATC code. Disease related treatments at baseline will be summarized by the categories given in Section 3.4.4. Concomitant medication beyond protocol allowed threshold will be summarized by preferred term.

4.2.4.3 Exposure of investigational product

Exposure will be summarized by treatment group (anifrolumab 300 mg, anifrolumab 150 mg, placebo 300 mg and placebo 150 mg), pooled treatment groups (pooled active arms and pooled placebo) and all subjects for the full analysis set.

Summary statistics will be provided for the duration of exposure. Additionally, the frequency and percentage of subjects treated ≥15 days, ≥29 days, and up to ≥365 days in 2-weekly intervals will be provided.

The frequency and percentage of subjects dosed will be presented in 2-weekly intervals (ie, 2 weeks, 4 weeks, 6 weeks, …, 50 weeks).

Furthermore, the time to discontinuation of IP will be presented as Kaplan-Meier plot including the number of subjects at risk (ie, still on IP).

Treatment compliance will be summarized by number, mean, SD, median, min and max for baseline up to Week 12 and baseline up to Week 52.

5. INTERIM ANALYSES

The primary analysis will be carried out after all subjects have completed the Week 12 visit or discontinued the study prior to Week 12. All subject data, including that collected after Week 12 will be used. At Week 12, the Sponsor personnel will be unblinded whereas investigators and subjects will remain blinded throughout the entire study. The DBL at study end will take place once all subjects have completed Week 60 or discontinued the study prior to Week 60. The Week 52 assessment is included in the treatment period.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The following changes have been made to the analysis from the protocol.

- Subject data collected for visits after Week 12 will be reported for if it was collected before the data-cut off for the primary DBL.
- The phrasing of "neutralization ratio" has been changed to "percent suppression of fold change" to be aligned with other anifrolumab studies.
- A pharmacodynamic analysis set has been added for clarity.
- The PGA VAS scale is not 0-100 mm but a 3-point PGA VAS.
- Skin tape test results will not be included in the study reports for the primary and end of study analyses.

7. REFERENCES

N/A

8. APPENDIX

Appendix A: Oral Corticosteroid Guidance

Appendix B: Derivation rules for missing components of efficacy variables

Appendix C: Derivation rules for imputation of partial or missing dates

Appendix D: Reference ranges and TELVC for laboratory values

Appendix E: Reference ranges and TELVC for vital signs

Appendix F: Percent suppression calculation

Appendix A Oral Corticosteroid Guidance

Examples of Equivalent Doses of Oral Prednisone

Oral Prednisone and Equivalents	**Equivalent Dose**				
Oral Prednisone	**7.5 mg**	**10 mg**	**20 mg**	**30 mg**	**40 mg**
Cortisone	37.5 mg	50 mg	100 mg	150 mg	200 mg
Hydrocortisone	30 mg	40 mg	80 mg	120 mg	160 mg
Methylprednisolone	6 mg	8 mg	16 mg	24 mg	32 mg
Prednisolone	7.5 mg	10 mg	20 mg	30 mg	40 mg
Triamcinolone	6 mg	8 mg	16 mg	24 mg	32 mg

Example of OCS Tapering Schedule

Time point	**Initial Dose of Oral Prednisone or Equivalent (mg/day)**						
	40	**35**	**30**	**25**	**20**	**15**	**10**
Week 12	35	30	25	20	15	12.5	10
Week 16	30	25	20	15	12.5	12.5	10
Week 20	25	20	15	12.5	12.5	12.5	7.5
Week 24	20	15	12.5	12.5	10	10	7.5
Week 28	15	12.5	12.5	10	10	10	7.5
Week 32	12.5	10	10	10	7.5	7.5	7.5
Week 36	10	10	7.5	7.5	7.5	7.5	7.5
Week 40	7.5	7.5	7.5	7.5	7.5	≤7.5	≤7.5

* Note: subjects on OCS doses equivalent to 10 mg prednisone/day may tolerate tapering by 1 mg/day per visit rather than an abrupt drop from 10 mg/day to 7.5 mg/day. The stepwise tapering of OCS dose should be performed at the discretion of the Investigator.

Appendix B Derivation rules for missing components of efficacy variables

If one or more components of SLEDAI 2K are missing, then the last observation carried forward approach will be used to impute the missing component score.

If one or more components of CLASI are missing, then the last observation carried forward approach will be used to impute the missing components with one exception. For CLASI damage imputation, if dyspigmentation is not present at a visit, the dyspigmentation duration will not be imputed.

Appendix C Derivation rules for imputation of partial or missing dates

If any medications reported are not able to be determined as prior or concomitant due to missing or partial start dates and/or stop dates, the following imputation rules will be implemented:

- If the year is present but the month and day are missing, then 01JAN will be imputed for the start date and 31DEC for the stop date.
- If the year and month are present but the day is missing, then 01 will be imputed for the start date and the last day of the month for the stop date.
- If the start date is completely missing and the end date is prior to the signing of the ICF, the medication will be considered prior.
- If the start date is completely missing and the end date is missing or on or after the signing of the ICF, the medication will be considered prior and concomitant.
- If the end date is completely missing and the start date is on or after the signing of the ICF the medication will be treated as concomitant.
- If the end date is completely missing and the start date is prior to the signing of the ICF the medication will be considered prior and concomitant.

Appendix D Reference ranges and TELVC for laboratory values

Parameter	Unit	Low value	Low decrease	High value	High increase
Haematology					
Haemoglobin	g/L	≤60	NA	≥200	NA
		≤70 and decrease from BL ≥15			
Haematocrit	V/V	≤0.18	NA	≥0.64	NA
		≤0.21 and decrease from BL ≥15%			
WBC	10E9/L	≤2, <1	NA	≥20	NA
Neutrophils	10E9/L	<0.5	NA	≥20	NA
		<1.0 and decrease from BL ≥0.5			
Lymphocyte	10E9/L	≤0.5, ≤0.25	NA	≥10.0	NA
Monocytes	10E9/L	NA	NA	≥1.4, ≥5.0	NA
Eosinophils	10E9/L	NA	NA	≥1.5, ≥5.0	NA
Basophils	10E9/L	NA	NA	≥1.0, ≥2.0	NA
Platelet Count	10E9/L	≤20		≥600	NA
		≤50 and decrease from BL ≥25			
INR		NA	NA	≥4.5	NA
Biochemistry					
ALT	IU/L	NA	NA	≥3 x ULN, ≥5 x ULN	NA
AST	IU/L	NA	NA	≥3 x ULN, ≥5 x ULN	NA
ALP	IU/L	NA	NA	≥3 x ULN	NA
CK	IU/L	NA	NA	≥500, ≥2000	NA
GGT	IU/L	NA	NA	≥5 x ULN	NA
Total Bilirubin	µmol/L	NA	NA	≥2 x ULN	NA

Parameter	Unit	Low value	Low decrease	High value	High increase
Albumin	g/L	≤20	NA	≥100	NA
		≤25 and decrease from BL ≥10		≥70 and increase from BL ≥10	
BUN	mmol/L	NA	NA	≥18	NA
Creatinine	umol/L	NA	NA	≥140, ≥190	NA
Sodium	mmol/L	≤132	NA	≥152	NA
Potassium	mmol/L	≤3	NA	≥5.5	NA
Chloride	mmol/L	≤90	NA	≥120	NA
Fasting Glucose	mmol/L	≤2.5	NA	≥7.0, ≥11.1	NA
Total Cholesterol	mmol/L	NA	NA	≥7.25	NA
IgG	mg/L	<=4.0	<6.5 and >=20% decrease from baseline	NA	NA
IgA	mg/L	NA	<=200 and > 20% decrease from baseline	>=6000	NA
IgM	mg/L	NA	<=200 and > 20% decrease from baseline	>=6000	NA
Bicarb	mmol/L	<=12	NA	>=40	NA
eGFR	mL/min/1.73m2	<=25	<=50 and >=25% decrease from baseline	>=150 and>=25% increase from baseline	
Urinalysis					
Urine protein/ creatinine ratio	g/mmol	NA	NA	≥0.395	NA
Fasting lipid profile					
HDL	mmol/L	≤0.8	NA	NA	NA
LDL	mmol/L	NA	NA	≥5.2	NA
Triglycerides	mmol/L	NA	NA	≥3.6, ≥5.4	NA

Appendix E Reference ranges and TELVC for vital signs

Parameter	Unit	Low value	Low decrease	High value	High increase
Pulse	Beats per minute	≤50	NA	≥120	NA
		≤50 and decrease from BL ≥20		≥120 and increase from BL ≥20	
Systolic blood pressure	mmHg	≤90	NA	≥160	NA
		≤90 and decrease from BL ≥20		≥160 and increase from BL ≥20	
Diastolic blood pressure	mmHg	≤50	NA	≥100	NA
		≤50 and decrease from BL ≥10		≥100 and increase from BL ≥10	

Appendix F Percent suppression calculation

1. Obtain Ct values for test samples (from clinical trial subjects) and the pooled normal control. This data consists of 3 endogenous control genes (18S, ACTB, and GAPDH) and 21 IFN-inducible genes.

2. Calculate ΔCt values for each sample (unique subject and time point) by subtracting the average endogenous control gene Ct value from each of the 21 IFN-inducible genes (done for both the test samples and the pooled control sample).

3. Calculate ΔΔCt values for each test sample by subtracting the pooled control ΔCt values from the test sample ΔCt values for each gene (e.g. Test Sample $\Delta Ct_{(EPSTI1)}$ - Pooled Control $\Delta Ct_{(EPSTI1)}$).

4. Multiply each ΔΔCt value by -1 (for magnitude directionality purposes). Calculate the power of 2 for each of the adjusted values. The ΔΔCt values are now in a linear scale format.

5. Calculate the observed target neutralization (tn) value for each gene for all available individual subject time points (X) relative to their baseline adjusted ΔΔCt values using the formula below;

$$tn = ((\text{Baseline adj. } \Delta\Delta Ct - \text{Day-X adj. } \Delta\Delta Ct)/ \text{Baseline adj. } \Delta\Delta Ct) * 100$$

6. Calculate the median target neutralization across all 21-gene for a particular subject and time point.

7. Adjust the median target neutralization value by subtracting it from 100. This normalizes all target neutralization values to a baseline value of 100%. This value is utilized as the final percent suppression value for further evaluation. A value <100% represent a target suppression relative to a particular subjects' baseline levels, while a value >100% represents an induction.