Revised Clinical Study Protocol	
Drug Substance	Anifrolumab (MEDI546)
Study Code	D3468C00003
Version	4.0
Date	19 May 2025

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase III Study Evaluating the Efficacy and Safety of Anifrolumab in Asian Participants with Active Systemic Lupus Erythematosus

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	01 Dec 2021		
2	07 Jul 2023		
3	19 May 2025		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

This CSP has been subject to a peer review according to AstraZeneca Standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	**19-May-2025**
Amendment 2	07-Jul-2023
Amendment 1	01-Dec-2021
Original Protocol	12-Nov-2020

Amendment 3 [19-May-2025]

Overall Rationale for the Modification:

[redacted] This change allows reduced reliance on the historical data [redacted].

Other changes are non-substantial changes are error corrections and administrative updates.

Summary of Changes:

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Protocol synopsis: Statistical methods Section 8.2: Sample size estimate Section 8.5.1: Analysis of the primary variable	[redacted]	To reduce reliance on the historical data [redacted]
	Updated [redacted] credible interval to [redacted] credible interval.	To be comparable with the conventional statistical practice.
	[redacted]	To provide comparison with different levels of thresholds

List of Non-Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Appendix U Protocol Amendment History	Added a new appendix to document protocol amendment history	Administrative
Section 3.1 Inclusion criteria	Inclusion criteria # 18: Changed Table 1 to Table 2.	Error correction.
Section 4.1 study plan: Table 4	Changed “verify eligibility criteria section 2.4” to “verify eligibility criteria sections 3.1 and 3.2”	Error correction.

PROTOCOL SYNOPSIS

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase III Study Evaluating the Efficacy and Safety of Anifrolumab in Asian Participants with Active Systemic Lupus Erythematosus

International Co-ordinating Investigator

[redacted], MD

[redacted]

Study site(s) and number of participants planned

Approximately 260 participants are planned to be randomised in Asia.

Study design

This is a Phase III, multicenter, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an intravenous (IV) treatment regimen of 300 mg anifrolumab vs placebo in Asian participants with moderate to severe active, autoantibody positive systemic lupus erythematosus (SLE) despite receiving standard of care (SOC). The study will be performed in participants aged 18 to 70 years of age.

Participants with a confirmed diagnosis of moderate to severe SLE and are currently receiving SOC comprising oral corticosteroids (OCSs), and/or immunosuppressants, and/or antimalarial, either alone or any combination of them, for a required duration of treatment at a stable dose, as described in the inclusion criteria may be eligible for randomization. Combination of ≥2 immunosuppressants should be avoided for safety reason. Participants must have eligible scores for SLE Disease Activity Index 2000 (SLEDAI-2K), British Isles Lupus Assessment Group (BILAG)-2004, and Physician's Global Assessment (PGA) as confirmed by the Disease Activity Central Review Team (DACRT).

Approximately 260 eligible participants receiving SOC treatment will be randomised in a 1:1 ratio to receive either a fixed IV dose of 300 mg anifrolumab or placebo every 4 weeks (Q4W) for a total of 13 doses (Week 0 to Week 48), with the primary endpoint evaluated at the Week 52 visit.

Randomisation will be stratified using the following factors: SLEDAI-2K score at screening (<10 points vs ≥10 points); Randomisation (Day 1) OCS dose (<10 mg/day vs ≥10 mg/day prednisone or equivalent); and region (Mainland China vs Not Mainland China).

This study includes:

- **A Screening Period**: Up to 35 days
- **Treatment Period**: A 52-week double-blind treatment period with anifrolumab or placebo administration as an intravenous (IV) infusion via an infusion pump over a minimum of 30 minutes, Q4W from Week 0 to Week 48 for a total of 13 doses.
- **Safety Follow-up Period:** After Week 52 (the completion of the double-blind treatment period), participants will continue in the study for further 8 weeks to complete the safety follow-up period, which is comprised of two visits, at Week 56 and Week 60.

From Week 0 (after randomisation) to Week 12, participants may receive **only** 1 burst of corticosteroids for an increase in SLE disease activity or to control non-SLE related disease (e.g., asthma or chronic obstructive pulmonary disease [COPD] exacerbation).

An important secondary objective in the study is assessing whether anifrolumab improves the ability to reduce oral corticosteroid dose in participants to ≤7.5 mg prednisone or equivalent per day. For this reason, steroid tapering to a target OCS dose of ≤7.5 mg/day **must** be attempted in all participants with a baseline OCS dose ≥10.0 mg/day. This will commence at Week 8 and continue stepwise until the target dose is reached, unless at least 1 of the following criteria is met:

- 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)
- Moderate to severe skin disease as reflected by a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score of ≥ 10
- Extensive joint disease as reflected by ≥8 tender and ≥8 swollen joints

Although a recommended steroid-tapering regimen is provided, investigators will have flexibility in how the OCS dose is reduced at each visit. If steroid tapering is not attempted in an eligible participant, the Sponsor or Sponsor's designee **must** be contacted immediately.

Investigators will not be required, but may continue, to taper OCS dose beyond the target of 7.5 mg/day up to Week 40 based on disease activity. If a participant has an increase in disease activity secondary to OCS tapering, they may increase the dose up to a maximum of the

baseline OCS therapy dose from Week 8 up to Week 40. Participants who require OCS dose above their baseline level may continue in the study following consultation with the Sponsor or Sponsor's designee, but may be considered as non-responders for efficacy endpoints. **Steroid tapering will not be permitted after Week 40** (details are defined in the SAP).

Participants with OCS dose adjustment beyond the protocol-allowed threshold may be considered as non-responders for efficacy endpoints (details are defined in the Statistical Analysis Plan).

Objectives and Endpoints

Objectives	Estimand Description/Endpoints/Outcome Measures
Primary	**Estimand Description**
To evaluate the effect of anifrolumab compared to placebo on disease activity	**Population:** Asian adults with moderate to severe active, autoantibody positive SLE despite receiving SOC **Endpoint:** BICLA, a composite binary endpoint defined by meeting all of the following criteria: • Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, where worsening is defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B • No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase from baseline of >0 points in SLEDAI-2K • No worsening from baseline in participants' lupus disease activity, where worsening is defined as an increase of ≥0.30 points on a 3-point PGA visual analogue scale (VAS) **Intercurrent events**: Use of restricted medications (RM) [a], premature end of treatment (PEOT) or death: composite strategy (non-responders from the time such events occur up to Week 52) **Summary measure**: difference in proportions of participants who are responders between anifrolumab and placebo at week 52
Key Secondary	**Endpoints**
To evaluate the effect of anifrolumab compared to placebo on:	
The proportion of participants who achieve SRI(4) response at week 52	SRI(4) response defined by meeting all of the following criteria: • Reduction from baseline of ≥ 4 points in the SLEDAI-2K. • No new organ systems affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline. • No worsening from baseline in the participants' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

The proportion of participants who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the sub-group of those with baseline OCS ≥10 mg/day	Maintained OCS reduction defined by meeting all of the following criteria: • Achieve an OCS dose of ≤ 7.5 mg/day prednisone or equivalent by Week 40 • Maintain an OCS dose ≤ 7.5 mg/day prednisone or equivalent from Week 40 to Week 52
The annualized flare rate through 52 weeks	Annualised flare rate with flare defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit
Other Secondary	**Endpoints/Outcome Measures**
To evaluate the effect of anifrolumab compared to placebo on the proportion of participants with a ≥ 50% reduction in CLASI activity score at Week 12 in the sub-group of those with baseline CLASI activity score ≥ 10	50% reduction in CLASI activity score compared to baseline defined by meeting the following criterion: • Achieve ≥ 50% reduction of CLASI activity score at Week 12 compared to baseline
To evaluate the effect of anifrolumab compared to placebo on the proportion of participants with reduction in the number of swollen and tender joints at Week 52 in the sub-group of those with ≥ 6 swollen and ≥ 6 tender joints at baseline:	Reduction defined by meeting the following criterion: • Achieve ≥ 50% reduction in the number of swollen and ≥ 50% reduction in the number of tender joints compared to baseline
To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamics of anifrolumab	Anifrolumab concentration and PK parameters, anti-drug antibodies (ADA), 21-gene type I IFN gene signature, anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, third component (C3), fourth component (C4), and total haemolytic complement (CH50) levels
Safety Objective	**Outcome Measures**
To evaluate the safety and tolerability of anifrolumab	Adverse events (including AESIs), vital signs, physical examination, 12 lead electrocardiograms (ECG), clinical laboratory tests (haematology, clinical chemistry, urinalysis), Columbia Suicide Severity Rating Scale (C-SSRS)

[a]: Restricted medication is described in Section 7.7. There may be some special cases of RM use intercurrent events where participants are eligible to respond after some duration of time. Additional details are given in the SAP.
BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; ECG = Electrocardiogram; OCS = oral corticosteroids; PGA = Physician's Global Assessment; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4) = Systemic Lupus Erythematosus Responder Index of ≥ 4; VAS = Visual analogue scale; LLDAS=Lupus Low Disease Activity State.

Note: Estimand descriptions for the key/other secondary endpoints are detailed fully in SAP. For Exploratory objectives and endpoints, see Section 2.

Target participant population

The study will be performed in Asian participants aged 18 to 70 years of age with moderate to severe SLE. Participants must be currently receiving OCSs, antimalarial, and/or immunosuppressants for a required duration of treatment at a stable dose, as described in the inclusion criteria. Participants must meet eligibility scores for SLEDAI-2K, BILAG-2004, and Physician's Global Assessment (PGA) as confirmed by the Disease Activity Central Review Team (DACRT) before randomization.

Duration of treatment

The treatment period duration is 52 weeks. Investigational medicinal product will be administered every 4 weeks from Week 0 to Week 48 for a total of 13 doses with the primary endpoint evaluated at Week 52. The total study duration could be up to approximately 65 weeks (including screening period and follow up period).

Investigational medicinal product, dosage and mode of administration

Approximately 260 participants receiving SOC treatment will be randomised in a 1:1 ratio to receive a fixed IV dose of anifrolumab 300 mg or placebo, as follows:

- Anifrolumab (MEDI-546) 300 mg IV administration Q4W OR
- Placebo IV administration Q4W

Statistical methods

The treatment effect of anifrolumab vs placebo measured by BICLA response at Week 52 will be estimated using the Bayesian robust meta-analytic-predictive (MAP) prior approach with borrowing from the pooled global phase III studies D3461C00005 (study 05) and D3461C00004 (study 04). The sample size is calculated based on the criterion of having greater than [redacted] posterior probability that anifrolumab 300mg is effective compared to placebo (difference in BICLA response rates at Week 52 greater than 0).

The BICLA response rates at Week 52 observed in the pooled study 05 and study 04 will be used as an informative prior for the response rates for anifrolumab 300 mg and placebo groups in the Asian population. A robust MAP prior approach (Schmidli et al, 2014) will be adopted to partially extrapolate the pooled response rates of study 05 and study 04 to the Asian population. The informative prior will be robustified with a prior weight, where the weight

represents the a priori degree of relevance of the pooled response rates of study 05 and study 04 to the Asian population. With a level of extrapolation ([redacted] weight), and the assumed proportions of BICLA response rates 47.5% and 30.8% in the anifrolumab 300 mg and placebo groups respectively (based on the pooled study 05 and study 04), 130 participants/arm yields [redacted] chance of having greater than [redacted] posterior probability that anifrolumab is effective compared to placebo (power: [redacted]). Under the assumptions of no treatment difference (30.8% vs 30.8%), 130 participants/arm and [redacted] prior weight will control the probability of having greater than [redacted] posterior probability of efficacy at approximately [redacted] (one-sided type I error: [redacted]). Expecting screen failure rate of 50%, approximately 520 participants shall be screened to obtain the required number of randomised participants.

The full analysis set (FAS) will be used as the primary population for reporting efficacy, which is defined as participants who are randomised and received at least 1 dose of investigational medicinal product (modified Intention-To-Treat [mITT]). The primary endpoint is response in BICLA, a composite binary endpoint whereby responders are defined by meeting all of the criteria specified in the above Objectives table at week 52. Otherwise, participants will be classified as non-responders. Intercurrent events RM, PEOT and death, result in a non-responder status using the composite strategy for the primary estimand. Study withdrawal will be imputed as a non-responder. If any of the criteria cannot be evaluated at Week 52 (e.g., due to missing values) that criterion will be imputed by carrying the Week 48 value forward and BICLA response will be derived based on the complete data. This applies only if Week 48 data is not missing, otherwise the participant will be defined as a BICLA non responder at Week 52. The primary analysis will be based on the initial 52-week, double-blind, placebo-controlled phase of the study and the assessment for the primary analysis will be based on the posterior probability that anifrolumab is effective compared to placebo using the Bayesian model. [redacted] posterior estimates for the treatment difference in BICLA response rates at Week 52 and the corresponding 95% credible intervals will be presented. Posterior probabilities of efficacy will also be estimated and compared with a number of thresholds, including [redacted] Results across a range of prior weights will also be presented for the primary endpoint. More details will be pre-specified in the statistical analysis plan (SAP).

In addition to the primary Bayesian analysis, the following analysis under the frequentist framework will be also performed for the FAS as supportive analysis. The treatment effect (i.e., the difference in response rate for anifrolumab vs placebo) will be estimated using a stratified Cochran-Mantel-Haenszel (CMH) method (Clowse et al, 2017; Cochran, 1954) with the same stratification factors as for the randomisation. The corresponding 95% confidence interval (CI), and 2-sided nominal p-value for the difference at Week 52, as well as the estimated response rate and the corresponding 95% CI within each treatment group will be presented. Further, longitudinal presentations of results by timepoint based on the same

method, with the corresponding 95% CI will be provided. Details for the CMH method will be pre-specified in the SAP.

There are 3 key secondary endpoints as listed in the Objectives section. The binary key secondary endpoints will be analyzed using the same CMH method as described above for the FAS. The effect on the annualized flare rate will be analyzed using a negative binomial regression model. The model will include covariates of treatment group, and the stratification factors. The logarithm of the follow-up time will be used as an offset variable in the model to adjust for participants having different exposure times. Nominal p-values will be reported for key secondary endpoints. No multiplicity adjustment will be applied.

The PK, PD and immunogenicity results will be summarized using descriptive statistics at each visit by treatment group. All safety parameters will be analyzed descriptively using safety analysis set.

The efficacy and safety in China subgroup will be analyzed to facilitate a benefit-risk assessment for regulatory submission in China. No interim analysis is planned.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Systemic lupus erythematosus (SLE) is a chronic, multisystemic, disabling autoimmune rheumatic disease of unknown aetiology. Systemic lupus erythematosus predominantly affects women of childbearing years (Cochran, 1954; Cooper et al, 1998; Lahita, 1999) with a review reporting the female-to-male ratio in the childbearing years to be about 12:1 (Okamoto et al, 2004; Pascual et al, 2006; Petri, 2001; Posner et al, 2007; Ramsey-Goldman and Manzi, 2000). There is substantial unmet medical need in the treatment of SLE, particularly in patients with moderate or severe disease. Although off-label therapy has improved management options in recent years, long-term prognosis remains poor for many patients. Compared to the general population, the overall mortality in SLE is increased with a standardized mortality ratio (SMR; defined as the ratio of the number of deaths observed to deaths expected) of 2.4, (2.3 to 2.5 95% confidence interval [CI]) in a large international cohort of 9,457 patients followed for over 70000 patient-years (Bernatsky et al, 2006).

SLE has been reported to be more prevalent among Asians than their white counterparts (Danchenko et al, 2006; D'Cruz, 2006). Asian patients were reported to have higher rates of lupus nephritis-associated autoantibodies, lupus nephritis, more active glomerulonephritis and higher overall damage scores compared with White patients (Merrill, 2014; Mok and Li, 2010).

Clinical manifestations of SLE include, but are not limited to, constitutional symptoms such as fatigue and fever, alopecia, rashes, serositis, arthritis, nephritis, vasculitis, lymphadenopathy, splenomegaly, haemolytic anaemia, cognitive dysfunction and other nervous system involvement. These disease manifestations cause a significant burden of illness and can lead to reduced physical function, loss of employment, lower health-related quality of life, and a lifespan shortened by about 10 years (ACR ad hoc committee, September 1999). Increased hospitalizations and side effects of medications including chronic oral corticosteroids (OCS) and other immunosuppressive treatments add to disease burden in SLE (Doria and Briani, 2008; Petri, 2001; Zonana-Nanach et al, 2000).

All of the therapies currently used for the treatment of SLE have well known adverse effect profiles and there is a medical need to identify new targeted therapies, particularly agents that may reduce the requirement for corticosteroids and cytotoxic agents.

Many agents currently used to treat SLE, such as azathioprine, cyclophosphamide, and mycophenolate mofetil/mycophenolic acid, have not been approved for the disease. Furthermore, these drugs all have well-documented safety issues and are not effective in all patients for all manifestations of lupus. Antimalarial agents (e.g., hydroxychloroquine) and

corticosteroids may be used to control arthralgia, arthritis, and rashes. Other treatments include nonsteroidal anti-inflammatory drugs (NSAIDs); analgesics for fever, arthralgia, and arthritis; and topical sunscreens to minimize photosensitivity. It is often difficult to taper patients with moderate or severe disease completely off corticosteroids, which cause long-term morbidity and may contribute to early cardiovascular mortality (Petri, 2001; Urowitz et al, 1976). (Belimumab (Benlysta®), a human Ig G1monoclonal antibody that binds to soluble B-lymphocyte stimulator protein (BlyS) biological activity, was the first new treatment to receive approval for SLE in over 50 years. Telitacicept, a human Ig G1 monoclonal antibody that binds to BlyS and a proliferation-inducing ligand (APRIL), was approved in Mainland China in 2021 for treatment of adult SLE patients. However, not all patients respond to those treatments and there is a substantial unmet need for novel therapies targeting other (central) disease driving pathways.

Multiple lines of evidence indicate a role of type I interferons (IFNs) in the pathogenesis of SLE:

- Genetic polymorphisms associated with type I IFNs are associated with susceptibility to SLE (Criswell, 2008; Rönnblom and Pascual, 2008; Schwartz et al, 2009; Sigurdsson, Göring et al, 2008; Sigurdsson, Nordmark et al, 2008).
- High IFN-α levels and type I IFN activity have been reported in SLE (Banchereau et al, 2004; Bengtsson et al, 2000; Dall'era et al, 2005).
- Increased levels of messenger ribonucleic acid (mRNA), whose transcription is induced by type I IFNs (type I IFN signature), are prominent in peripheral blood mononuclear cells and whole blood in approximately 60% of SLE participants and are associated with greater disease activity (Baechler et al, 2003; Bennett et al, 2003; Crow and Wohlgemuth, 2003; Feng X et al, 2006; Hylton et al, 1986; Kirou et al, 2004; Kirou et al, 2005). Transcripts induced by type I IFN are the most overexpressed transcripts in SLE (Yao et al, 2010).
- Proteins induced by IFN are increased in participants with SLE (Huang et al, 2008; Hylton et al, 1986; Okamoto et al, 2004).
- Overexpression of type I IFN, type I IFN signature, and proteins induced by type I IFNs have been associated with greater disease activity and organ system involvement in SLE.

Patients with high anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody titres, lupus nephritis, and progressive skin rashes have high serum levels of type I IFN (Banchereau et al, 2004; Bengtsson et al, 2000). In addition, patients with acute skin involvement tend to have elevated IFN in blood and skin (Dall'era et al, 2005). Skin biopsies from participants with SLE also show increased type I IFN signature (Blomberg S et al, 2001; Dobkin et al, 1999; Doria and Briani, 2008; Farkas et al, 2001; World Health Organization, 2014; Yao et al,

2009). Proteins induced by IFN are increased in patients with active central nervous system (CNS) symptoms (Okamoto et al, 2004).

Immune complexes containing SLE autoantibodies, such as anti-dsDNA or antiribonucleoprotein (anti-RNP) antibodies, can activate type I IFN production (Banchereau et al, 2004; Bengtsson et al, 2000; Rönnblom and Alm, 2003). After internalization through Fc receptors, autoantibody-containing immune complexes bind endosomal toll-like receptor 7 (TLR7) and toll-like receptor 9 (TLR9), stimulating production of type I IFN. Type I IFN stimulates monocyte derived dendritic cell maturation, which promotes loss of tolerance and generation of autoreactive T and B cells, autoantibody production, immune complex formation, and further production of type I IFN, creating a self-perpetuating cycle of autoimmunity (Banchereau et al, 2004; Pascual et al, 2006; Rönnblom and Pascual, 2008).

Anifrolumab, a type I IFN receptor antagonist, is the first-in-class type I IFN targeted therapy approved in multiple countries for the treatment, as administered intravenously, of adult patients with moderate to severe SLE despite standard therapy. In addition, anifrolumab is being investigated as a novel treatment for adults with active, proliferative LN based on encouraging Phase II results. Anifrolumab will potentially also be investigated as a novel treatment modality in other type I IFN driven diseases such as SSc and myositis.

Anifrolumab inhibits type I IFN signaling by blocking the biologic activity of type I IFNs, and multiple lines of evidence indicate a role of type I IFNs in the pathogenesis of SLE. Most adult patients with SLE (approximately 60% to 80%) express elevated levels of type I IFN-inducible genes (Yao et al, 2010, Kennedy et al 2015, Hoffman et al 2017), and they have been associated with increased SLE disease activity and severity (Bengtsson et al, 2000, Baechler et al, 2003, Kirou et al, 2005, Postal et al, 2012).

Anifrolumab administered IV has been studied for the treatment of adults with moderate to severe SLE who were receiving standard of care in 3 phase III studies and 3 phase II studies. The phase III studies of anifrolumab IV were studies D3461C00005 (hereafter referred to as "study 05") and D3461C00004 (hereafter referred to as "study 04"), and the placebo - controlled LTE study D3461C00009 (hereafter referred to as "Study 09") (included patients who completed either study 05 or study 04). The safety evaluation of anifrolumab IV 300 mg Q4W over 52 weeks was based on pooled data from the phase III studies 05 and 04, and data from phase II study CD IA-MEDI- 546-1013 (hereafter referred to as "study 1013"). The evaluation of the long-term safety profile of anifrolumab IV 1000 mg/300 mg Q4W was based on 2 long-term extension studies (each up to 3 years): open-label Ph II CD-IA-MEDI-546-1145 (hereafter referred to as "study 1145") and randomized, placebo-controlled phase III study (study 09). Overall, based on safety data reported from unblinded and open-label studies as of the data cut-off (29 Jan 2023), anifrolumab with IV administration has been well

tolerated and has an acceptable safety profile in adult patients with moderate to severe SLE while receiving standard of care treatment during 52 weeks of treatment and for up to 4 years.

A detailed description of the chemistry, pharmacology, efficacy, and safety of anifrolumab is provided in Investigator's Brochure (IB).

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design

This is a Phase III, multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of an IV treatment regimen of 300 mg anifrolumab vs placebo in adult Asian participants with moderate to severe active, autoantibody-positive SLE while receiving standard of care (SOC) treatment.

To ensure adequate treatment, all participants will receive SOC treatment with at least 1 of the following: OCS, antimalarial, or immunosuppressants, in addition to investigational medicinal product (IMP). This is consistent with both the European League Against Rheumatism (EULAR) (Bertsias et al, 2008) and American College of Rheumatology (ACR) (ACR ad hoc committee, September 1999) management guidelines of moderate to severe SLE.

The study will be randomised, placebo-controlled, and double-blind to ensure a robust design and minimize bias. This is the preferred design as outlined in the Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products for the treatment of SLE, cutaneous lupus and lupus nephritis (CHMP, February 2015).

Randomisation will be stratified by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K, see Appendix E) score at screening (<10 points vs ≥10 points), Day 1 OCS dose (<10 mg/day vs ≥10 mg/day of prednisone or equivalent), and region (Mainland China vs Not Mainland China). Stratification is implemented in order to minimize the risk for baseline imbalance(s) across treatment arms on potentially confounding variables. Baseline imbalances of these factors could impact efficacy and/or safety assessments of anifrolumab vs placebo.

A treatment period of 52 weeks is an appropriate study duration to determine the IMP's efficacy and safety profile. To ensure adequate safety and immunogenicity follow up, all participants that complete the study treatment shall be assessed for an additional 8 weeks in safety follow up period, which is comprised of two visits at Week 56 and Week 60.

The global Phase II and III studies showed consistent efficacy and safety profiles across the range of ethnicities, including Asian patients, included in the studies. As a novel design, Bayesian borrowing from the pooled global Phase III studies could improve feasibility for

evaluating efficacy given a positive treatment effect observed in study 04 and study 05, whilst it would not jeopardize the scientific value in evaluating treatment effects of anifrolumab vs placebo in the Asian (including Chinese) SLE population. The statistical method has been updated to using the Bayesian borrowing approach to estimate the treatment effect of anifrolumab vs placebo in terms of reducing disease activity in the Asian SLE population, with data borrowing from the pooled global Phase III study 05 and study 04. More details of the approach are described in Section 8 and additional details are given in the SAP.

1.2.2 Rationale for primary endpoint selection

The primary outcome measure is the proportion of participants achieving the British Isles Lupus assessment Group-based Composite Lupus Assessment (BICLA) response at Week 52.

Two composite endpoints, the SLE Responder Index (SRI) and BICLA, have been widely used in clinical trials, and accepted by SLE experts and health authorities. Both SRI(4) and BICLA have been used in anifrolumab clinical program. In study 04 using BICLA as primary endpoint, anifrolumab demonstrated a statistically significant and clinically meaningful benefit compared with placebo (47.8% vs 31.5%; difference 16.3%, 95% CI 6.3, 26.3; p=0.0013). While study 05 did not achieve its primary endpoint SRI(4), clinical meaningful responses were observed on secondary endpoint (BICLA response at Week 52) (47.1% vs 30.2%; difference 17.0%, 95% CI 7.2, 26.8; nominal $p < 0.001$), which is consistent with study 04 result.

There are advantages of using BICLA. BILAG, the main disease activity index that drives BICLA, registers both partial and complete clinically meaningful improvement within multiple organ domains and requires improvement in all organ systems affected at baseline. In addition, BILAG applies equal weighting to all organ systems in its scoring. BICLA has produced consistent results in phase III study 05 and study 04, and a phase IIb study 1013, and across time (Furie et al, 2017; Mikdashi and Nived, 2015; Thanou et al, 2014; Clowse et al, 2017). Consequently, BICLA is the focus of the efficacy assessment of anifrolumab.

Based on the evidence above, this study selects BICLA as the primary efficacy endpoint.

1.2.3 Rationale for dose selection

The selection of a dose of 300 mg anifrolumab Q4W for this study is based on safety and efficacy results from the results of anifrolumab clinical program.

The first phase III study (study 05) did not meet the primary endpoint of a statistically significant reduction in disease activity, as measured by SRI(4) at Week 52. However, clinically meaningful numerical responses to anifrolumab 300 mg on several key secondary endpoints were observed: individual disease manifestations (skin activity measured by

CLASI, and joint disease) and maintained OCS reduction. The annualized flare rate was numerically lower for anifrolumab 300 mg compared with placebo. Other secondary endpoints (including BICLA response at Week 52) also suggested benefit of anifrolumab 300 mg.

The second phase III study (study 04) met its primary endpoint with anifrolumab 300 mg demonstrating a statistically significant and clinically meaningful benefit compared with placebo in overall disease activity, as measured by BICLA response at Week 52. Anifrolumab also demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoints: BICLA response in IFN test-high participants, ability to taper steroids, and improvement in skin disease. A numerically higher reduction in the rate of flares was observed for anifrolumab compared with placebo; however, statistical significance could not be concluded. No difference was seen in the proportion of participants achieving at least 50% reduction in the number of swollen and tender joints at Week 52.

The totality of evidence from phase III studies (study 04, study 05), and phase IIb study 1013 including the highly consistent treatment benefit observed across the studies, and across a range of clinically meaningful endpoints, lead to the conclusion that anifrolumab 300 mg IV Q4W provides clinical benefit over 52 weeks compared to placebo in moderate to severe SLE participants. To date, no significant ethnic difference in PK profile, efficacy and safety has been observed in different populations and anifrolumab has been approved across regions worldwide. The Phase I study (D3468C00002) also shows the tolerable safety profile and consistent PK/PD response of 300 mg anifrolumab IV in Chinese patients with SLE. For these reasons, the selection of a dose of 300 mg anifrolumab is justified for this study which expects to observe similar positive benefits/risk profile of anifrolumab 300 mg IV in Asian (including Chinese) population.

1.2.4 Rationale for duration of infusion

In a Phase IIb study 1013 where 2 doses of anifrolumab (300 mg and 1000 mg) in combination with SOC were compared to placebo, all doses were administered over approximately [redacted]. The frequency of infusion related reactions did not differ substantially between the 300 mg [redacted]) and 1000 mg ([redacted]) groups, and both were lower than that observed in the placebo group ([redacted]). In the two Phase III studies (study 05 and study 04), the infusion time was reduced to a minimum of [redacted]. In these phase III studies, the infusion related AE was a slightly higher in 300 mg dose group than placebo in study 05 [redacted] and study 04 ([redacted] Overall, infusions of anifrolumab were generally well tolerated as most AEs temporally associated with infusions were nonserious and mild or moderate in intensity.

For those reasons, the infusion time in this study is kept as a minimum of [redacted].

1.3 Benefit/risk assessment

A detailed assessment of the overall benefit/risk of anifrolumab is discussed in the IB.

1.3.1 Risk assessment

As of 29 Jan 2023, anifrolumab safety has been evaluated in 11 unblinded or open-label completed studies: 8 in participants with SLE (study 05, study 04, study 1013, study 1145, study 02, study 08, D3468C00002 and study 09), 1 in participants with SSc (study MI-CP180), 1 in healthy volunteers (study 06) and 1 in participants with LN (study 07). Four studies are ongoing: 2 in participants with SLE (D3465C00001 and D3468C00003), 1 in participants with LN (D3466C00001) and 1 in healthy volunteers (D3465C00002).

Approximately 1968 patients and/or healthy volunteers have been enrolled in the clinical development program, of which 1317 participants have been exposed to at least 1 dose of anifrolumab, and 651 participants have been exposed to placebo.

Anifrolumab 300 mg vs placebo data from 52-week SLE study 04, study 05, and study 1013 were pooled to establish the overall safety profile of the drug. The long-term safety profile was based on 2 LTE studies: study 1145 and study 09.

A summary of the risk assessment for anifrolumab is provided in Table 1. More detailed information about the known and expected benefits and potential risks of anifrolumab may be found in the IB.

Table 1 Risk for Anifrolumab and Study Procedures

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Anifrolumab Risks		
Important Identified Risk: Herpes zoster **Identified Risks** Upper respiratory tract infection, bronchitis, respiratory tract infection, hypersensitivity, anaphylactic reaction, infusion-related reaction [a]	Refer to the IB for the most up-to-date safety data.	Patients will be excluded from participation in the study if they have: recurrent or opportunistic infection requiring hospitalization and IV antibiotics; live or attenuated vaccine or clinically significant infection within 8 weeks prior to signing the ICF; history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the participant to infection, or a positive HIV result; active HBV, HCV, CMV, or Epstein-Barr virus infection; severe HZ infection; or any infection requiring oral anti-infectives within 2 weeks prior to signing the ICF. See Section 3.2. Infections, including non-opportunistic serious infections, opportunistic infections, TB, and latent TB will be monitored closely in this study. See Section 3.2, Section 5.2.6, and Section 6.3. The incidence of severe allergic reactions has been low after IV administration of anifrolumab. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions will be immediately available, and site staff will be trained to recognize and treat anaphylaxis. See Section 3.2 and Section 6.10.1.
Important Potential Risks Based on Anifrolumab Mechanism of Action: Malignancy and serious infections	Refer to the IB for the most up to date safety data	Mitigation strategies for malignancy include exclusion of patients from participation in this study if they have a medical history of cancer, except for squamous or basal cell carcinoma of the skin and cervical cancer in situ, which have been treated with curative therapy that has been documented successful, as defined in the protocols. Participants will be closely monitored for the presence of neoplasms, and study intervention will be discontinued in the case of malignancy, based on the judgment of Investigator/AstraZeneca. See Section 3.2, and Section 6.3.4. For mitigation strategies for serious infections, see Section 3.2, Section 3.9 and Section 6.10.2. Malignancy and serious infections are important potential risks for anifrolumab based on its mechanism of action and will continue to be closely monitored during the study.

Abbreviations: CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; IB = Investigator's Brochure; ICF = informed consent form; IV = intravenous; SC = subcutaneous; TB = tuberculosis.

[a] Only for intravenous route of administration.

1.3.2 Benefit assessment

Across the 3 double-blind, global phase II/III studies (04, 05, and 1013), the efficacy of anifrolumab 300 mg IV Q4W in participants with moderate to severe SLE was observed across a range of clinically important endpoints. Anifrolumab showed an early and sustained effect on overall disease activity, the ability to taper steroid use to a clinically beneficial level (≤ 7.5 mg/day) and maintain this level to Week 52, an early and sustained benefit on cutaneous skin activity, and leads to a clinically meaningful reduction in the rate of flares.

In study 04, anifrolumab 300 mg demonstrated a statistically significant and clinically meaningful benefit compared with placebo in overall disease activity, as measured by BICLA response at Week 52, as well as in the ability to achieve a sustained taper of glucocorticoids and improvement in skin disease. Treatment with anifrolumab also resulted in a numerical reduction in the annual flare rate compared with placebo. The efficacy results in study 04 are supported by data from study 05 and study 1013.

A clinically meaningful numerical difference in overall disease activity measured by SRI(4) at Week 52 in favor of anifrolumab 300 mg was observed in 2 out of the 3 studies (study 04 and study 1013). In study 05, SRI(4) response rate at Week 52 was generally similar between participants in the anifrolumab 300 mg group compared with participants in the placebo group; the difference between treatment groups did not meet statistical significance.

1.3.3 Overall benefit: risk conclusion

Treatment with anifrolumab 300 mg IV Q4W was well tolerated, and had an acceptable safety profile in adult patients with moderate to severe SLE for up to 4 years of treatment.

Herpes zoster is an important identified risk for anifrolumab. Upper respiratory tract infection, bronchitis, respiratory tract infection, hypersensitivity, anaphylactic reaction, and infusion related reaction are identified risks for anifrolumab. Malignancy and serious infection are important potential risks for anifrolumab. Identified and important potential risks undergo careful enhanced monitoring in the development program. In additional to the ongoing blinded review provided by the study physician, an independent Data and Safety Monitoring Board (DSMB) will review blinded and unblinded safety data on a regular basis throughout the study (see Appendix A 6).

Overall, anifrolumab 300 mg as administered IV Q4W provides a favorable benefit-risk profile in the SLE population. Anifrolumab is the first-in-class type I IFN targeted therapy approved for the treatment of adult patients with moderate to severe SLE despite standard therapy.

1.4 Study design

This is a Phase III, multicenter, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an IV treatment regimen of 300 mg anifrolumab vs placebo in participants with moderate to severe, autoantibody positive SLE while receiving SOC treatment. The study will be performed in Asian participants aged 18 to 70 years of age.

Participants with a confirmed diagnosis of moderate to severe active SLE and are currently receiving SOC comprising of OCSs and/or antimalarial, and/or immunosuppressants, either alone or any combination of them, for a required duration of treatment at a stable dose, as described in the inclusion criteria. Participants must have eligible scores for SLEDAI-2K, BILAG-2004, and PGA as confirmed by the DACRT.

Eligible participants will be randomised in a 1:1 ratio to receive either a fixed intravenous dose of 300 mg anifrolumab plus SOC or placebo plus SOC Q4W for a total of 13 doses (Week 0 to Week 48), with the primary endpoint evaluated at the Week 52 visit.

Randomisation will be stratified using the following factors:

- SLE Disease Activity Index 2000 (SLEDAI-2K) score at screening (< 10 points vs ≥ 10 points);
- Randomisation (Day 1) OCS dose (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent);
- Region (Mainland China vs Not Mainland China).

This study includes:

- **A Screening Period**: Up to 35 days
- **Treatment Period:** A 52-week double-blind treatment period with anifrolumab or placebo administration as an IV infusion via an infusion pump over a minimum of 30 minutes, Q4W from Week 0 to Week 48 for a total of 13 doses.
- **Safety Follow-up Period:** After the completion of the double-blind treatment period (Week 52), participants will continue in the study for further 8 weeks to complete the safety follow-up period which is comprised of two visits at Week 56 and Week 60.

The total study duration could be up to approximately 65 weeks including screening period.

The safety of study participants will be reviewed by an independent DSMB; see Appendix A 6 for details.

1.4.1 Steroid burst

Section 7.7.3 provides specific details on steroid burst and tapers. From Week 0 (after randomisation) to Week 12, participants may receive **only** 1 burst of corticosteroids for an increase in SLE disease activity or to control non-SLE related disease (e.g., asthma or chronic obstructive pulmonary disease [COPD] exacerbation).

1.4.2 Protocol-specified steroid tapering

An important secondary objective in the study is assessing whether anifrolumab improves the ability to reduce oral corticosteroid dose in participants to ≤ 7.5 mg prednisone or equivalent per day. For this reason, steroid tapering to a target OCS dose of ≤ 7.5 mg/day **must** be attempted in all participants with a baseline OCS dose ≥ 10.0 mg/day. This will commence at Week 8 and continue stepwise until the target dose is reached, unless at least 1 of the following criteria is met:

- 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).
- Moderate to severe skin disease as reflected by a CLASI activity score of ≥ 10.
- Extensive joint disease as reflected by ≥ 8 tender and ≥ 8 swollen joints.

Although a recommended steroid-tapering regimen is provided, Investigators will have flexibility in how the OCS dose is reduced at each visit. If steroid tapering is not attempted in an eligible participant, the Sponsor or Sponsor's designee **must** be contacted immediately.

Investigators will not be required, but may continue, to taper OCS dose beyond the target of 7.5 mg/day up to Week 40 based on disease activity. If a participant has an increase in disease activity secondary to OCS tapering, they may increase the dose up to a maximum of the baseline OCS therapy dose from Week 8 up to Week 40. Participants who require OCS dose above their baseline level may continue in the study following consultation with the Sponsor or Sponsor's designee, but may be considered as non-responders for efficacy endpoints. Steroid tapering will not be permitted after Week 40. Section 7.7.3 provides specific details on steroid use during the double-blind treatment period.

1.4.3 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis

- The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and

considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

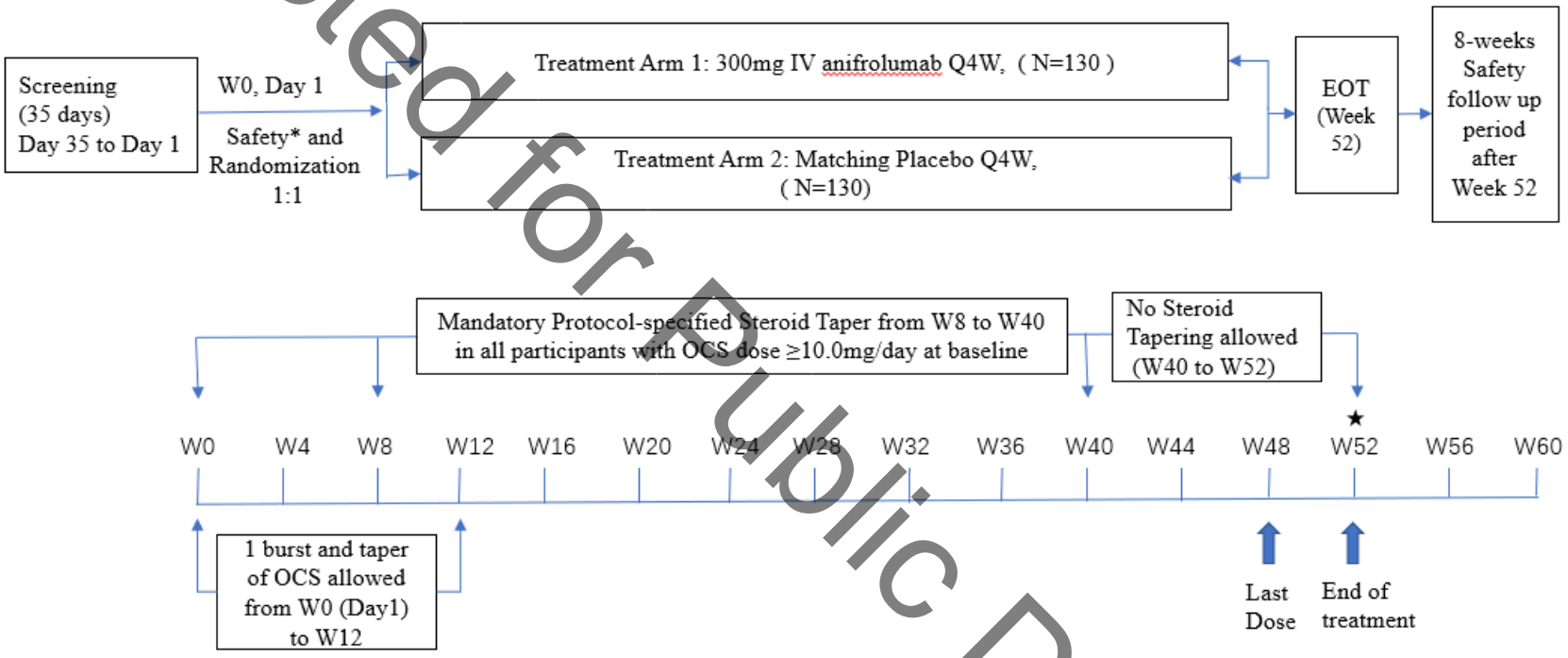
- To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

  Where allowable by local health authorities, ethics committees, healthcare provider guidelines (e.g., hospital policies), or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. Investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix M.

Figure 1 Study flow chart



★=Primary Endpoint at Week 52
*Stratification: SLEDAI Score (<or ≥10 mg); Region (Mainland China vs not Mainland China)
EOT=end of treatment; IV=intravenous; N=number of subjects; OCS=oral corticosteroid; Q4W= every 4 weeks; W=Week

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Estimand Descriptions:
To evaluate the effect of anifrolumab compared to placebo on disease activity	**Population:** Asian adults with moderate to severe active, autoantibody positive SLE despite receiving SOC **Endpoint:** BICLA, a composite binary endpoint defined by meeting all of the following criteria: • Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, where worsening is defined as ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B • No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase from baseline of > 0 points in SLEDAI-2K • No worsening from baseline in participants' lupus disease activity, where worsening is defined as an increase of ≥ 0.30 points on a 3-point PGA visual analogue scale (VAS) **Intercurrent events:** Use of restricted medications (RM)[a], premature end of treatment (PEOT) or death: composite strategy (non-responders from the time such events occur up to Week 52) **Summary measure:** difference in proportions of participants who are responders between anifrolumab and placebo at week 52

2.2 Secondary objectives

Key Secondary Objectives:	Endpoints:
To evaluate the effect of anifrolumab compared to placebo on:	
The proportion of participants who achieve SRI(4) response at week 52	SRI(4) response defined by meeting all of the following criteria: • Reduction from baseline of ≥ 4 points in the SLEDAI-2K. • No new organ systems affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline. • No worsening from baseline in the participants' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

The proportion of participants who achieve an oral corticosteroid (OCS) dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the sub-group of those with baseline OCS ≥10 mg/day	Maintained OCS reduction defined by meeting all of the following criteria: • Achieve an OCS dose of ≤ 7.5 mg/day prednisone or equivalent by Week 40. • Maintain an OCS dose ≤ 7.5 mg/day prednisone or equivalent from Week 40 to Week 52.
The annualized flare rate through 52 weeks	Annualised flare rate with flare defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit.
Other Secondary Objective	**Endpoints/Outcome Measures**
To evaluate the effect of anifrolumab compared to placebo on the proportion of participants with a ≥ 50% reduction in CLASI activity score at Week 12 in the sub-group of participants with baseline CLASI activity score ≥ 10	50% reduction in CLASI activity score compared to baseline defined by meeting the following criterion: • Achieve ≥ 50% reduction of CLASI activity score at Week 12 compared to baseline.
To evaluate the effect of anifrolumab compared to placebo on the proportion of participants with reduction in the number of swollen and tender joints at Week 52 in the sub-group of those with ≥ 6 swollen and ≥ 6 tender joints at baseline	Reduction defined by meeting the following criterion: • Achieve ≥ 50% reduction in the number of swollen and ≥ 50% reduction in the number of tender joints compared to baseline.
To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamics of anifrolumab	Anifrolumab concentration and PK parameters, ADA, 21-gene type I IFN gene signature, dsDNA antibodies, C3, C4, and CH50 levels

2.3 Safety objectives

Safety Objective	Outcome Measures
To evaluate the safety and tolerability of anifrolumab	Adverse events (including AESIs), vital signs, physical examination, 12 lead ECG, clinical laboratory tests (haematology, clinical chemistry, urinalysis), C-SSRS

2.4 Exploratory objectives

Exploratory Objectives	Endpoints/Outcome Measures
To explore the difference between anifrolumab and placebo on measures of disease activity including levels [redacted]	[redacted]
To explore the difference between anifrolumab and placebo on [redacted]	[redacted]

To explore the difference between anifrolumab and placebo on [redacted]	[redacted]

Note: Estimand descriptions for the key/other secondary endpoints are detailed fully in the SAP.

[a]: Restricted medication is described in Section 7.7. There may be some special cases of RM use intercurrent events where participants are eligible to respond after some duration of time. Additional details are given in the SAP.

ADA = Anti-drug antibody; BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; C3 = Third component of complement; C4 = Fourth component of complement; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; dsDNA = double stranded deoxyribonucleic acid; ECG = Electrocardiogram; EQ-5D-5L= EuroQoL 5 dimensions; LLDAS=Lupus Low Disease Activity State; OCS = oral corticosteroids; PGA = Physician's Global Assessment; PK = Pharmacokinetic(s); SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4) = Systemic Lupus Erythematosus Responder Index of ≥4; VAS = Visual analogue scale.

3 PARTICIPANT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

3.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Written informed consent and any locally required authorization (if applicable) obtained from the participant prior to performing any protocol-related procedures, including Screening evaluations.
3. In the opinion of Investigator, must be able to comprehend the ICF and all protocol related assessments, such that the participant can complete all study required documents, procedures, and outcome measures.
4. Completion of Screening procedures within 35 days after signing the ICF.

Age

5. Participant must be 18 to 70 years of age inclusive, at the time of signing the ICF.

Disease Characteristics

6. Participants who have a diagnosis of paediatric or adult SLE according to the ACR 1997 revised criteria (Stoll et al, 2004; Tan et al, 1982; see Appendix D) for ≥ 24 weeks prior to signing the ICF.
7. Must be receiving at least one of the following standard therapy regimens at Screening:
   (a) Oral prednisone (or equivalent) monotherapy:
      - Start date: minimum daily dose: ≥ 7.5 mg/day for at least 8 weeks prior to Day 1 (randomisation)
      - Must be stable for > 2 weeks before Day 1 (randomisation)
      - Maximum daily dose: ≤ 40 mg/day

   (b) Antimalarials and/or immunosuppressant(s) with or without OCS:
      - Permitted medications include: antimalarials, azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, mizoribine, tacrolimus, and cyclosporine (Note: The combination of azathioprine and methotrexate is not allowed due to known safety issues. The combinations of tacrolimus/cyclosporine

with other immunosuppressants above should be avoided. Combination with antimalarials is allowed.)

- Start date: ≥ 12 weeks prior to signing the ICF.
- Must be stable ≥ 8 weeks prior to signing the ICF.
- The daily dose should follow the local medical practice and not exceed the maximum allowed daily dose:
  - Azathioprine: ≤ 200 mg/day.
  - Mycophenolate mofetil ≤ 2 g/day or mycophenolic acid ≤ 1.44 g/day.
  - Oral, subcutaneous (SC), or intramuscular methotrexate ≤ 25 mg/week.
  - Mizoribine ≤ 150 mg/day.
  - Tacrolimus ≤ 0.2 mg/kg/day or cyclosporine ≤ 5 mg/kg/day, monitoring of serum concentration may be performed at the discretion of Investigator where local practice guidelines mandate or in case of safety concerns.

(c) Oral prednisone (or equivalent) plus immunosuppressant(s):

- Start dates for OCS and immunosuppressants must be met.
- Stability requirements for each medication must be met.
- No minimum daily dose for OCS when in combination with immunosuppressants.
- Maximum daily dosages for each medication in (a) and (b) must not be exceeded.

8. Autoantibody-positive at Screening, as determined by the central laboratory, for at least one of the following:
   (a) Antinuclear antibody (ANA) immunofluorescent assay test (titer ≥ 1:80).
   (b) Anti-dsDNA.
   (c) Anti-Smith (anti-Sm).
9. To be eligible a participant must have SLEDAI-2K ≥ 6 points, with ≥ 4 points coming from clinical components ("Clinical" SLEDAI-2K") at screening.

   In addition, the following criteria for "Clinical" SLEDAI-2K must be met:

   (a) Clinical SLEDAI of at least ≥ 4 points at Day 1 (randomization).

   Note: The "Clinical" SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures:

   - Includes points from the following clinical components: arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, or vasculitis.
   - Excludes points attributed to a fever, an SLE headache, and organic brain syndrome.

(b) In order to qualify for SLEDAI-2K score for arthritis at screening, participant must have at least 3 joints with tenderness AND swelling (same joints) due to SLE.

(c) In order to qualify for SLEDAI-2K score for rash at screening, participant must have rash with significant erythema (not only faint pink erythema).

(d) Clinical SLEDAI-2K points at screening cannot only be due to alopecia and mucosal ulcers.

10. At screening, BILAG-2004 (Appendix F) with at least 1 of the following:
    (a) BILAG-2004 level A disease in ≥ 1 organ system.
    (b) BILAG-2004 level B disease in ≥ 2 organ systems.
11. PGA score ≥ 1.0 on a 0 to 3 visual analogue scale (VAS) at Screening.
12. Participants with concurrent diagnosis of fibromyalgia must have either positive anti-dsDNA or low C3 or C4 during screening or must be on immunosuppressive treatment (excluding antimalarials) other than oral corticosteroids only.
13. Chest radiograph (obtained during Screening or within 12 weeks prior to signing of the informed consent) or a CT scan of the chest (within 12 weeks of signing the informed consent) which meets all of the following:
    (a) No evidence of current active infection (e.g., pneumonia, TB) or previous TB; and
    (b) No evidence of malignancy or no radiological findings of pulmonary nodules suspicious for lung cancer (as per applicable guidance, e.g., ACR Lung-RADS v2022 https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf) without appropriate follow up prior to enrolment; and
    (c) No clinically significant abnormalities (unless due to SLE).
14. Meets all of the following TB criteria:
    (a) No medical history or signs or symptoms of active TB prior to or during any Screening visit.
    (b) A chest radiograph during the Screening Period or within 12 weeks prior to signing of the informed consent with no evidence of active or signs of prior TB infection.
    (c) No recent contact with a person with active TB OR if there has been such contact, referral to a physician specializing in TB to undergo additional evaluation prior to randomisation (documented comprehensively in source), and, if warranted, receipt of appropriate treatment for latent TB initiated before the first administration of IMP.
    (d) No history of latent TB prior to initial Screening visit, with the exception of latent TB with documented completion of appropriate treatment.

Testing for Inclusion in the Study:

The participant must undergo an Interferon gamma (IFN-γ) release assay (IGRA) (e.g., QuantiFERON-TB Gold [QFT-G] test) test for TB obtained from the study Central Laboratory at screening with any of the following results:

(a) Negative test result.

(b) Positive test result: referral to a TB specialist for evaluation and for which active TB has been ruled out (as described in the protocol definition), and initiation of treatment for latent TB prior to the first administration of IMP in accordance with local standard of care.

(c) Indeterminate test result confirmed by repeat test using the same assay.

- If in an endemic region*, the participant must be referred to a TB specialist for evaluation (with assessment and treatment recommendation comprehensively documented in source) and initiation of appropriate latent TB treatment, if warranted, prior to the first administration of IMP. If no latent TB treatment is warranted, the participant may enter the study without latent TB treatment, but must be retested every 3 months for the first 6 months. If retest result at 6 months is indeterminate or negative, the participant may continue in the study without further testing.
- If in a non-endemic region, the participant may enter the study without referral to a TB-specialist and latent TB treatment, but must be administered a retest every 3 months for the first 6 months. If, upon retest by the end of the 6 months the result is indeterminate, the participant may continue in the study without treatment and with routine TB testing.

*Endemic region as defined based on World Health Organization (WHO) lists of High Burden Countries (HBC) for TB and multi-resistant (MDR) TB.

Notes:

- A participant with a positive IGRA [QFT-G] test result upon retest (after an initial indeterminate result) regardless if in endemic or non-endemic region should be referred to a TB-specialist for assessment to rule out active TB as described in protocol and initiation of appropriate latent TB treatment (with the assessment and treatment comprehensively documented in source) before any further IMP administration.

15. Any negative PCR or antigen test result (central or local labs as appropriate) at screening in addition to no known or suspected COVID-19 exposure within 2 weeks prior to screening based on the COVID-19 questionnaire.

- If there is a known or suspected exposure, a participant must be negative upon re-test result (central lab or local lab) obtained after 2 weeks and must remain asymptomatic for inclusion in the study.

Note: Following study specific rescreening procedures, participants positive at screening may be re-screened after 6 weeks of mild/asymptomatic infections or at the discretion of Investigator, provided there has been no development of severe COVID-19 disease or sequelae. Participants may also be re-screened a second time following rescreening procedures, if the primary reason for screen failure was due to positive COVID-19 test.

16. Willing to forego other forms of experimental treatment during the study.

Weight

17. Body weight ≥ 40 kg.

Sex

18. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male participants:

- All fertile males who are sexually active must use condom from Day 1 until at least 16 weeks after receipt of the final dose of IMP. It is strongly recommended that the female partner of a male participant also use an effective method of contraception from Table 2 (other than a barrier method) throughout this period.
- Men are considered fertile after puberty unless they have previously had bilateral orchidectomy or undergone vasectomy, which should be documented in the participant's medical records. Male participants must not donate sperm during the course of the study and for 16 weeks after the last dose of the investigational medicinal product.

(b) Female participants:

Women of child-bearing potential (WOCBP)

- Negative serum β-human chorionic gonadotropin (β-hCG) test at screening (females of childbearing potential only).
- Women of child-bearing potential must have a negative urine pregnancy test at randomisation (Day 1), prior to administration of investigational medicinal product.
- Females of childbearing potential must use 1 highly effective method of contraception, plus a male condom, from Screening until 16 weeks after the final dose of IMP, unless the participant is surgically sterile (e.g., bilateral oophorectomy or complete hysterectomy), has a sterile/non-fertile male partner, is at least 12 months postmenopausal, or practices sustained abstinence consistent with the participant's customary lifestyle. Highly effective methods of birth control include those listed in Table 2.

Women of non-childbearing potential

- Women of non-childbearing potential must be postmenopausal or have been surgically sterilized (i.e., bilateral oophorectomy, or complete hysterectomy), which should be documented in the participant's medical records.
- A post-menopausal state may be inferred for women not taking hormone replacement therapy (HRT) by a history of ≥ 12 months amenorrhoea and follicle stimulating hormone (FSH) levels in a sample collected during screenings in the laboratory's normal range for post-menopausal women.
  - A post-menopausal state may be inferred for women who are taking HRT and > 40 years of age if:
    - Menopause was documented in medical records before initiation of HRT

    OR
    - At least 2 FSH levels are within postmenopausal range while on the HRT

The table below lists highly effective methods of contraception. Female participants of childbearing potential must use one of the following non-hormonal or hormonal methods **along with a male condom**. Highly effective methods (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

Table 2 Highly effective methods of birth control

Non-hormonal	• Vasectomised partner (confirmed absence of sperm in semen) • Bilateral tubal occlusion (caveat: failure rate > 1%) • Intrauterine device (copper) • True sexual abstinence in line with the preferred and usual lifestyle choice of the participant
Hormonal	• Intrauterine hormone-releasing systems (IUS) • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation – oral, intravaginal, or transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation- oral (Cerazette only), injectable, or implantable

- Ineffective methods that should **not** be used are as follows:
  - Periodic abstinence (calendar, sympto-thermal, post-ovulation methods)
  - Coitus interruptus (withdrawal method)
  - Spermicides
  - Lactational amenorrhea
  - Non-copper containing intrauterine devices (or others not listed in the acceptable methods of contraception)
  - Some low dose or triphasic COCs (combined oral contraceptives)

- Progesterone only oral contraceptives (except Cerazette)
- Sponge, diaphragm, male or female condoms without secondary methods

3.2 Exclusion criteria

Participants should not enter the study if any of the following exclusion criteria are fulfilled.

Medical Conditions

1. History of, or current diagnosis of, a clinically significant non-SLE related vasculitis syndrome (see Appendix J). Vasculitis due to SLE is allowed in the study.
2. History or evidence of suicidal ideation (severity of 4 [active: method and intent, but no plan] or 5 [active: method, intent, and plan]) within the past 6 months; or any suicidal behavior within the past 12 months or recurrent suicidal behaviour in the lifetime of the participant based on an assessment with the C-SSRS (Appendix Q) at screening or at baseline.
3. Active severe or unstable neuropsychiatric SLE including, but not limited to aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy); acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; and mononeuritis multiplex:
   (a) Where, in the opinion of the Principal Investigator (PI), delegated Sub-Investigator (SI) or Sponsor, protocol specified standard therapy is insufficient and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, is indicated.
4. Active severe SLE-driven renal disease where, in the opinion of the PI or delegated SI or Sponsor, protocol specified standard therapy is insufficient and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, is indicated.
5. Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE and systemic sclerosis (SSc), as noted in (a) or (b) below:
   (a) An overlap syndrome of SLE with myositis or rheumatoid arthritis at Screening is permitted provided the participant also meets the criteria for the classification as SLE; or
   (b) A history of mixed connective tissue disease, which over time has developed into a diagnosis of SLE, is permitted provided diagnosis of SLE has been present for at least 1 year.

6. History of, or current diagnosis of, catastrophic anti-phospholipid syndrome (APS) within 1 year prior to signing the ICF. Participants with other degrees of APS adequately controlled by anticoagulants or aspirin for at least 12 weeks can be recruited to the study.
7. History of, or current, inflammatory joint or skin disease other than SLE that, in the opinion of Investigator, could interfere with the inflammatory arthritis or skin assessments and confound the disease activity assessments.
8. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF.

Exclusion criteria related to infection and malignancy risk factors

9. History of recurrent infection requiring hospitalization and IV antibiotics (e.g., 3 or more of the same type of infection over the previous 52 weeks).
10. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the participant to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at Screening.
    (a) An HIV test must be performed during screening, and the result should be available prior to randomisation. The participant is ineligible to participate in the study when positive for HIV antibody or infection (i.e., positive nucleic acid test) performed by the central laboratory. Participants refusing HIV testing during the screening period will not be eligible for study participation.
11. At Screening, confirmed positive test for hepatitis B serology, as confirmed by central laboratory, for:
    (a) Hepatitis B surface antigen (HBsAg);

    Or

    (b) Hepatitis B core antibody (HBcAb) and hepatitis B virus (HBV) DNA detected above the lower limit of quantitation (LLOQ) by reflex testing by the central laboratory at screening.

    Note: Participants who are HBcAb positive at screening will be tested every 3 months for HBV DNA. To remain eligible for the study, the participant's HBV DNA levels must remain below the LLOQ as per the central laboratory.
12. Active hepatitis C infection (defined as positive hepatitis C virus [HCV] antibody and detectable HCV RNA as confirmed by central laboratory.
13. Any severe case, as defined by study guidelines, of herpes zoster infection at any time prior to Week 0 (Day 1), including, but not limited to, non-cutaneous herpes (ever), herpes encephalitis (ever), recurrent herpes zoster (defined as 2 episodes within 2 years) or ophthalmic herpes involving the retina (ever).

Any herpes zoster infection that has not completely resolved within 12 weeks prior to signing the ICF.

14. Any clinical cytomegalovirus (CMV) or Epstein-Barr virus infection that has not completely resolved within 12 weeks prior to signing the ICF.
15. Opportunistic infection (see section 6.3.2) requiring hospitalization or IV antimicrobial treatment within 3 years of randomisation.
16. Any history of severe COVID-19 infection (e.g., prolonged hospitalization [hospitalization for observational purposes is not exclusionary]) or any prior COVID-19 infection with documented long COVID and/or clinically significant unresolved sequelae.
17. Any mild/asymptomatic COVID-19 infection (lab confirmed or suspected based on clinical symptoms) within the last 6 weeks prior to first dosing.
18. Any of the following:
    (a) Clinically significant chronic infection (i.e., osteomyelitis, bronchiectasis, etc) within 8 weeks prior to signing the ICF (chronic nail infections are allowed).
    (b) Any infection requiring hospitalization or treatment with IV anti-infectives not completed at least 4 weeks prior to signing the ICF.
19. Any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to Day 1.
20. History of cancer, apart from:
    (a) Squamous or basal cell carcinoma of the skin treated with documented success of curative therapy ≥ 3 months prior to Week 0 (Day 1)
    (b) Cervical cancer in situ treated with apparent success with curative therapy ≥ 1 year prior to Week 0 (Day 1).
21. Females with abnormal cervical cancer screening results as specified in Appendix H:
    (a) All females who have been or are sexually active with an intact cervix must have documentation of a normal cervical cancer screening (Pap smear or HPV tests as per local guidelines) result within 2 years prior to randomisation. Any abnormal cervical cancer screening result documented within 2 years prior to randomisation must be repeated to confirm participant eligibility.
    (b) Females aged < 25 years, who have never been sexually active or have well-documented HPV vaccination records may not require a cervical cancer screening test.

Prior/Concomitant Therapy

22. Prior receipt of anifrolumab.

23. Any change in route of administration of oral, SC, or intramuscular methotrexate anytime within the 8 weeks prior to signing of the informed consent through Day 1
24. Receipt of any commercially available biologic agent within 5 half-lives (refer to Section 7.7.1 and Appendix I for a complete list) prior to signing of the ICF.
25. Receipt of any of the following prior to signing the ICF (refer to Section 7.7.1 and Appendix I for a complete list):
    a. Receipt of B cell-depleting therapy (e.g., rituximab or obinutuzumab see Appendix I):
    - ≤26 weeks prior to signing the ICF;
    - or if therapy was administered >26 weeks ago, if absolute B cell count is below the lower limit of normal or baseline value prior to receipt of B cell-depleting therapy (whichever is lower).

    b. Belimumab within 12 weeks (< 12 weeks) prior to signing the ICF
26. A known history of allergy or reaction to any component of the IMP formulation or history of anaphylaxis to any human gamma globulin therapy
27. Any history of an anaphylactic reaction to human proteins, or monoclonal antibodies
28. Regular use of > 1 NSAID within 2 weeks prior to Week 0 (Day 1); OR receipt of fluctuating doses of a NSAID within 2 weeks prior to Week 0 (Day 1)
29. Receipt of any of the following:
    (a) Intra-articular, intramuscular or IV glucocorticosteroids within 6 weeks prior to Day 1
    (b) Any live or attenuated vaccine within 8 weeks prior to signing the ICF (Administration of killed vaccines is acceptable. The Sponsor recommends Investigators ensure all participants are up to date on required vaccinations, including influenza [inactivated/recombinant] vaccine prior to study entry)
    (c) Any restricted medication listed in Section 7.7.1
    (d) Blood transfusion or receipt of blood products (except serum albumin) within 4 weeks prior to signing the ICF
30. Receipt of >2 investigational medicinal products for the disease under study (SLE) since time of diagnosis and through signing the ICF.
31. Receipt of any commercially available Janus kinase (JAK) inhibitor (e.g., tofacitinib or baricitinib) ≤ 12 weeks or Bruton's tyrosine kinase (BTK) inhibitor (e.g., ibrutinib, acalabrutinib, zanubrutinib) ≤ 24 weeks prior to signing the ICF.
32. Receipt of any investigational medicinal product (small molecule or biologic agent) within 4 weeks or 5 half-lives prior to signing of the ICF, whichever is greater

Laboratory Assessments

33. At Screening (within 35 days of randomisation), any of the following (note: retesting of laboratory test results during Screening may be repeated once):
    (a) Aspartate aminotransferase (AST) > 2.0 × upper limit of normal (ULN).
    (b) Alanine aminotransferase (ALT) > 2.0 × ULN.
    (c) c
    (d) Serum creatinine > 2.0 mg/dL (or > 181 µmol/L)
    (e) Urine protein/creatinine ratio > 2.0 mg/mg (or > 226.30 mg/mmol)
    (f) Neutrophil count < 1000/µL (or < 1.0×10^9/L)
    (g) Platelet count < 25000/µL (or < 25×10^9/L)
    (h) Hemoglobin < 8 g/dL (or < 80 g/L), or < 7 g/dL (or < 70 g/L) if related to participant's SLE such as in active hemolytic anemia
    (i) Glycosylated hemoglobin (HbA1c) > 8% (or > 0.08) at Screening (diabetic participants only)

Other Exclusions

34. Any condition that, in the opinion of Investigator or Sponsor, would interfere with efficacy or safety evaluation of the investigational medicinal product or put participant at safety risk
35. Concurrent enrolment in another clinical study with an investigational medicinal product
36. Individuals involved with the conduct of the study, their employees, or immediate family members of such individuals
37. Lactating, breastfeeding or pregnant females or females who intend to become pregnant or begin breastfeeding anytime from initiation of Screening until the end of 16 weeks post last dose of IMP.
38. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to signing the ICF.
39. Current alcohol, drug or chemical abuse, or a history of such abuse within 1 year before randomisation.
40. Major surgery within 8 weeks before signing the ICF or elective major surgery planned during the study period.

Procedures for withdrawal of incorrectly enrolled participants see Section 3.4.

3.3 Participant enrolment and randomisation

Investigator(s) should keep a record, the participant screening log, of participants who enter pre-study screening.

Investigator(s) will:

1 Obtain signed informed consent from the potential participant before any study specific procedures are performed. The participant is considered enrolled when the ICF is signed and the enrolment call is done via IVRS/IWRS.

2 Assign potential participant a unique enrolment number, beginning with 'E#'.

3 Determine participant eligibility. See Section 3. During screening, the DACRT (see Section 5.1.2) will confirm eligibility criteria based on the data captured in the electronic case report form (eCRF) and from the Central Laboratory. Sites will be notified to either randomise or screen fail the participant.

4 On Day 1, Investigator will confirm that all eligibility criteria still are fulfilled (including that the "Clinical" SLEDAI-2K score is ≥ 4 points, OCS dose has been stable for the last 2 weeks) and will then perform the randomisation transaction in the IVRS/IWRS.

5 Assign eligible participant unique randomisation code and blinded investigational medicinal product kit number(s) via IVRS/IWRS.

Specific information concerning the use of the IVRS/IWRS will be provided in the separate user manual.

At the start of the screening period, each participant must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the center number and the participant number within that particular center. This number is the participant's unique identifier and is used to identify the participant on the eCRF.

Investigational medicinal product (anifrolumab or placebo) should, if possible, be administered the same day the investigational medicinal product kit number is assigned and the same day all randomisation study procedures are performed.

Randomisation codes will be assigned strictly sequentially as participants become eligible for randomisation. If a participant withdraws from participation in the study, then his/her enrollment/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomised participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Participants who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study. The participants are considered as screen failure.

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, Investigator should inform the AstraZeneca study physician

immediately, and a discussion should occur between the AstraZeneca study physician and Investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The treatment assigned to individual participants will be determined according to a randomisation scheme that has been loaded into the IVRS/IWRS database. The randomisation code will be assigned from a randomisation list prepared by the AstraZeneca randomisation system (AZRand).

Block randomisation using an IVRS/IWRS will be used to randomise participants in a 1:1 ratio to receive a fixed IV dose of 300 mg anifrolumab or placebo.

The randomisation will be stratified using the following factors:

- SLEDAI-2K score at screening (< 10 points vs ≥ 10 points)
- Randomisation (Day 1) OCS dose (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent)
- Region (Mainland China vs Not Mainland China)

Once a randomisation number has been assigned, no attempt should be made to use that number again. The randomisation schedule and treatment code will not be revealed to the participants, study personnel, or AstraZeneca or its representative until after the database lock.

3.6 Methods for ensuring blinding

This study will be double-blind with regard to IV treatment (anifrolumab or placebo). Anifrolumab and placebo are distinguishable during the final preparation step of the investigational infusion bag. All packaging and labelling of investigational medicinal product is done in such way as to ensure blinding for all Sponsor and site staff other than the unblinded pharmacist/designee at site. The kits on the shelf, and the infusion bags when prepared, look identical. Since anifrolumab and placebo can be distinguished at the preparation step, the unblinded pharmacist/designee will be responsible for maintaining accountability and preparing the blinded IV study therapy according to the handling instructions.

Neither the participant nor any of the study center personnel (with the exception of the unblinded pharmacist/designee) or Sponsor staff/designee who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the treatment received until the database has been locked and the study has been unblinded. In the event that the treatment allocation for a participant becomes known to Investigator or other study staff

involved in the management of study participants, the Sponsor, or designee must be notified immediately by Investigator.

3.7 Methods for unblinding

In the event of a medical emergency, Investigator may unblind an individual participant's investigational medicinal product allocation. Instructions for unblinding an individual participant's investigational medicinal product allocation are contained in the IVRS/IWRS manual. Investigator should promptly document and explain any premature unblinding to the Sponsor, without revealing the treatment given to participant to the Sponsor. Investigator will record in the source documentation the date and reason for revealing the blinded treatment assignment for that participant. In general, unblinding should only occur if management of the medical emergency would be different based on the participant having received investigational medicinal product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational medicinal product was received by the participant. If this was the case, the investigational medicinal product allocation should not be unblinded.

AstraZeneca or its designee retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational medicinal product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Participants who have been unblinded by AstraZeneca Patient Safety or designee (and who have not been unblinded to Investigator or AstraZeneca study physician) will not, based on the unblinding alone, be discontinued from further receipt of investigational medicinal product.

3.7.1 Unblinding for data and safety monitoring board

An independent DSMB will review safety data throughout the study. The DSMB will be provided with partially unblinded data (data that are summarized by treatment group using masked treatment group labels). The DSMB may choose to unblind the data for additional review as specified in the DSMB charter. The Sponsor and the study team will remain blinded to all data transfers provided to the DSMB. Details about the DSMB will be included in the DSMB Charter. For further details on the DSMB, see Appendix A 6.

3.7.2 Unblinding for performing the primary analysis at Week 52

There will be 2 clinical database locks (CDLs) in the study. The primary analysis CDL, will occur after all randomized participants have completed Week 52 (or have withdrawn from the study). The primary analysis CDL includes the assessments of the primary, key secondary, and secondary objectives, including safety. Exploratory objectives available at the time of the

primary CDL may also be included. No changes to the clinical database up to Week 52 will be made once the primary CDL has occurred. The final analysis CDL will be performed after all participants have completed their last visit/assessment. Investigators, participants, and site staff will remain blinded on the treatment assignments for individual participants who are in the follow up period at least until these participants have completed the study including follow up periods.

3.8 Restrictions

3.8.1 Fasting lipid profile

Participants will be required to fast for at least 8 hours prior to assessment of lipid profile at the visits described in the Treatment Period Study Plan (Table 4). If the participant has not fasted, he/she should fast before the next visit, and the test can be done at that visit.

3.8.2 Donation of blood or other biological samples

Participants must not donate blood from date of randomisation and within 16 weeks after the last IMP dose. Male participants must not donate sperm during the course of the study and for 16 weeks after the last dose of the investigational medicinal product.

3.8.3 Perioperative management of investigational medicinal product

Elective surgeries should be avoided during the study if clinically feasible.

3.8.4 Major surgery

Pre-operative management of investigational medicinal product: if a non-urgent major surgical procedure becomes necessary during the study, it should be scheduled at least 4 weeks after the last administration of investigational medicinal product, if clinically feasible (see Appendix O).

3.8.5 Non-major surgery

The decision to withhold IMP administration is at Investigator's discretion.

Post-operative management of investigational medicinal product: Investigational medicinal product administration can be resumed at Investigator's discretion after all of the following criteria are met:

- External wound healing is complete and
- Any postoperative antibiotic course is completed and
- All acute surgical complications have resolved.

3.9 Discontinuation of study intervention

Participants may be discontinued from investigational medicinal product in the following situations:

1. Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. The primary reason should be documented as 1 of the following:
   (a) Participant perceives the investigational medicinal product to be ineffective.
   (b) Participant is unable to comply with protocol-specified visits and/or procedures due to conflicts not related to clinical trial.
   (c) Participant perceives logistics to be unacceptable.
   (d) Participant wishes to participate in another clinical trial.
   (e) Participant wishes to take a treatment that is not allowed in this study.
   (f) An AE or laboratory abnormality is of concern to the participant, but not clinically significant to physician.
   (g) Other, please specify reason.
2. Lost to follow-up
3. AE that, in the opinion of Investigator or the AstraZeneca study physician, contraindicates further dosing with investigational medicinal product.
4. Severe non-compliance with the study protocol.
5. Investigator or the AstraZeneca study physician deems withdrawal as being in the participant's best interest.
6. Pregnancy, positive pregnancy test, non-compliance with protocol-defined contraceptive recommendations or participant expresses an interest to become pregnant.
7. Isolated HBc positivity with HBV DNA confirmed by the central laboratory.
8. Positive HIV test.
9. Confirmed diagnosis of non-cutaneous herpes zoster.
10. Anaphylactic reaction or severe hypersensitivity reaction suspected to be related to IMP.
11. Participants that develop malignancies during the study should be discontinued from IMP. Exception for non-melanoma skin cancers where discontinuation is at the discretion of investigator and/study physician.
12. Receipt of any prohibited medications identified in Section 7.7.1.2.
13. The use of restricted medications listed in Section 7.7.1.3 if, in consultation with the sponsor, the AstraZeneca study physician determines the participant must be discontinued.
14. A diagnosis of active TB, premature discontinuation of treatment for latent TB, or noncompliance with TB therapy. Note: duration of treatment for latent TB should follow

the local practice. If local practice is not defined, then Centres for Disease Control guidance should be used.

Additional restrictions related to concomitant medications are discussed in Section 7.7.2.

3.9.1 IMP discontinuation in relation to COVID-19

- Participants who develop confirmed or suspected severe COVID-19 infection requiring hospitalization, ICU care or assisted ventilation must have their IMP permanently discontinued.
- Participants with laboratory (central or local) confirmed non-severe COVID-19 infection must have their IMP temporary withheld with no further IMP dosing until complete resolution of symptoms for at least 2 weeks and without any sequalae. Restart of IMP must be discussed with AZ study physician or designee.
- Participants with suspected symptomatic COVID-19 or known exposure to COVID-19 (close contact) infection i.e., no antigen or PCR test result available, must have their IMP temporary withheld and should undergo antigen or RT-PCR test (central or local lab) with no further IMP dosing until complete resolution of symptoms for at least 2 weeks and without any sequalae, or remain asymptomatic for at least 2 weeks. Restart of IMP must be discussed with AZ study physician or designee.

3.9.2 Participant decision to discontinue investigational medicinal product

If the participant decides to discontinue investigational medicinal product for any reason, including but not limited to those outlined in Section 3.9 above, the participant will not receive any further investigational medicinal product. The participant may also refuse to continue any further study observation.

3.9.3 Procedures for discontinuation of a participant from investigational medicinal product

At any time, participants are free to discontinue investigational medicinal product or withdraw from the study (i.e., investigational medicinal product and assessments – see Section 3.10), without prejudice to further treatment. A participant that decides to discontinue investigational medicinal product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. AE will be followed up (See Section 6); questionnaires (e.g., for participant reported outcomes) if applicable and all study drugs should be returned by the participant.

Discontinuation of investigational medicational product does not necessarily mean discontinuation of follow-up or termination of study participation. Participants who discontinue IMP will be asked to return for all regularly scheduled clinic visits for the full treatment period (Table 4) in order to support the final efficacy and safety analysis for

anifrolumab (see Section 8). Participants with early IMP discontinuation do not need to return for further safety follow-up assessments if they have been followed up for at least 12 weeks after the last dose during regularly scheduled clinical visits.

If the participant is unwilling to complete all regularly scheduled clinic visits, the participants should complete the Week 52/EDV within 4 weeks of the last dose of IMP, as well as Follow-up Visit 1 and Follow-up Visit 2 (8 and 12 weeks after the last dose) unless consent is withdrawn. Every effort should be made to have the participants return to the site based on the regular visit schedule to conduct the EDV. In the event this is not feasible, the EDV should be conducted as soon as possible but no later than 4 weeks post-last dose. Participants already followed up for at least 12 weeks do not need to return for further safety follow-up visits.

The reason for premature discontinuation of investigational medicinal product will be documented in the source documents and recorded in the eCRF.

It is essential to collect as much data as possible for all participants throughout the study and especially all potential endpoint events. Complete withdrawal from the study (i.e., withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible. If the participant permanently discontinues investigational medicinal product prior to their completion of the study and wishes to continue with only selected study assessments; prioritised assessments are listed in Section 4.3.1.

If a participant is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are participants who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These participants should have the reason for study withdrawal recorded as ‘Eligibility Criteria Not Fulfilled’ (i.e., participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised participants). Rescreening of a participant will be permitted once.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

3.10.2 Withdrawal of the informed consent

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an EDV visit should be conducted, as shown in the SoA. See SoA and section 4.3.1 **Follow up visits after premature discontinuation of IMP** for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
    - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

A participant who withdraws consent will always be asked about the reason(s) (see Section 3.9) and the presence of any AEs. Investigator will follow-up AEs outside of the clinical study.

If a participant withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn participants will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial participants are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant,
- Are assessed as causally related to study intervention,
- Are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the participant at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the participants' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

The Study plan detailing the procedures at screening, during the treatment and follow-up period are presented in Table 3, Table 4 and Table 5.

4.1 Study plan

Table 3 Study plan detailing the procedures at Screening

Study Period	Screening	Details in Section
Written informed consent /assignment of E#	X	10.4
Medical history [a]	X	5.1.4
Complete physical examination, weight and height	X	5.2.2
Vital signs	X	5.2.3
ECG	X	5.2.2.5
Serum chemistry, haematology, and urinalysis	X	5.2.1
Urine protein/creatinine ratio	X	5.2.1
ANA, anti-dsDNA antibodies, anti-Sm antibody [b]	X	5.4.3
B cell count [c]	X	5.2.1
Chest X-ray (only in participants who have not had a chest radiograph within 12 weeks prior to signing the ICF) [d]	X [e]	5.2.6.1
FSH in postmenopausal females	X	5.2.1
Serum pregnancy test in all females of childbearing potential	X	5.2.1
Blood test for TB [f]	X	5.2.6.1
Hepatitis B and C	X	5.2.1
HIV test	X	5.2.1
COVID-19 test and COVID-19 questionnaire	X	5.2.7 5.2.1
Cervical Cancer Screening Test (HPV/Pap smear) [i]	X [e]	5.2.2.3
C3, C4, CH50 complement	X	5.2.1
BILAG-2004 associated laboratory tests (anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs [g])	X	5.2.1
C-SSRS	X	5.2.5
BILAG-2004	X [h]	5.1.4
CLASI	X [h]	5.1.8
SLEDAI-2K	X [h]	5.1.3
PGA	X [h]	5.1.5
Joint count	X [h]	5.1.9
TB questionnaire	X	5.2.6.3
Assessment of AEs/SAEs/AESIs	X	6; 6.3; 6.6
ACR classification criteria	X	Appendix D
Concomitant medications, including SLE medications	X	7.7
Verify eligibility criteria	X	3.1; 3.2

ACR = American College of Rheumatology; AE = adverse event; AESI = adverse event of special interest; ANA = antinuclear antibody; anti-Sm= Anti-Smith; BILAG = British Isles Lupus Assessment Group; C3 = third component of complement; C4 = fourth component of complement; CH50 = total hemolytic complement; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia Suicide Severity Rating Scale; CT = computed tomography; dsDNA = Double stranded deoxyribonucleic acid; ECG = electrocardiogram; FSH = Follicle-stimulating hormone; HIV= Human immunodeficiency virus; HPV= Human Papilloma Virus; IGRA =Interferon-gamma release assay; PGA = Physician's Global Assessment; QFT-G= QuantiFERON®-TB Gold In-Tube; SAE = serious adverse event; SLE =Systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis

[a]Medical History will include details for each body system contained in the BILAG-2004 assessment (BILAG Related History)

[b]Redraw for ANA and anti-dsDNA can be done within the 35 days screening window, however, results must be available within the 35 days screening window for participants to be randomised.

[c]Receipt of B cell-depleting therapy (including but not limited to, ocrelizumab, ofatumumab, atacicept, obinutuzumab, or rituximab) < 26 weeks prior to signing the ICF (< 40 weeks for atacicept), and if therapy was administered ≥ 26 weeks ago (40 weeks for atacicept), absolute B cell less than the lower limit of normal or baseline value prior to receipt of B cell-depleting therapy (whichever is lower).

[d]Anterio- posterior, and lateral images are required whenever possible, or per standard of care.

[e]Assessments required to determine eligibility and stratification are allowed anytime during the screening period as long as they are completed within 35 days after signing the ICF.

[f]Interferon-gamma release assay (IGRAs) using QuantiFERON®-TB Gold In-Tube (QFT-G) Test

[g]Direct Coombs test samples will only be collected per Investigator's opinion, measured by local laboratory, and applicable BILAG assessment requirements for determining haemolytic anaemia.

[h]These assessments must all be completed at the same visit (SLEDAI-2K, BILAG-2004, joint count, PGA, and CLASI).

[i]Female participants with an intact cervix should have a Cervical Cancer Screening Test (HPV/Pap smear) within 2 years prior to randomization (unless female < 25 years old which is specified in Exclusion Criteria #21). Since access to a HPV/Pap smears may vary by county, the Sponsor recommends that local guidelines for obtaining HPV/Pap smears in participants who have received immunomodulators or immunosuppressive treatment be followed.

Table 4 Study plan detailing the procedures during the Treatment Period (double-blind period)

Visit Number	V1 [a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT-DB)	EDV-DB [o]	Details in Section
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**NA**	**NA**
Procedure/Visit Window		**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**NA**	**NA**
EQ-5D-5L, Lupus QoL, WPAI	X			X			X			X				X	X	5.3.1 5.3.3 5.3.4
Medical history	X															5.1.4
Complete physical examination	X						X							X	X	5.2.2.1
Focused physical examination		X	X	X	X	X		X	X	X	X	X	X			5.2.2.2
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.2
Assessment of Cushingoid features	X						X							X	X	5.2.2.4
ECG	X													X	X	5.2.2.5
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.3
Serum chemistry, haematology, and urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1

Visit Number	V1 [a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT-DB)	EDV-DB [o]	Details in Section
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**NA**	**NA**
Procedure/Visit Window		**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**NA**	**NA**
Cervical cancer screening（HPV/Pap smear）														X [b]	X [b]	5.2.2.3
Urine pregnancy test [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
TB blood test (QFT-G)				X [d]			X [d]							X	X	5.2.6.1
HBV DNA [m]				X			X			X			X			3.2
Immunology profile [k]	X						X							X	X	5.2.1.1
Lipid profile [e]	X						X							X	X	5.2.1.1
Cardiovascular risk assessment	X													X	X	5.2.4
IFN 4-gene sample collection [f]	X															5.4.4
PK blood sample (predose) [g]	X	X		X			X			X			X	X	X	5.4.1

Visit Number	V1 [a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT-DB)	EDV-DB [o]	Details in Section
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**NA**	**NA**
Procedure/Visit Window		**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**NA**	**NA**
PK blood sample (postdose) [g]	X												X			5.4.1
Immunogenicity blood sample (predose) [n]	X			X			X			X			X	X	X	5.4.3
SLEDAI-2K associated laboratory tests [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
[redacted] (PD marker) [i]	■	■		■			■			■				■	■	5.4.2.1
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.5
BILAG-2004	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.1.4
BILAG-2004 associated laboratory tests [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.1.8
SLEDAI-2K	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.1.3
SDI	X						X							X	X	5.1.7

Visit Number	V1 [a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT-DB)	EDV-DB [o]	Details in Section
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**NA**	**NA**
Procedure/Visit Window		**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**NA**	**NA**
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.1.5
Joint count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.1.9
Protocol-specified steroid tapering (if indicated)			X	X	X	X	X	X	X	X	X					7.7
Medical Resource Use Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.3.2
TB questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.6.3
Assessment of AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Verify eligibility criteria	X															3.1, 3.2
Randomisation	X															3.3

Visit Number	V1 [a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT-DB)	EDV-DB [o]	Details in Section
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**NA**	**NA**
Procedure/Visit Window		**±7D**	**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**NA**	**NA**
Investigational medicinal product administration [l]	X	X	X	X	X	X	X	X	X	X	X	X	X			7

AE = adverse event; AESI = Adverse Event of Special Interest ; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia Suicide Severity Rating Scale (C-SSRS); dsDNA = double stranded deoxyribonucleic acid; ECG = electrocardiogram; EDV = Early Discontinuation Visit; EQ-5D- 5L = EuroQoL 5 dimensions; HBV = hepatitis B virus; HPV = Human Papilloma Virus; IFN = interferon; PD = pharmacodynamic; PGA = Physician's Global Assessment; PK = pharmacokinetic; QFT-G = QuantiFERON® -TB Gold In-Tube; SAE = serious adverse event; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis; WPAI = Work Productivity and Activity Impairment.

[a]Once screening assessments needed to confirm eligibility and stratification are complete, all laboratory results are reported, and central review is complete, a participant may be randomised. There does not need to be 35 days between screening and Randomisation (Day 1).

[b]Female participants should have a Cervical Cancer Screening Test (HPV/Pap smear) per local standard of care, if possible, between Week 48 and Week 52 to ensure that there is no evidence of new cervical dysplasia (unless female < 25 years old which is specified in Exclusion Criteria #21). Since access to HPV/Pap smears may vary by county, the Sponsor recommends that local guidelines for obtaining HPV/Pap smears in participants who have received immunomodulators or immunosuppressive treatment be followed. For participants who early discontinue investigational medicinal product, and is willing to return for all regularly clinic scheduled visits, the HPV/Pap smear should be done between Week 48 and Week 52.

[c]Urine pregnancy test in females of childbearing potential.

[d]Only for participants with indeterminate QFT-G result at screening but no latent TB treatment is warranted. The QFT-G will be retested at Week 12 and Week 24 for the first 6 months. See section 6.3.5 for more instruction.

[e]Lipid profile (cardiovascular assessment) - participants will be required to fast for at least 8 hours prior to this assessment. If a participant has not fasted, the assessment should be performed under fasted conditions at the next visit.

[redacted]

[h]SLEDAI-2K associated laboratory tests are C3, C4, CH50 complement, anti-dsDNA antibodies, urine protein/creatinine ratio. If Central laboratory results are not available for SLEDAI-2K associated samples drawn on the date of visit, labs should be redrawn one time within 14 days of SLEDAI-2K assessment date.

[redacted]

[j]BILAG-2004 laboratory tests to include Coombs (if applicable), anticardiolipin, lupus anticoagulant, haptoglobin. Note: In order to avoid having to bring the participant back for a separate phlebotomy, the blood specimen for anticardiolipin, lupus anticoagulant, haptoglobin will be collected at the specified visits, however the blood will be stored at the central laboratory, and the analyses performed only if Investigator indicates that these tests need to be completed because of clinical suspicion of haemolytic anaemia or

antiphospholipid syndrome. Direct Coombs test samples will only be collected per Investigator's opinion at local laboratory and applicable BILAG assessment requirements for determining haemolytic anaemia.

[k]Immunology profile includes ANA, anti-Sm, anti-RNP, anti-SSA, and anti-SSB, and quantitative immunoglobulins.

[l]Investigational medicinal product will be administered as an IV infusion via an infusion pump over a minimum of 30 minutes.

[m]Participants who are HBcAb positive at screening will be tested every 3 months for HBV DNA. To remain eligible for the study, participant's HBV DNA levels must remain below the LLOQ as per central laboratory

[n] In order to help understand the potential drug-relatedness of any hypersensitivity or anaphylaxis reaction, possible additional ADA testing (if not already scheduled for a visit) may be collected and analysed

[o]If the participant is unwilling to complete all regularly scheduled clinic visits, the participant should complete the EDV within 4 weeks of the last dose of investigational medicinal product, as well as Follow-up Visit 1 and Follow-up Visit 2 (8 and 12 weeks after the last dose) unless consent is withdrawn. If the participant is unwilling to continue with any study visits, including EDV visit, at a minimum, the assessments mentioned in section 4.3.1 should be completed.

Table 5 Study plan detailing the procedures during follow-up

Visit Number Study Week Procedure/Visit Window	Follow-up Visit 1 [a] 8 weeks post last dose ±7D	Follow-up Visit 2 [a] 12 weeks post last dose ±7D	Details in Section
EQ-5D-5L, WPAI		X	5.3.1; 5.3.4
Complete physical examination, weight		X	5.2.2
Vital signs	X	X	5.2.3
Serum chemistry, haematology, and urinalysis	X	X	5.2.1
Urine pregnancy test in females of childbearing potential	X	X	5.2.1
PK blood sample	X	X	5.4.1
Immunogenicity blood sample [d]		X	5.4.3
TB questionnaire	X	X	5.2.6.3
[redacted]		[redacted]	[redacted]
SLEDAI-2K associated laboratory tests [b]	X	X	5.2.1
BILAG-2004 associated laboratory tests [c]	X	X	5.2.1
C-SSRS	X	X	5.2.5
BILAG-2004	X	X	5.1.4
CLASI	X	X	5.1.8
SLEDAI-2K	X	X	5.1.3
PGA	X	X	5.1.5
Joint count	X	X	5.1.9
Medical Resource Use Questionnaire	X	X	5.3.2
Assessment of AESIs	X	X	6.3; 6.6
Assessment of AEs/SAEs	X	X	6
Concomitant medications	X	X	7.7

AE = adverse event; AESI = Adverse Event of Special Interest; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus; Disease Area and Severity Index; EQ-5D-5L = EuroQoL 5 dimensions; IFN = interferon; PD = pharmacodynamic; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis; WPAI = Work Productivity and Activity Impairment; C-SSRS= Columbia Suicide Severity Rating Scale.

[a]Follow-up assessments are to be completed when participants complete the study (e.g., early termination or after the treatment period). Participants with early IMP discontinuation do not need to return for further safety follow-up assessments if they have been followed up for at least 12 weeks after the last dose during regularly scheduled clinical visits.
[b]SLEDAI-2K associated laboratory tests are C3, C4, CH50 complement, anti-ds DNA, urine protein/creatinine ratio. If central laboratory results are not available for SLEDAI-2K associated samples drawn on the date of visit, labs should be redrawn one time within 14 days of the SLEDAI assessment date.
[c]BILAG-2004 laboratory tests to include Coombs (if applicable), anticardiolipin, lupus anticoagulant, haptoglobin. Note: In order to avoid having to bring the participants back for a separate phlebotomy, the blood specimen for anticardiolipin, lupus anticoagulant, haptoglobin will be collected at the specified visits, however the blood will be stored at the central laboratory, and the analyses performed only if Investigator indicates that these tests need to be completed because of clinical suspicion of haemolytic anaemia or antiphospholipid

syndrome. Direct Coombs test samples will only be collected per Investigator's opinion at local laboratory and applicable BILAG assessment requirements for determining haemolytic anaemia.
[d]In order to help understand the potential drug-relatedness of any hypersensitivity or anaphylaxis reaction, possible additional ADA testing (if not already scheduled for a visit) may be collected and analysed.

4.2 Enrolment/screening period

At Screening, participants are assessed to ensure that they meet eligibility criteria. Once the participant signs theICF, they are considered enrolled in the study. Participants who do not meet these criteria must not be randomised into the study.

Screening procedures will be performed according to the Screening Study Plan (Table 3), from Day -35 to Day -1. Once screening assessments needed to confirm eligibility and stratification are complete, all laboratory results are reported, and central review is complete, a participant may be randomised. There does not need to be 35 days between screening and Randomisation (Day 1).

Chest radiograph and Cervical Cancer Screening Test may be completed anytime during the screening period as long as all results have been reviewed by Investigator prior to randomisation.

If a participant does not meet eligibility criteria on the basis of a laboratory value then the laboratory value may be repeated once within the screening period.

4.2.1 Other considerations for screening

4.2.1.1 Oral examination

In several biological programs there have been serious infections and/or death related to Ludwig's angina. Although this has not been seen in the anifrolumab program, Investigators should check a participant's oral cavity and review their dental health carefully during the screening process. While a dental examination is not required prior to enrolment in this study, Investigators are cautioned to consider carefully whether participants have active caries or a dental infection that might impact on participant safety prior to enrolment.

4.2.1.2 Mammography

As participants with SLE have impaired immune response, are treated with immunosuppressants and are at potential risk for malignancy, it is recommended that participants enrolled into the study are compliant and up to date with local recommendations for mammography or other screening procedures for breast cancer.

4.2.2 Re-screening participants who screen fail

If a participant fails screening for inadequate disease activity, or other reason, which, in the opinion of Investigator, may change to make the participant eligible, the participant may be re-screened **1 time**. The same E-code that the participant received at the first enrolment will be used. In this case, the participant will re-sign the informed consent document. If the participant fails screening twice, they may not undergo further screening for this study. Initial screening procedures completed within the 35 days prior to participant randomisation need not be repeated during the re-screen visit.

4.3 Treatment period

Procedures during the Treatment Period will be performed according to the Treatment Period Study Plan (Table 4), from Randomisation (Week 0) to Week 52. The participant-reported outcome assessments should be completed by the participant (unassisted by spouse, family members or friends) prior to all other evaluations, and prior to the infusion, as disease assessments/clinical evaluations may confound the results.

Before scheduling the Randomisation (Day 1) visit, ensure notification from the DACRT has been received, confirming that participant meets disease activity eligibility (Inclusion Criterion No. 9, 10 and 11). The DACRT will review all data necessary to characterize participant SLE in relation to the SLEDAI-2K, BILAG-2004, and PGA assessments (including central laboratory results).

On Day 1, ensure participant meets eligibility criteria, including Day 1 assessments according to the Treatment Period Study Plan (Table 4). Participants confirmed to be eligible will be randomised. Investigational medicinal product (anifrolumab or placebo) should be administered the same day the investigational medicinal product kit number is assigned and the same day all randomisation study procedures are performed.

Participants will have scheduled visits at 4-week (±7 days) intervals to complete protocol-specified assessments and investigational medicinal product administration according to the Treatment Period Study Plan (Table 4). From Week 4 through Week 48, Investigational medicinal product (anifrolumab or placebo) administration and required study procedures are preferred to be completed in the same day, but are also allowed to be completed within 24 hours if needed.

The last dose of investigational medicinal product will be administered on Week 48. At Week 52, participants will have an End of Treatment (EOT) visit. For participants who prematurely discontinue investigational medicinal product and are not willing to continue to participate in the study refer to Section 3.9 and Section 4.3.1.

4.3.1 Follow up visits after premature discontinuation of investigational medicinal product

Participants who discontinue investigational medicinal product (see Section 3.9) will be asked to return for all regularly scheduled clinic visits. If the participant is unwilling to complete all regularly scheduled clinic visits, the participant should complete the EDV within 4 weeks of the last dose of investigational medicinal product, as well as Follow-up Visit 1 and Follow-up Visit 2 (8 and 12 weeks after the last dose) unless consent is withdrawn.

If the participant is unwilling to continue with any study visits, including EDV visit, at a minimum, the following assessments should be completed:

- SLEDAI-2K and the associated laboratory tests (anti-dsDNA antibodies, C3, C4, CH50).
- BILAG-2004 laboratory tests to include anticardiolipin, lupus anticoagulant, haptoglobin and Coombs (Coombs will be performed at local laboratory as applicable per BILAG assessment requirements).
- Note: In order to avoid having to bring the participant back for a separate phlebotomy, the anticardiolipin, lupus anticoagulant, and haptoglobin blood specimen will be collected at all specified visits, however the blood will be stored at the central laboratory, and the analyses performed only if Investigator indicates that these tests need to be completed because of clinical suspicion of haemolytic anaemia or antiphospholipid syndrome. Direct Coombs test samples will only be collected per Investigator's opinion at local laboratory and applicable BILAG assessment requirements for determining haemolytic anaemia.
- CLASI
- PGA
- Joint count

The following safety assessments will also be completed:

- Serum chemistry, haematology, urinalysis
- Urine for protein, creatinine and urine-protein-creatinine ratio
- Lipid Profile defined in Section 5.2.1.1
- Immunology Profile defined in Section 5.2.1.1
- Vital signs
- Complete physical examination, weight
- AE including AESIs
- Cardiovascular risk assessment

- TB questionnaire
- Concomitant medications

If the participant does not agree to do this, they will be asked if they can be followed on a monthly basis via telephone calls until 12 weeks post the last dose of IMP. At these calls, they will be asked about AEs/SAEs, lupus symptoms, and lupus medications. Steroid bursts will also be captured.

Adverse events will be followed up per Section 6.4.2.

4.3.2 Lost to follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

4.4 Unscheduled visit

There may be times a participant needs to have an unscheduled visit. Investigator should determine the assessments to be completed based on the reason for the unscheduled visit and for participant safety. Concomitant medications and AEs should be completed whenever a participant has an unscheduled visit.

If a participant presents for an unscheduled visit in lieu of a regularly scheduled visit (i.e., the participant is seen for safety and efficacy assessments when a regularly scheduled dosing or follow-up visit is missed), Investigator should complete all possible safety and efficacy assessments applicable to the missed visit. Unscheduled efficacy assessments should not be collected in between completed regular study visits.

4.5 Follow-up period

Procedures will be performed according to the Follow-up Period Study Plan (Table 5).

Participants who complete the double-blind treatment period will have follow-up visits at Week 56 and Week 60. Participants who are withdrawn from the investigational medicinal product and do not agree to complete the 52-week study period, should complete the EDV visit within 4 weeks of the last dose of IMP, and be followed 8 and 12 weeks after the last dose by completing the Follow-up Visit 1 and 2 assessments (see Section 3.9).

4.6 Study completion and end of study

An individual participant will be considered to have completed the study if the participant was followed up until the end of the study (Week 60, or Week 52 for those participants who prematurely discontinue the investigational medicinal product and complete a minimum of 12 weeks of follow-up) regardless of the number of doses of investigational medicinal product that were received. The end of the study ("study completion") is defined as the date of the last protocol specified visit/assessment for the last participant in the study.

5 STUDY ASSESSMENTS

The Web Based Data Capture (WBDC) system will be used for data collection and query handling. Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

5.1 Efficacy assessments

Efficacy measurements will be made at the times indicated in the Study Plan (see Table 3 for assessments to be performed at Screening, Table 4 for Treatment Period, and Table 5 for Follow-up). Participant-reported outcome assessments should be completed by the participant, unassisted by spouse, family members or friends.

5.1.1 Training and certification for Systemic Lupus Erythematosus assessments

In order to maintain consistent evaluation of SLE disease activity across study sites, training and certification of Investigators and designated site personnel who will be completing the disease evaluations listed below will be conducted.

- SLEDAI-2K
- BILAG-2004
- PGA
- SDI
- CLASI
- Swollen and tender joint count evaluation

The SLEDAI-2K, BILAG-2004, PGA, and CLASI must be administered by Investigator or another qualified physician, unless prior sponsor approval has been obtained for any other clinically trained site personnel with documentation of adequate assessment experience per the study central review plan. The joint count evaluation can be completed by other site personnel who, as per Investigator discretion, are qualified to perform the assessments and have at least one year of experience administering the joint count evaluation. Training will include printed training materials, digital media and formal presentations, as well as web-based training modules.

After attending study presentations (i.e., Investigator Meeting) or after completion of online training modules, all Investigators and designated site physicians must pass an online

examination in order to obtain certification for all disease evaluation assessments, with the exception of the joint count evaluation. Investigators and designated site personnel must be trained and certified prior to participants entering screening at their respective sites. All assessments and certifications must be renewed via the study online training website prior to expiration and must remain current (not expire) throughout the course of the study. If there is a change in site personnel over the course of the study, new Investigators or physicians must be certified prior to performing the SLEDAI-2K, BILAG-2004, PGA, and CLASI assessments.

It is expected that Investigator will ensure all joint count assessors have adequate experience (minimum of 1 year) and training qualifications to perform the swollen and tender joint count assessment. Assessors (including any new Investigators or site personnel) must complete the online joint count training module and obtain certification prior to performing any joint assessment.

Documentation of all training will be maintained in the site's study file.

Over the course of the study, Investigator assessments for a given participant should be completed by the same trained and/or certified Investigator, designated physician, or qualified site personnel (as described above) whenever possible.

5.1.2 Disease activity central review team

The study has a DACRT made up of individuals who are medically-qualified individuals and/or support staff who assist in the ongoing management of this trial. The DACRT will review all data necessary to characterize participant SLE; however, the group will remain blinded for the duration of the study. DACRT Group members will have access to an independent expert on SLE disease activity indices for unanticipated issues with regards to interpretation of these indices.

The DACRT will be utilized to confirm eligibility during screening and will be utilized throughout the study to confirm SLEDAI-2K, BILAG-2004, and PGA scoring. The DACRT will also ensure that the completion of efficacy assessments by Investigators is of proper quality and consistency.

If there is inconsistency between assessments, additional clarification and training on these assessments will be provided through the DACRT.

5.1.3 Systemic Lupus Erythematosus Disease Activity Index 2000

The SLEDAI-2K index (see Appendix E) consists of a list of organ manifestations, each with a definition. A certified Investigator or designated physician will complete the SLEDAI-2K assessment and decide whether each manifestation is "present" or "absent" in the last 4 weeks.

The assessment also includes the collection of blood and urine for assessment of the laboratory categories of the SLEDAI-2K.

The SLEDAI-2K assessment consists of 24 lupus-related items. It is a weighted instrument, in which descriptors are multiplied by a particular organ's "weight". For example, renal descriptors are multiplied by 4 and central nervous descriptors by 8 and these weighted organ manifestations are totalled into the final score. The SLEDAI-2K score range is 0 to 105 points with 0 indicating inactive disease. The SLEDAI-2K scores are valid, reliable, and sensitive clinical assessments of lupus disease activity. The SLEDAI-2K calculated using a timeframe of 30 days prior to a visit for clinical and laboratory values has been shown to be similar to the SLEDAI-2K with a 10-day window (Touma et al, 2010). A timeframe of 28 days will be used in this study.

The "Clinical" SLEDAI-2K score is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures. Its use may permit earlier clinical decisions to be made without waiting for immunologic measures (including anti-dsDNA antibodies and C3, C4, and CH50 complement levels). However, in any circumstance where the "Clinical" SLEDAI-2K score is used, sites must subsequently update the SLEDAI-2K assessment when laboratory data become available so that the full SLEDAI-2K score is made available to the Sponsor.

A quick Reference Guide will be provided to all study personnel, which contains detailed protocol-specific clarifications and extensions of SLEDAI-2K clinical parameter definitions and a guidance for correlating SLEDAI-2K and BILAG-2004 clinical parameters.

5.1.4 British Isles Lupus Assessment Group 2004

The BILAG-2004 is a translational index with 9 organ systems (General, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic, Renal and Haematology) that is able to capture changing severity of clinical manifestations (see Appendix F). It has ordinal scales by design and does not have a global score; rather it records disease activity across the different organ systems at a glance by comparing the immediate past 4 weeks to the 4 weeks preceding them. It is based on the principle of physicians' Intention-to-Treat and categorizes disease activity into 5 different levels from A to E:

- Grade A represents very active disease requiring immunosuppressive drugs and/or a prednisone dose of > 20 mg/day or equivalent
- Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressives, antimalarials, or NSAIDs
- Grade C indicates mild stable disease
- Grade D implies no disease activity, but the system has previously been affected

- Grade E indicates no current or previous disease activity

Although the BILAG-2004 was developed based on the principle of Intention-to-Treat, the treatment has no bearing on the scoring index. Only the presence of active manifestations influences the scoring.

5.1.4.1 Protocol-specific clarification and extension of BILAG-2004 definitions

A quick Reference Guide will be provided to all study personnel, which contains detailed protocol-specific clarifications and extensions of BILAG-2004 clinical parameter definitions and guidance for correlating SLEDAI 2K and BILAG-2004 clinical parameters. Please refer to this guide when completing disease activity assessments. Important extensions of selected BILAG-2004 glossary definitions are included as follows:

Protocol-specific extensions of BILAG-2004 and SLEDAI-2K clinical parameter definitions:

(a) BILAG-2004 A or B score in the musculoskeletal organ system due to active polyarthritis, defined as follows:

- "BILAG 2004 A": severe arthritis (BILAG 2004 #41) manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living (ADL), that has been present on several days cumulatively over the past 4 weeks, including at the time of the Screening visit. Basic ADLs are defined as the following activities which require assistance or assistive devices (at least 1 must be present and documented in source): ambulation, toileting, grooming including bathing, dressing, feeding oneself.
- For scoring BILAG-2004 as severe arthritis (A), the affected joints must have clear signs of synovitis (tender AND swollen) that is due to SLE activity with significant impact on basic daily activities and need for assistance as above and non-SLE related causes that may affect joint activity and basic ADLs such as osteoarthritis or obesity must be ruled out. The joint activity would require treatment with high dose systemic steroids and/or immunomodulators/immunosuppressives including biologics. Although activity in only 2 joints could qualify for a BILAG A score for arthritis, this is expected to occur very rarely.
- BILAG 2004 B": moderate arthritis or tendonitis or tenosynovitis (BILAG 2004 #42) defined as tendonitis/tenosynovitis or active synovitis in ≥ 1 joint (observed or through history) with some loss of functional range of movements which leads to some loss of functional range of motion as manifested by effects on instrumental ADLs (such as cooking, driving, using the telephone or computer, shopping, cleaning, etc), which has been present on several days over the last 4 weeks and is present at the time of the Screening visit. The joint activity must be due to SLE with other causes excluded and with activity that would need treatment with

moderate systemic steroid doses, intraarticular steroid injection and/or antimalarials. Although activity in only 1 joint could qualify for a BILAG B score for arthritis, this is expected to occur very rarely

(b) BILAG-2004 and SLEDAI-2K "lupus headache": lupus headache is rare, migraine, tension or cluster headaches should not be recorded. Lupus headache should only be recorded if it is disabling, lasts at least 3 days, and does not respond to narcotics. It is expected that its severity would prompt formal testing (lumbar puncture, magnetic resonance imaging [MRI], CT, etc) and require corticosteroids and/or immunosuppressants and potentially hospitalisation for treatment. Lupus headache is considered a manifestation of lupus cerebritis.

5.1.4.2 Modified BILAG 2004

The majority of BILAG As and BILAG Bs assigned via the scoring algorithms of the BILAG 2004 are considered a legitimate representation of clinically significant worsening disease activity; however, there is a feature within the BILAG-2004 Index Scoring algorithms that can result in an A or B assigned to a body system which had improved, and then remained at the 'same' level of improvement compared to previous visits. Items marked 'same' frequently warrant assignment of an A or a B category following the BILAG-2004 Index Scoring based on the BILAG principle of Intention-to-Treat. These are "false" A or B categories because they are not true worsening of disease activity but are due to unchanged or the same disease activity that has previously improved. These "false" A and B can only be determined and subsequently re-scored after a participant had completed a series of visits that define true state of SLE disease activity.

The DACRT will differentiate "false" A and B scores from true clinically significant worsening by reviewing all BILAG-2004 Index scores for each participant's visits. A modified BILAG-2004 Index Scoring Rules will be used. The modified BILAG rules and the review process and scoring as well as references used that justify the modification are detailed in a charter developed for this exercise.

5.1.5 Physician global assessment

A trained and certified Investigator will complete the PGA (see Appendix G). The PGA represents the physician's overall assessment of average SLE disease severity on a VAS scale with 0 (no disease) to 3 (severe) disease activity over the last 4 weeks. The PGA for a given participant should be completed by the same physician whenever possible.

The PGA is a modification of the classic analogue scale in that it is anchored with numbers from 0 to 3 demarcating no, mild, moderate and severe disease. The number 3 indicates severe disease and is at the end of the scale. This refers to the most severe possible disease, and does not reflect the most severe seen in a particular participant, but the most severe disease ever seen in all SLE participants. Therefore, the line made by the physician along this scale should

virtually never get to this edge. Any disease rated greater than 2.5 is very severe. The range of moderate disease covers approximately 1.5 to 2.4. Mild disease falls below 1.5. The instrument is similar to a logarithmic scale, with greater distances or demarcations possible among more mild-moderate symptoms.

When scoring the PGA, the score from the previous visit should be reviewed and the mark should be moved relative to the score from the previous visit. This is a global assessment, factoring in all aspects of the participant's lupus disease activity. It should not reflect non-lupus medical conditions.

5.1.6 Oral corticosteroid reduction

Please refer to Section 7.7.3 for all information regarding steroid tapering.

5.1.7 Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

The SDI has been developed to assess irreversible damage in SLE participants independently of its cause (SLE activity, therapy, comorbidities) but occurring after disease onset (see Appendix K). Damage, i.e., irreversible impairment since onset of SLE is usually defined as a clinical feature that has to be continuously present for at least 6 months to score. In addition, some irreversible events such as MI or a cerebrovascular accident score as damage on their occurrence. Briefly, damage is defined for 12 organ systems; peripheral vascular, ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, endocrine (diabetes), gonadal, and malignancies. Damage over time can be stable or increase, to a maximum of 45 points, however there should be no decrease in the number of points (Schwartz et al, 2009).

5.1.8 Cutaneous Lupus Erythematosus Disease Area and Severity Index inflammatory disease activity

The CLASI is a validated index used for assessing the cutaneous lesions of SLE and consists of 2 separate scores: the first summarises the inflammatory activity of the disease; the second is a measure of the damage done by the disease (see Appendix L). The activity score takes into account erythema, scale/hypertrophy, mucous membrane lesions, recent hair loss, and non-scarring alopecia. The damage score represents dyspigmentation, scarring/atrophy/panniculitis, and scarring of the scalp. Participants are asked if their dyspigmentation lasted 12 months or longer, in which case the dyspigmentation score is doubled. Each of the above parameters is measured in 13 different anatomical locations, included specifically because they are most often involved in cutaneous lupus erythematosus (CLE). The most severe lesion in each area is measured.

5.1.9 Joint count

The swollen and tender joint count is based on left and right shoulder, elbow, wrist, metacarpophalangeal (MCP) 1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP) 1, PIP2, PIP3, PIP4, PIP5 joints of the upper extremities and left and right knee of the lower extremities. Conventionally, an active joint for the SLEDAI-2K calculation is defined as a joint with pain and tenderness and at least 1 of the following (warmth, erythema, swelling, or effusion) (Merrill, 2014). However, in this study an active joint for the joint count assessment is defined as a joint with tenderness and swelling only. Each of 28 joints will then be evaluated separately for tenderness (by palpating the joint) and swelling. Joints with intra-articular injection within 4 weeks are not evaluable for the assessment.

The joint count assessment will include questions regarding limitation of range of movements and effects of joint symptoms on basic and functional ADLs.

The joint counts must be performed by an assessor with experience in performing these assessments; see Section 5.1.1 for details.

5.1.10 Lupus Low Disease Activity State

A conceptual definition of LLDAS is 'a state, which if sustained, is associated with a low likelihood of adverse outcome, considering disease activity and medication safety' (Franklyn et al, 2016). As a composite endpoint employed in clinical trials, LLDAS is defined and measured by attaining all of the following 5 criteria:

- SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis) or fever;
- no new lupus disease activity compared with the previous assessment (SLEDAI-2K);
- a PGA ≤ 1 (scale 0–3);
- a current prednisone (or equivalent) dose ≤ 7.5 mg daily;
- standard maintenance doses of immunosuppressive drugs and approved biological agents (Golder et al, 2019). This criterion on immunosuppressive medications will be handled through the intercurrent event of RM.

5.2 Safety assessments

Key safety assessments are AEs, AESIs, vital signs, physical examination, safety laboratory tests, and ECGs. Safety assessments will be made at the times indicated in the Study Plan (see Table 3 for assessments to be performed at Screening, Table 4 for Treatment Period, and Table 5 for Follow-up). Participant-reported outcome assessments should be completed by the participant, unassisted by spouse, family members or friends.

5.2.1 Clinical laboratory assessments

All clinical laboratory tests will be performed in a central clinical laboratory at the times indicated in the study plans(Table 3, Table 4 and Table 5).

A serum pregnancy test (or serum FSH in postmenopausal females with menses absent for ≥1 year) will be performed at screening at the central laboratory. Urine pregnancy tests (for females of childbearing potential) will be performed at the site using a dipstick. Direct Coombs test samples will only be collected per Investigator's opinion at local laboratory and applicable BILAG assessment requirements for determining haemolytic anaemia. Abnormal safety laboratory results should be repeated as clinically indicated, as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of Investigator. The date, time of collection will be recorded on the appropriate eCRF.

Every attempt should be made to redraw any missing safety laboratory tests, even if the participant has received the investigational medicinal product.

Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.4.7.

In case a participant shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix C. Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

The following laboratory variables will be measured:

Table 6 Clinical laboratory tests

Screening
ANA, anti-dsDNA antibodies, anti-Sm antibody, anti-RNP, anti-Sjogren's Syndrome-related antigen A [SSA] and anti-Sjogren's Syndrome-related antigen B [SSB]
HbA1c in diabetic participants only
Peripheral blood B lymphocyte count (only for participants who received B cell depleting therapy prior to signing ICF, including but not limited to ocrelizumab, ofatumumab, atacicept, obituzumab, or rituximab)
BILAG-2004 associated laboratory tests analysed for all participants at screening (anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs [Coombs will be performed at local laboratory as applicable per BILAG assessment requirements]) *
Hepatitis B surface antigen
Hepatitis B core antibody (reflex DNA testing if isolated HBc positive)
Hepatitis C antibody
HIV test

CK
C3, C4, CH50 complement
Urine protein/creatinine ratio
SARS-Cov-2 RT-PCR
QFT-G test

Haematology (whole blood)

Haematology/Haemostasis (whole blood)
White blood cell count with differential
Red blood cell count
Haematocrit
Haemoglobin
Platelet count
Mean corpuscular volume (MCV)
Mean corpuscular haemoglobin concentration (MCHC)

Serum Chemistry

Calcium
Chloride
Potassium
Sodium
Aspartate transaminase* (AST)
Alanine transaminase* (ALT)
Alkaline phosphatise* (ALP)
Gamma glutamyl transferase (GGT)
Blood urea nitrogen (BUN)
Creatinine
Bilirubin, total* (reflexively fractionated if elevated)
Glucose
Albumin
Creatine kinase (CK)
*Note for serum chemistry: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Urinalysis

Colour
Appearance
Specific gravity
pH
Protein dipstick
Glucose
Ketones
Blood
Bilirubin
Microscopy including WBC/HPF, RBC/HPF, casts
Urine creatinine and protein, urine protein/creatinine ratio

Pregnancy Test

Serum β-hCG (at screening only)
Urine β-hCG (at every visit after screening, using a dipstick)
Serum FSH (at screening only) in postmenopausal females with menses absent for ≥1 year

Disease Evaluations

SLEDAI-2K-associated laboratory tests (C3, C4, CH50 complement, anti-ds DNA, urine protein/creatinine ratio)
Note: If central laboratory results are not available for SLEDAI 2K associated tests, samples should be redrawn one time within 14 days of the SLEDAI assessment date.

BILAG-2004 associated laboratory tests, including anticardiolipin, lupus anticoagulant, haptoglobin and Coombs (as applicable). Coombs will be performed at local laboratory as applicable per BILAG assessment requirements. *

* In order to avoid having to bring the participant back for a separate phlebotomy, the anticardiolipin, lupus anticoagulant, and haptoglobin blood specimen will be collected at the specified visits, however the blood will be stored at the central laboratory, and the analyses performed only if Investigator indicates that these tests need to be completed because of clinical suspicion of haemolytic anaemia or antiphospholipid syndrome. Direct Coombs test samples will only be collected per Investigator's opinion at local laboratory and applicable BILAG assessment requirements for determining haemolytic anaemia.

5.2.1.1 Laboratory assessments for cardiovascular risk assessments

Fasting lipid profile

Participants will have a fasting lipid profile (high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) completed at times indicated in the Study Plan (Table 3, Table 4, and Table 5). Participants will be required to fast for at least 8 hours prior to this assessment (see Section 3.8.1).

Immunology profile

Participants will have tests to determine immunology profile (ANA, anti-Sm, anti-RNP, anti-SSA and anti-SSB), and quantitative immunoglobulins completed at times indicated in the Study Plan (Table 3, Table 4, and Table 5).

5.2.2 Physical examination

Body height will be captured at screening only. Participants will be weighed at each study visit. Medically significant changes from the Screening physical examination will be recorded as AEs.

5.2.2.1 Complete physical examination

A complete physical examination will be performed at the visits specified in the Study Plan (Table 3, Table 4, and Table 5), and will include an assessment of the following: general appearance, head and neck, breast, respiratory, cardiovascular, abdomen, musculoskeletal/extremities, neurological, skin, lymph nodes, and thyroid.

5.2.2.2 Focused physical examination

The focused physical examination will include an assessment of the organ systems required to complete protocol-specified assessment tools (SLEDAI-2K, BILAG-2004, joint count, and CLASI). Additional assessments should be done as clinically indicated. Abnormal findings will be recorded as part of AE, SAE, AESI, or lupus activity, as appropriate.

5.2.2.3 Cervical Cancer Screening Test (Pap Smear/HPV Test)

Most cases of cervical cancer appear to be related to infection with papilloma virus. Because of the potential for viral reactivation due to blockade of the interferon pathway, we are

assessing cervical dysplasia in this study, although to date there has been no signal in the anifrolumab studies.

A Cervical Cancer Screening Test (Pap smear/HPV test which is in align with local practice) is required at screening in women who have not had their cervix surgically removed. If a Cervical Cancer Screening Test was performed within 2 years prior to screening with no documented malignancy (e.g., cervical intraepithelial neoplasia grade III [CIN III], carcinoma in situ [CIS], or adenocarcinoma in situ [AIS]) or no High-risk HPV was found, it does not need to be repeated. Abnormal Cervical Cancer Screening Test results received anytime within the 2 years prior to randomisations must be repeated to ensure eligibility. Please refer to Appendix H for guidance.

Participants should have a Pap Smear or HPV Test at the end of treatment per local standard of care, if possible, between Week 48 and Week 52, to ensure that there is no evidence of new cervical dysplasia. Since access to a Pap Smear or HPV Test may vary by county, the Sponsor recommends that local guidelines for obtaining Pap Smear or HPV Test in participants who have received immunomodulators or immunosuppressive treatment be followed. If a Pap Smear was performed at the EOT was not normal but showed no evidence of malignancy (e.g., CIN III, CIS or AIS), it should be repeated as per the participant's gynaecologists recommendation. If the participant's gynaecologist has recommended a repeat Pap Smear be performed at a specified interval, the Pap Smear should be obtained as recommended and the report provided in source document.

Females aged < 25 years, who have never been sexually active or have well documented HPV vaccination records may not require a cervical cancer screening test.

5.2.2.4 Assessment of Cushingoid features

Participants will be assessed for Cushingoid features at the visits specified in the Treatment Period Study Plan (Table 4). Features, such as moon face, buffalo hump, purple or violaceous striae, central obesity, hirsutism, acne, easy bruising, and fragile skin, will be captured separately to evaluate whether resolution of same can occur overtime with OCS reduction.

5.2.2.5 ECG

12-lead ECGs for all participants at all centers will be conducted at the centers using standardised ECG machines throughout the study. ECGs will be performed at Screening, Randomisation, and at Visit 14 (Week 52). ECGs will be obtained after the participant has been resting supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the participant in the same physical position.

Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically

significant and the reason for the abnormality will be recorded on the eCRF, if the Investigator considers it clinically significant. Abnormal values shall not be recorded as AEs unless deemed clinically significant.

5.2.3 Vital signs

Vital signs (ear temperature, blood pressure [BP], pulse rate, and respiratory rate) will be obtained at each visit. Vital signs should be taken with the participant resting in a sitting position. Temperature should be taken the same way at all visits for a given participant. Specific information on vital signs surrounding the infusion is included in Section 7.2.4 (Participant Monitoring/Procedures During and After Infusions).

5.2.4 Assessment of cardiovascular risk

To understand the contribution of the chronic inflammatory response in SLE to dyslipidaemia (as a potential risk for accelerated subclinical arteriosclerotic cardiovascular disease) and the potential effects of anifrolumab treatment, both lipid (including LDL and HDL, triglycerides [see Section 5.2.1.1]) and inflammatory profiles will be obtained during the study. Various risk factors for atherosclerosis will be assessed as part of the participant demographics at screening according to the Adult Treatment Panel (ATP) III Guidelines. Current and previous concomitant medications received for cardiovascular indications should be collected and recorded.

5.2.5 Columbia Suicide Severity Rating Scale

The C-SSRS (Appendix Q) is a unique, simple, and short method of assessing both behaviour and ideation that tracks all suicidal events, and provides a summary of suicidality (Posner et al, 2007). It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be administered at all study visits by a trained rater. The trained rater will record the clinical observation on the scale, which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS. An Investigator physician will review completed C-SSRS responses on the day of assessment and document review within the source.

If a participant indicates having a rating of type 4 or 5 suicidal ideation on the C-SSRS suicidal ideation scale at any time since the previous visit when the C-SSRS was administered or indicates having had any suicidal behaviour since the previous visit, the participant should be referred to a mental health professional immediately. If the C-SSRS is administered by a

rater other than the Primary Investigator, it is recommended that the Primary Investigator confirms suicidal ideation before making a referral to mental health services; however this should not delay the referral.

5.2.6 Tuberculosis screening and monitoring

5.2.6.1 Screening evaluation

A blood test for TB will be done at screening using the IGRAs test (i.e., QuantiFERON® -TB Gold In-Tube [QFT-G] Test). Evaluation of all participants by QFT-G test will be performed by the central clinical laboratory, and chest imaging will be completed at screening. If an adequate (antero-posterior and lateral or per local standard of care) chest radiograph has been performed within 12 weeks prior to signing the ICF, it does not need to be repeated at the screening visit.

Compared to culture confirmed TB, overall, 87.6% of participants have a positive QFT-G result (Cellestis, 2005). The false negative rate in this setting appears to be over 12%. Further, the performance of the test in the setting of immunosuppressant drugs has not been evaluated. Nor has it been evaluated in individuals with medical conditions other than, or in addition to, latent TB or tuberculosis disease. The guide also states that “Medical treatments or conditions that impair immune functions can potentially reduce IFN-γ responses and prevent detection of a specific response to the (secretory proteins) ESAT-6 and CFP-10 (the test stimulators)”.

Given the population to be enrolled in the SLE study, false negative tests are possible, so a chest radiograph is a relevant technique for detecting active pulmonary disease and minimizing potential risk to study participants.

5.2.6.2 Tuberculosis results from screening evaluations

The procedures, and guidance for the evaluation of tuberculosis test results which must be performed based on the screening IGRA (i.e., QFT-G) test can be found in Section 3.1, Inclusion Criterion # 14.

5.2.6.3 Tuberculosis monitoring during the study

All participants will be monitored for signs and symptoms of TB over the course of the reatment Period and at the follow up visits using the standardized New or Reactivated TB Surveillance Questionnaire. This questionnaire must be completed at every onsite visit prior to receiving study intervention. If a participant presents with signs/symptoms of TB or positive findings on the routine questionnaire, an IGRA TB (QFT-G) test should be administered.

Participants, with indeterminate QFT-G results for both the initial and retest **at Screening and for whom latent TB treatment is not warranted**, must undergo repeat retesting every 3 months for 6 months see study plan (Section 4.1).

- If the retest QFT-G result is still indeterminate at Week 24, no further retesting is required until the Week 52 QFT-G required for all participants.
- Positive QFT-G test result, the participant should be referred to a TB specialist. If a TB specialist is not available, the local country guidelines should be followed for further diagnostic work up and anti-TB treatment regimens. If no local guidelines exist for immunocompromised individuals, then USA guidelines may be followed. This should also be reported as an AESI.
- Negative QFT-G test result, then the participant does not need to continue TB testing outlined for participants with indeterminate results at screening.

All participants must undergo QFT-G testing from the central laboratory for TB at Week 52. For participants with negative QFT at baseline and no symptoms of active TB:

- Week 52 QFT-G negative: no further testing.
- Week 52 QFT-G indeterminate: repeat at Week 56. If negative no further testing, however if indeterminate repeat again at Week 60.
- Week 52 QFT-G positive: repeat QFT-G test as soon as possible. If confirmed follow recommendations for positive QFT-G results during study. If repeat test is indeterminate or negative follow recommendation for indeterminate results above. Consider referral to TB specialist.

Tuberculosis questionnaire

To aid in the early detection of new or reactivated TB, a TB questionnaire will be used to evaluate participants for signs and symptoms of TB at every visit prior to receiving investigational medicinal product. If the evaluation raises suspicion that a participant may have new or reactivated TB, an immediate and thorough investigation should be undertaken including, where possible, consultation with experts specialising in TB.

Investigators should be aware that TB in immunocompromised participants may present as disseminated disease or with extrapulmonary features and should be referred for appropriate treatment.

5.2.7 COVID-19 questionnaire

Investigator should do SARS-Cov-2 exposure risk assessment throughout the study. A COVID-19 questionnaire will be used at screening visit to support COVID-19 risk assessment. After randomization, COVID-19 risk will be collected during routine AE assessment. If a participant becomes exposed or acutely infected during study, IMP should be temporary withheld as specified in Section 3.9.1. International/local guidelines for isolation should be followed. Refer to Section 3.9.1 for details.

5.3 Patient reported outcomes/pharmacoeconomic assessments

Health-related quality of life (HRQoL) and pharmacoeconomic assessments will be made at the times indicated in the Study Plan (Table 3, Table 4, and Table 5). Participant-reported outcome assessments should be completed by the participant, unassisted by spouse, family members or friends.

Participants will be completing the following participant-reported questionnaires to assess treatment effects.

5.3.1 EuroQoL 5 dimensions

The EQ-5D-5L is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (EuroQoL Group, 1990). Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems) that reflect increasing levels of difficulty. EQ-5D-5L health states will be converted into a single index value using values sets from the EQ-5D-5L Crosswalk Project. The questionnaire also includes a VAS, where the participants are asked to rate their health on a scale of 0-100, with 0 being worst imaginable health state and 100 being best imaginable health state.

5.3.2 Medical resource use questionnaire

Medical resource use will be determined by completing the Medical Resource Use Questionnaire Edition Number 3, which collects information on: 1) the number of unscheduled emergency department visits; 2) unscheduled hospitalisations; 3) the length of stay for hospitalisations; 4) the number of intensive care unit (ICU) stays and the length of ICU stays; 5) unscheduled medical provider visits; and 6) the cause(s) of hospitalisation over duration of the study.

Site personnel will administer the questionnaire by interviewing the participant at every visit. Further, site personnel are required to obtain source documentation (i.e., medical records) for these visits and make the records available to the monitor. Appropriate SAE/AE forms need to be completed for hospitalisation and emergency department visits.

5.3.3 Lupus quality of life

Lupus QoL is a 34-item SLE-specific health-related QoL measure. It was developed in the United Kingdom for use in adults with SLE (McElhone et al, 2007) and was further validated in the USA (Jolly et al, 2010). The instrument consists of 8 domains (physical health [8 items], pain [3 items], planning [3 items], intimate relationships [2 items], burden to others [3 items], emotional health [6 items], body image [5 items] and fatigue [4items]).

5.3.4 Work Productivity and Activity Impairment

The Work Productivity and Activity Impairment (WPAI) is a validated, self-administered questionnaire consisting of 6 questions, assessing the impact of disease on productivity. The WPAI yields 4 types of scores: absenteeism (work time missed), presenteeism (VAS [scored from 0 to 10] rating of impairment while working), work productivity loss (overall work impairment /absenteeism plus presenteeism), and activity impairment (VAS [scored from 0 to 10] rating of daily activities, other than work at a job) (Reilly et al, 1993).

5.4 Clinical pharmacology assessments

Clinical pharmacology assessments will be made at the times indicated in the Study Plan (Table 3, Table 4, and Table 5).

5.4.1 Pharmacokinetics

- Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix R.
- Samples will be stored for a maximum of 5 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.
- Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years following issue of the CSR.

5.4.1.1 Collection of samples

Blood samples for determination of anifrolumab in serum will be taken at the times presented in the study plan table (Table 4, Table 5). Pre-dose should be drawn within 30 minutes before the investigational medicinal product administration. Post-dose samples should be collected at 15 minutes ±5 minutes after completion of investigational medicinal product administration. Post-dose specimens should not be drawn through the IV line used to administer the investigational medicinal product.

For the PK analysis it is important that the date, start and stop time for the IV infusion, and the sample collection time are recorded. Instructions for sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual provided to the centers.

5.4.1.2 Determination of drug concentration

Samples for determination of anifrolumab concentration in serum will be analyzed by an external laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.2 Pharmacodynamics

5.4.2.1 Collection of samples

[redacted]

Samples will be collected, labelled, stored, and shipped as detailed in the separate Laboratory Manual.

5.4.3 Immunogenicity

Instructions for immunogenicity (ADA and neutralising antibodies [nAb]) sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

5.4.3.1 Anti-drug antibodies

Pre-dose serum samples to measure the presence of ADA will be collected according to the Study Plan (Table 4 and Table 5). The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Full details of the analytical method used will be described in a separate bioanalytical report. In order to help understand the potential drug-relatedness of any hypersensitivity or anaphylaxis reaction, possible additional ADA testing (if not already scheduled for a visit) may be collected and analyzed.

5.4.3.2 Neutralising antibodies

Neutralising antibodies testing will only occur on samples that are ADA positive. Samples that are ADA negative will not be tested for nAb. The presence or absence of neutralising ADA will be determined using a validated bioanalytical method. At the end of study, study team will decide whether or not to take neutralising antibodies testing based on overall ADA positive status. This testing result (if required) might not be available at the end of study.

[redacted]

5.4.5 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the participant unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, or surrogate).

Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix P to the Clinical Study Protocol.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’

criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

6.3 Adverse events of special interest

An AESI is an AE of scientific and medical concern specific to understanding biologics and requires close monitoring and rapid communication by Investigator to the Sponsor/Sponsor's delegate. An AESI may be serious or non-serious.

AESIs will be assessed at each visit and recorded in the eCRF. Currently, the following are AESIs for SLE studies.

- Serious non-opportunistic infection
- Opportunistic infection
- Herpes zoster
- Tuberculosis including Latent Tuberculosis
- Malignancy
- Major adverse cardiovascular events

An AESI that meets 1 of the seriousness outcomes listed in Section 6.2 will be categorised as an SAE for the purposes of follow-up responsibility and safety reporting. A nonserious AESI will be categorised as an AE. For reporting of AESIs, see Section 6.6.

6.3.1 Serious non-opportunistic infection

A serious, non-opportunistic infection is any infection that meets the SAE criteria in Section 6.2. Serious infection AEs are reported as SAEs. It is expected that microorganism culture results and all diagnostic or therapeutic procedure results performed on a participant experiencing a serious infection will be provided as an SAE update.

6.3.2 Opportunistic infection

An opportunistic infection is an invasive infection caused by microorganisms that are normally non-pathogenic or rarely pathogenic in individuals with normal immune function or

cause an infection of a type or severity not seen in the normal host. The absence of an invasive infection (i.e., colonization), irrespective of the type of microorganism, is not considered an opportunistic infection. It is expected that microorganism culture results and all diagnostic or therapeutic procedure results performed on a participant experiencing an opportunistic infection will be provided as an update.

6.3.3 Herpes zoster

Herpes zoster (HZ) is a viral infection usually characterized by a cutaneous vesicular eruption on an erythematous base presenting along dermatome(s) and usually associated with prodromal pain. HZ results from the reactivation of Varicella-zoster virus.

The following criteria for the evaluation of herpes zoster manifestations should be used:

1. Cutaneous localised is defined as ≤ 3 contiguous dermatomes (unilateral).
2. Cutaneous disseminated is defined as > 3 contiguous dermatomes (unilateral) OR "Skip lesions" - involving non-contiguous dermatomes OR Bilateral distribution rather than unilateral.
3. Visceral disseminated is defined as visceral complications including pneumonitis, hepatitis, and meningoencephalitis.
4. Involvement of the anterior or posterior structures of the eye, with or without zoster dermatitis (herpes zoster ophthalmicus) is classified as visceral disseminated.

Characteristics of cutaneous presentations should be captured and include a list of all dermatomes affected, whether the rash crosses the midline (unilateral or bilateral involvement) and whether affected dermatomes are contiguous.

Specific details of ophthalmic and nervous tissue involvement as well as other visceral involvement (for example, pneumonitis, hepatitis, and meningoencephalitis) must be provided. These visceral disseminated HZ events should be reported as an AESI of herpes zoster and not as an AESI of opportunistic infection. Seriousness, intensity/severity, clinical presentation and outcome should be included in the adverse event report along with existing laboratory and test results and imaging. Polymerase chain reaction testing of samples from vesicles, biopsy or other specimens (e.g., cerebrospinal fluid) may confirm the presence of *Varicella zoster* virus. Where Varicella zoster virus involvement is suspected in the absence of a rash, PCR or other diagnostic test results should be documented in the AE report.

Primary infections caused by *Varicella zoster* virus (VZV, i.e., chickenpox) should be reported using the diagnosis of chickenpox or an appropriate descriptor of the infection. A VZV infection is not an AESI.

6.3.4 Malignancy

Malignancy is a neoplasm characterized by cells with abnormal features, uncontrolled rapid growth with invasive and/or metastatic tendencies diagnosed based on pathologic and clinical standards. Understanding risk, if any, of developing different malignancies is critical to establishing the benefit-risk profile for anifrolumab. Investigators are therefore requested to obtain biopsy results and have pertinent biomarker and/or genetic testing results performed and to report these for any malignancies reported during the study or follow-up. Malignancies other than non-melanoma skin cancers (NMSC; cutaneous basal cell and squamous cell carcinomas) are generally considered serious and reported as SAEs.

6.3.5 Tuberculosis including latent tuberculosis

Tuberculosis (TB) is a mycobacterial infectious disease generally presenting as cough with systemic symptoms of infection diagnosed by skin test (purified protein derivative), blood test (IGRA), radiographic imaging, body fluid and tissue sampling; presentation may include disseminated or latent disease. An infection may be new (including conversion of a TB test to positive) or reactivation of dormant disease (new active disease in a previously TB test positive participant without prior evidence of active disease).

- **A bacteriologically confirmed** TB case is one where a biological specimen is positive by smear microscopy, culture or rapid diagnostic such as PCR or nucleic acid amplification test (Xpert MTB/RIF).
- **A clinically diagnosed TB** case is one that does not fulfil the criteria for bacteriological confirmation but has been diagnosed as active TB by a clinician or other medical practitioner who has decided to give the participant a full course of TB treatment. This definition includes cases diagnosed on the basis of radiograph abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to: anatomical site of disease; history of previous treatment; drug resistance; HIV status (World Health Organization, 2014 and 2020).

Latent TB is a mycobacterial infection without clinical, bacteriological, or radiologic findings consistent with active TB, but results in a positive TB blood test such as an IGRA (QuantiFERON-TB Gold). All participants must undergo IGRA[QFT-G] testing from the Central Laboratory for TB at screening and every 12 months through the duration of study (including the treatment and follow-up period) for both TB endemic and non-endemic regions as identified by the WHO (World Health Organization, 2020). Participants with a positive TB

blood test result, but no accompanying clinical or radiological work up should not be classified as having latent TB, but should be reported as being IGRA [QFT-G] test positive.

Participants should be monitored and a standardized TB questionnaire conducted at each required visit according to study plan. If a participant presents with signs/symptoms of TB or positive findings in the routine questionnaire, an IGRA [QFT-G] TB test should be administered.

The following guidelines must be followed based on TB test results:

- Participants with a negative IGRA [QFT-G] test result must be tested for TB again every 12 months from randomisation in both endemic and non-endemic regions.
- Participants testing positive at any time for TB must be referred to a TB specialist for evaluation. Active TB must be ruled out and initiation of treatment for latent TB prior to the first administration of study intervention in accordance with local standard of care.
- If a participant has an indeterminate IGRA [QFT-G] test result, he/she must be retested immediately using the same assay
  (a) If in an endemic region*, and the results upon immediate retest remain indeterminate, the participant must be referred to a TB specialist for evaluation (with assessment and treatment recommendation properly documented in source) before any further IMP administration. If warranted, appropriate latent TB treatment must be initiated prior to continued administration of IMP. If no latent TB treatment is warranted, the participant may continue to receive IMP without latent TB treatment, but must be administered a retest every 3 months for 6 months. If upon retest by the end of the 6 months, the result is indeterminate, the participant may continue in the study without latent TB treatment and continue with routine TB testing.
  (b) If in a non-endemic region, and the results upon immediate retest remain indeterminate, the participant may continue in the study without latent TB treatment, but must be administered a retest every 3 months for 6 months. If, upon retest by the end of the 6 months, the result is indeterminate, the participant may continue in the study without treatment.

  * Endemic region as defined based on WHO lists of High Burden Countries (HBC) for TB and multi-resistant (MDR) TB. (See current list, World Health Organization, 2020).

  NOTE:

  - It is recommended that any participant with an indeterminate test result be referred to a TB specialist for care and treatment per local guidelines. A participant with a negative IGRA [QFT-G] test result upon retest (after an initial indeterminate result) need not receive any treatment for TB prior to receiving IMP. A participant with a positive IGRA [QFT-G] rest result upon retest (after

an initial indeterminate result) should begin treatment for latent TB as outlined above.

- If no local guidelines exist for immunocompromised individuals, then WHO guidelines may be followed (World Health Organization, 2014). Once latent TB is confirmed, treatment must be instituted immediately, and no IMP may be administered until treatment of latent TB has begun. IMP may be administered within an appropriate time frame following treatment initiation as per local guidelines.

6.3.6 Major adverse cardiovascular events

Major adverse cardiovascular events (MACE) are designated as AESIs in the anifrolumab program. These events include non-fatal myocardial infarction, non-fatal stroke and cardiovascular (CV) death.

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

Adverse Events and SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period until Follow-up Visit 2 (12 weeks post final dose). All SAEs, including ongoing or new SAEs occurring within the follow-up period12 weeks after last dose of intravenous IMP, will be followed to resolution/stabilization regardless of the date of study completion. Events that reach a point of resolution/stabilization but with consequences are recorded as “resolved with sequalae.”

6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the participant’s last visit in the study are followed up by Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

If Investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, Investigator shall, without undue delay, report the serious adverse event to the sponsor.

6.4.3 Variables

The following variables will be collected for each AE

- AE (verbatim)
- The date and time when the AE started and stopped

- Maximum intensity (mild, moderate, or severe)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational medicinal product (yes or no)
- Action taken with regard to investigational medicinal product
- Outcome of AE

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to:
  (a) Death
    - Date of death
    - Autopsy performed
    - Primary/secondary cause of death
  (b) Life threatening
  (c) Inpatient hospitalisation or prolongation of existing hospitalization
    - Date of hospitalization
    - Date of discharge
  (d) Persistent or significant disability/incapacity
  (e) Congenital abnormality or birth defect
  (f) Important medical event
- Description of AE
- Investigator causality assessment to concomitant medications
- Investigator causality assessment to study procedures (yes or no)

6.4.4 Assessment of severity

The determination of severity should be made by Investigator, using the severity categories as below:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2. Investigator should provide an assessment of the severity of each AE/SAE.

6.4.5 Causality collection

Investigator should assess causal relationship between Investigational medicinal product and each Adverse Event, and answer 'yes' or 'no' to the question '*Do you consider that there is a reasonable possibility that the event may have been caused by the investigational medicinal product?*'

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug (such as OCS, azathioprine, antimalarials, mycophenolate mofetil/mycophenolic acid, methotrexate, and mizoribine). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix P to the Clinical Study Protocol.

6.4.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study *personnel: 'Have you/the child had any health problems since the previous visit/you were last asked?' or* revealed by observation will be collected and recorded in the CRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.7 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria

- are the reason for discontinuation of treatment with the investigational medicinal product
- are considered to be clinically relevant as judged by Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia vs low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

6.4.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3×ULN together with total bilirubin ≥ 2×ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4.9 Disease progression

Disease progression can be considered as a worsening of a participant's condition attributable to SLE. It may be an increase in the activity or severity of the existing manifestations of SLE or the appearance of new manifestations. **Worsening of SLE should not be reported as an AE**, **unless the signs and symptoms meet criteria for an SAE or lead to discontinuation of the investigational medicinal product.** New manifestation or worsening of existing manifestations of SLE should be reported as "new" or "worsening" in the BILAG-2004, and recorded in the SLEDAI-2K, as appropriate.

6.5 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational medicinal product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once Investigators or other site personnel indicate an AE is serious or is an AESI in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative(s).

If the WBDC system is not available, then Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise Investigator/study site personnel how to proceed.

6.6 Reporting of adverse events of special interest

Adverse Events of Special Interest will be assessed by Investigator for severity, relationship to the investigational medicinal product, possible aetiologies, and whether the event also meets criteria of an SAE. All AESIs (serious or nonserious) will be recorded on the AE CRF (using a recognized medical term or diagnosis that accurately reflects the event).

The reporting period for AESIs is the period immediately following the time that written informed consent is obtained through the end of participant participation in the study. Following detection of an AESI (non-serious), reporting is required within 72 hours of knowledge of the event, and for serious AESIs the standard 24-hour timeline for reporting to the appropriate AstraZeneca representative or designee applies.

6.7 Overdose

An overdose (i.e., having been administered a greater dose of study intervention than specified in this protocol) with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, then Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

The designated AstraZeneca representative works with Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for overdoses associated with an SAE, see Section 6.5. and within 30 days for all other overdoses.

6.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention.

6.8.1 Maternal exposure

If a participant becomes pregnant during the course of the study, investigational medicinal product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational medicinal product under study may have interfered with the effectiveness of a contraceptive medication. **Congenital anomaly/birth defects and spontaneous miscarriages should be reported and handled as SAEs.** Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study until 16 weeks after the last dose of IP, then Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for pregnancies associated with SAEs (see Section 6.5) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

6.8.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 16 weeks following the last dose.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first investigational medicinal product administration until 16 weeks after the last investigational medicinal product administration should be followed up and documented in the Pregnancy Report Form. Information on the pregnancy of a participant's partner must be obtained directly from the participant's partner. Therefore, prior to obtaining information about the pregnancy, Investigator must obtain the consent of the participant's partner.

6.9 Medication error, drug abuse and drug misuse

6.9.1 Timeline

If an medication error, drug abuse, **or** drug misuse occurs in the course of the study, then Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**,i.e., immediately but **no later than 24 hours** of when they become aware of it.
The designated AstraZeneca representative works with Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 6.9.4) and within 30 days for all other medication errors.

6.9.2 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix P (P 3).

6.9.3 Drug abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix P (P 3).

6.9.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix P (P 3).

6.9.5 Reporting of overdose

Refer to Section 6.7 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If a medication error occurs on an IMP in the course of the study, then Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within **1or 5 calendar days** for overdoses associated with an SAE (see Section 6.5) and within 30 days for all other overdoses.

6.10 Management of IMP related toxicities

6.10.1 Anaphylaxis, hypersensitivity, and infusion-related reactions

Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Pre-medication for infusions is not planned. However, i f a prior infusion-related reaction has been documented or if a potential benefit from pre-medication is expected based on investigator justification, Investigator may elect to administer prophylactically an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the participant

prior to subsequent infusions. **Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted** (see Appendix I).

6.10.2 Infections

When an infection is reported as an SAE or AESI, cultures should be obtained and culture results should be reported with the event. Other specific laboratory or other investigations (e.g., chest imaging for pneumonia) that confirm or aid in the diagnosis or treatment should be obtained when indicated and results should be reported with the SAE or AESI.

Participants who develop a new infection while undergoing treatment with investigational medicinal product should receive appropriate medical therapy, as determined by local standards, and be monitored closely until the condition resolves. Investigational medicinal product should not be administered to a participant with a clinically significant, active infection as determined by Investigator (see Section 3.9). For any active infection (e.g., *varicella zoster* infection/chickenpox) or significant exposure to any infection (e.g., *varicella zoster* infection in a naive participant, bacterial pneumonia), Investigator should consider whether to interrupt investigational medicinal product administration and should notify the AstraZeneca study physician.

Similarly, if a participant presents with signs or symptoms where opportunistic infections are considered (e.g., CNS symptoms consistent with progressive multifocal leukoencephalopathy or *herpes encephalitis* or atypical pneumonia suggesting *pneumocystis jiroveci* pneumonia), investigational medicinal product should be interrupted until Investigator confirms the symptoms and signs of infection have resolved or that no active infection has developed.

If dosing is resumed after resolution of a safety concern (i.e., infection or other AE) the investigational medicinal product must be administered within 14 days of the scheduled time of the missed dose. If this is not possible, dosing should be resumed at the time of the next scheduled dose.

6.11 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

The study will have a DSMB for independent safety monitoring. For details on the DSMB, refer to Appendix A6.

The study will have a central review team for the confirmation of diagnosis and disease activity assessments (Disease Activity Central Review Team). Details related to DACRT, refer to Section 5.1.2.

7 STUDY INTERVENTION AND OTHER TREATMENTS

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo, or medical device(s) intended to be administered to or medical device(s) utilised by a study participant according to the study protocol.

7.1 Identity of investigational medicinal product(s)

Anifrolumab (MEDI-546) and placebo will be supplied to Investigator by AstraZeneca.

Investigational medicinal product	Dosage form and strength	Manufacturer
Anifrolumab (MEDI-546)	150 mg/mL solution of anifrolumab (Clear to opalescent, colorless to yellow liquid, free from or practically free from visible particles) intended for IV administration following dilution into 0.9% (w/v) saline	AstraZeneca Nijmegen B.V.
Placebo to match Anifrolumab	Solution (clear) intended for IV administration following dilution into 0.9% (w/v) saline	AstraZeneca Nijmegen B.V.

Excipients include 25 mM histidine/histidine-HCl, 50 mM lysine-HC1, 130 mM trehalose dihydrate, 0.05% (w/v) plant-derived polysorbate 80, pH 5.9.

Investigational medicinal product and placebo will be provided as a vial packaged within a carton. Each kit will contain 2 mL label-claim volume. Every kit will have a unique number that will be printed on all the labels within the kit (i.e., the outer carton label and the vial label).

Preparation of investigational medicinal product and placebo must be performed by an unblinded qualified person (e.g., pharmacist or study nurse) at the site, using aseptic technique. When diluted as directed in the investigational medicinal product study manual provided by the Sponsor, placebo and investigational drug appear identical. See Section 7.2 below for diluent and infusion vessel and tubing specifications.

7.2 Dose and treatment regimens

The investigational medicinal product, anifrolumab 300 mg or placebo, will be administered via controlled IV infusion pump into a peripheral vein over a minimum of [redacted] Q4W from Week 0 to Week 48 for a total of 13 doses. **Each dose must be at least 14 days apart.**

7.2.1 Dose preparation steps

From a pre-filed 100 mL IV infusion bag of 0.9% (w/v) saline, withdraw and discard a volume of saline equal to 2.0 mL. Then add 2.0 mL anifrolumab from the vial in the kit to the infusion bag and mix by gentle inversion. Due to approximately 10% overfill of 0.9% (w/v) saline, the final volume of the dilution will be greater than 100 mL.

The dose of anifrolumab or placebo for administration must be prepared by Investigator's or site's designated IMP manager using aseptic technique.

7.2.2 Prior to administering the investigational medicinal product

- Confirm participant was evaluated for signs and symptoms of TB.
- Women of childbearing potential must have a negative urine pregnancy test prior to receiving investigational medicinal product.
- Participants should not have clinically significant, active infection as determined by Investigator.
- **There should be at least 14 days between doses**. If the previous investigational medicinal product infusion was given within 14 days, delay visit until >14 days has elapsed and contact the AstraZeneca study physician.
- Pre-dose blood samples will be collected.
- If a prior infusion-related reaction has been documented, Investigator may elect to administer prophylactically an antihistamine or acetaminophen/paracetamol for the comfort and safety of the participant prior to subsequent infusions. The medications should be given after visit assessments have been completed. Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted.

7.2.3 Investigational medicinal product administration procedures

- Total in-use storage time from needle puncture of the anifrolumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36 to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials.
- Investigational medicinal product must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational medicinal product.
- Because compatibility of anifrolumab with IV medications and solutions other than 0.9% (w/v) saline, is not known, the investigational medicinal product solution should not be

infused through an IV line in which other solutions or medications are being administered.

- Investigational medicinal product should be delivered through an IV administration set with a 0.20 µm or 0.22 µm filter.
- Investigational medicinal product should be administered over a minimum of [redacted]. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 4 hours at room temperature. Infusion time does not include the final flush time.
- Immediately following the initial dosing, up to an additional **25 mL of** 0.9% (w/v) **saline** will be given via infusion pump at the same pump speed utilized at the completion of the initial dosing.
- An emergency cart should be available in the infusion suite.
- Investigational medicinal product does not contain preservatives, and any unused portion must be discarded.

7.2.4 Participant monitoring/procedures during and after the infusion

Participants will be monitored during the administration of the investigational medicinal product and for at least 2 hours after the first 4 infusions (Weeks 0, 4, 8, and 12). If there are no safety concerns, for subsequent infusions participants will be monitored during administration of the investigational medicinal product and for a minimum of 1 hour after completion of the IV infusion thereafter (Week 16 to Week 48).

Monitoring will include vital signs (ear temperature, BP, pulse rate, respiratory rate) in a sitting position at the following times:

- Shortly before the IV infusion (within 15 ±5 minutes of the beginning of the investigational medicinal product infusion).
- Every 15 ±5 minutes during infusion.
- Immediately after completion of administration of investigational medicinal product, including post-dose saline flush (within 15 ±5 minutes after completion of investigational medicinal product administration).
- Every 30 ±5 minutes after completion of investigational medicinal product administration (not including saline flush) for at least 2 hours after the first 4 doses (Randomisation [Day 1] to Week 12) of investigational medicinal product are administered, and for at least 1 hour, thereafter (Week 16 to 48).
- Samples for PK laboratory assessments should be collected 15 ±5 minutes after completion of investigational medicinal product administration (not including saline flush) after dosing on Randomisation (Day 1) and Week 48.

Vital signs may be taken more frequently, based on Investigator judgment.

7.2.5 Discharge

The participant should only be discharged from the site after the minimum monitoring period and when judged stable in the opinion of Investigator/designee. Blood pressure and pulse rate will be taken prior to discharge from the site.

7.2.6 Documentation of investigational medicinal product administration

The duration of the investigational medicinal product infusion will be recorded and calculated as follows:

- Duration of infusion: the amount of time elapsed from the infusion start time to the infusion stop time. Infusion start time is defined as the time point where investigational medicinal product is first infused into the participant. Infusion stop time is defined as the time point where the infusion pump completes infusion of the investigational medicinal product, not including the saline flush.

For example: an infusion with a start time of 12:00 PM would have a duration of infusion recorded as 30 minutes (a time between 12:00 PM and 12:30 PM).

The start time of IMP infusion, end time of IMP infusion, and the end time of salin flush should be documented accurately in source document.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study interventions should be kept in a secure place under appropriate storage conditions. The investigational medicinal product should be stored at 2 to 8°C (36 to 46°F) and must not be frozen.

7.5 Compliance

The administration of all study interventions (including investigational medicinal products) should be recorded in the appropriate sections of the Case Report Form. The investigational medicinal product will be administered by qualified study site personnel, who will monitor compliance.

7.6 Accountability

The study intervention provided for this study will be used only as directed in the study protocol.

The study site personnel will account for all study interventions dispensed to and returned from the participant.

Investigator or pharmacist is required to maintain accurate investigational medicinal product accountability records. Upon completion of the study, copies of investigational medicinal product accountability records will be returned to AstraZeneca or designee. Each administration of IV study therapy will be documented in the eCRF.

The unblinded AstraZeneca representative can perform complete IV study therapy accountability during each unblinded monitoring visit, including verifying documentation of drug receipt, dispensing, return, and destruction of IV study therapy and consistency of this documentation with physical inventory and IVRS/IWRS.

All unused investigational medicinal product will be returned to an AstraZeneca or designee-authorised depot or disposed of upon authorisation by AstraZeneca or designee or other written instructions provided by AstraZeneca or designee (for contact information and specific shipping instructions). Investigator or pharmacist should sign certificates of delivery and return.

Details regarding supplies, dose preparation, process for reporting product complaints, and accountability for the investigational medicinal product will be provided to the sites.

7.7 Concomitant and other treatments

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting Investigator.

7.7.1 Prohibited/restricted medications

7.7.1.1 Excluded medications: pre-study

Any medication listed in Appendix I must be discontinued prior to signing of the ICF.

7.7.1.2 Excluded medications: during double-blind treatment period

Medications leading to immediate discontinuation of investigational medicinal product.

- Cyclophosphamide
- Biologic immunomodulators (e.g., belimumab, rituximab)
- JAK inhibitors (e.g., tofacitinib, baricitinib)

- BTK inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib)
- Plasmapheresis
- Any immunoglobulin therapy
- IFN therapy (alpha 2a and 2b, beta 1a and 1b, and pegylated IFNs alpha 2a and 2b)
- Investigational agents
- Live or attenuated vaccines (e.g., BCG, herpes zoster, yellow fever); the Sponsor recommends that Investigators ensure all participants are up to date with required vaccinations prior to entry into the study
- Any medication listed in Appendix I , except restrictions (e.g., sulfasalazine, danazol, and dapsone restrictions) as listed below in Section 7.7.1.3.
- Intravenous corticosteroids > 1 g methylprednisolone or equivalent

If any of the prohibited medications listed in Appendix I are used, except restricted drug listed below in Section 7.7.1.3, IMP must be immediately discontinued and participant will be regarded as non-responder for efficacy endpoints. Additional details are given in the SAP.

7.7.1.3 Restricted medications during double-blind treatment period

As anifrolumab is an investigative immunomodulatory agent, non-protocol permitted changes to immune modifiers or immunosuppressants on study are not permitted unless necessary to treat an adverse event or increased disease activity.

If a participant receives any of the following during study treatment period **the study physician must be notified immediately**. Sponsor will determine if the participant may continue to receive investigational medicinal product. Details on handling the analysis of data from participants who may use restricted medications are described in the SAP.

1 Sulfasalazine
2 Danazol, GnRH agonists or GnRH antagonists
3 Dapsone
4 Azathioprine > 200 mg/day or at a daily dose greater than that at Week 0 (Day 1)
5 Mycophenolate mofetil > 2.0 g/day or mycophenolic acid > 1.44 g/day or at a daily dose greater than that at Week 0 (Day 1)
6 Oral, SC, or intramuscular methotrexate > 25 mg/week or at a daily dose greater than that at Week 0 (Day 1)
7 Mizoribine > 150 mg/day or at a daily dose greater than that at Week 0 (Day 1)
8 Any change in route of administration of oral, SC, or intramuscular methotrexate
9 Intravenous corticosteroids > 40 mg/day but ≤ 1 g/day methylprednisolone or equivalent
10 Intramuscular corticosteroids > 80 mg/day methylprednisolone or equivalent

11 Subcutaneous or intramuscular corticosteroid precursors

12 Treatment with OCS > 40 mg/day prednisone or equivalent

13 Treatment with OCS above Day 1 dose for a dosing period > 14 days

14 Corticosteroids with a long biologic half-life (e.g., dexamethasone, betamethasone)

15 Tacrolimus (including topical) or cyclosporine, at a daily dose greater than that at Week 0 (Day 1)

16 Other immunosuppressants including but not limited to leflunomide.

Note: Cyclosporine eye drops are acceptable for use in the study. Topical tacrolimus is only acceptable if it's initiated **before** study and on stable regimen during study.

7.7.1.4 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the participant's safety and well-being, may be given at the discretion of Investigator and recorded in the appropriate sections of the Case Report Form.

Inhaled corticosteroids:

Use of inhaled corticosteroids is allowed as needed for management of asthma or COPD.

Vitamins and herbal products:

Use of naturopathic, herbal or ayurvedic products should be avoided and participants should not start treatment with any of these or of nutritional/dietary supplements, vitamins, and/or minerals without discussing with Investigator.

Medicinal cannabinoid use:

Any new medicinal cannabinoid should not be started during the course of the study. Participants who are already on a stable regimen 8 weeks prior to screening may continue their regimen at the same stable dose through the course of study. Increases in strength or frequency is not allowed. Decrease or discontinuation is allowed for safety reasons.

7.7.2 Systemic Lupus Erythematosus therapy during double-blind treatment period

Permitted medications for SOC SLE are described below. Concomitant medications should only be administered after all visit assessments, including investigational medicinal product administration and post-infusion PK blood draws (if applicable), with the exception of a participant with a previous infusion-related reaction who is to receive acetaminophen (paracetamol) or equivalent. The acetaminophen or equivalent should be given after all visit assessments other than the infusion have been completed, and prior to starting the infusion.

Table 7 Permitted medications for SOC SLE

Permitted SOC SLE	Limitations of Use
OCS	• Oral prednisone or equivalent up to ≤ 40 mg/day is permitted from at **least 2 weeks prior to signing of the informed consent**. The dose of oral prednisone must remain stable **at least 2 weeks prior to Randomisation.** • Where prednisone is the single SOC medication [i.e., the participant is not concurrently receiving any medications listed in Section 3.1 #7], a dose of oral prednisone ≥ 7.5 mg/day but ≤ 40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to Randomisation is required.
Intramuscular corticosteroids	• Participants with increased SLE disease activity may receive 1 intramuscular injection of corticosteroids (methylprednisolone ≤ 80 mg or equivalent) instead of a burst and taper of OCS described above between Day 1 and Week 12. • May only be administered after all assessments and investigational medicinal product infusion have been completed at the visit.
Corticosteroid bursts and tapers	• Participants with increased SLE disease activity may receive 1 permitted burst and taper of corticosteroids between Day 1 and Week 12. Additional details on burst and taper for SLE and non-SLE (e.g., asthma or COPD exacerbation) disease activity are provided in Sections 7.7.1.4 to 7.7.3.
Intra-articular/tendon sheath/bursal corticosteroid injections	• Intra-articular/tendon sheath/bursal injection should be minimised. Participants may receive a maximum of 2 injections (for a total dose of ≤80 mg methylprednisolone or equivalent) instead of a burst and taper of OCS described above, between Day 1 and Week 12. • An intra-articular/tendon sheath/bursal injection may be allowed for non-SLE related disorders up to Week 40 if the symptoms of the disorder do not interfere with the ability to assess SLE-related endpoints. Investigator must contact the AstraZeneca study physician for permission to administer an intra-articular/tendon sheath/bursal corticosteroid injection prior to administration of corticosteroids for non-SLE related disorders. • If permission is given, the injection should not be administered until after the completion of all assessments, including investigational medicinal product administration and post-infusion PK blood draw (if applicable).
Antimalarials and immunosuppressants (azathioprine, methotrexate, and mycophenolate mofetil/mycophenolic acid, and mizoribine)	• Antimalarials and immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil/mycophenolic acid, and mizoribine) are permitted, and at least 1 is required, as part of SLE therapy on Day 1 if the participant is not on OCS. • Dose regimens must remain stable from Day 1 to the completion of Week 52 but may be decreased for toxicity or to optimise management of an AE, such as infection. The toxicity/event must be confirmed as a documented AE. The dose can be returned to the Day 1 level if the toxicity/event resolves and if clinically indicated. • Antimalarials/immunosuppressants should not be changed if a participant has increased SLE disease activity during the OCS tapering period.

Nonsteroidal anti-inflammatory drugs (NSAIDs)	• Prescription NSAIDs must remain stable from screening through Week 52 but can be reduced for reasons of toxicity but not efficacy. Prescription NSAIDs cannot be administered with other NSAIDs (including over-the-counter non-steroidals) except for low-dose aspirin. • On a given visit day, prescription or non-prescription NSAIDs should not be taken until after all assessments have been completed. • NSAIDs for analgesic purposes that never exceed label-approved doses of NSAIDs may be used for pain as required, based on Investigator judgment for up to 1 week at a time
Acetaminophen, paracetamol or equivalent	• Pain medications should not be used within a minimum of 6 to 12 hours (based on known duration of effect) of a scheduled visit. • Normal release (not extended release) acetaminophen or equivalent (e.g., paracetamol) may be used for pain as required. • In a participant with a previous infusion-related reaction, acetaminophen or equivalent can be given after all visit assessments have been completed and prior to starting the infusion.
Low-dose aspirin	• Low-dose aspirin (maximum of 325 mg/day) for cardiovascular disease is permitted.
Topical therapy	• Concurrent use of topical therapy for cutaneous lupus erythematosus (e.g., corticosteroids) is permitted. Topical moisturisers are also permitted. • Topical therapy must be the same being used at signing of the informed consent and the dose and frequency of application must be stable during screening. • During the study, topical therapy may be reduced or discontinued based on clinical manifestations and Investigator discretion. Should cutaneous skin manifestations reoccur, the same topical therapy may be resumed up to the Day 1 dose. • It is encouraged that no new dermatologic preparations be used for the duration of the study. It is also recommended that participants use sunscreen (list as concomitant medication for SLE) and avoid sun exposure during the study.

All permitted SOC SLE therapies received from initiation of screening through the end of the study will be recorded on the source document and CRF, and will include the specific indication for use (e.g., general SLE activity, skin involvement, nephritis, pleurisy) as well as the dose, start and stop dates, frequency, and route of administration. In addition, any change in permitted SOC SLE therapy and the reason for change must be documented.

If concurrent SOC medication requirements, e.g., glucocorticoids, immunosuppressants or anti-malarials, are not followed, participants may be considered as non-responders for efficacy endpoints. Additional details are given in the SAP.

7.7.3 Steroid use during the double-blind treatment period

7.7.3.1 Steroid burst and taper from Week 0 (Day 1) to Week 12

In order to allow adequate time for the investigational medicinal product to achieve significant clinical benefit, Investigators may administer **1** burst and taper of corticosteroids between Week 0 (Day 1) and Week 12 for increased SLE disease activity/non-SLE causes.

A steroid burst as described below is defined as 1 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. Any course of OCS above the Day 1 dose must not extend beyond Week 12, regardless of when the course was started;

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. Participants who receive any intra-articular/tendon sheath/bursal injections should not receive OCS or intramuscular burst between Day 1 and Week 12.

Participants who receive more than 1 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 may be considered as non-responders for efficacy endpoints (details are defined in the SAP), regardless of whether the OCS burst was administered for increased SLE activity or non-SLE causes.

7.7.3.2 Increase in corticosteroids from Week 12 to Week 40

Between Week 12 and Week 40, an increase in corticosteroid dose for increased SLE activity is not allowed. Participant receiving a steroid dose above their Week 0 (Day 1) dose may continue in the study, but may be considered as non-responders for efficacy endpoints (details are defined in the SAP).

An increase in OCS for non-SLE causes (e.g., asthma or COPD exacerbation) is allowed ONCE with AstraZeneca study physician approval between Week 12 and Week 40. This might include a non-SLE OCS up to ≤20 mg/day of prednisone (or equivalent) for up to a total of 14 days and must be fully administered and tapered to less than or equal to the Day 1 dose by the end of the 14th day and by the Week 40 visit day. This will be captured as burst and taper not attributable to SLE. The non-SLE indication must be clearly indicated in the source documents.

Participants who receive prednisone (or equivalent) for non-SLE indication at a total dose > 20 mg/day but ≤ 40 mg/day for a dosing period of greater than 14 days may continue in the study, but may be considered as non-responders for efficacy endpoints (details are defined in the SAP). If a participant receives > 40 mg prednisone or equivalent or a dose above baseline level for more than 14 days, it must be reported to the AstraZeneca study physician. The AstraZeneca study physician will determine if the participant may continue to receive investigational medicinal product.

7.7.3.3 Increase in oral corticosteroids after Week 40

An increase in OCS is NOT allowed after Week 40 (except for the management of AEs or as a prophylaxis for adrenal insufficiency as described below). Participants who receive an increase in their OCS after Week 40 will be considered as non-responders for efficacy endpoints (details are defined in the SAP).

7.7.3.4 Increase in oral corticosteroids for intercurrent disease or to prevent adrenal insufficiency

In addition to the burst and tapers described above, participants who are taking ≤ 7.5 mg/day prednisone or equivalent will be allowed to receive up to an additional 7.5 mg/day to a total of 15 mg/day prednisone or equivalent for a total of up to 14 days or a single dose of IV hydrocortisone (≤ 100 mg hydrocortisone followed by half that dose for 2 days before returning to their usual dose) for severe illness, surgery, or symptoms of adrenal insufficiency or corticosteroid withdrawal if clinically warranted at any time. Use of corticosteroids should be minimised for patient safety reasons.

7.7.3.5 Protocol-specified steroid tapering Week 8 to Week 40

All participants with a baseline prednisone (or equivalent) dose of ≥ 10.0 mg/day must attempt tapering of their dose to ≤ 7.5 mg/day. Tapering will start at Week 8 and continue through Week 40, unless there are signs of increased disease activity, including:

- SLEDAI-2K scores for renal, CNS, cardiopulmonary, vasculitis, fever, hemolytic anemia, thrombocytopenia or gastrointestinal activity; and/or
- SLEDAI-2K scores showing new activity in any organ system, except serological abnormalities (dsDNA, hypocomplementemia); and/or
- Moderate to severe skin disease as reflected by a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score of ≥ 10; and/or
- Extensive joint disease as reflected by ≥8 tender and ≥8 swollen joints

If steroid tapering is not attempted in an eligible participant, the Sponsor or Sponsor's designee must be contacted immediately. The recommended steroid-tapering regimen is provided in Appendix N. However due to variability in participant responses to steroid

treatment and tolerability of taper, 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 Week 40 based on disease activity.

When available, if the lab values from the current visit at which tapering occurs, show increased SLE activity, the tapering can be reversed. If a participant has an increase in disease activity secondary to OCS tapering between Week 8 and Week 40, the OCS dose should be increased back to, but should not exceed, the Day 1 baseline dose. Participants who require OCS dose above their baseline level may continue in the study following consultation with the Sponsor or Sponsor's designee, but may be considered as non-responders for efficacy endpoints (details are defined in the SAP).

Steroid tapering will not be permitted after Week 40.

7.8 Dose modification

There are no provisions for IMP dose modification or retreatment in this study.

7.9 Intervention after the end of the study

Participants are to be treated with standard therapy after they have concluded study treatment. There are no provisions for administration of IMP following the Week 52 end of treatment visit.

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until CDL and protocol violators identified. Analyses will be performed by AstraZeneca or its representatives.

Two CDLs are planned in this study. The primary CDL will be conducted after the last participant completes 52-week double blind treatment period, and the final CDL will be conducted once the last participant completes the last visit/assessment. After the primary CDL, the treatment allocation for participants will become known to the sponsor staff. The blind will be maintained for investigators, investigational site staff, and for the participants until the final CDL.

A comprehensive SAP was prepared within 90 days of first participant enrolment into the study. Any subsequent amendments to the SAP will be documented, with final amendment completed prior to unblinding of the data for the analysis. Details of all analyses, including sensitivity analyses, will be fully documented in the SAP.

8.2 Sample size estimate

A total of 260 participants receiving SOC treatment will be randomised 1:1 to treatment with anifrolumab or placebo.

The treatment effect of anifrolumab vs placebo measured by BICLA response at Week 52 will be estimated using the Bayesian robust MAP prior approach with borrowing from the pooled global phase III studies (study 05 and study 04). The sample size is calculated based on the criterion of having greater than [redacted] posterior probability that anifrolumab 300mg is effective compared to placebo (difference in BICLA response rates at Week 52 greater than 0).

In study 05, a difference of 17.0% in BICLA response rates at Week 52 was observed for anifrolumab 300 mg compared with placebo (47.1% vs 30.2%, 95% CI 7.2, 26.8; nominal $p < 0.001$). In study 04, participants treated with anifrolumab 300 mg had a statistically significant higher BICLA response rate at Week 52, compared with participants in the placebo group (47.8% vs 31.5%; difference 16.3%, 95% CI 6.3, 26.3; $p=0.0013$). The pooled BICLA response rates for anifrolumab 300 mg and placebo groups based on study 05 and study 04 are 47.5% and 30.8%, respectively. Results for BICLA responses at Week 52 in study 05 and study 04 trials are also listed in Table 8.

Table 8 BICLA response rates at Week 52 in study 05 and study 04

		Response Rates **BICLA at 52 weeks**	**Treatment difference (95% CI)** **BICLA at 52 Weeks**
Study 05	Placebo	55/184 (30.2%)	-
	Anifrolumab 300mg	85/180 (47.1%)	17.0% (7.2%, 26.8%)
Study 04	Placebo	57/182 (31.5%)	-
	Anifrolumab 300mg	86/180 (47.8%)	16.3% (6.3%, 26.3%)
Pooled study 05 & study 04	Placebo	112/366 (30.8%)	-
	Anifrolumab 300mg	171/360 (47.5%)	16.6% (9.7%, 23.6%)

The current study mirrors study 04's design with the same target population (moderate to severe SLE patients), treatment groups and randomization ratio. The primary endpoint BICLA response at Week 52 is also evaluated with the same definition as study 05 and study 04. Given the robust response rates in study 05 and study 04, the pooled BICLA response rates at Week 52 in will be used as an informative prior for the response rates of anifrolumab 300 mg and placebo groups in the Asian population. The robust MAP prior approach (Schmidli et al, 2014) will be adopted to partially extrapolate the pooled response rates of study 05 and study 04 to the Asian population. The informative prior will be robustified with a prior weight, where the weight represents the a priori degree of relevance of the pooled response rates of study 05 and study 04 to the Asian population. With a level of extrapolation ([redacted]), and the assumed proportions of BICLA response rates 47.5% and 30.8% in the anifrolumab 300 mg and placebo groups respectively (based on the pooled study 05 and study 04), 130 participants/arm yields [redacted] chance of having have greater than [redacted] posterior probability that anifrolumab is effective compared to placebo, i.e., the lower limit of [redacted] credible interval of treatment difference is greater than 0 in a Bayesian framework (power: [redacted]). In mathematical notation, it can be written as

$$P(\pi_1 - \pi_0 > 0 | data) > [redacted]$$

where π_1 and π_0 represent the underlying response rates of anifrolumab 300 mg and placebo groups respectively. Under the assumptions of no treatment difference (30.8% vs 30.8%), 130 participants/arm and [redacted] prior weight will control the probability of having greater than [redacted] posterior probability of efficacy at approximately [redacted] (one-sided type I error: [redacted]). Expecting screen failure rate of 50%, approximately 520 participants shall be screened to obtain the required number of randomised participants.

8.3 Definitions of analysis sets

8.3.1 All participants analysis set

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

8.3.2 Full analysis set

The full analysis set will be used as the primary population for reporting efficacy. This comprises all participants randomised into the study who receive at least 1 dose of investigational medicinal product and will be analyzed according to randomised treatment (modified Intention-To-Treat).

8.3.3 Safety analysis set

The safety analysis set will be used as the primary population for reporting safety data. It consists of all participants who have received at least 1 dose of IMP. Erroneously treated participants, who are randomized to receive anifrolumab but are actually given placebo for the entirety of their time in the study, will be accounted for in the placebo arm. A participant who has on one or several occasions received anifrolumab is classified in the respective anifrolumab group.

8.3.4 Pharmacokinetic analysis set

All participants who received anifrolumab and who had at least 1 quantifiable serum PK observation post first dose that are assumed not to be affected by factors such as protocol deviations, will be included in the PK analysis dataset. All PK data summaries will be based on this analysis set.

8.4 Outcome measures for analyses

Baseline is defined as the last measurement prior to randomisation and dose administration on Day 1. If the Day 1 value is missing or is invalid or is collected after administration of investigational medicinal product, the latest assessment prior to dose administration on Day 1 will serve as baseline.

When applicable, adjudicated values of BILAG-2004, SLEDAI-2K, CLASI, and PGA will be used for all assessments.

8.4.1 Primary outcome variable

The primary endpoint, BICLA response at Week 52, is a composite endpoint where a participant is a BICLA responder if all of the following criteria are met:

- Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B;
- No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase from baseline of > 0 points in SLEDAI-2K;
- No worsening from baseline in the participants' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

As supportive to the primary endpoint, time to BICLA response sustained up to Week 52 will also be assessed.

8.4.2 Key secondary outcome variables

8.4.2.1 SRI(4)

The secondary endpoint used to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity is the difference in proportion of participants achieving SRI(4) at Week 52, where a participant achieves SRI(4) if all of the following criteria are met:

- Reduction from baseline of ≥ 4 points in the SLEDAI-2K;
- No new organ systems affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline;
- No worsening from baseline in the participants' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

8.4.2.2 Oral corticosteroid management

The secondary endpoint used to evaluate the effect of anifrolumab vs placebo on the ability to reduce the OCS dose in participants with baseline OCS ≥ 10 mg/day prednisone or equivalent is the difference in proportions of participants meeting all the following criteria:

- Achieve an OCS dose of ≤ 7.5 mg/day prednisone or equivalent by Week 40;
- Maintain an OCS dose ≤ 7.5 mg/day prednisone or equivalent from Week 40 to Week 52.

8.4.2.3 Flares

The secondary endpoint used to evaluate the effect of anifrolumab vs placebo on flares is the annualised flare rate through Week 52. A flare is defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit (i.e., a worsening from an E, D, or C score to a B score in at least 2 organ systems or a worsening from an E, D, C, or B to an A score in any one organ system compared to the previous visit).

8.4.3 Other secondary outcome variables

8.4.3.1 Skin lesions

The secondary endpoint used to evaluate the effect of anifrolumab vs placebo on inflammatory cutaneous lupus lesions in participants with baseline CLASI activity score ≥ 10 is the difference in proportions of participants who meet the following criterion:

- Achieve ≥ 50% reduction of CLASI activity score at Week 12 compared to baseline.

In addition, the maintenance of effect in the CLASI activity score will be evaluated using the proportion of participants with a CLASI activity score ≥ 10 at baseline who achieve at least a 50% reduction in CLASI activity score at Week 12 and maintain response at Week 52.

The difference between anifrolumab and placebo in the mean change from baseline in CLASI activity as well as CLASI damage score will be evaluated longitudinally over time up to Week 52.

8.4.3.2 Joints

The other secondary endpoint used to evaluate the effect of anifrolumab vs placebo on joints are:

- Difference in the proportion of participants with at least 6 swollen and at least 6 tender joints at baseline who achieve at least a 50% reduction from baseline in both the number of swollen and tender joints at Week 52;

A reduction of at least 50% is reached if all the following criterion are met:

- The percentage reduction from baseline in both the number of swollen joints and the number of tender joints, separately, is 50%.

8.4.4 Exploratory variables

[redacted]

[redacted]

[redacted]

8.4.5 Patient-reported outcome variables

8.4.5.1 Lupus quality of life scale

The difference between anifrolumab and placebo in the mean change from baseline in Lupus QoL score to Week 52 will be assessed.

8.4.5.2 EuroQoL 5 dimensions

The proportion of participants in each EQ-5D-5L health state (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems), by dimension, as well as the VAS Score and single summary utility index, including changes from baseline, will be explored over time.

8.4.5.3 Work Productivity and Activity Impairment – Lupus

The WPAI score levels (percentages) at baseline, Week 24 and Week 52 will be assessed.

8.4.5.4 Medical resource use questionnaire

The following endpoints will be assessed:

- Number of participants with unscheduled health care visits;
- Number of unscheduled specialist visits;
- Number of unscheduled primary care visits;
- Number of participants with unscheduled emergency department visits;
- Of participants with visits, number of unscheduled emergency department visits;
- Number of participants with hospital stays;
- Of participants with visits, number of hospital visits;
- Length of hospital stay.

8.4.6 Safety variables

The following safety data will be collected: vital signs, 12-lead ECG, haematology, clinical chemistry, urinalysis, C-SSRS, and reported AEs (including AEs of special interest, see Section 6.4).

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. Occurrence of suicidal behaviour and ideation, based on the C-SSRS, from baseline up to Week 52 will be explored. AEs will be utilizing by means of descriptive statistics and qualitative summaries.

8.4.6.1 Other significant adverse events

During the evaluation of the AE data, a medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the AstraZeneca Global Patient Safety Physician, be considered other significant AEs and reported as such in the CSR.

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

8.4.7 Immunogenicity variables

ADA assessments will be conducted utilising a tiered approach (screen, confirm, titre). The presence of nAb will be tested in all ADA-positive samples time points of week 12 and later using a ligand binding assay.

8.4.8 Pharmacokinetic variables

Due to the limited sampling schedule, the PK assessment will be primarily based on the [redacted]

8.4.9 Pharmacodynamic outcome variables

The outcome variable for C3, C4, and CH50 complement levels will be the mean change from baseline to Week 52 in participants with abnormal complement level at baseline, defined as complement level below lower limit of normal. The outcome variable for anti-dsDNA antibodies will be proportion of participants with positive anti-dsDNA test result.

[redacted]

8.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 52-week treatment period, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence.

In general, the analyses will be based on the FAS unless otherwise stated. Intercurrent events are defined as events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. In this study the intercurrent events are:

- Restricted medication use,
- Premature end of treatment,
- Death

The strategy for dealing with the intercurrents events will be detailed for the primary analyses of the primary endpoint. The strategy for all other endpoints will be detailed in the SAP.

Supplementary estimand/sensitivity analyses for the primary and key secondary endpoints for assessing the robustness of results will explore different methods for handling intercurrent events and different assumptions for missing data. The impact of non-compliance due to COVID-19 on PEOT will also be evaluated using hypothetical strategy with multiple imputation as supplementary analysis. Full details will be provided in the SAP.

Missing Data

The study was designed to reduce the risk for missing data as much as possible through the following measures:

- From Randomisation (Day 1) to Week 12, the study design allows for 1 burst and taper of OCS in order to allow adequate time for investigational medicinal product to achieve significant clinical benefit.

- One burst of OCS to ≤ 20 mg/day between Week 12 and Week 40 is also allowed for non-SLE causes.
- Participants who require additional bursts of OCS will still be encouraged to remain in the study.

Participants who discontinue investigational medicinal product will be asked to come to each visit for the scheduled assessments through the Week 52 end of treatment visit. The definition of the primary estimand includes a criterion that corresponds to non-response for participants who prematurely discontinue from investigational medicinal product, or who receive restricted medications beyond the protocol-allowed threshold. Supplementary estimands exploring different methods for handling intercurrent events, and/or sensitivity analyses for assessing the robustness of results under different assumptions for missing data may be carried out. Details will be pre-specified in the SAP.

Presentation of Results

All data will be presented by treatment group. Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

95% CIs will be presented for treatment comparisons. If a model is used to estimate the treatment difference, the corresponding CI according to the model will be presented. Otherwise, the unadjusted CI will be used.

Demography and baseline characteristics will be summarized by treatment group for the full analysis set.

8.5.1 Analysis of the primary variable

The primary endpoint is BICLA response at Week 52 (as defined in Section 8.4.1).The intercurrent events: discontinuation of investigational medicinal product, receipt of restricted medications and death are unfavourable outcomes. Therefore, participants treated with restricted medications beyond protocol-allowed threshold, those who discontinued the investigational medicinal product for any reasons, and those who died will be non-responders. Study withdrawal results in true missing data and will be imputed as a non-responder. This composite approach for the estimand answers a clinically relevant question comparing the number of participants able to both complete the study treatment and to achieve adequate response without further medication being required.

The assessment for the primary analysis will be based on the posterior probability of efficacy using the Bayesian model. [redacted] posterior estimates for the treatment difference in BICLA response rates at Week 52 and the corresponding [redacted] credible intervals will be presented. Posterior probabilities of efficacy (treatment difference greater

than 0) will also be estimated and compared with a number of thresholds, [redacted] Results across a range of prior weights will also be presented for the primary endpoint. More details will be pre-specified in the SAP.

In addition to the primary Bayesian analysis, the following analysis under the frequentist framework will be also performed for the FAS as supportive analysis.

The treatment effect (i.e., the difference in BICLA response rate at Week 52 for anifrolumab vs placebo) in the FAS will be estimated using the CMH method (Clowse et al, 2017; Cochran, 1954) stratified by:

- SLEDAI-2K score at screening (< 10 points vs ≥ 10 points)
- Randomisation (Day 1) OCS dose (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent)
- Region (Mainland China vs Not Mainland China)

Details for the CMH method will be pre-specified in the SAP.

The corresponding 95% CI, and 2-sided nominal p-value for the difference, as well as the response rate and the corresponding 95% CI within each treatment group will be presented.

Time to BICLA response sustained up to Week 52 will be analyzed as a supportive measure to the primary endpoint to assess if treatment with anifrolumab reduces the time needed to achieve an improvement in disease activity that is maintained throughout the study compared with placebo. A Cox proportional hazard model will be fitted to data including the covariates of treatment and the stratification factors. Details will be presented in the SAP.

Further, longitudinal presentations of results over time based on the same CMH method, with the corresponding 95% CI, will be created. In addition, the individual components of the composite BICLA endpoints will be summarized by treatment group.

8.5.2 Analysis of the secondary variables

8.5.2.1 Analysis methods for secondary efficacy variables

Secondary endpoints SRI(4), OCS will be analyzed and presented using the CMH method as described in Section 8.5.1 for the FAS. In addition, the individual components of the composite SRI endpoints will be summarized by treatment group. Details will be described in the SAP.

The flare rate in the anifrolumab treatment group will be compared to the flare rate in the placebo group using a negative binomial model for the FAS. The response variable in the model will be the number of flares over the 52-week treatment period. The model will include covariates of treatment group, and the stratification factors. The logarithm of the follow-up time will be used as an offset variable in the model to adjust for participants having different

exposure times. The estimated treatment effect and the corresponding 95% CI as well as the 2-sided nominal p-value will be presented. In addition, supportive analyses only including flares while on treatment will be carried out. Details will be described in the SAP.

Time to first flare will be analyzed as a supportive analysis to the assessment of reduction of flares to explore the extent to which treatment with anifrolumab delays the time to first flare compared with placebo. A Cox proportional hazard model will be fitted to data including the covariates of treatment, and the stratification factors. Details will be presented in the SAP.

Other secondary binary responder endpoints will be assessed using the CMH method as described in Section 8.5.1.

8.5.3 Analysis methods for exploratory variables

[redacted]

8.5.3.1 Analysis methods for safety variables

AEs (including AESIs) will be summarized by means of counts summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term (PT) for the study periods (treatment period and treatment period including follow-up period), if not stated otherwise. All AEs will be listed.

Laboratory data for haematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and minimum/maximum post-treatment values will be tabulated. Frequencies of clinically noteworthy values (defined in the

SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and last post-baseline time point will be evaluated for urinalysis.

The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarized by treatment group.

The proportion of participants with suicidal behavior and suicidal ideation throughout the study based on the C-SSRS will be presented for each treatment group. The proportion of participants within each of the 4 suicidal behavior categories and within each of the 5 suicidal ideation sub-categories will also be presented for each treatment group. Descriptive statistics on the total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be summarized for each treatment group.

Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

8.5.3.2 Analysis method for immunogenicity variables

Anti-drug antibodies to anifrolumab will be summarized using descriptive statistics at each visit by treatment group. ADA titres-time profiles of anifrolumab by treatment group will be generated. The impact of ADA on PK and PD will be assessed. The potential association of ADA with safety and efficacy will be explored.

8.5.3.3 Analysis methods for pharmacokinetic variables

Anifrolumab serum concentrations will be summarized using [redacted] Serum concentrations of anifrolumab, summary statistics, and PK profiles will be provided in the CSR or as an addendum to the CSR.

8.5.3.4 Analysis methods for pharmacodynamic variables

Pharmacodynamic variables will be summarized as appropriate.

8.5.4 Subgroup analysis

To explore the uniformity of the detected overall treatment effect on the primary, and when applicable, some secondary efficacy endpoints, subgroup analyses may be performed for the following factors:

- SLEDAI-2K score at screening (< 10 points vs ≥ 10 points)
- OCS dose at baseline (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent)

- Sex (male vs female)
- Age (≥ 18 to < 65 vs ≥ 65 years)
- Onset of disease (adult vs paediatric onset)
- BMI (≤ 28, > 28 kg/m^2)
- Region (Mainland China vs Not Mainland China)
- 4-gene IFN test (4-gene IFN test high vs low)

Full details of the subgroup analyses will be pre-specified in the SAP.

The efficacy and safety in China subgroup will be analyzed to facilitate a benefit-risk assessment for regulatory submission in China. Details of the subgroup analysis will be specified in SAP.

8.5.5 Interim analysis

No interim analysis for efficacy/futility is planned for this study.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first participant is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC or eCOA system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study intervention accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the participant's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating participants. This will require direct access to all original records for each participant (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the participant's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the participant.

The AstraZeneca representative will be available between visits if Investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Unblinded monitoring

In order to maintain the integrity of the study blind, separate unblinded monitoring visits will be conducted as outlined in the study clinical monitoring plan.

9.2.2 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.3 Study agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of participants and in all other respects, not relating to study conduct or treatment of participants, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or participants are enrolled.

9.2.4 Archiving of study documents

Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with anifrolumab.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff or other party, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre or other party.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Participant data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the participants. Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. Investigator should submit the written approval to AstraZeneca before enrolment of any participant into the study.

The Ethics Committee should approve all advertising used to recruit participants for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any participant into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted

with the investigational medicinal product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

Regulatory Reporting Requirements for SAEs

- Prompt notification by Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each participant is notified that they are free to discontinue from the study at any time
- Ensure that each participant is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each participant provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICFs is/are stored in Investigator's Study File
- Ensure a copy of the signed ICF is given to the participant
- Ensure that any incentives for participants who participate in the study as well as any provisions for participants harmed as a consequence of study participation are described in the ICF that is approved by an Ethics Committee.

10.5 Changes to the protocol and ICF

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's Ethics Committee are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, ICH, and any applicable regulatory requirements. Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

11 LIST OF REFERENCES

ACR ad hoc committee, September 1999
ACR ad hoc committee. Guidelines for Referral and Management of systemic Lupus Erythematosus in Adults. Arthritis & Rheumatism Vol. 42, No. 9, September 1999, pp 1785–1796).

American Psychiatric Association, 1994
American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. American Psychiatric Association, Washington, DC.

Anifrolumab Investigator's Brochure edition 12 dated 02 August 2020

Apor et al, 2014
Apor E, O'Brien J, Stephen M, Castillo JJ. Systemic lupus erythematosus is associated with increased incidence of hematologic malignancies: a meta-analysis of prospective cohort studies. Leuk Res 2014;38(9):1067-71.

Baechler et al, 2003
Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci USA. 2003;100(5):2610-5.

Banchereau et al, 2004
Banchereau J, Pascual V, Palucka AC. Autoimmunity through cytokine-induced dendritic cell activation. Immunity. 2004;20:539–50.

Bengtsson et al, 2000
Bengtsson AA, Sturfelt G, Truedsson L, Blomberg J, Alm G, Vallin H, et al. Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies. Lupus. 2000;9:664-71.

Bennett et al, 2003
Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, et al. Interferon and granulopoiesis signatures in systemic lupus erythmatosus blood. Journal of Experimental Medicine. 2003;197(6):711-23.

Bernatsky et al, 2006
Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54(8):2550-7.

Bernatsky et al, 2013
Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin J-F, Petri M, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013;42:130-5.

Bertsias et al, 2008
Bertsias G, Ioannidis JPA, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics, Ann Rheum Dis 2008;67:195–205).

Blomberg S et al, 2001
Blomberg S, Eloranta ML, Cederblad B, Nordlin K, Alm GV, Rönnblom L. Presence of cutaneous interferon-alpha producing cells in patients with systemic lupus erythematosus. Lupus. 2001;10(7):484-90.

Burman, 2009
Burman CF, Sonesson C, Guilbaud O, 2009. A recycling framework for the construction of Bonferroni-based multiple tests. Stats in Med. 2009;28:739–761.

Cellestis, 2005
Clinicians Guide to QuantiFERON®-TB Gold.

CHMP, February 2015
CHMP Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus, and lupus nephritis (26 February 2015; EMA/CHMP/51230/2013).

Clowse et al, 2017
Clowse ME, Wallace DJ, Furie RA, et al. Efficacy and safety of epratuzumab in moderately to severely active systemic lupus erythematosus: results from two phase iii randomised, double-blind, placebo-controlled trials. Arthritis Rheumatol 2017;69:362–75.

Cochran, 1954
Cochran, W. G. 1954. Some Methods for Strengthening the Common χ2 Tests. Biometrics 10:417-451.

Cooper et al, 1998
Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Parks CG, Gilkeson GS. Hormonal, environmental, and infectious risk factors for developing systemic lupus erythematosus. Arthritis Rheum. 1998;41(10):1714-24.

Criswell, 2008
Criswell LA. The genetic contribution to systemic lupus erythematosus. Bull NYU Hosp Jt Dis. 2008;66(3):176-83.

Crow and Wohlgemuth, 2003
Crow MK, Wohlgemuth J. Microarray analysis of gene expression in lupus. Arthritis Res Ther. 2003;5:279-87.

Dall'era et al, 2005
Dall'era MC, Cardarelli PM, Preston BT, Witte A, Davis Jr, JC. Type I Interferon correlates with clinical and serologic manifestations of systemic lupus erythematosus. Ann Rheum Dis. 2005; 64:1692-7.

Danchenko et al, 2006
Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus Erythematosus: a comparison of worldwide disease burden. Lupus 2006; 15:308-18.

D'Cruz, 2006
D'Cruz DP. Systemic lupus Erythematosus. BMJ 2006;332(7546):890-4.

Dobkin et al, 1999
Dobkin PL, Da Costa D, Dritsa M, Fortin PR, Senécal JL, Goulet JR, et al. Quality of life in systemic lupus erythematosus patients during more and less active disease states: differential contributors to mental and physical health. Arthritis Care Res. 1999;12(6):401-10.

Doria and Briani, 2008
Doria A, Briani C. Lupus: improving long-term prognosis. Lupus. 2008;17(3):166-70.

Dörner and Furie, 2019
Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet. 2019;393(10188):2344-2358. doi:10.1016/S0140-6736(19)30546-X

EuroQoL Group, 1990
EuroQol - a new facility for the measurement of health-related quality of life,Health Policy,Volume 16, Issue 3,1990,Pages 199-208

Farkas et al, 2001
Farkas L, Beiske K, Lund-Johansen F, Brandtzaeg P, Jahnsen FL. Plasmacytoid dendritic cells (natural interferon-alpha/beta-producing cells) accumulate in cutaneous lupus erythematosus lesions. Am J Pathol. 2001;159(1):237-43.

Feng X et al, 2006
Feng X, Wu H, Grossman JM, Hanvivadhanakul P, FitzGerald JD, Park GS, et al. Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus. Arthritis Rheum. 2006;54(9):2951-62.

Franklyn et al, 2016
Franklyn K, Lau CS, Navarra SV for the Asia-Pacific Lupus Collaboration, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS)Annals of the Rheumatic Diseases 2016;75:1615-1621.

Furie et al, 2017
Furie R, Khamashta M, Merrill JT, Werth VP4, Kalunian K5, Brohawn P, et al. Anifrolumab, an anti-interferon-alpha receptor monoclonal antibody, in moderate to severe SLE. Arthritis Rheum 2017;69:376-86.

Golder et al, 2019
Golder V, et al. Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. The Lancet Rheumatology, 2019, 1(2).

Goobie et al, 2015
Goobie GC, Bernatsky S, Ramsey-Goldman R, Clarke AE. Malignancies in systemic lupus erythematosus: a 2015 update. Curr Opin Rheumatol 2015;27(5):454-60.

Hall and Rosen, 2010
Hall JC, Rosen A. Type I interferons: crucial participants in disease amplification in autoimmunity. Nat Rev Rheumatol. 2010;6:40–9.

Hoffman et al 2017
Hoffman RW, Merrill JT, Alarcon-Riquelme ME, Petri M, Dow ER, Nantz E, et al. Gene expression and pharmacodynamic changes in 1,760 systemic lupus erythematosus patients from two phase III trials of BAFF blockade with tabalumab. Arthritis Rheumatol 2017;69(3):643-54.

Huang et al, 2008
Huang X, Yang N, Ou X, Li D, Wang Z, Xie Q, et al. Sequential activation of protein kinase C delta and JNK is required for interferon-alpha-induced expression of IFIT4. Cell Signal. 2008 Jan;20(1):112-9.

Hylton et al, 1986
Hylton W, Cayley J, Dore C, Denman AM. 2',5'-oligoadenylate synthetase induction in lymphocytes of patients with connective tissue diseases. Ann Rheum Dis. 1986 Mar;45(3):220-4.

Ivashkiv and Donlin, 2014
Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nat Rev Immunol. 2014;14:36–49.

James C et al, 2017
James C and Bernstein A. Current and future therapies for the treatment of histamine-induced angioedema. Expert Opin Pharmacother 2017;18: 253-62.

Jolly et al, 2010
MEENAKSHI JOLLY, SIMON A. PICKARD, RACHEL A. MIKOLAITIS, ROGER A. RODBY, WINSTON SEQUEIRA, JOEL A. BLOCK, LupusQoL-US Benchmarks for US Patients with Systemic Lupus Erythematosus, The Journal of Rheumatology Sep 2010, 37 (9) 1828-1833; DOI: 10.3899/jrheum.091443

Kirou et al, 2004
Kirou KA, Lee C, George S, Louca K, Papagiannis IG, Peterson MG, et al. Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus. Arthritis Rheum. 2004;50(12):3958-67.

Kirou et al, 2005
Kirou KA, Lee C, George S, Louca K, Peterson MG, Crow MK. Activation of the interferon alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. Arthritis Rheum. 2005;52(5):1491-503.

Kennedy et al 2015
Kennedy WP, Maciuca R, Wolslegel K, Tew W, Abbas AR, Chaivorapol C, et al. Association of the interferon signature metric with serological disease manifestations but not global activity scores in multiple cohorts of patients with SLE. Lupus Sci Med 2015;2(1):e000080.

Lahita, 1999
Lahita RG. The role of sex hormones in systemic lupus erythematosus. Curr Opin Rheumatol. 1999;11(5):352-6.

McElhone et al, 2007
Kathleen McElhone, Janice Abbott, Joanna Shelmerdine et al. Development and validation of a disease-specific health-related quality of life measure, the LupusQoL, for adults with systemic lupus erythematosus. Arthritis & Rheumatism.Vol.57,No.6, August 15, 2007, 972-979

Merrill, 2014
Merrill, J.M. Guidelines for use of the SLEDAI-2K to assess disease activity (modified for assessment over one month). Lupus Foundation of America. Accessed 08 December 2014 at:http://www.lupus.org/

Mok and Li, 2010
Mok ML and Li WL. Do Asian patients have worse lupus? Lupus. 2010;19:1384-90.

Mikdashi and Nived, 2015
Mikdashi J, Nived O. Measuring disease activity in adults with systemic lupus erythematosus: the challenges of administrative burden and responsiveness to patient concerns in clinical research. Arthritis Res Ther 2015;17:183.

Mok and Li, 2010
Mok ML and Li WL. Do Asian patients have worse lupus? Lupus. 2010;19:1384-90.

Muskardin and Niewold, 2018
Muskardin TLW, Niewold TB. Type I interferon in rheumatic diseases. Nature. 2018;14:214-28.

Okamoto et al, 2004
Okamoto H, Katsumata Y, Nishimura K, Kamatani N. Interferon-inducible protein 10/CXCL10 is increased in cerebrospinal fluid of patients with central nervous system lupus. Arthritis Rheum. 2004;50:3729-32.

Pascual et al, 2006
Pascual V, Farkas L, Banchereau J. Systemic lupus erythematosus: all roads lead to type I interferons. Curr Opin Immunol. 2006;18(6):676-82.

Petri, 2001
Petri M. Long-term outcomes in lupus. Am J Managed Care. 2001;7(16) Suppl: S480-5.

Posner et al, 2007
Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants Am J Psychiatry 2007; 164(7):1035-1043

Postal et al, 2012
M. Postal, L. T. Costallat, and S. Appenzeller, "Biological therapy in systemic lupus erythematosus," International Journal of Rheumatology, vol. 2012, Article ID 578641, 9 pages, 2012

Ramsey-Goldman and Manzi, 2000
Ramsey-Goldman R, Manzi S. Systemic lupus erythematosus. Women and health. Academic Press 2000:704.

Reilly et al, 1993
Reilly, M.C., Zbrozek, A.S. & Dukes, E.M. The Validity and Reproducibility of a Work Productivity and Activity Impairment Instrument. PharmacoEconomics 4, 353–365 (1993).

Rönnblom and Alm, 2003
Rönnblom L, Alm GV. Systemic lupus erythematosus and the type I interferon system. Arthritis Res Ther. 2003;5:68-75.

Rönnblom and Pascual, 2008
Rönnblom L, Pascual V. The innate immune system in SLE: type I interferons and dendritic cells. Lupus. 2008;17(5):394-9.

Sampson HA et al, 2006
Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.

Schwartz et al, 2009
Schwartz N, Rubinstein T, Burkly LC, Collins CE, Blanco I, Su L, et al. Urinary TWEAK as a biomarker of lupus nephritis: a multicenter cohort study. Arthritis Res Ther. 2009;11(5):R143.

Schmidli et al, 2014
Heinz Schmidli, Sandro Gsteiger, Satrajit Roychoudhury, Anthony O'Hagan, David Spiegelhalter, Beat Neuenschwander, Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics. 2014;70(4): 1023-1032

Sigurdsson, Göring et al, 2008
Sigurdsson S, Göring HH, Kristjansdottir G, Milani L, Nordmark G, Sandling JK, et al. Comprehensive evaluation of the genetic variants of interferon regulatory factor 5 (IRF5) reveals a novel 5 bp length polymorphism as strong risk factor for systemic lupus erythematosus. Hum Mol Genet. 2008;17(6):872-81.

Sigurdsson, Nordmark et al, 2008
Sigurdsson S, Nordmark G, Garnier S, Grundberg E, Kwan T, Nilsson O, et al. A risk haplotype of STAT4 for systemic lupus erythematosus is over-expressed, correlates with anti-dsDNA and shows additive effects with two risk alleles of IRF5. Hum Mol Genet. 2008;17(18):2868-76.

Stoll et al, 2004
Stoll T, Sutcliffe N, Mach J, Klaghofer R, Isenberg DA. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus - a 5-yr prospective study. Rheumatology (Oxford). 2004;43(8):1039-44.

Tan et al, 1982
Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis and Rheum 1982; 25:1271-1277.

Thanou et al, 2014
Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Sci Med 2014;1:e000005.

Touma et al, 2010
Touma Z, Urowitz MB, Gladmann DD. SLEDAI-2K for a 30-day window. Lupus. 2010;19:49-50.

Urowitz et al, 1976
Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smyth HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med. 1976 Feb;60(2):221-5.

Wallace et al, 2011
Wallace DJ, Strand V, Furie R, Petri MA, Kalunian K, Pike M, et al. Evaluation of treatment success in systemic lupus erythematosus clinical trials: Development of the British Isles Lupus Assessment Group-Based Composite Lupus Assessment endpoint. Presented at: ACR 2011: Poster 2265.

Wallace et al, 2014
Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M, et al. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomized, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis. 2014 Jan;73(1):183-90.

World Health Organization, 2014
World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014) and January 2020.
http://apps.who.int/iris/bitstream/10665/79199/1/ 9789241505345 eng.pdf

World Health Organization, 2020
World Health Organization. Global Tuberculosis Report-2020.
https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

Yao et al, 2009
Yao Y, Richman L, Higgs BW, Morehouse CA, de los Reyes M, Brohawn P, et al. Neutralization of interferon-alpha/beta-inducible genes and downstream effect in a phase I trial of an anti-interferon-alpha monoclonal antibody in systemic lupus erythematosus. Arthritis Rheum. 2009 Jun;60(6):1785-96.

Yao et al, 2010
Yao Y, Higgs BW, Richman L, White B, Jallal B. Use of type I interferon-inducible mRNAs as pharmacodynamic markers and potential diagnostic markers in trials with sifalimumab, an anti-IFNalpha antibody, in systemic lupus erythematosus. Arthritis Res Ther. 2010 Apr 14;12 Suppl 1:S6.

Yee et al, 2009
Yee CS, Farewell V, Isenberg DA, Griffiths B, Teh LS, Bruce IN, et al. The BILAG-2004 index is sensitive to change for assessment of SLE disease activity. Rheumatology (Oxford) 2009; 48: 691-5.

Zonana-Nanach et al, 2000
Zonana-Nanach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis Rheum. 2000;43(8):1801-8.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

A 2 Regulatory Reporting Requirements for SAEs

- Prompt notification by Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
  - Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

Prompt notification by Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator should have a process in place to ensure that:

- The site staff or service providers delegated by Investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 3 Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 4 Informed Consent Process

- Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

A 5 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 6 Committees Structure

An independent DSMB will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. The DSMB will be provided with data that are summarized by treatment group using masked treatment group labels (e.g., A and B). After reviewing the data by masked treatment group, the DSMB may choose to unblind the treatment groups for additional review. The DSMB may also ask for unblinded efficacy data, if during the performance of a

benefit/risk assessment the Board feels there is a potential safety issue or concern. The DSMB will not routinely review efficacy data (blinded or unblinded).

At any time during the study, as well as on an ad hoc basis, the DSMB will also review any safety data assessed by the study physician as medically relevant. Additional information, including frequency of DSMB review, can be found in the DSMB charter.

If any event(s) occur that, in the opinion of the DSMB, contraindicates further dosing of additional patients, the Sponsor will conduct a prompt cumulative review of safety data and the circumstances of the event in question to determine whether dosing and study randomisation should be stopped, whether the protocol will be modified, or whether the study will be discontinued permanently. Review by the DSMB and Sponsor decision to resume (with or without modifications) is required for resumption of the study in the event the study is interrupted. Where applicable, the regulatory authorities and Institutional Review Board/Independent Ethics Committee (IRBs/IECs) will be notified of any actions taken with the study.

A 7 Dissemination of Clinical Study Data Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 8 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data, electronic Lupus Assessment Suite [eLAS]). Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be predefined in the separate study document to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.

- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in GCP, i.e., all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

A 10 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by Investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

B 1 Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are participant to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

C 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study Investigator will remain vigilant for increases in liver biochemistry. Investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational medicinal product (IMP).

Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

C 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3×Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3×ULN together with TBL ≥ 2×LN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

C 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3×ULN
- AST ≥ 3×ULN
- TBL ≥ 2×ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to Investigator (also sent to AstraZeneca representative).

Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results Investigator will without delay:

- Determine whether the participant meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local Laboratories Being Used:

Investigator will without delay review each new laboratory report and, if the identification criteria are met, will:

- Notify the AstraZeneca representative
- Determine whether the participant meets potential Hy's Law criteria (see Appendix C2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF

C 4 Follow-up

Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

Potential Hy's Law Criteria met

If the participant does meet PHL criteria Investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study intervention (see Appendix C6)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, Investigator is not required to submit a potential Hy's Law SAE unless there is a significant change# in the participant's condition.
- The Study Clinical Lead contacts Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available

C 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

According to the outcome of the review and assessment, Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

C 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory. Any test results need to be recorded.

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) c
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin saturation

[a]HBV DNA is only recommended when IgG anti-HBc is positive
[b]HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c]CD-transferrin and Transferrin are not available in China.

Appendix D American College of Rheumatology Criteria for Systemic Lupus Erythematosus Classification

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis or pericarditis	a. Pleuritis--convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR b. Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria > 0.5 gm per day or > 3+ if quantitation not performed OR b. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	a. Seizures--in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance OR b. Psychosis--in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	a. Hemolytic anemia with reticulocytosis OR b. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions OR c. Lymphopenia--< 1,500/mm^3 on ≥ 2 occasions

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Item	Definition
	OR d. Thrombocytopenia--< 100,000/mm^3 in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies based on: 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; 2) a positive test result for lupus anticoagulant using a standard method; or 3) a false-positive test result for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.
Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug.

Appendix E Systemic Lupus Erythematosus Disease Activity Index 2000

These are for information purposes and representation only and serve as an example to be used in the study.

SLEDAI 2K Index Must be present at the time of visit or in the preceding 30 days and SLE-Related to be checked!			
Wt	(√) If Present	Descriptor	Definitions **If descriptor is checked as present, please check appropriate condition(s) in definition and/or specify in the space provided.**
8	☐	Seizure	Recent onset (last 30 days). Exclude metabolic, infectious or drug causes. **Specify if checked:**
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, and □ 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, and at least 2 of the following: □ perceptual disturbance, □ incoherent speech, □ insomnia or daytime drowsiness, □ 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, and □ 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. (Must have been severe enough to warrant lumbar puncture and/or MRI or head CT, perhaps hospitalization, and is thought to be due to active lupus cerebritis.) **Specify if checked:**
8	☐	CVA	New onset of cerebrovascular accident(s) (CVA). Exclude arteriosclerosis. **Specify if checked:**
8	☐	Vasculitis	□ Ulceration, □ gangrene, □ tender finger nodules, □ periungual infarction, □ splinter hemorrhages, or □ biopsy or □ angiogram proof of vasculitis.

SCREENING SLEDAI 2K Index Must be present at the time of visit or in the preceding 30 days and SLE-Related to be checked!			
4	☐	Arthritis	≥ 2 joints with pain and signs of inflammation (□ tenderness, □ swelling or □ effusion). **(Complete Joint Count)**
4	☐	Myositis	Proximal muscle aching/weakness associated with □ elevated creatine phosphokinase (CK)/aldolase or □ EMG changes or □ a biopsy showing myositis.
4	☐	Urinary Casts	Heme-granular or red blood cell casts. NOT granular casts. (See labs)
4	☐	Hematuria	>5 RBC/high power field. Exclude stone, infection, or other cause. (See labs)
4	☐	Proteinuria	>0.5 gm/24-hour equivalent. (See labs)
4	☐	Pyuria	>5 WBC/high power field. Exclude infection. (See labs)
2	☐	Rash	Inflammatory-type rash. **Specify on BILAG Worksheet Diagram and complete CLASI if checked:**
2	☐	Alopecia	□ Abnormal, □ patchy or □ diffuse loss of hair. **(Complete CLASI if checked.)**
2	☐	Mucosal Ulcers	□ Oral or □ □nasal ulcerations. **(Complete CLASI if checked.)**
2	☐	Pleurisy	Pleuritic chest pain with □ pleural rub or □ effusion, or □ pleural thickening. MUST be confirmed with objective finding.
2	☐	Pericarditis	Pericardial pain with at least one (1) of the following: □ rub or □ effusion, or □ ECG or □ □echocardiogram confirmation.
2	☐	Low Complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory. (See labs)
2	☐	Increased DNA Binding	Above normal range for testing laboratory. (See labs)
1	☐	Fever	>38°C (100.4F). Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets / x10^9/L, exclude drug causes. (SLEDAI definition/units) <100,000 platelets/µL (< 100 x10^9/L) -Conversion to conventional (Covance) units for site
1	☐	Leukopenia	<3,000 white blood cells / x10^9/L, exclude drug causes. (SLEDAI definition/units) <3,000 white blood cells/µL (< 3 x10^9/L) -Conversion to conventional (Covance) units for site
	TOTAL SCORE (Sum of all of weights next to descriptors marked present)		

INVESTIGATOR SIGNATURE: _____ DATE: __ __ / _____ / _____
DD/ MMM/ YYYY

Appendix F British Isles Lupus Assessment Group-2004

These are for information purposes and representation only and serve as an example to be used in the study.

BILAG-2004 INDEX Centre:_____Date:_____Initials/Hosp No:_____

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND** Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
***Y/N** Confirm this is due to SLE activity (Yes/No)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) Y/N*
79. Diastolic blood pressure (mm Hg) value ( ) Y/N*
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) Y/N*
82. Urine albumin-creatinine ratio mg/mmol ( ) Y/N*
83. Urine protein-creatinine ratio mg/mmol ( ) Y/N*
84. 24 hour urine protein (g) value ( ) Y/N*
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) Y/N*
87. GFR (calculated) ml/min/1.73 m^2 ( ) Y/N*
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

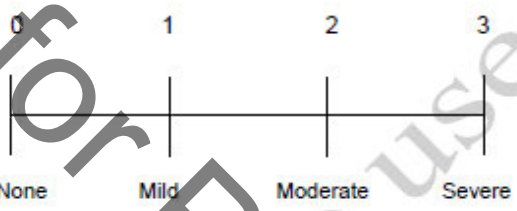
HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) Y/N*
91. Total white cell count (x 10^9/l) value ( ) Y/N*
92. Neutrophils (x 10^9/l) value ( ) Y/N*
93. Lymphocytes (x 10^9/l) value ( ) Y/N*
94. Platelets (x 10^9/l) value ( ) Y/N*
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 1/Sep/2009

Appendix G Physician Global Assessment

These are for information purposes and representation only and serve as an example to be used in the study.

PHYSICIAN GLOBAL ASSESSMENT (PGA)



PGA Visual Analogue Scale Measurement = ____.____ inches (measure to the nearest 1/10 of an inch

Appendix H Guidance for Cervical Cancer Testing Results

Guidance for Abnormal Pap Smear Results

Pap Smear Result	Abbreviation	Also Known As	Suggested Action
Atypical squamous cells–undetermined significance	ASC–US	—	Permitted to enter study
Atypical squamous cells–cannot exclude HSIL	ASC–H	—	Permitted to enter study
Atypical glandular cells	AGC	—	Permitted to enter study
Low-grade squamous intraepithelial lesion	LSIL	Mild dysplasia Cervical intraepithelial neoplasia–1 (CIN–1)	Permitted to enter study
High-grade squamous intraepithelial lesion	HSIL	Moderate dysplasia CIN-2 / CIN II	Permitted to enter study
High-grade squamous intraepithelial lesion	HSIL	CIN–3 / CIN III Carcinoma in situ (CIS)	**Exclude/discontinue participant**
Endocervical adenocarcinoma in situ	AIS	—	**Exclude/discontinue participant**

Guidance for HPV Test Results

Test Result	Interpretation	Suggested Action
Negative HPV test result	High-risk HPV was not found	Permitted to Enter Study
Positive HPV test result	High-risk HPV was found	Exclude/discontinue participant

Appendix I Prohibited Medications

Medications to be Discontinued Prior to signing ICF

Medicine	Discontinuation prior to signing ICF	Medicine	Discontinuation prior to signing ICF
Abatacept (CTLA 4 Ig)	24 weeks	Leflunomide	36 weeks
Actnar® gel	6 weeks	Lenalidomide	8 weeks
Adalimumab	12 weeks	Lupuzor (IPP-201101)	12 weeks
Alefacept	12 weeks	Memantine	4 weeks
Anakinra	12 weeks	Natalizumab	24 weeks
Apremilast	4 weeks	Obinutuzumab*	26 weeks
Atacicept (TACI-Ig)*	40 weeks	Ocrelizumab*	26 weeks
B cell depleter*	26 weeks	Ofatumumab*	26 weeks
Baricitinib	12 weeks	Plasmapheresis	24 weeks
Belimumab	12 weeks	Retinoids	4 weeks
Blisibimod (AMG 623)	8 weeks	Rituximab*	26 weeks
BI655064 (anti-CD40)	12 weeks	Siltuximab	12 weeks
BIIB059 (anti-BDCA2)	12 weeks	Similar to Study drug	26 weeks
Certolizumab pegol	24 weeks	Sirolimus	4 weeks
Cyclophosphamide	12 weeks	Tabalumab	26 weeks
Cytokines (e.g., IFN, low dose IL-2)	Washout Time	Telitacicept	12 weeks
Eculizumab	12 weeks	Thalidomide	8 weeks
Efalizumab	12 weeks	Tocilizumab	12 weeks
Epratuzumab	26 weeks	Tofacitinib	4 weeks
Etanercept	4 weeks	Topical Pimecrolimus	4 weeks
Golimumab	12 weeks	Tripteryguim wilfordii (“thunder god vine”)	4 weeks
Iberdomide	12 weeks	Ustekinumab	26 weeks

Immunosuppressants	Washout Time	VIB4920 (anti-CD40L)	12 weeks
Infliximab	12 weeks	Voclosporin	8 weeks
Intravenous Globulin	4 weeks	Zanubrutinib	12 weeks

* Provided B cell count is above lower limit of normal or has returned to pre-B cell treatment level at screening

Appendix J Vasculitis Syndromes Excluded from the Study

Participants with a history of current diagnosis of the following vasculitis syndromes are excluded from participating in the study. Vasculitis due to SLE is allowed in the study.

- Behçet's Disease
- Buerger's Disease
- Central Nervous System Vasculitis
- Churg-Strauss Syndrome
- Cryoglobulinemia
- Giant Cell Arteritis
- Henoch–Schönlein Purpura
- Kawasaki Disease
- Microscopic Polyangiitis
- Polyarteritis Nodosa
- Polymyalgia Rheumatica
- Takayasu's Arteritis
- Wegener's Granulomatosis

Appendix K Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

These are for information purposes and representation only and serve as an example to be used in the study.

SLICC/ACR Damage Index

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (eg 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 > 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 **OR**	1
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 (eg 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 > 1site)	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)

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)
Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996;39(3):363

Appendix L Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

These are for information purposes and representation only and serve as an example to be used in the study.

Cutaneous LE Disease Area and Severity Index (CLASI)

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

	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-dyspigmentation	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 – tick appropriate box)
☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) ☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

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, Mucous membrane involvement and Alopecia)		(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Figure 1. The Cutaneous Lupus Erythematosus (LE) Disease Area and Severity Index instrument. Post indicates posterior; incl, includes.

study reflected a broad group of patients with CLE in terms of disease type, skin type, and therapy. To reflect different skin types, we decided to have at least 3 patients, but not more than 7 patients, with Fitzpatrick skin type V or VI, and at least 3 patients with Fitzpatrick skin type I, II, or III. A major inclusion criterion was a biopsy-proven CLE, with or without systemic involve-

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174

Appendix M Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

M 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, e.g., remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the Section 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

M 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. Investigator should confirm this with the AstraZeneca Study Physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with study intervention.

If this delay is outside the Screening window specified in Table 1, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 4.2. The procedures detailed in Sections 3.1 and 3.2 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

M 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the participants' home/remote location as per local standard operating procedures, as applicable.

Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

M 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology, including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication, and efficacy data to be collected, reported, and documented according to study requirements.

M 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured in the source documents by the qualified HCP from the study site or TPV service, or by the participant.

Appendix N Oral Corticosteroid Guidance

Table 9 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	6mg	8 mg	16 mg	24 mg	32 mg

Table 10 Example of OCS Tapering Schedule

Time point	**Initial Dose of Oral Prednisone or Equivalent**			
	40 mg	**30 mg**	**20 mg**	**10 mg***
Day 8	35 mg	27.5 mg	17.5 mg	10 mg
Day 28	30 mg	25 mg	15 mg	10 mg
Day 42	25 mg	20 mg	10 mg	10 mg
Day 56	15 mg	15 mg	10 mg	7.5 mg
Day 70	10 mg	10 mg	7.5 mg	≤ 7.5 mg
Day 84	7.5 mg	7.5 mg	≤ 7.5 mg	≤ 7.5 mg

* Note: participants 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 Investigator.

Appendix O General Guidance for Determination of Major Surgery

The goal of this guidance is to maximize the benefit/risk for each patient entering this study. An important aspect to this goal is taking into account all relevant history, including recent surgeries and/or injuries that could influence the safety of the patient potentially being exposed to an additional immunomodulatory medication or could bias the efficacy endpoints of the trial.

Given the advancement and availability of surgical techniques, major surgery is in the judgment of Investigator and his/her evaluation of the following criteria, regardless of the specific surgical procedure:

- Has the patient completely recovered (mentally, emotionally, and physically) from the surgery and is not receiving additional medications related to the prior surgery (i.e., antibiotics)?
- Has the patient completed all follow-up visits related to the surgery, including ancillary services such as physical and/or occupational therapy?
- Has the patient resumed all of their prior activities?
- Has the patient returned to his/her baseline medications for SLE and non-SLE indications?

Appendix P Additional Safety Information

P 1 Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the participant or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

P 2 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

P 3 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified** and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix Q COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Q 1 Columbia Suicide Severity Rating Scale (Baseline/Screening Version)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self; gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Q 2 Columbia Suicide Severity Rating Scale (Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix R Handling of Human Biological Samples

R 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

Investigator keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

R 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

Investigator:

1) Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
2) Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

3) Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

R 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, for example, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, for example, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

1) UN 3373 – Biological Substance, Category B
2) are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subjects to these Regulations unless they meet the criteria for inclusion in another class.

1) Clinical study samples will fall into Category B or exempt under IATA regulations.
2) Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
3) Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix S Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips, tongue and/or uvula)

AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
   (b) Reduced BP (see number 3 below for definition) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch, flush, swollen lips, tongue and/or uvula)
   (b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
   (c) Reduced BP (see number 3 below for definition) or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours); for adults a systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP (taken at or immediately prior to start of the infusion), whichever BP is lower.

The following definitions are provided for the purposes of this study:

Hypersensitivity reaction: Onset of an illness, distinct from the underlying and/or comorbid disease, occurring usually within the first 48 hours after exposure to an allergy-causing substance with involvement of skin and/or mucosal tissue (eg, local areas of hives, itch, rash, flush, or mildly swollen lips, tongue, and/or uvula), respiratory tract, CV system, and/or gastrointestinal symptoms. The symptoms associated with (non-serious) hypersensitivity do not require immediate intervention (steroids or epinephrine) to prevent deterioration of cardiorespiratory function, ie, they are not life-threatening.

Angioedema: Angioedema is a self-limited, localized swelling of subcutaneous (or submucosal) tissue that results from extravasation of fluid into interstitial tissues. It presents with rapid, localized swelling, large welts, and pain. The lips, mouth, throat, eyes, hands, and feet are most commonly affected. Rarely, angioedema can be life-

threatening when swelling of the throat interferes with breathing. Angioedema may be acute or chronic (eg, hereditary angioedema), may occur with or without urticaria (hives), and is generally self-limited (James and Bernstein 2017).

Angioedema may be associated with IgE and may infrequently be a component of an anaphylactic reaction. In the absence of confirmatory IgE antibody, the Sampson Criteria should be used as the case definition for anaphylaxis.

Angioedema may be the result of histamine activation (often associated with urticaria), bradykinin generation, or unknown pathophysiology. The clinical presentation of these types of angioedema may be analogous in nature, but their treatment algorithms differ significantly.

Infusion-related Reaction: Infusion-related reactions are any other reaction occurring during infusion of study intervention or felt to be temporally related to the infusion within 24 hours of study intervention administration.

Appendix T Abbreviations

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADL	Activity of daily living
AE	Adverse event
AESI	Adverse event of special interest
AIS	Adenocarcinoma in situ
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
AND	
anti-dsDNA	Anti-double stranded deoxyribonucleic acid
Anti-Sm	Anti-Smith
Anti-RNP	Anti-Ribonucleoprotein
Anti-SSA	Anti-Sjogren's Syndrome-related antigen A
Anti-SSB	Anti-Sjogren's Syndrome-related antigen B
AST	Aspartate aminotransferase
APRIL	A proliferation-inducing ligand
APS	Anti-phospholipid syndrome
ATP	Adult Treatment Panel
β-hCG	β-human chorionic gonadotropin
BCG	Bacillus Calmette-Guerin
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BlyS	B-lymphocyte stimulator protein
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
BTK	Bruton's tyrosine kinase
C3	Third component of complement
C4	Fourth component of complement
CDL	Clinical Database Lock
CH50	Total haemolytic complement
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIN III	Cervical intraepithelial neoplasia grade III
CIS	Carcinoma in situ
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	Cutaneous Lupus Erythematosus
CMV	Cytomegalovirus
CNS	Central nervous system
COCs	Combined oral contraceptives
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	coronavirus disease-19
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report

Abbreviation or special term	Explanation
CT	Computed tomography
CV	Cardiovascular
dsDNA	Double stranded deoxyribonucleic acid
DNA	Deoxyribonucleic acid
DACRT	Disease Activity Central Review Team
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic case report form
EDV	Early Discontinuation Visit
EOT	End of Treatment
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5 dimensions
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBC	High Burden Countries
HBV	Hepatitis B virus
HCP	Health Care Professional
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HZ	Herpes zoster
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFN	Interferon
IFNAR1	Subunit 1 of the type I interferon receptor
Ig	Immunoglobulin
IgG1κ	Immunoglobulin G1 kappa
IGRA	Interferon-gamma release assay
IMP	Investigational medicinal product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JAK	Janus kinase
LLDAS	Lupus Low Disease Activity State
LLOQ	Lower limit of quantitation
LN	lupus nephritis
MACE	Major adverse cardiovascular events
MCP	Metacarpophalangeal
MDR	Multi-resistant
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
mRNA	Messenger ribonucleic acid
nAb	Neutralising antibodies
NIMP	Non-investigational medicinal product
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCS	Oral corticosteroids
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PI	Principal Investigator
PMDA	Pharmaceuticals and Medical Devices Agency
PIP	Proximal interphalangeal
PK	Pharmacokinetic(s)
RM	Restricted medications
PEOT	Premature end of treatment
Q4W	Every 4 weeks
QFT-G	QuantiFERON-TB Gold
QoL	Quality of life
RNA	Ribonucleic acid
SD	Standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SI	Sub-investigator
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SMR	Standardised mortality ratio
SoA	Standard of Activity
SOC	Standard of care
SRI	SLE Responder Index
SRI(4)	Systemic Lupus Erythematosus Responder Index of ≥4
SSc	systemic sclerosis
TB	Tuberculosis
ULN	Upper limit of normal
TLR7	Toll-like receptor 7
TLR9	Toll-like receptor 9
TPV	Third-party vendor
VAS	Visual analogue scale
WBDC	Web Based Data Capture
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
w/v	Weight/volume

Appendix U Protocol Version History

The Summary of Changes Table for the current revision is located directly before the PROTOCOL SYNOPSIS.

Amendment 2 [07-Jul-2023]

Overall Rationale for the Amendment:

The main purpose of this amendment is to update the study design, sample size and statistical analysis method using Bayesian borrowing approach. One endpoint, CLASI, is adjusted from "key" secondary to "other" secondary endpoints which allows key secondary endpoints to reflect most clinically relevant endpoints. In addition, this amendment includes the modifications of some inclusion and exclusion criteria to align with anifrolumab program safety requirements, to ensure correct interpretation by site personnel, to address current COVID-19 landscape and to decrease identified recruitment barriers. The changes in inclusion and exclusion criteria would not impact target patient population and patient safety. This amendment also includes template updates to reflect the latest regulatory and process changes implemented within AstraZeneca. Other minor corrections, revisions, and/or reordering of text that were made to improve consistency, accuracy, and clarity, but do not substantively affect the content of this document, may not be individually listed below.

Section # and Name	Description of Change	Brief Rationale
Throughout Protocol SYNOPSIS, 2 Study Objectives 8 Statistical analyses by AstraZeneca	Update the language for estimand description; clarify death as an intercurrent event	To align with the estimand framework defined in ICH E9 (R1) addendum; clarification
	Move CLASI from key secondary to other secondary endpoints	To reflect most clinically relevant endpoints
SYNOPSIS, Section 8.1, Section 8.2, Section 8.5.1	Update statistical method and sample size estimate	To align with the updated study design of using Bayesian borrowing approach
1.1 Background and rationale for conducting this study, 1.2 Rationale for study design, doses and control groups, 1.3 Benefit/risk assessment	Reflect the latest approved biologics for SLE in Market; Update according to latest IB.	Information update
1.2.1 Rationale for study design	Rationale for study design updated	To provide the rationale why Bayesian borrowing is considered
1.4.3 Study flow chart, 3.1 Inclusion Criteria #4, 3.2 Exclusion Criteria #33, 4.1 study plan and throughout	Extend screening period to 35 days	To allow sufficient time for collection of eligibility data.
3.1 Inclusion criteria #6	Update the description of SLEDAI-2K at screening	To clarify that to count as “active” a joint must be both tender and swollen, and to strengthen requirement for rash
3.1 Inclusion criteria #7	Update Permitted immunosuppressants to include tacrolimus and cyclosporine	Revise SOCs to meet real world treatment practice

Section # and Name	Description of Change	Brief Rationale
3.1 Inclusion criteria #13	Clarify assessment of incidental pulmonary nodule findings	Provide clear guidance for sites
3.1 Inclusion criteria#14, 6.3.5 Tuberculosis including Latent Tuberculosis	Revise for clarification, update management procedure for patient with positive TB result	Clarification and keep consistency with anifrolumab program update
3.1 Inclusion criteria #15 3.2 Exclusion criteria #16 and #17 3.9.1 IP discontinuation due to COVID-19	Add COVID-19 antigen as alternative test; Change rescreening restriction to at least 6 weeks before the 1st dosing for mild recovered patient with COVID-19; Revise text and add Long COVID sequelae to exclusion	Adapted in accordance with evolved knowledge of COVID-19 diagnostics and disease course
3.2 Exclusion criteria #21, 5.2.2.3 Cervical Cancer Screening Test, Appendix H, and throughout	Rename to “Cervical cancer screening test” throughout; Add alternative HPV test criteria; No requirement of cervical cancer screening testing in females aged < 25 years with fully HPV vaccination or without sexual experience	Revise to reflect local cervical cancer screening guidelines.
3.2 Exclusion Criteria #31, Appendix I	Adjustment of JAK and BTK washout time	Correction for consistency
3.2 Exclusion Criteria #3, #4, #34	Expand and add "as per Sponsor opinion"	Clarification
3.2 Exclusion Criteria #37	Add “breastfeeding”	Clarification
3.7.2 Unblinding for Performing the Primary Analysis at Week 52	Added section “Unblinding for Performing the Primary Analysis at Week 52”	To clarify the timepoint for clinical database lock
3.9.3 Procedures for discontinuation of a participant from Investigator Product	Clarify what visits required after participants confirmed discontinuation from Investigator Product	Simplification of the phrasing
3.10.2 Withdrawal of the informed consent	Correct Follow-up Visit 1 to 8 weeks after last IMP dose. Delete repetitive decription regarding of actions after a participant discontinued Investigator Product	Correction
5.1.4.1 Protocol-specific clarification and extension of BILAG-2004 definitions	Update for BILAG arthritis extended definition.	Clarification
5.2.6.2 Tuberculosis results from screening evaluations	Revise description to keep consistent with inclusion TB criteria and 6.3.5TB including latent TB	Correction and keep consistency
5.2.6.3 Tuberculosis monitoring during the study	Add text regarding TB monitoring and use QFT-G for consistence	Clarification
6.9 Medication Error, Drug Abuse and Drug Misuse, Appendix P3	Add sub-sections: ‘Timeline’, ‘Drug Abuse’, ‘Drug Misuse’, ‘Reporting of Overdose’ and related content in Appendix	Update per AZ SOPs
7.7.1.3 Restricted Medications During Double-blind treatment period	Update the restricted maximum dose range for cyclosporine and tacrolimus.	Keep consistency with the SOCs change

Section # and Name	Description of Change	Brief Rationale
8.4.9 Pharmacodynamic outcome variables	Update the outcome variable for anti-dsDNA antibodies	Revise to keep consistency with C-lab reporting
8.5.2 Analysis of the secondary variables 8.5.3 Analysis methods for exploratory variables	Clarify analysis methods for binary endpoints	Clarification
Appendix A Regulatory, Ethical, and Study Oversight Considerations	A2 Regulatory Reporting Requirements for SAEs: add paragraph of "Regulatory Reporting Requirements for Serious Breaches" A8 Data Quality Assurance: Add CSR reporting requirement for important deviations from tolerance limits (QTLs) and remedial actions taken. Update the maintenance period of study related records and documents including signed ICFs from 15 years to 25 years.	Align with sponsor latest CSP template
Appendix C Actions required in Cases of increases in Liver Biochemistry and Evaluation of Hy's Law	Correct formatting and numbering of sub sections under Appendix C. C3 Identification of Potential Hy's Law Cases: add "local laboratories being used" paragraph C4 Follow-up: clarify investigator actions under "Potential Hy's Law Criteria met" section. C6 Laboratory Tests: add "Alcoholic hepatitis" test, including footnote C	Update per AZ SOPs
Appendix I Prohibited Medication	Updated prohibited drugs list	Corrections and keep consistency with anifrolumab program update in SLE
Appendix U Protocol Amendment History	Added a new appendix to document protocol amendment history	Administrative

Amendment 1 01-Dec-2021

Overall Rationale for the Amendment:

Modifications have been made to include changes in key secondary endpoints and exploratory endpoints, to update safety information, and to provide clarification to ensure correct interpretation. Other minor corrections and revisions that are made to improve accuracy and consistency, and clarity which do not substantively affect the content of this document are not individually listed below. Except for the substantial changes of secondary and exploratory endpoints all other modifications are considered to be non-substantial.

Section # and Name	Description of Change	Brief Rationale
Throughout, 3.1 Inclusion Criteria #18, 3.8.2 Donation of blood or other biological samples, 6.8.1 Maternal	Extended required time period for contraception after maternal or paternal exposure as well as blood or sperm donation from 12 to 16 weeks after last dose of investigational product (IP).	Extended per latest internal guidance in Project Specific Safety Requirements (PSSR) v5.0

Section # and Name	Description of Change	Brief Rationale
exposure and 6.8.2 Paternal exposure		
Throughout	Clarify stratification factor Region definition as 'Mainland China vs Others'	To clarify stratification setting
Throughout	Clarify the duration of safety follow up visits is 8 and 12 weeks after the last dose	Correction and to keep consistent throughout the CSP
Protocol Synopsis, 2.1 Primary Endpoints	Revise description format to include 'population', 'intercurrent event strategy' and 'summary measure'	To keep consistent with the latest CSP template on estimand description
Protocol Synopsis, 2.2 Secondary Endpoints, 8.4.2 Key secondary outcome variables	Upgrade SRI(4) as one of the key secondary endpoints	As recommended by Chinese Health Authority and to reflect importance of SRI(4) as an validated endpoint for assessment of overall disease activity
Protocol Synopsis, 2.2 Secondary Endpoints, 2.4 Exploratory Objectives, 8.4.3 Other secondary outcome variables, 8.4.4 Exploratory variables	Downgrade below secondary endpoints to exploratory endpoints. • Measures of disease activities including SRI (5-8) response, the individual components of BICLA and SRI, the number of swollen and joint counts, LLDAS, as well as BICLA and SRI over time • SDI at Week52 • Patient reported outcome measures at Week 52	The scientific value of the downgraded endpoints is more adequately reflected as exploratory
2.4 Exploratory Objectives, 8.4.3 Other secondary outcome variables, 8.4.4 Exploratory variables	Add 'BICLA and SRI(4) dual response' to exploratory endpoint	To explore dual endpoint response
1.1 Introduction	Revise text to reflect Anifrolumab approval information	To update regulatory information
1.3.1 Risk Assessment, 1.3.1.1 Identified Risks, 1.3.1.2 Important potential risks based on mechanism of action, 1.3.3 Overall Benefit: Risk Conclusion	Revise text to reflect 'herpes zoster' as important identified risk and 'serious infection' as important potential risk, and other safety background update	To align safety information updated in the latest IB V13
1.4.2 Protocol-specified steroid tapering	Revise descriptive text for joint related OCS Tapering criteria	To clarify the joint criteria
1.4.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Add text for mitigation options and remove "At-home IP administration from mitigations options	Update applicable mitigation options for Anifrolumab IV
3.1 Inclusion Criteria #9	Add text to clarify Day 1 requirement for "Clinical" SLEDAI score and remove 'excluding knees' from joint related "clinical" SLEDAI criteria.	Clarification on clinical SLEDAI criteria

Section # and Name	Description of Change	Brief Rationale
3.1 Inclusion Criteria #10	Add 'at screening' for BILAG criteria	Clarification
3.1 Inclusion Criteria #12	Add 'excluding antimalarials' after immunosuppressive treatment	Clarification
3.1 Inclusion Criteria #15, and 3.9.1 IP discontinuation in relation to COVID-19	Allow 'local lab' testing for SARS-CoV-2 and revise text to clarify	Facilitate COVID-19 testing and provide clarification
3.1 Inclusion Criteria #18	Update contraception requirements and Table 1 Effective methods of birth control and ineffective methods	Update to align with AZ internal Women of Childbearing Potential guidance
3.2 Exclusion Criteria #17	Add WHO definition of COVID-19 infection	Clarification for COVID-19 definition
3.2 Exclusion Criteria #37	Extend required time period from 12 weeks to 16 weeks post last dose of IP for females who intend to become pregnant or breastfeeding after study	To be consistent with latest PSSR
3.9 Discontinuation of study intervention, 3.9.1 IP discontinuation in relation to COVID-19	Modify text on IP discontinuation criteria and COVID-19 related IP discontinuation	To be consistent with latest PSSR
3.10.1 Screen failures	Add CRF entry minimal requirements for SF participants	Clarify data collection requirement for SF
3.10.2 Withdrawal of the informed consent	Add text to clarify follow-up requirement for participants who withdraw consent	To keep consistent with CSP latest template and ICF content
4.1 Study Plan Table 3 footnote g	Add text to clarify time requirement on PK sample collection	Clarification
4.1 Study Plan Table 3 footnote o and Table 4 footnote a	Add text to clarify Follow-up requirements	Clarification
5.2.3 Vital signs	Add text to clarify that body temperature should be taken by same method throughout the study for individual participant	Clarification
5.4.1 Pharmacokinetic	Add text to provide instruction of sample collection, handling and disposal	To clarify sample storage requirement for PK/ADA samples
6 Safety Reporting and Medical Management 6.1 Definition of adverse events	Modification of the description of AE and SAE	To keep consistent with the latest CSP template
6.3 AESI and 6.3.6 Major adverse cardiovascular events	Add "MACE" to AESI and provide definition	Update information to keep consistent with the latest PSSR
6.3.3 Herpes Zoster	Add criteria for HZ evaluation	Clarification
6.7 Overdose	Update overdose reporting timeline	Clarification and to keep consistency with AZ SOP
6.11 Study governance and oversight	Add text to clarify study specific DSMB and DACRT	Clarification
7.1 Identify of investigational product(s)	Update manufacturer information	Information update

Section # and Name	Description of Change	Brief Rationale
7.2.4 Participant monitoring/procedures during and after the infusion	Add text to clarify PK sample collection time window	Clarification
7.2.6 documentation of IP administration	Delete definition of 'duration of IP administration' to avoid confusion and clarify documentation requirement	Clarification
8 Statistical Analyses by AstraZeneca	Clarify sample size estimate; update outcome variables; add definition of safety analysis set	To keep consistent with the changes in objectives. To clarify analysis set for safety variables.
9.3 Study timetable and end of study	Delete expected study timeline	Correction
Administrative Changes	Change wording from 'Medical monitor' to 'Study physician', from 'congenital abnormality' to 'congenital anomaly' and from 'Patients' to 'Participants' across the document	Administrative changes
Appendix I Prohibited/ Restricted Medicines	Correction in footnote and modify washout duration for Leflunomide	Correction
Appendix M Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Nature Disaster, or Public Health Crisis	Add text to provide additional instruction on mitigations	Information update and keep consistent with CSP section 1.4.3
Appendix N Table 7	Correct 6mg Triamcinolone is equal to 7.5mg prednisone	Correction
Appendix Q, R,S	Add C-SSRS template, and instructions for human biological sample handling and Anaphylaxis	Information for reference