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Revised Clinical Study Protocol

Drug Substance	Anifrolumab (MEDI-546)
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A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT number: 2014-004632-19

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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
01	09 April 2015		
02	01 February 2016		
03	23 March 2016		
04	18 May 2016		
05	23 May 2019		

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

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol 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.

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PROTOCOL SYNOPSIS

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

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Study site(s) and number of subjects planned

Approximately 360 subjects are planned at approximately 135 sites.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2015	3
Estimated date of last subject completed	Q3 2018	

Study design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an intravenous (IV) treatment regimen of 300 mg anifrolumab versus placebo in subjects with moderately to severely active, autoantibody-positive systemic lupus erythematosus (SLE) while receiving standard of care (SOC) treatment. The study will be performed in adult subjects aged 18 to 70 years of age.

Approximately 360 subjects receiving SOC treatment will be randomised in a 1:1 ratio to receive 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. Investigational product will be administered as an IV infusion via an infusion pump over a minimum of 30 minutes, Q4W. Subjects must be taking either 1 or any combination of the following: oral corticosteroids (OCS), antimalarial, and/or immunosuppressants.

Randomisation will be stratified using the following factors: SLE Disease Activity Index 2000 (SLEDAI-2K) score at screening (<10 points versus ≥10 points); Week 0 (Day 1) OCS dose

(<10 mg/day versus ≥10 mg/day prednisone or equivalent); and results of a type 1 interferon (IFN) test (high versus low).

This study includes:

- **A Screening Period**: Up to 30 days
- **Treatment Period**: A 52-week double-blind treatment period with investigational product administration Q4W from Week 0 to Week 48 for a total of 13 doses
- **At Week 52**, subjects will have 2 options:
  - If eligible, enrol into the long-term extension (LTE) study

    OR
  - Continue in the current study for another 8 weeks to complete a 12-week safety follow-up after the last dose of investigational product (last dose of investigational product will be given in Week 48)

Objectives

Primary Objective:	**Outcome Measures:**
To evaluate the effect of anifrolumab compared to placebo on disease activity as measured by the difference in the proportion of subjects achieving the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Week 52	Composite endpoint (BICLA), defined by meeting all of the following criteria: - Reduction of all baseline British Isles Lupus Assessment Group (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 subjects' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS) - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment

Key Secondary Objectives:	**Outcome Measures:**
To evaluate the effect of anifrolumab compared to placebo on:	
The proportion of subjects with BICLA response at Week 52 in the IFN test-high subgroup	BICLA (see outcome measure for primary objective)
The proportion of subjects who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the subgroup of subjects 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 - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with a ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score at Week 12 in the subgroup of subjects with baseline CLASI activity score ≥10	50% reduction in CLASI activity score compared to baseline defined by meeting all of the following criteria: - Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with ≥50% reduction in joint counts at Week 52 in the subgroup of subjects with ≥6 swollen and ≥6 tender joints at baseline	50% reduction in the number of swollen and tender joints compared to baseline defined by meeting all of the following criteria: - Achieve ≥50% reduction in the number of swollen and tender joints, separately - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The annualised 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

[redacted]

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of anifrolumab	Adverse events (AEs) (including adverse events of special interest [AESIs]), vital signs, physical examination, 12-lead electrocardiograms, flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K, clinical laboratory tests (haematology, clinical chemistry, urinalysis), Columbia Suicide Severity Rating Scale, and Personal Health Questionnaire Depression Scale-8

[a] Restricted medication is described in Section 3.3 and additional details are given in the Statistical Analysis Plan.

Target subject population

The study will be performed in adult subjects aged 18 to 70 years of age with moderately to severely active SLE. Subjects 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. Subjects must have eligible scores for SLEDAI-2K, BILAG-2004, and PGA as confirmed by the Disease Activity Adjudication Group.

Duration of treatment

Investigational product will be administered every 4 weeks from Week 0 to Week 48 for a total of 13 doses. The total study duration could be up to approximately 64 weeks for subjects who do not enrol into the LTE study (including screening period) and up to approximately 56 weeks (including screening period) for those subjects who do enrol into the LTE study.

Investigational product, dosage and mode of administration

Approximately 360 subjects 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 sample size and power estimations are based on the primary endpoint and key secondary endpoints. An update was made to the primary and 2 key secondary endpoints; therefore, a power analysis was conducted based on the updated primary endpoint, the proportion of subjects achieving BICLA response at Week 52.

The primary estimand of interest is the difference in change from baseline in disease activity between anifrolumab and placebo, to reflect the effect of the initially assigned and dosed investigational product. This is measured by the primary efficacy endpoint, which was [redacted] later updated to the difference in the proportion of subjects achieving BICLA response at Week 52. The intercurrent events of discontinuation of the investigational product and receipt of restricted medications were incorporated into the primary and key secondary endpoints (except flares). The full analysis set will be used as the primary population for reporting efficacy and safety data. The full analysis set is defined as subjects who are randomised and received at least 1 dose of investigational product (modified Intention-To-Treat).

Original sample size and power estimation

The sample size is primarily driven by the need to acquire an adequate safety database size, as well as the ability to assess key secondary endpoints. [redacted]

[redacted]

Updated power estimation

An updated power analysis was performed based on the previously planned sample size and amended primary and key secondary endpoints. There were no changes made to the study sample size. Power calculations were performed solely to justify the update to the primary and key secondary endpoints.

The primary endpoint is the difference in the proportion of subjects achieving BICLA response at Week 52, comparing anifrolumab 300 mg to placebo. With assumed proportions of BICLA responders of 30% and 46% in the placebo and anifrolumab 300 mg groups, respectively, 180 subjects/arm yields approximately 88% power to reject the hypothesis of no difference using a 2-sided alpha of 0.05. The minimal detectable difference in BICLA response between anifrolumab 300 mg versus placebo is approximately 10% with this sample size. Calculations are based on a 2-group chi-squared test of equal proportions (nQuery version 8.1.2.0).

The assumptions for effect sizes used in the above calculations are based on the observed results from study D3461C00005.

A stratified Cochran-Mantel-Haenszel test with the same stratification factors as for the randomisation, ie, disease activity at screening (SLEDAI-2K <10 points versus ≥10 points), Day 1 OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent), and results of the IFN test (high versus low) will be used for the assessment of the primary objective.

The key secondary endpoints will be analysed similarly, with the exception of the effect on the annualised flare rate, which will be analysed 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 subjects having different exposure times. The multiplicity of the key secondary variables will be controlled using a weighted procedure with pre-determined weights for each of the key secondary variables.

All safety parameters will be analysed descriptively.

TABLE OF CONTENTS PAGE

[redacted]

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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 antibodies
ADL	Activity of daily living
AE	Adverse event
AESI	Adverse event of special interest
AIS	Adenocarcinoma in situ
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
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
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
BP	Blood pressure
C3	Third component of complement
C4	Fourth component of complement
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

Abbreviation or special term	Explanation
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	Computed tomography
CV-EAC	Cardiovascular Event Adjudication Committee
dECG	Digital electrocardiogram
DEHP	Diethylhexyl phthalate
DSMB	Data and Safety Monitoring Board
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
[redacted]	[redacted]
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV DNA	Hepatitis B virus DNA
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IFA	Immunofluorescent assay
IFIGx	Interferon-inducible gene expression
IFN	Interferon
Ig	Immunoglobulin
IGRA	Interferon-gamma release assay
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IV	Intravenous
IXRS	Interactive voice/web response system
[redacted]	[redacted]
LLOQ	Lower limit of quantitation
LTE	Long-term extension
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCS	Oral corticosteroids
[redacted]	[redacted]
PGA	Physician's Global Assessment
PHQ-8	Personal Health Questionnaire Depression Scale-8
PI	Principal Investigator
PIP	Proximal interphalangeal
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation or special term	Explanation
PVC	Polyvinyl chloride
Q4W	Every 4 weeks
QFT-G	QuantiFERON-TB Gold
[redacted]	[redacted]
RGQ	Rotor-Gene Q
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
[redacted]	[redacted]
[redacted]	[redacted]
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SMR	Standardised mortality ratio
SOC	Standard of care
[redacted]	[redacted]
TB	Tuberculosis
ULN	Upper limit of normal
VAS	Visual analogue scale
[redacted]	[redacted]

1. INTRODUCTION

1.1 Background

Systemic lupus erythematosus (SLE) is a chronic, multisystemic, disabling autoimmune rheumatic disease of unknown aetiology. Systemic lupus erythematosus predominantly affects women of childbearing years (Cooper et al, 1998; Lahita, 1999) with a review reporting the female-to-male ratio in the childbearing years to be about 12:1 (Ramsey-Goldman and Manzi, 2000). There is substantial unmet medical need in the treatment of SLE, particularly in subjects with moderate or severe disease. Although off-label therapy has improved management options in recent years, long-term prognosis remains poor for many subjects. Compared to the general population, the overall mortality in SLE is increased with a standardised 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 subjects followed for over 70000 subject-years (Bernatsky et al, 2006).

Clinical manifestations of SLE include, but are not limited to, constitutional symptoms, 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 (QoL), and a lifespan shortened by about 10 years (ACR ad hoc committee, September 1999). Increased hospitalisations 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.

There has been only 1 new treatment (belimumab) for SLE approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in the approximately 50 years since hydroxychloroquine was approved for use in discoid lupus and SLE. However, belimumab is not approved everywhere, and the uptake has been modest. 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 (eg, 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 minimise photosensitivity. It is often difficult to taper subjects 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). Even small daily doses of 5 to 10 mg prednisone used long-term carry increased risks of side effects such as cataracts, osteoporosis, and coronary artery disease (Petri, 2001).

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, Sigurdsson, Göring et al, 2008; Sigurdsson, Nordmark et al, 2008).
- High IFN-α levels and type I IFN activity have been reported in SLE (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 subjects and are associated with greater disease activity (Baechler et al, 2003, Bennett et al, 2003, Crow and Wohlgemuth, 2003, Feng X et al, 2006, 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 subjects 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.

Subjects 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 (Bengtsson et al, 2000). In addition, subjects with acute skin involvement tend to have elevated IFN in blood and skin (Dall'era et al, 2005). Skin biopsies from subjects with SLE also show increased type I IFN signature (Blomberg S et al, 2001, Farkas et al, 2001, Yao et al, 2009). Proteins induced by IFN are increased in subjects 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 (Bengtsson et al, 2000, Rönnblom and Alm, 2003). After internalisation 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).

With the growing evidence that type I IFNs play an important role in autoimmune diseases such as SLE, inhibition of the biological activity of type I IFNs with anifrolumab may, therefore, be a novel efficacious therapy for the treatment of SLE and its significant unmet medical need.

Anifrolumab (MEDI-546) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against subunit 1 of the type I interferon receptor (IFNAR1). It is composed of 2 identical light chains and 2 identical heavy chains, with an overall molecular weight of approximately 148 kDa. Anifrolumab inhibits binding of type I IFN to type I interferon receptor (IFNAR) and inhibits the biologic activity of all type I IFNs.

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an intravenous (IV) treatment regimen of 300 mg anifrolumab versus placebo in adult subjects with moderately to severely active, autoantibody-positive SLE while receiving standard of care (SOC) treatment.

It is thought that neutralisation of IFN signalling through the human type I IFN receptor with anifrolumab will reduce the severity of disease activity in subjects with chronic, moderately to severely active SLE, and that anifrolumab will be well tolerated when given at the proposed dose for the duration of the study.

To ensure adequate treatment, all subjects will receive SOC treatment with at least 1 of the following: OCS, antimalarial, or immunosuppressants, in addition to investigational product. This is consistent with the 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 minimise bias. This is the preferred design as outlined in the June 2010 FDA Guidance for Industry Systemic Lupus Erythematosus-Developing Medical Products for Treatment and in the Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products for the treatment of SLE and lupus nephritis (CHMP, February 2015).

Randomisation will be stratified by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K, see [redacted] score at screening (<10 points versus ≥10 points), Day 1 OCS dose (<10 mg/day versus ≥10 mg/day of prednisone or equivalent), and the results of the IFN test (high versus low). Stratification is implemented in order to minimise 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 versus placebo.

A treatment period of 52 weeks is an appropriate study duration to determine the investigational product's long-term efficacy and safety profile.

1.2.2 Rationale for primary endpoint selection

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

The BICLA is driven by improvement in the BILAG-2004 score, which measures organ-specific activity (Wallace et al 2011). The BILAG-2004 incorporates a comprehensive, organ-specific, 97-question assessment, which requires the Investigator to score organ manifestations as improving, same, worse, or new over the previous 4 weeks. The scores (A, B, C, D) derived from the assessments (improving, same, worse, or new) will determine whether further treatment is needed to resolve disease activity. The change in treatment does not determine the scoring (Yee et al 2009). The BICLA was used as the primary endpoint in a Phase 2b (Wallace et al 2014) and in a Phase 3 SLE trial of epratuzumab (Clowse et al 2017). It was also used as a secondary endpoint in the anifrolumab Phase 2b study and the Phase 3 study D3461C00005.

Given the clinical relevance for the use of BICLA and its ability to discern effect as suggested in the anifrolumab Phase 2b study and the Phase 3 study D3461C00005, the BICLA was chosen as the primary endpoint.

1.2.3 Rationale for dose selection

The selection of a dose of 300 mg anifrolumab every 4 weeks (Q4W) for this study is based on safety and efficacy results from the interim analysis of a Phase 2b study where 2 doses of anifrolumab (300 mg and 1000 mg) are evaluated relative to placebo as well as dose-response modelling and simulation. In the interim analysis of the Phase 2b study, clinically meaningful benefit was observed with the 300 mg dose, with no incremental benefit at 1000 mg, see Section 1.3 for details. In addition, a higher proportion of subjects reporting *Herpes zoster* reactivations was observed at 1000 mg compared to 300 mg. Given the comparable efficacy between the 300 and 1000 mg anifrolumab doses and the increased frequency of *Herpes zoster* events in the 1000 mg dose group relative to the 300 mg dose group, the benefit:risk profile appears to favour the 300 mg dose. Further, from the PK/efficacy model, minimal improvement in efficacy was predicted for doses higher than 300 mg, consistent with the observed Phase 2b study interim analysis data. The model also predicted that doses lower than 300 mg will result in lower efficacy since trough concentrations (C_{trough}) from doses lower than 300 mg will fall below the model-predicted concentrations corresponding to 80% of maximum SRI(4) efficacy. The non-linear PK properties of anifrolumab cause a large increase in C_{trough} variability at doses below 300 mg, so as anifrolumab dose is lowered, a large proportion of subjects are predicted to have very rapid clearance and negligible exposure to anifrolumab. For these reasons, the selection of a dose of 300 mg anifrolumab is justified for this study.

A companion 3-arm study (D3461C00005) evaluating the efficacy, safety, and PK of anifrolumab is being conducted to verify that a lower dose (150 mg) of anifrolumab will be suboptimal.

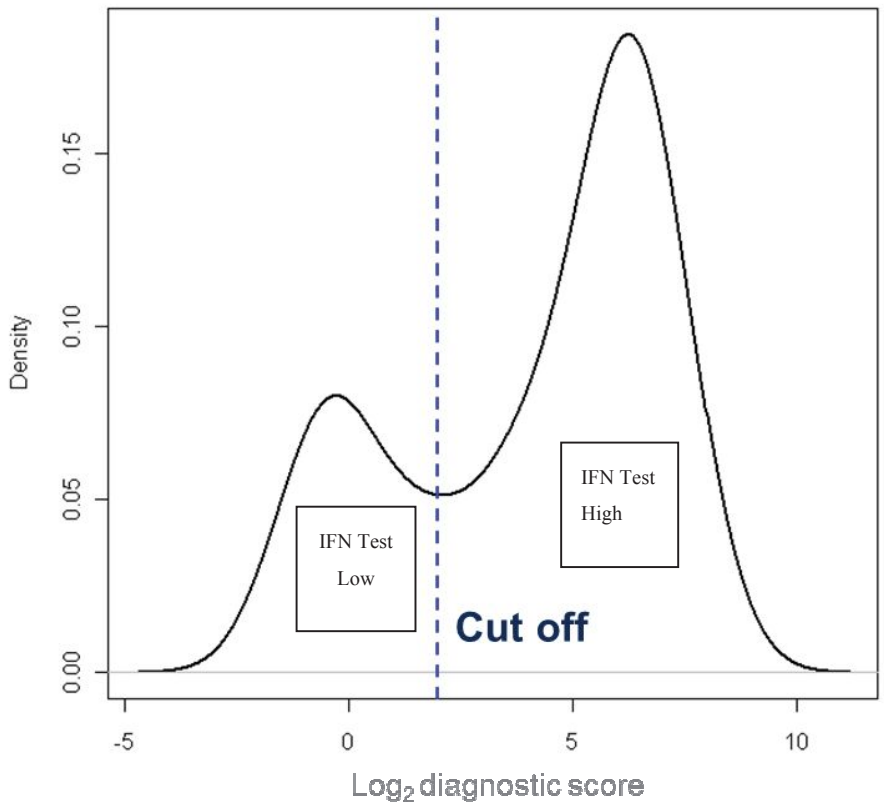
1.2.4 Rationale for duration of infusion

In a Phase 2b study where 2 doses of anifrolumab in combination with SOC (300 mg and 1000 mg) were compared to placebo, combined with SOC, all doses were administered over approximately 60 minutes. The frequency of infusion-related reactions did not differ substantially between the 300 mg (2.0%) and 1000 mg (3.8%) groups and both were lower than that observed in the placebo group (5.9%). Therefore, in this study the infusion time was reduced to a minimum of 30 minutes.

1.2.5 Interferon test background

Type I IFN has been considered to be important in SLE disease pathogenesis and inhibition of this pathway is targeted by anifrolumab. To understand the relationship between type I IFN expression and response to anti-IFN therapy, it is necessary to know if a subject's disease is driven by type I IFN activation. However, direct measurement of the target protein remains a challenge. As such, a transcript-based marker was developed to evaluate the effect of over expression of the target protein on a specific set of mRNA markers. The expression of these markers is easily detected in whole blood and demonstrates a correlation with expression in diseased tissue such as skin in SLE. The bimodal distribution of the transcript scores for SLE subjects supports defining an IFN test-high and low subpopulation as shown in the figure below:

Figure 1 Distribution of IFN transcript scores



1.3 Benefit/risk and ethical assessment

A detailed up-to-date assessment of the overall risk/benefit of anifrolumab is discussed in the Investigator's Brochure (IB).

There is significant unmet medical need for the treatment of subjects with chronic, moderately to severely active SLE. Since type I IFNs have a role in SLE, a therapy such as anifrolumab, that targets type I IFN receptors, may be beneficial in the treatment of these subjects.

Anifrolumab has been or is being investigated in 5 MedImmune/AstraZeneca-sponsored clinical studies in adult subjects with systemic sclerosis or SLE as follows:

- Study MI-CP180 was a Phase 1, open-label, dose-escalation study of single and multiple IV doses of anifrolumab in adult subjects with systemic sclerosis (completed study).
- Study CD-IA-MEDI-546-1013 is an ongoing Phase 2b, randomised, double-blind, placebo-controlled study of anifrolumab (300 and 1000 mg) in adult subjects with moderately to severely active SLE (ongoing at the time of writing this protocol).
- Study CD-IA-MEDI-546-1145 is the ongoing open-label extension (OLE) for subjects completing Study CD-IA-MEDI-546-1013 (ongoing at the time of writing this protocol).
- Study D3461C00002 is an ongoing study in Japanese adult subjects with SLE (ongoing at the time of writing this protocol).
- Study D3461C00007 is an ongoing study in adult subjects with lupus nephritis (ongoing at the time of amending this protocol).

Study CD-IA-MEDI-546-1013 is a Phase 2b, randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of anifrolumab in adult subjects with chronic, moderately to severely active SLE with an inadequate response to SOC treatment for SLE. Subjects were randomised 1:1:1 to placebo, anifrolumab 300 mg or anifrolumab 1000 mg while continuing their SOC treatment. Enrolment in the study is complete. An interim analysis (including the analysis of the primary endpoint) was conducted after all subjects completed the Day 169 visit or discontinued from study treatment early. As of the data cut-off date of August 15, 2014, a total of 305 subjects had been treated with investigational product (2 subjects discontinued from the study prior to dosing).

Efficacy in anifrolumab Phase 2b study

The primary efficacy endpoint of the Phase 2b study was the proportion of subjects achieving response in Systemic Lupus Erythematosus Responder Index (4) (SRI[4]) with sustained reduction of OCS (<10 mg/day and less than or equal to the dose received on Day 1 by Day 85 and maintained between Days 85 and 169) at Day 169. There were higher proportions of subjects in the 300 mg (34.3%) and 1000 mg (28.8%) anifrolumab groups than in the placebo (17.6%) group who met the primary endpoint at Day 169. Similar results were also observed in the other co-primary population, the IFN test-high subjects (representing approximately

75% of the study population) but not in the IFN test-low subjects at Day 169 (it is important to note that the sample size is low in this subpopulation). Further, compared to the placebo group, numerically higher proportions of subjects in the anifrolumab groups met the secondary endpoints of SRI(4) with sustained reduction of OCS (<10 mg/day and less than or equal to the dose received on Day 1 by Day 281 and maintained between Days 281 and 365) at Day 365 (placebo [25.5%], 300 mg [51.5%] and 1000 mg [38.5%]) and reduction of background OCS dose to ≤7.5 mg/day at Day 365 in those taking ≥10 mg/day at baseline (placebo [26.6%], 300 mg [56.4%], and 1000 mg [31.7%]).

The efficacy observed with the primary and secondary endpoints was supported by a wide range of evidence. A numerically higher proportion of subjects receiving anifrolumab met SRI response criteria without the OCS taper requirement at Day 169 and Day 365 compared to placebo. Furthermore, compared to the placebo group numerically higher proportions of anifrolumab treated subjects achieved SRI(5), SRI(6), SRI(7), and SRI(8) response, as well as BICLA response.

Higher response rates were also observed in organ specific measures for anifrolumab-treated subjects compared with placebo. In subjects with moderate or severe skin disease (Cutaneous Lupus Erythematosus Disease Area and Severity Index [CLASI] activity score ≥10) at baseline, a numerically higher proportion of subjects achieved at least 50% improvement from baseline in the CLASI activity score following anifrolumab treatment compared to subjects receiving placebo. In subjects with moderate or severe arthritis (≥8 swollen and tender joints) at baseline, a numerically higher proportion of subjects treated with 300 mg anifrolumab achieved at least 50% improvement in swollen and tender joint counts compared to subjects treated with placebo.

Amongst subjects with a dose of ≥10 mg/day oral prednisone or equivalent at baseline, a numerically higher proportion of subjects in the 300 mg anifrolumab group than in the placebo group were able to reduce OCS to ≤7.5 mg/day prednisone or equivalent by Day 169. Similar results were seen at Day 365. No apparent differences were seen when comparing the 1000 mg anifrolumab and placebo groups.

Serum complement and anti-dsDNA antibody levels are often indicative of active disease in SLE. In subjects with detectable anti-dsDNA autoantibody levels at baseline, those treated with 300 mg anifrolumab demonstrated a numerically larger decrease from baseline in anti-dsDNA antibody levels at Day 365 than those who were treated with placebo. In subjects with abnormal third component of complement (C3) levels at baseline, those treated with anifrolumab demonstrated a numerically larger increase from baseline in C3 levels at Day 169 and 365 than those who were treated with placebo.

Expression of type I IFN-inducible genes in whole blood using a 21-gene panel (pharmacodynamic [PD] marker) decreased following anifrolumab administration for all dose groups in subjects with a baseline positive type I IFN signature in whole blood. Both the 300 mg and 1000 mg anifrolumab dose achieved and maintained 82 to 90% neutralisation of the gene signature. In the placebo group no neutralisation of the gene signature (>6%) was observed at any time point.

Safety experience in anifrolumab Phase 2b study through August 2014

Although the safety profile for anifrolumab is acceptable, an imbalance was seen in the rate of occurrence of uncomplicated *Herpes zoster* reactivation.

The overall number of subjects with adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) (new or reactivated tuberculosis [TB], malignancy, infusion or hypersensitivity or anaphylactic reaction and non SLE-related vasculitis) were similar between the placebo and anifrolumab groups. Serious adverse events related to the investigational product were observed in 5.9% of the subjects in the placebo, 3.0% in the 300 mg and 1.0% in the 1000 mg anifrolumab group. Adverse events leading to discontinuation of the investigational product were observed in 7.9% in the placebo, 3.0% in the 300 mg and 9.5% in the 1000 mg anifrolumab group. There was 1 death in the 1000 mg anifrolumab group (acute colitis) and none in the other 2 treatment groups.

There was a higher number of subjects with infection-related AEs in both the 300 mg (63.6%) and 1000 mg (61.9%) anifrolumab groups compared with the placebo group (51.5%). This was due primarily to more reports of uncomplicated cases of *Herpes zoster* in the anifrolumab treated subjects (300 mg: 5.1%; 1000 mg: 9.5%) compared to placebo (2.0%). Importantly, subjects with *Herpes zoster* infection responded to standard antiviral treatment. One treatment-emergent SAE of transverse myelitis with a positive varicella zoster virus polymerase chain reaction in cerebrospinal fluid was reported. The subject recovered following treatment with pulsed steroid and standard antiviral medication.

There was a higher number of subjects with infections reported as influenza in the anifrolumab groups (300 mg: 6.1%; 1000 mg: 7.6%) compared to placebo (2.0%); however, the protocol did not require objective evidence confirming the aetiology of these infections.

Infusion-related reactions were observed in 5.9% of placebo treated subjects: 2.0% in the 300 mg anifrolumab group and 3.8% in the 1000 mg anifrolumab group. The characteristics and severity of these reactions were similar in all 3 treatment groups.

Overall benefit:risk assessment

Anifrolumab demonstrated a clinically relevant benefit in subjects with moderate to severe SLE treated with SOC. The efficacy was supported by a broad range of clinical measures of global (various levels of SRI responses, BICLA) and organ specific disease activity (CLASI, joint count). A clinically relevant increase in the proportion of subjects achieving pre-specified corticosteroid reduction in the 300 mg group was also observed compared with placebo, while no apparent difference was observed comparing the 1000 mg group and placebo.

Anifrolumab was generally well tolerated. A dose-related increase in the number of subjects with uncomplicated *Herpes zoster* infections was observed in subjects receiving anifrolumab compared with placebo. To date, in clinical trials of anifrolumab, hypersensitivity events or anaphylaxis/anaphylactoid events have not occurred more frequently in subjects who were

treated with anifrolumab as compared to placebo, although careful monitoring for such events will continue.

The administration of any foreign protein may be associated with acute allergic reactions that may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, and unresponsiveness. Reports of infusion-related reactions from clinical trials conducted to date suggest that the frequency, severity and characteristics of these reactions are similar across all treatment groups.

Although anifrolumab is a human monoclonal antibody, subjects can develop anti-anifrolumab antibodies that may neutralise the activity of the drug or may be associated with acute or delayed hypersensitivity reactions including anaphylaxis. Subjects will be monitored for clinical manifestations that may be associated with the formation of specific antibodies to anifrolumab generated during the study, as well as for the presence of such antibodies.

In this study, anifrolumab will be administered at a fixed IV dose of 300 mg Q4W for 52 weeks, equivalent to the lower dose in the Phase 2 study (CD-IA-MEDI-546-1013). Anifrolumab has been generally well tolerated to date with no dose-related safety signal observed with the exception of an imbalance in observed events of uncomplicated *Herpes zoster* infections.

In order to minimise the risk of treatment with anifrolumab, subjects with risk factors for serious infection, malignancy, or immune deficiency disorders are specifically excluded from participation.

Serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, *Herpes zoster*, TB (including latent TB), influenza, vasculitis (non SLE), and major adverse cardiovascular events (MACE) (including stroke, myocardial infarction [MI], or cardiovascular death) are designated as AESIs in this study.

Major adverse cardiovascular events are also designated as AESIs. An external independent adjudication committee will assess all deaths and cardiovascular SAEs to determine if they meet criteria for MACE (stroke, MI, or cardiovascular death). Specific details will be addressed in a cardiovascular event adjudication charter. There have been no imbalances in reporting rates of MACE or other non-MACE cardiovascular events observed either with anifrolumab or other agents sharing a similar mechanism of action compared to controls/placebo to date. However, since accelerated coronary artery disease and cerebrovascular accidents are recognised complications of SLE, the adjudication process is put in place to support rigorous signal detection activity across treatment arms.

Compared to the general population, subjects with SLE have a higher rate of depression and suicide. Therefore, subjects will be screened for suicidality and those who are at high risk at baseline will be excluded from participation in the study.

In order to provide an independent periodic review of safety throughout the trial, in addition to the ongoing, blinded review provided by the Medical Monitor, an independent Data and Safety Monitoring Board (DSMB) will review blinded and unblinded safety data on a regular basis throughout the study (see Section 6.10.1).

In conclusion, AstraZeneca believes that the available nonclinical and clinical data indicate an acceptable safety profile for anifrolumab. The proposed dosing regimens for Protocol D3461C0004 are adequately justified and the management plan for potential risks associated with anifrolumab is appropriate. The emerging safety profile has not identified any risks that would preclude continued investigation of anifrolumab. AstraZeneca believes that anifrolumab continues to demonstrate an overall positive benefit-risk balance to support its further clinical evaluation in subjects with active SLE.

1.4 Study design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an IV treatment regimen of 300 mg anifrolumab versus placebo in adult subjects with moderately to severely active, autoantibody-positive SLE while receiving SOC treatment. The study will be performed in adult subjects aged 18 to 70 years of age.

Approximately 360 subjects receiving SOC treatment will be randomised in a 1:1 ratio to receive a fixed IV dose of 300 mg anifrolumab or placebo Q4W for a total of 13 doses (Week 0 to Week 48) with the primary endpoint evaluated at the Week 52 visit. Investigational product will be administered as an IV infusion via an infusion pump over a minimum of 30 minutes, Q4W.

Subjects must be taking either 1 or any combination of the following: OCS, antimalarial, or immunosuppressants. Specific medication restrictions are contained in the eligibility criteria and Section 3.3. See Figure 2 for an outline of the study design.

Randomisation will be stratified using the following factors:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
- Results of the IFN test (high versus low)

This study includes:

- **A Screening Period**: Up to 30 days
- **Treatment Period**: A 52-week double-blind treatment period with investigational product administration Q4W from Week 0 to Week 48 for a total of 13 doses
- **At Week 52**, subjects will have 2 options:
  - If eligible, enrol into the long-term extension (LTE) study

OR

- Continue in the current study for another 8 weeks to complete a 12-week safety follow-up after the last dose of investigational product (last dose of investigational product will be given in Week 48)

The total study duration could be up to approximately 64 weeks for subjects who do not enrol into the LTE study (including screening period) and up to approximately 56 weeks (including screening period) for those subjects who do enrol into the LTE study.

1.4.1 Steroid burst

Section 3.3.2 provides specific details on steroid burst and tapers. From Week 0 (Day 1) to Week 12, subjects may receive **only** 1 burst of corticosteroids for an increase in SLE disease activity or to control non-SLE related disease (eg, asthma or chronic obstructive pulmonary disease [COPD] exacerbation). Subjects receiving more than 1 burst during the first 12 weeks of treatment will be considered non-responders for subsequent assessments of disease activity (details are defined in the Statistical Analysis Plan [SAP]), regardless of the reason for the burst (SLE or non-SLE activity).

1.4.2 Protocol-specified steroid tapering

An important secondary objective in this study is assessing whether anifrolumab improves the ability to reduce corticosteroid dose in patients 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 subjects 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
- Moderate to severe arthritis disease as reflected by an active joint count of ≥8 tender and/or swollen joints

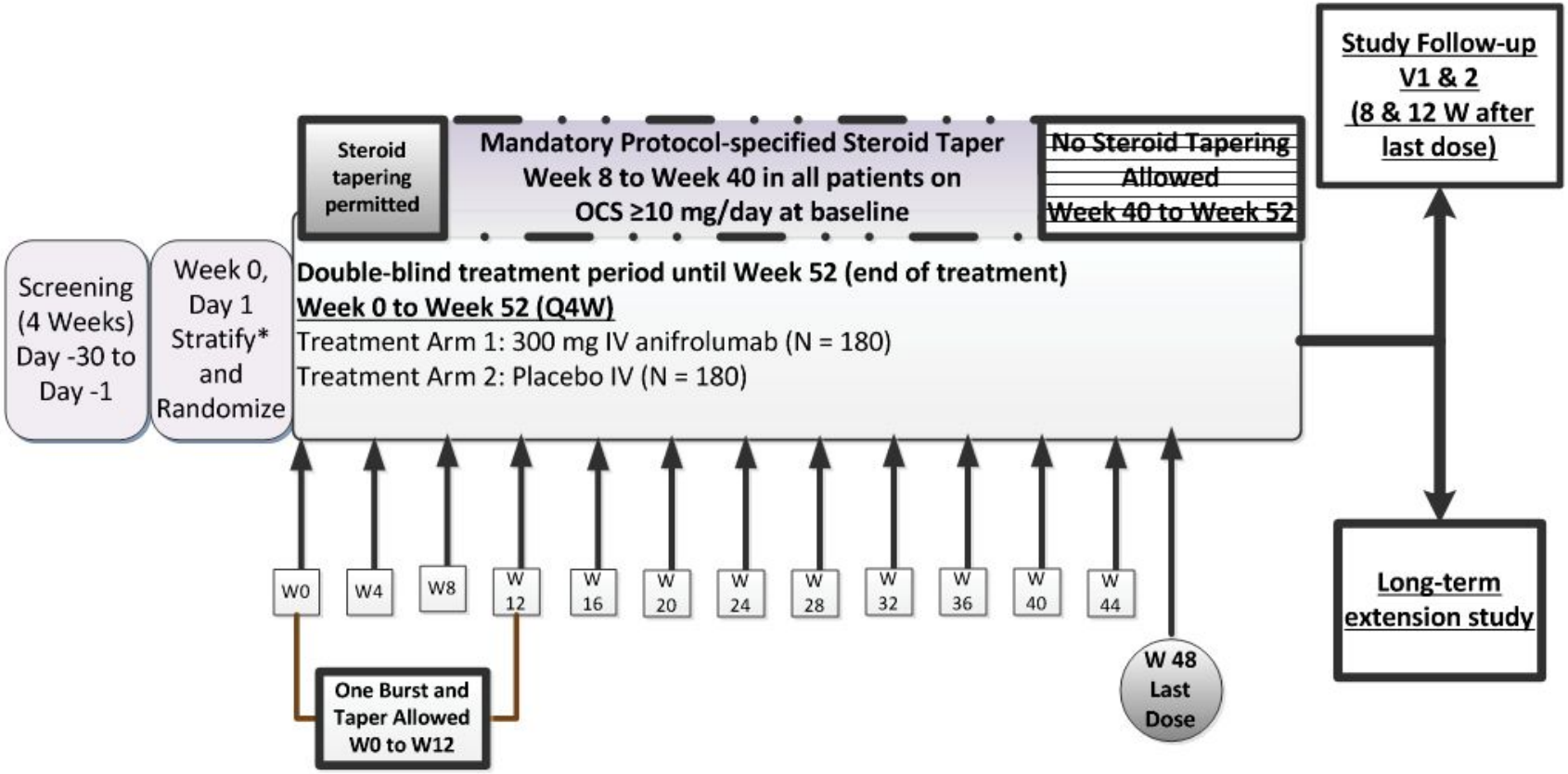
A recommended steroid-tapering regimen is provided in [redacted] but Investigators will have flexibility in how the OCS dose is reduced at each visit. If steroid tapering is not attempted in an eligible subject, the Sponsor or Sponsor's designee **must** be contacted immediately.

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 subject 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 without the subject being considered a non-responder for subsequent assessments of disease activity (details are defined in the

SAP). Subjects who require OCS dose above their baseline level may continue in the study but could be considered non-responders for subsequent assessments of disease activity.

Steroid tapering will not be permitted after Week 40.

Figure 2 Study flow chart



*** Stratification:**
SLEDAI Score (< or ≥10 points)
OCS Dose (< or ≥10 mg)
IFN Test (Low or High)

IFN = interferon; IV = intravenous; N = number of subjects; OCS = oral corticosteroid; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; Q4W = every 4 weeks; V = Visit; W = Week

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measures:
To evaluate the effect of anifrolumab compared to placebo on disease activity as measured by the difference in the proportion of subjects achieving BICLA response at Week 52	Composite endpoint (BICLA), 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, 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 subjects' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS) - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment

[a] Restricted medication is described in Section 3.3 and additional details are given in the SAP.

2.2 Secondary objectives

Key Secondary Objectives:	Outcome Measures:
To evaluate the effect of anifrolumab compared to placebo on:	
The proportion of subjects with BICLA response at Week 52 in the IFN test-high subgroup	BICLA (see outcome measure for primary objective)
The proportion of subjects who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the subgroup of subjects 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 - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment

The proportion of subjects with a ≥50% reduction in CLASI activity score at Week 12 in the subgroup of subjects with baseline CLASI activity score ≥10	50% reduction in CLASI activity score compared to baseline defined by meeting all of the following criteria: - Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with ≥50% reduction in joint counts at Week 52 in the subgroup of subjects with ≥6 swollen and ≥6 tender joints at baseline	50% reduction in the number of swollen and tender joints compared to baseline defined by meeting all of the following criteria: - Achieve ≥50% reduction in the number of swollen and tender joints, separately - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The annualised 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
[redacted]	[redacted]

[redacted]

2.3 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of anifrolumab	Adverse events (including AESIs), vital signs, physical examination, 12-lead electrocardiograms (ECG), flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K, clinical laboratory tests (haematology, clinical chemistry, urinalysis), Columbia Suicide Severity Rating Scale (C-SSRS), and Personal Health Questionnaire Depression Scale-8 (PHQ-8)

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

Subjects must meet *all* the following criteria:

1. Aged 18 through 70 years at the time of screening
2. Written informed consent and any locally required authorisation (eg, Health Insurance Portability and Accountability Act [HIPAA] in the USA, Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
3. Completion of all screening procedures needed to determine subject eligibility and stratification within 30 days after signing the informed consent form (ICF)
4. Weigh ≥40.0 kg at Screening
5. Adequate peripheral venous access
6. Diagnosis of paediatric or adult SLE with a diagnosis of SLE according to the ACR 1982 revised criteria (Tan et al, 1982) ≥24 weeks prior to signing the ICF

7. Currently receiving at least 1 of the following*:

   (a) Where prednisone is the single SOC medication (ie, the subject is not concurrently receiving any medication listed in inclusion criterion 7(c)), a dose of oral prednisone ≥7.5 mg/day but ≤40 mg/day (or prednisone equivalent**) for a minimum of 8 weeks prior to Day 1. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation

   (b) Where prednisone is not the single SOC medication (ie, the subject is concurrently receiving at least one medication listed in inclusion criterion 7(c)), a dose of oral prednisone ≤40 mg/day (or prednisone equivalent**) for a minimum of 2 weeks prior to signing of the ICF. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation

   (c) Any of the following medications administered for a minimum of 12 weeks prior to signing the informed consent, and at a stable dose for a minimum of 8 weeks prior to signing the informed consent through Day 1:

      (i) Azathioprine ≤200 mg/day

      (ii) Antimalarial (eg, chloroquine, hydroxychloroquine, quinacrine)

      (iii) Mycophenolate mofetil ≤2 g/day or mycophenolic acid ≤1.44 g/day

      (iv) Oral, subcutaneous (SC), or intramuscular methotrexate ≤25 mg/week

      (v) Mizoribine ≤150 mg/day

   *If receiving oral prednisone (or equivalent) and an additional agent, the dose duration and maximum allowable dosages for both (b) and (c) must be met

   **See [redacted] for examples of prednisone equivalency

8. Fulfils at least 4 of the 11 ACR modified 1982 classification criteria for SLE (see [redacted] at least 1 of which must be:

   (a) Positive antinuclear antibody (ANA) test at screening by immunofluorescent assay (IFA) at the central laboratory with titre ≥1:80; OR

(b) Anti-dsDNA antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; OR

(c) Anti-Smith (anti-Sm) antibody at screening elevated to above normal (including indeterminate) as per the central laboratory

9. At Screening, Disease Activity Adjudication Group confirmation of:

(a) SLEDAI-2K Criteria: SLEDAI-2K score ≥6 points and "Clinical" SLEDAI-2K score ≥4 points. 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:

(i) Includes points from the following clinical components: arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, or vasculitis

(ii) Excludes points attributed to a fever, an SLE headache, and organic brain syndrome

(b) BILAG-2004 Level Criteria: At least 1 of the following:

(i) BILAG-2004 level A disease in ≥1 organ system

(ii) BILAG-2004 level B disease in ≥2 organ systems

(c) Physician's Global Assessment (PGA) score ≥1.0 on a 0 to 3 VAS at screening

10. Negative serum β-human chorionic gonadotropin (β-hCG) test at screening (females of childbearing potential only)

11. Females of childbearing potential must use 2 effective methods of avoiding pregnancy, one of which is a barrier method, from Screening until 12 weeks after the final dose of investigational product unless the subject is surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a sterile male partner, is 1 year postmenopausal, or practices abstinence. Cessation of birth control after the 12-week follow-up period should be discussed with a responsible physician

- Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception

- Postmenopausal is defined as at least 1 year since last menses and the subject has an elevated follicle-stimulating hormone (FSH) level within the central laboratory value of postmenopausal at screening

Effective methods of birth control include those listed in Table 1.

Table 1 Effective methods of birth control

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom (with spermicide*)	Progesterone T	Implants
Cap (with spermicide cream or jelly*)	Copper T	Hormone shot or injection
Diaphragm (with spermicide cream or jelly*)		Combined pill
		Minipill
		Patch

*where commercially available

12. Nonsterilised males who are sexually active with a female partner of childbearing potential must use a condom (with spermicide where commercially available) from Day 1 until at least 12 weeks after receipt of the final dose of investigational product

13. Females with an intact cervix must have documentation of a normal Pap smear with no documented malignancy (eg, cervical intraepithelial neoplasia grade III [CIN III], carcinoma in situ [CIS], or adenocarcinoma in situ [AIS]) within 2 years prior to randomisation (see [redacted] for guidance on abnormal Pap smear results)

    *Any abnormal Pap smear result documented within 2 years prior to randomisation must be repeated to confirm patient eligibility

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

15. Meets all of the following TB criteria:

    (a) No history of active TB prior to any Screening visit

    (b) No history of latent TB prior to initial Screening visit, with the exception of latent TB with documented completion of appropriate treatment

    Note: Subjects with no history of latent TB prior to the initial Screening visit, but who are diagnosed with latent TB during screening, may be considered eligible if appropriate treatment is initiated prior to randomisation. Such subjects may be re-screened if necessary to allow

for local guidelines on latent TB treatment initiation.

(c) No signs or symptoms suggestive of active TB from medical history or physical examination

(d) No recent contact with a person with active TB OR if there has been such contact, referral to a physician specialising in TB to undergo additional evaluation prior to randomisation (documented appropriately in source), and, if warranted, receipt of appropriate treatment for latent TB at or before the first administration of investigational product

(e) Must meet 1 of the following criteria:

(i) Negative QuantiFERON-TB Gold [QFT-G] test result for TB obtained from the study Central Laboratory within 3 months prior to randomisation OR

(ii) Positive QFT-G test result for TB obtained during the Screening Period from the study Central Laboratory for which active TB has been ruled out and appropriate treatment for latent TB has been initiated prior to the first investigational product administration OR

(iii) Indeterminate (confirmed on retest) QFT-G test result for TB obtained during the Screening Period from the study Central Laboratory with ongoing QFT-G testing for TB according to the Study Plan

(f) A chest radiograph with no evidence of current active infection (eg, TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to SLE) obtained during the Screening Period or anytime within 12 weeks prior to signing of the informed consent

16. Day 1 “Clinical” SLEDAI-2K score ≥4 points

17. OCS dose stable for at least 2 weeks prior to randomisation

18. Stable SLE SOC treatment (see Section 3.3.2) at the time of randomisation

19. Women of childbearing potential must have a negative urine pregnancy test at randomisation (Day 1), prior to administration of investigational product

20. In the opinion of the Investigator, must be able to comprehend the ICF and all protocol related assessments, such that the patient can complete all study required documents, procedures, and outcome measures

3.2 Exclusion criteria

Any of the following would exclude the subject from participation in the study:

3.2.1 General exclusion criteria

1. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results

2. Concurrent enrolment in another clinical study with an investigational product

3. Individuals involved with the conduct of the study, their employees, or immediate family members of such individuals

4. Lactating or pregnant females or females who intend to become pregnant anytime from initiation of Screening until the 12-week safety follow-up period following last dose of investigational product

5. Current alcohol, drug or chemical abuse, or a history of such abuse within 1 year before Week 0 (Day 1)

6. Major surgery within 8 weeks before signing the ICF or elective major surgery planned during the study period (see [redacted])

7. Spontaneous or induced abortion, still or live birth, or pregnancy ≤4 weeks prior to signing the ICF

8. At Screening (within 4 weeks before Week 0 [Day 1]), any of the following:

   (a) Aspartate aminotransferase (AST) >2.0 × upper limit of normal (ULN)

   (b) Alanine aminotransferase (ALT) >2.0 × ULN

   (c) Total bilirubin >ULN (unless due to Gilbert's syndrome)

   (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 $<1.0 \times 10^9$/L)

   (g) Platelet count <25000/μL (or $<25 \times 10^9$/L)

   (h) Haemoglobin <8 g/dL (or <80 g/L), or <7 g/dL (or <70 g/L) if related to subject's SLE such as in active haemolytic anaemia

(i) Glycosylated haemoglobin (HbA1c) >8% (or >0.08) at screening (diabetic subjects only)

Note: Abnormal screening laboratory tests may be repeated ONCE on a separate sample before subject is declared a screen failure.

3.2.2 Exclusion criteria related to concomitant medications

9. Receipt of any of the following:

(a) Where prednisone is the single SOC medication (ie, the subject is not concurrently receiving any medication listed in inclusion criterion 7(c)), any addition of a new oral prednisone therapy (or equivalent) any time in the 8 weeks prior to Day 1, OR any change in/ discontinuation of current oral prednisone dose (or equivalent) anytime within the 2 weeks prior to randomisation (see [redacted] for examples of prednisone equivalency)

(b) Where prednisone is not the single SOC medication (ie, the subject is concurrently receiving at least one medication listed in inclusion criterion 7(c)):

(i) Any addition of a new oral prednisone therapy (or equivalent) any time from 2 weeks prior to signing of the ICF through Day 1, OR any change in/ discontinuation of current oral prednisone dose (or equivalent) anytime within the 2 weeks prior to randomisation (see [redacted] for examples of prednisone equivalency)

(ii) Any addition of a new dose of any of the following anytime in the 12 weeks prior to signing of the informed consent through Day 1, or change in / discontinuation of current dose anytime in the 8 weeks prior to signing of the informed consent through Day 1: azathioprine; any antimalarial (eg, chloroquine, hydroxychloroquine, quinacrine); mycophenolate mofetil/mycophenolic acid; oral, SC, or intramuscular methotrexate; mizoribine

10. Receipt of any of the following:

(a) Azathioprine >200 mg/day

(b) Mycophenolate mofetil >2 g/day or mycophenolic acid >1.44 g/day

(c) Oral, SC, or intramuscular methotrexate >25 mg/week

(d) Mizoribine >150 mg/day

(e) 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

11. Receipt of any investigational product (small molecule or biologic agent) within 4 weeks or 5 half-lives prior to signing of the ICF, whichever is greater (see [redacted]

12. Prior receipt of anifrolumab

13. Receipt of any commercially available biologic agent within 5 half-lives (see [redacted] prior to signing of the ICF

14. 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 (see [redacted])
- or 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)

15. Receipt of epratuzumab or tabalumab <26 weeks prior to signing the ICF, or belimumab <12 weeks prior to signing the ICF

16. A known history of allergy or reaction to any component of the investigational product formulation or history of anaphylaxis to any human gamma globulin therapy

17. 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)

18. 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 subjects are up to date on required vaccinations, including influenza [inactivated/recombinant] vaccine prior to study entry)

(c) Bacillus Calmette-Guerin (BCG) vaccine within 1 year of signing the ICF

(d) Any restricted medication listed in [redacted] if the washout period is not met

(e) Blood transfusion within 4 weeks prior to signing the ICF

3.2.3 Exclusion criteria related to systemic lupus erythematosus and other diseases

19. History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome (see [redacted] Vasculitis due to SLE is allowed in the study

20. 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 behaviour within the past 12 months based on an assessment with the C-SSRS at screening or at baseline

21. 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) That would make the subject unable to fully understand the ICF OR

    (b) Where, in the opinion of the Principal Investigator (PI), protocol-specified SOC is insufficient and utilisation 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

22. Active severe SLE-driven renal disease where, in the opinion of the PI, protocol-specified SOC is insufficient and utilisation 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

23. Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE and systemic sclerosis, as noted in A or B below:

    (a) An overlap syndrome of SLE with myositis or rheumatoid arthritis at screening is permitted provided the subject also meets the criteria for the classification as SLE; or

(b) A past 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

24. History of or current diagnosis of catastrophic or severe anti-phospholipid syndrome within 1 year prior to signing the ICF. Antiphospholipid syndrome adequately controlled by anticoagulant therapy for at least 3 months is acceptable.

25. History of, or current, inflammatory joint or skin disease other than SLE that, in the opinion of the Investigator, could interfere with the inflammatory arthritis or skin assessments and confound the disease activity assessments

26. 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

3.2.4 Exclusion criteria related to infection and malignancy risk factors

27. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the subject to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at screening. Subjects refusing HIV testing during the screening period will not be eligible for study participation

28. Confirmed positive test for hepatitis B serology 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: Subjects who are HBcAb positive at screening will be tested every 3 months for HBV DNA. To remain eligible for the study, the subject's HBV DNA levels must remain below the LLOQ as per the central laboratory.

29. Positive test for hepatitis C antibody as confirmed by central laboratory

30. Any severe herpes infection at any time prior to Week 0 (Day 1), including, but not limited to, disseminated herpes (ever), herpes encephalitis (ever), recurrent *Herpes zoster* (defined as 2 episodes within 2 years) or ophthalmic herpes (ever)

31. Any *Herpes zoster*, cytomegalovirus (CMV) or Epstein-Barr virus infection that has not completely resolved within 12 weeks prior to signing the ICF

32. Opportunistic infection requiring hospitalisation or IV antimicrobial treatment within 3 years of randomisation

33. Any of the following:

    (a) Clinically significant chronic infection (ie, osteomyelitis, bronchiectasis, etc) within 8 weeks prior to signing the ICF (chronic nail infections are allowed)

    (b) Any infection requiring hospitalisation or treatment with IV anti-infectives not completed at least 4 weeks prior to signing the ICF

34. Any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to Day 1

35. 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)

3.3 Restrictions and concomitant medications

3.3.1 Excluded medications: Day 1 through the end of the study

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

3.3.1.1 Medications that lead to immediate discontinuation of investigational product

(a) Cyclophosphamide

(b) IFN therapy (alpha 2a and 2b, beta 1a and 1b, and pegylated IFNs alpha 2a and 2b)

(c) Investigational agents

(d) Biologic immunomodulators (including, but not limited to, belimumab, abatacept, or rituxumab)

(e) Live or attenuated vaccines (the Sponsor recommends that Investigators ensure all subjects are up to date with required vaccinations prior to entry into the study)

(f) Plasmapheresis

(g) BCG vaccine

(h) Any immunoglobulin (Ig) therapy

(i) Intravenous corticosteroids >1 gm methylprednisolone or equivalent

(j) Any medications listed in [redacted] (please see the sulfasalazine, danazol, and dapsone restrictions in Section 3.3.1.2), except restrictions below.

3.3.1.2 Restricted medications

As anifrolumab is an investigative immunomodulatory agent, non-protocol permitted changes to immune modifiers or immunosuppressants on study are strongly discouraged.

If a subject receives 1 of the following, the Investigator must notify the PRA Medical Monitor immediately. The PRA Medical Monitor will determine with the Sponsor if the subject may continue to receive investigational product. Details on handling the analysis of data from subjects who may use restricted medications are described in the SAP.

(a) Sulfasalazine

(b) Danazol

(c) Dapsone

(d) Azathioprine >200 mg/day or at a daily dose greater than that at Week 0 (Day 1)

(e) 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)

(f) Oral, SC, or intramuscular methotrexate >25 mg/week or at a daily dose greater than that at Week 0 (Day 1)

(g) Mizoribine >150 mg/day or at a daily dose greater than that at Week 0 (Day 1)

(h) Any change in route of administration of oral, SC, or intramuscular methotrexate

(i) Intravenous corticosteroids >40 mg/day but ≤1 gm/day methylprednisolone or equivalent

(j) Intramuscular corticosteroids >80 mg/day methylprednisolone or equivalent

(k) Subcutaneous or intramuscular corticosteroid precursors

(l) Treatment with OCS >40 mg/day prednisone or equivalent

(m) Treatment with OCS above Day 1 dose for a dosing period >14 days

(n) Corticosteroids with a long biologic half-life (eg, dexamethasone, betamethasone)

(o) Other immunosuppressants including but not limited to calcineurin inhibitors (eg, cyclosporine, tacrolimus [including topical]) or leflunomide.

Note: Cyclosporine eye drops are acceptable for use in the study.

3.3.1.3 Other concomitant medications

Medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report form (CRF).

3.3.2 Concomitant medications for Systemic Lupus Erythematosus standard of care during the study

Permitted medications for SOC SLE are described below. Concomitant medications should only be administered after all visit assessments, including investigational product administration and post-infusion PK blood draws (if applicable), with the exception of a subject with a previous infusion-related reaction who is to receive acetaminophen 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.

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 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 (ie, the subject is not concurrently receiving any medication listed in inclusion criterion 7(c)), a dose of oral prednisone ≥7.5 mg/day but ≤40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to Day 1 is required - Subjects with increased SLE disease activity may receive 1 permitted burst and taper of OCS between Day 1 and Week 12. Additional details on burst and taper for SLE and non-SLE (eg, asthma or COPD exacerbation) disease activity are provided in Sections 3.3.2.1 to 3.3.2.4
Intramuscular corticosteroids	- Subjects 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 product infusion have been completed at the visit - Additional details on burst and taper for SLE and non SLE disease activity are provided in Sections 3.3.2.1 to 3.3.2.4

Permitted SOC SLE	Limitations of Use
Intra-articular/tendon sheath/bursal corticosteroid injections	- Intra-articular/tendon sheath/bursal injection should be minimised. Subjects 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. The Investigator must contact the medical monitor 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 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 subject 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 subject has increased SLE disease activity during the OCS tapering period
Prescription 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 NSAIDs should not be taken until after all assessments have been completed and should be taken according to SOC

Permitted SOC SLE	Limitations of Use
Non-prescription NSAIDS	- NSAIDs should not be taken on the day of a scheduled visit until all assessments are complete - 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 - NSAIDs cannot be used in combination with another NSAID at any dose, except low-dose aspirin (≤325 mg/day); topical NSAIDs may be used in combination with one oral NSAID
Acetaminophen 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 (eg, paracetamol) may be used for pain as required - In a subject 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 (eg, 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 subjects use sunscreen (list as concomitant medication for SLE) and avoid sun exposure during the study

NSAIDs = nonsteroidal anti-inflammatory drugs; OCS = oral corticosteroids; SLE = systemic lupus erythematosus; SOC = standard of care

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 (eg, 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.

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

In order to allow adequate time for the investigational 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 activity.

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

Subjects who receive more than 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 will be considered non-responders for subsequent assessments of disease activity (details are defined in the SAP), regardless of whether the OCS burst was administered for increased SLE activity or non-SLE causes.

3.3.2.2 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. A subject receiving a steroid dose above his or her Week 0 (Day 1) dose may continue in the study, but will be considered a non-responder for subsequent assessments of disease activity (details are defined in the SAP).

An increase in OCS for non-SLE causes (eg, asthma or COPD exacerbation) is allowed **ONCE** with medical monitor 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.

Subjects who receive non-SLE prednisone (or equivalent) 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 will be

considered non-responders for subsequent assessments of disease activity (details are defined in the SAP). If a subject receives >40 mg prednisone or equivalent) or a dose above baseline level for more than 14 days, it must be reported to the PRA Medical Monitor. The PRA Medical Monitor will determine with the Sponsor if the subject may continue to receive investigational product.

3.3.2.3 Increase in oral corticosteroids after Week 40

No increase in OCS is allowed after Week 40 (except for the management of AEs or as a prophylaxis for adrenal insufficiency as described below). Subjects who receive an increase in their OCS after Week 40 will be considered non-responders for subsequent assessments of disease activity.

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

In addition to the burst and tapers described above, subjects 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 from Day 1 to Week 40.

3.3.2.5 Protocol-specified steroid tapering Week 8 to Week 40

On treatment days, tapering will start after all assessments have been completed and investigational product has been administered. Tapering can be started on the scheduled study visit day (eg, Week 8 Visit) based on clinical manifestations and the laboratory values from the previous visit. If laboratory values of the current visit show SLE activity consistent with exception rule No. 1 or No. 2 below, the tapering can be reversed.

Beginning at Week 8 and continuing through Week 40, steroid tapering to an OCS dose of ≤7.5 mg/day MUST be attempted in all subjects with OCS dose ≥10.0 mg/day at Baseline, 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
- Moderate to severe arthritis disease as reflected by an active joint count of ≥8 tender and/or swollen joints

Steroid tapering must be started within 14 days of the visit. If steroid tapering is not attempted in an eligible subject, the Sponsor or Sponsor's designee must be contacted immediately. The recommended steroid-tapering regimen is provided in [redacted], but due to variability in

subject 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. **Steroid tapering will not be permitted after Week 40.**

A subject experiencing an increase in disease activity secondary to OCS tapering may increase the dose up to a maximum of the baseline OCS therapy dose from Week 8 up to Week 40 without the subject being considered a non-responder for subsequent assessments of disease activity. Subjects who require OCS dose above their baseline level may continue in the study but could be considered non-responders for subsequent assessments of disease activity (details are defined in the SAP).

3.3.3 Other restrictions

3.3.3.1 Fasting lipid profile

Subjects 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 3). If the subject has not fasted, they should fast before the next visit, and the test can be done at that visit.

3.3.3.2 Perioperative management of investigational product

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

Major surgery

Pre-operative management of investigational 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 product, if clinically feasible.

Non-major surgery

The decision to withhold investigational product administration is at the Investigator's discretion.

Postoperative management of investigational product: investigational product administration can be resumed at the 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

3.4 Subject enrolment and randomisation

Investigator(s) should keep a record of subjects considered for, and included in the study. The pre-screening/screening log will be evaluated periodically during routine monitoring visits. The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study-specific procedures are performed. The subject is considered enrolled when the ICF is signed and the enrolment call is done in the interactive voice/web response system (IXRS).

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

3. Determine subject eligibility. During screening, the Disease Activity Adjudication Group (see Section 5.2.2) will confirm eligibility criteria based on the data captured in the electronic data capture (EDC) system and from the Central Laboratory. Sites will be notified to either randomise or screen fail the subject.

4. On Day 1, the Investigator will confirm that all eligibility criteria still are fulfilled (including that the "Clinical" SLEDAI-2K score is ≥4 points [see Inclusion Criterion No. 9 for "Clinical SLEDAI-2K" definition], OCS dose has been stable for the last 2 weeks) and will then perform the randomisation transaction in the IXRS.

5. At randomisation the IXRS will assign eligible subjects a unique randomisation code and blinded investigational product kit number(s) to the subject.

Specific information concerning the use of the IXRS will be provided in the separate user manual.

Block randomisation using an IXRS will be used to randomise subjects in a 1:1 ratio to receive a fixed IV dose of 300 mg anifrolumab or placebo. AstraZeneca Biostatistics group is responsible for generating the randomisation scheme for this study using the GRand system.

The randomisation will be stratified using the following factors:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
- Results of the IFN test (high versus low)

Investigational product (anifrolumab or placebo) should, if possible, be administered the same day the investigational product kit number is assigned.

3.5 Methods for ensuring blinding

This is a double-blind study in which anifrolumab and placebo are distinguishable during the final preparation step of the investigational infusion bag. All packaging and labelling of investigational product is done in such way as to ensure blinding for all Sponsor and investigational site staff other than the unblinded investigational product manager. The kits on the shelf, and the infusion bags when prepared, look identical. Since anifrolumab and placebo can be distinguished at the preparation step, investigational product will be prepared by an unblinded investigational product manager at the site, who will not be involved in the management of study subjects.

Neither the subject nor any of the Investigator or Sponsor staff/designee who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. In the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor, or designee must be notified immediately by the Investigator.

3.6 Unblinding

In the event of a medical emergency, the Investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. The Investigator should promptly document and explain any premature unblinding to the Sponsor, without revealing the treatment given to patient to the Sponsor. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational 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 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 subject have been made and documented.

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

3.6.1 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 summarised 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 at PRA 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 Section 6.10.1.

3.7 Discontinuation of investigational product

Subjects may be discontinued from investigational product in the following situations:

1. Subject decision. The subject 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) Subject perceives the investigational product to be ineffective

    (b) Subject is unable to comply with protocol-specified visits and/or procedures due to conflicts not related to clinical trial

    (c) Subject perceives logistics to be unacceptable

    (d) Subject wishes to participate in another clinical trial

    (e) Subject wishes to take a treatment that is not allowed in this study

    (f) An AE or laboratory abnormality is of concern to the subject, but not clinically significant to physician

    (g) Other, please specify reason

2. Lost to follow-up: must be documented by time and date of telephone calls, emails, text messages, numbers called, individuals spoken to if not subject, and at least 2 attempts to contact the subject via certified letter

3. AE that, in the opinion of the Investigator or the Sponsor/Sponsor's delegate Medical Monitor, contraindicates further dosing with investigational product

4. Severe noncompliance with the study protocol

5. The Investigator or Sponsor/Sponsor's delegate Medical Monitor deems withdrawal as being in the subject's best interest

6. Pregnancy, positive pregnancy test, or subject expresses an interest to become pregnant

7. Isolated HBc positivity with HBV DNA confirmed by the central laboratory

8. Receipt of any medications identified in Section 3.3.1.1

9. The use of restricted medications listed in Section 3.3.1.2. if the PRA Medical Monitor, in consultation with the Sponsor, determines the subject must be discontinued

10. 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 Centers for Disease Control guidance should be used.

Additional restrictions related to concomitant medications are discussed in Section 3.3.1.3.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment, and will not be eligible for the LTE study.

3.7.1 Subject decision to discontinue investigational product

If the subject decides to discontinue investigational product for any reason, including but not limited to those outlined in Section 3.7 above, the subject will not receive any further investigational product. The subject may also refuse to continue any further study observation.

3.7.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) (see Section 3.7) and the presence of any AEs. The Investigator will follow-up AEs outside of the clinical study.

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

3.7.3 Lost to follow-up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at Follow-up Visit 2. A subject is considered lost to follow up when the following attempts to contact the subject are unsuccessful:

- Either phone calls, faxes or emails, and
- Having sent 2 registered letters/certified mail, and
- One attempt to check the status of the subject using publicly available sources, if allowed by local regulations

"Lost to follow-up" as a reason for study discontinuation must be documented by time and date of telephone calls, emails, text messages, numbers called, individuals spoken to if not subject, and documentation that 2 certified/registered letters were sent.

3.7.4 Study completion and end of study

An individual subject will be considered to have completed the study if the subject was followed up until the end of the study (Week 60, or Week 52 for those enrolling in the LTE

study, or Week 52 for those subjects who prematurely discontinue the investigational product and complete a minimum of 12 weeks of follow-up), regardless of the number of doses of investigational 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 subject in the study.

3.7.5 Procedures for discontinuation of a subject from investigational product

Discontinuation of investigational product does not necessarily mean discontinuation of follow-up or termination of study participation. Compliant subjects who are discontinued from the investigational product should be encouraged to continue to undergo all study-related visits/procedures for the full treatment period (Table 3) in order to support the final efficacy and safety analysis for anifrolumab (see Section 8). The reason for premature discontinuation of investigational product will be documented in the source documents and recorded in the CRF.

It is essential to collect as much data as possible for all subjects throughout the study and especially all potential endpoint events. Complete withdrawal from the study (ie, withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible. If the subject permanently discontinues investigational product prior to their completion of the study and wishes to continue with only selected study assessments; prioritised assessments are listed in Section 4.2.1.

For subjects who wish to withdraw from the study completely refer to Section 3.7.2.

3.8 Criteria for withdrawal

3.8.1 Screen failures

Screening failures are subjects who have provided informed consent and who subsequently do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These subjects should have the reason for study withdrawal recorded as "Eligibility Criteria Not Fulfilled" (ie, subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised subjects). Rescreening of a subject will be permitted once.

3.9 Discontinuation of the study

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

- Meet individual stopping criteria or are otherwise considered significant (see Section 3.7 for reasons for discontinuation of investigational product)
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for subjects at the time of discontinuation of follow-up must be recorded in the CRF.

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study plan detailing the procedures at screening

Study Period	Screening
Written informed consent / assignment of E#	X
Medical history [a]	X
Physical examination, weight and height	X
Vital signs	X
ECG	X
Serum chemistry, haematology, and urinalysis	X
Urine protein/creatinine ratio	X
ANA, anti-dsDNA antibodies, anti-Sm antibody [b]	X
B cell count [c]	X
Chest x-ray (only in subjects who have not had a chest x-ray within 12 weeks prior to signing the ICF) [d]	X [e]
FSH in postmenopausal females	X
Serum pregnancy test in all females of childbearing potential	X
Blood test for TB [f]	X
Hepatitis B and C	X
HIV test [g]	X
IFN test [b]	X
Pap smear (only in females with an intact cervix who have not had a normal Pap smear within 2 years prior to randomisation)	X [e]
C3, C4, CH50 complement	X
BILAG-2004 associated laboratory tests (anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs [h])	X
C-SSRS	X
BILAG-2004	X [i]
CLASI	X [i]
Skin photography, if applicable [j]	X [i]
SLEDAI-2K	X [i]
PGA	X [i]

Study Period	Screening
Joint count	X [i]
TB questionnaire	X
Assessment of AESIs	X
Assessment of AEs/SAEs	X
ACR classification criteria	X
Concomitant medications, including SLE medications	X
Verify eligibility criteria	X

ACR = American College of Rheumatology; AE = adverse event; AESI = adverse event of special interest; ANA = antinuclear antibody; BILAG = British Isles Lupus Assessment Group; C3 = third component of complement; C4 = fourth component of complement; CH50 = total haemolytic complement; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia Suicide Severity Rating Scale; dsDNA = Double stranded deoxyribonucleic acid; ECG = electrocardiogram; PGA = Physician's Global Assessment; SAE = serious adverse event; 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/anti-dsDNA, or IFN test can be done within the 30-day screening window, however, results needed to determine eligibility and stratification must be available within the 30-day screening window for subjects 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 [see [redacted]) 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 are allowed anytime during the screening period as long as they are completed within 30 days after signing the informed consent form.

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

[g] Subjects within the treatment or follow-up period at the time of amendment 4 approval will undergo HIV testing at the time of amendment 4 ICF signature.

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

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

[j] Photography will be conducted at selected sites in subjects who sign an additional optional consent, and have a screening CLASI score of ≥10. If no baseline skin activity or photos can be captured at the patient's Screening or Day 1 visit, no further photography will be done.

Table 3 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 (EDV)** [b]
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Procedure/Visit Window		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
[redacted]														
PHQ-8	X			X			X			X				X
[redacted]														
[redacted]														
[redacted]														
Medical history	X													
Complete physical examination	X						X							X
Focused physical examination		X	X	X	X	X		X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Cushingoid features	X						X							X
ECG	X													X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry, haematology, and urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pap smear														X [c]

Visit Number	**V1** [a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 (EDV)** [b]
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Procedure/Visit Window		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
Urine pregnancy test [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB blood test (QFT-GIT)			X [e]				X [e]			X [e]				X
HBV DNA [f]				X			X			X			X	
Immunology profile	X						X							X
Lipid profile [g]	X						X							X
Cardiovascular risk assessment	X													X
IFN Test [h]							X							X
[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]
[redacted]	[redacted]												[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]
SLEDAI-2K associated laboratory tests [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	[redacted]			[redacted]			[redacted]			[redacted]				[redacted]
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BILAG-2004	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	**V1** [a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 (EDV)** [b]
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Procedure/Visit Window		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
BILAG-2004 associated laboratory tests [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin photography, if applicable [m]	X	X	X	X			X			X				X
SLEDAI-2K	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Modified flare index	X			X			X			X			X	
[redacted]	[redacted]						[redacted]							[redacted]
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Joint count	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protocol-specified steroid tapering (if indicated)			X	X	X	X	X	X	X	X	X			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TB questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X													

Visit Number	V1 [a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EDV) [b]
Study Week	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Procedure/Visit Window		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
Randomisation	X													
Investigational product administration [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	

AE = adverse event; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia Suicide Severity Rating Scale (C-SSRS); [redacted]; ECG = electrocardiogram; EDV = Early Discontinuation Visit; [redacted]; IFN = interferon; [redacted]; PGA = Physician's Global Assessment; PHQ-8: Personal Health Questionnaire Depression Scale-8; [redacted]; SAE = serious adverse event; [redacted]; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis

[a] Once screening assessments are complete, all necessary laboratory results are reported, and adjudication is complete, a subject may be randomised. There does not need to be 30 days between screening and Week 0 (Day 1).

[b] Subjects continuing in the LTE study will have all assessments, then receive investigational product as part of the LTE protocol.

[c] Subjects should have a Pap smear between Week 48 and Week 52 to ensure that there is no evidence of new cervical dysplasia. Since access to a Pap smear may vary by country, the Sponsor recommends that local guidelines for obtaining Pap smears in subjects who have received immunomodulators or immunosuppressive treatment be followed.

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

[e] Only done if indeterminate at screening/previous visit using the IGRAs test that was used during screening (ie, QFT-GIT).

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

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

[h] Whole blood will be collected in PAXgene tubes to measure the overexpression of mRNA for certain types of type I IFN-inducible genes using a 4-gene test.

[i] [redacted]

[j] In order to help understand the potential drug-relatedness of any hypersensitivity or anaphylaxis reaction, possible additional [redacted] testing [redacted] may be done.

[k] 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 the SLEDAI assessment date.

[l] BILAG-2004 laboratory tests to include anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs (Coombs will be performed as applicable per BILAG assessment requirements). Note: In order to avoid having to bring the subject back for a separate phlebotomy, the anticardiolipin, lupus anticoagulant, and haptoglobin blood specimens will be collected at all specified visits, however the blood will be stored at the central laboratory and the analyses performed only if the 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 the Investigator's opinion, measured by local laboratory, and applicable BILAG assessment requirements for determining haemolytic anaemia.

[m] Photography will be conducted at selected sites in subjects who sign an additional optional consent, and have a screening CLASI score of ≥10. If no baseline skin activity or photos can be captured at the patient's Screening or Day 1 visit, no further photography will be done.

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

Table 4 Study plan detailing the procedures during Follow-up

Visit Number	**Follow-up Visit 1** [a]	**Follow-up Visit 2** [a]
Study Week	**8 weeks post final dose**	**12 weeks post final dose**
Procedure/Visit Window		
[redacted]		[redacted]
PHQ-8		X
Physical examination, weight		X
Vital signs	X	X
Serum chemistry, haematology, and urinalysis	X	X
Urine pregnancy test in females of childbearing potential	X	X
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
TB questionnaire	X	X
[redacted]		[redacted]
SLEDAI-2K associated laboratory tests [b]	X	X
BILAG-2004 associated laboratory tests [c]	X	X
C-SSRS	X	X
BILAG-2004	X	X
CLASI	X	X
Skin photography, if applicable [d]		X
SLEDAI-2K	X	X
PGA	X	X
Joint count	X	X

Visit Number	**Follow-up Visit 1** [a]	**Follow-up Visit 2** [a]
Study Week	**8 weeks post final dose**	**12 weeks post final dose**
Procedure/Visit Window		
[redacted]	[redacted]	[redacted]
Assessment of AESIs	X	X
Assessment of AEs/SAEs	X	X
Concomitant medications	X	X

AE = adverse event; AESI = Adverse Event of Special Interest; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; [redacted]; IFN = interferon; [redacted]; PGA = Physician's Global Assessment; PHQ-8 = Personal Health Questionnaire Depression Scale-8; [redacted]; SAE = serious adverse event; [redacted] SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis; VAS = visual analogue scale; [redacted]

[a] Follow-up assessments are to be completed when subjects complete the study (eg, early termination or after the treatment period) and are not going to participate in the LTE study.

[b] SLEDAI-2K associated laboratory tests are [redacted], 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 anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs (Coombs will be performed as applicable per BILAG assessment requirements). Note: In order to avoid having to bring the subject back for a separate phlebotomy, the anticardiolipin, lupus anticoagulant, and haptoglobin blood specimens will be collected at all specified visits, however the blood will be stored at the central laboratory and the analyses performed only if the 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 the Investigator's opinion, measured by local laboratory, and applicable BILAG assessment requirements for determining haemolytic anaemia.

[d] Photography will be conducted at selected sites in subjects who sign an additional optional consent, and have a screening CLASI score of ≥10. If no baseline skin activity or photos can be captured at the patient's Screening or Day 1 visit, no further photography will be done.

4.1 Enrolment/Screening Period

At Screening, subjects are assessed to ensure that they meet eligibility criteria. Once the subject signs the informed consent, they are considered enrolled in the study. Subjects 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 2), from Day -30 to Day -1.

Once screening assessments are complete, all necessary laboratory results are reported, and adjudication is complete, a subject may be randomised. There does not need to be 30 days between screening and Week 0 (Day 1).

Chest x-rays and Pap smears may be completed anytime during the screening period as long as all results have been reviewed by the Investigator prior to randomisation.

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

4.1.1 Other considerations for screening

4.1.1.1 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 subject'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 subjects have active caries or a dental infection that might impact on subject safety prior to enrolment.

4.1.1.2 Mammography

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

4.1.2 Re-screening subjects who screen fail

If a subject fails screening for inadequate disease activity, or other reason, which, in the opinion of the Investigator, may change to make the subject eligible, the subject may be re-screened 1 time. In this case, the subject will re-sign the informed consent document. If the subject fails screening twice, they may not undergo further screening for this study. Initial screening procedures completed within the 30 days prior to subject randomisation need not be repeated during the re-screen visit.

4.2 Treatment Period

Procedures during the Treatment Period will be performed according to the Treatment Period Study Plan (Table 3), from Week 0 (Day 1) to Week 52. The subject-reported outcome assessments should be completed by the subject (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 Week 0 (Day 1) visit, ensure notification from the Disease Activity Adjudication Group has been received, confirming that subject meets adjudicated eligibility criteria (Inclusion Criterion No. 9). The Disease Activity Adjudication Group will review all data necessary to characterise subject SLE in relation to the SLEDAI-2K, BILAG-2004, and PGA assessments (including central laboratory results).

On Day 1, ensure subject meets eligibility criteria, including Day 1 assessments according to the Treatment Period Study Plan (Table 3).

Subjects confirmed to be eligible will be randomised.

Subjects will have scheduled visits at 4-week intervals to complete protocol-specified assessments and investigational product administration according to the Treatment Period Study Plan (Table 3).

The last dose of investigational product will be administered on Week 48. At Week 52, subjects will have an End of Treatment (EOT) visit. For subjects who prematurely discontinue investigational product and are not willing to continue to participate in the study refer to Section 3.7.

4.2.1 Premature discontinuation of investigational product

Subjects who discontinue investigational product will be asked to return for all regularly scheduled clinic visits. If the subject is unwilling to complete all regularly scheduled clinic visits, the subject should complete the EDV (Week 52) visit within 4 weeks of the last dose of investigational product, as well as Follow-up Visit 1 and Follow-up Visit 2 (8 and 12 weeks after the EDV visit) unless consent is withdrawn. If the subject is unwilling to continue with any study visits, including EDV, at a minimum, the following assessments should be completed:

- SLEDAI-2K and the associated laboratory tests (anti-dsDNA antibodies, C3, C4, CH50)
- BILAG-2004 and the associated laboratory tests (anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs [Coombs will be performed as applicable per BILAG assessment requirements]). Note: In order to avoid having to bring the subject back for a separate phlebotomy, the anticardiolipin, lupus anticoagulant, and haptoglobin blood specimens will be collected at all specified visits, however the blood will be stored at the central laboratory and the analyses performed only if the 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 the Investigator's opinion, measured by local laboratory, and applicable BILAG assessment requirements for determining haemolytic anaemia.

- CLASI
- PGA (physician global assessment)
- Skin photography, if indicated
- 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 5.3.11.1
- Immunology Profile defined in Section 5.3.11.2
- Vital signs
- Physical examination, weight
- Adverse events including AESIs
- Cardiovascular risk assessment
- TB questionnaire
- Concomitant medications

If the subject does not agree to do this, they will be asked if they can be followed on a monthly basis via telephone calls. 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 6.6.2.

4.3 Unscheduled Visit

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

If a subject presents for an unscheduled visit in lieu of a regularly scheduled visit (ie, the subject is seen for safety and efficacy assessments when a regularly scheduled dosing or follow-up visit is missed), the 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.

4.4 Follow-up Period

Procedures will be performed according to the Follow-up Period Study Plan (Table 4).

Subjects who complete the Week 52 visit may be eligible to participate in a LTE study.

Subjects who complete the double-blind treatment period will have follow-up visits at Week 56 and Week 60, unless they enrol in the LTE study. Subjects who are withdrawn from the study, and do not agree to complete the 52-week study period, should complete the early discontinuation visit (Week 52 procedures) within 4 weeks of the last dose of investigational product, and be followed 8 and 12 weeks after the EDV visit by completing the Follow-up Visit 1 and 2 assessments (see Section 3.7).

5. STUDY ASSESSMENTS

5.1 Description of study procedures

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

5.2 Efficacy assessments

Efficacy measurements will be made at the times indicated in the Study Plan (see Table 2 for assessments to be performed at Screening, Table 3 for Treatment Period, and Table 4 for Follow-up). Subject-reported outcome assessments should be completed by the subject, unassisted by spouse, family members or friends.

5.2.1 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
- CLASI
- Swollen and tender joint count evaluation

The SLEDAI-2K, BILAG-2004, PGA, and CLASI must be administered by the 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 1 year of experience administering the joint count evaluation. Training will include printed

training materials, digital video disks (DVDs) and formal presentations, as well as web-based training modules.

After attending study presentations (ie, 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 subjects 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 the 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 subject should be completed by the same trained and/or certified Investigator, designated physician, or qualified site personnel (as described above) whenever possible.

5.2.2 Disease Activity Adjudication Group

PRA has a Disease Activity Adjudication Group who are medically-qualified individuals and/or support staff who assist in the ongoing management of this trial. The Disease Activity Adjudication Group will review all data necessary to characterise subject SLE in relation to the SLEDAI-2K, BILAG-2004, and PGA assessments (including central laboratory results); however, the group will remain blinded for the duration of the study. Adjudication group members will have access to an independent expert on SLE disease activity indices for unanticipated issues with regard to interpretation of these indices.

The Disease Activity Adjudication Group will be utilised to confirm eligibility during screening and will be utilised throughout the study to confirm SLEDAI-2K, BILAG-2004, and PGA scoring. The Adjudication Group 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 Disease Activity Adjudication Group.

5.2.3 Systemic Lupus Erythematosus Disease Activity Index 2000

The SLEDAI-2K disease activity index (see [redacted]) 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 [redacted]
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.

5.2.4 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 [redacted] 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 categorises 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.

5.2.4.1 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:

(i) 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 ADL 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 (not responsive to steroids up to 10 mg/day, antimalarials, NSAIDs).
- "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.

(ii) 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], computed tomography [CT], etc) and require corticosteroids and/or immunosuppressants and potentially hospitalisation for treatment. Lupus headache is considered a manifestation of lupus cerebritis.

5.2.4.2 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 subject had completed a series of visits that define true state of SLE disease activity.

The Disease Activity Adjudication Group will differentiate "false" A and B scores from true clinically significant worsening by reviewing all BILAG-2004 Index scores for each subject'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.

5.2.5 Physician Global Assessment

A trained and certified Investigator will complete the PGA (see [redacted]). 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 subject 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 subject, but the most severe disease ever seen in all SLE subjects. 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 subject's lupus disease activity. It should not reflect non-lupus medical conditions.

5.2.6 Oral corticosteroid reduction

Please refer to Section 3.3.2 for all information regarding steroid tapering.

[redacted]

5.2.8 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 [redacted] 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. Subjects 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.

5.2.9 Skin photography

Skin photography is an optional assessment. Subjects will sign an additional consent for photography if they agree to participate in these assessments. Photography will be conducted at selected sites in subjects who sign an additional consent, and have a screening CLASI score of ≥10.

Site staff will be trained to take photographs. The person who performs the CLASI will identify a single, active skin lesion (the target lesion) that is suitable for being photographed, and is considered to be the most significant inflammatory lesion due to SLE. The same target lesion will be photographed throughout the study at time points specified in the Study Plan (Table 2, Table 3, and Table 4). If no baseline skin activity or photos can be captured at the patient's Screening or Day 1 visit, no further photography will be done. In addition to the target lesion, photograph(s) including the anatomic area (eg, arm, back, scalp) with the target lesion should also be taken. If feasible, photographs of other areas with active skin disease should also be taken to demonstrate changes in the overall burden of cutaneous disease activity. Additional details about photography are provided in the photography manual.

5.2.10 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 be 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.

[redacted]

5.3 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 2 for assessments to be performed at Screening, Table 3 for Treatment Period, and Table 4 for Follow-up). Subject-reported outcome assessments should be completed by the subject, unassisted by spouse, family members or friends.

5.3.1 Adverse events

Adverse events, SAEs, and AESIs are defined in Sections 6.1, 6.2, and 6.5, respectively.

Recording of AEs is described in Section 6.6 and reporting of SAEs in Section 6.7.

5.3.2 Vital signs

Vital signs (oral temperature, blood pressure [BP], pulse rate, and respiratory rate) will be obtained at each visit. Specific information on vital signs surrounding the infusion is included in Section 7.2.4 (Subject Monitoring/Procedures During and After Infusions).

5.3.3 Physical examination

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

5.3.3.1 Complete physical examination

A complete physical examination will be performed at the visits specified in the Study Plan (Table 2, Table 3, and Table 4), 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.

5.3.3.2 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.

5.3.3.3 Pap smear

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.

Abnormal Pap smear results received anytime within the 2 years prior to randomisation must be repeated to ensure subject eligibility. If a Pap smear performed within 2 years prior to randomisation was normal with no documented malignancy (eg, CIN III, CIS, or AIS), it does not need to be repeated. Subjects with abnormal Pap smear results of atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells where high-grade squamous intraepithelial lesion (HSIL) cannot be ruled out (ASC-H), atypical glandular cells (AGC), or CIN grades I and II (CIN I and II) will be allowed to enter the study; please refer to [redacted] for guidance.

Subjects should have a Pap smear between Week 48 and Week 52 to ensure that there is no evidence of new cervical dysplasia. Since access to a Pap smear may vary by country, the Sponsor recommends that local guidelines for obtaining Pap smears in subjects who have received immunomodulators or immunosuppressive treatment be followed. If a Pap smear was performed between Week 48 and Week 52 and was not normal but showed no evidence of malignancy (eg, CIN III, CIS, or AIS), it should be repeated as per the patient's gynaecologist's recommendations. If the patient'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 the source document.

5.3.3.4 Assessment of Cushingoid features

Subjects will be assessed for Cushingoid features at the visits specified in the Treatment Period Study Plan (Table 3). 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.

5.3.4 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 5.3.11.1]) and inflammatory profiles will be obtained during the study. Various risk factors for atherosclerosis will be assessed as part of the subject 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.

5.3.5 Columbia Suicide Severity Rating Scale

The C-SSRS 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 (see [redacted]

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 subject 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 subject 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.

5.3.6 Personal Health Questionnaire Depression Scale-8

The PHQ-8 consists of 8 of the 9 criteria on which the DSM-IV diagnosis of depressive disorders is based (American Psychiatric Association, 1994, see [redacted] It assesses symptoms of depression over the last 2 weeks. The PHQ-8 is completed by the subject and scored by the Investigator at visits specified in the Treatment and Follow-up Study Plans

(Table 3 and Table 4). In addition to the 8 questions on depression, there is also a non-scored question to assess how the depressive symptoms affect the subject's level of functioning.

5.3.7 Electrocardiogram

Digital ECGs (dECG) for all subjects at all centres will be conducted at the centre using a machine provided by the central ECG vendor and will be transmitted to the central ECG laboratory. Digital ECGs will be performed at Screening, Randomisation, and at Visit 14 (Week 52). Digital ECGs will be performed in triplicate at Randomisation and at Visit 14 (Week 52). Digital ECGs will be obtained after the subject has been resting in a supine position for at least 10 minutes. All dECGs will be documented by recording the date, time, heart rate, QRS duration, PR interval, RR interval, QT, and corrected QT interval. The corrected QT intervals will be calculated using the Fridericia formula.

The 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.

Quality assurance of the ECG waveform and subject demographics will be conducted by a central ECG laboratory operator at the central ECG laboratory. Electrocardiogram reports will be provided to the study sites once the analysis is complete. It is the Investigator's judgment whether the findings/results on the central ECG laboratory report are clinically relevant or not.

5.3.8 Tuberculosis screening and monitoring

5.3.8.1 Screening evaluation

A blood test for TB will be done at screening using the interferon-gamma release assay (IGRAs) test (ie, QuantiFERON® -TB Gold In-Tube Test [QFT-GIT]). Evaluation of all subjects by QFT-GIT test will be performed by the central clinical laboratory, and chest x-rays will be completed at screening. If an adequate (anterio-posterior and lateral or per local SOC) chest x-ray was 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 subjects have a positive QFT-GIT 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 x-ray is a relevant technique for detecting active pulmonary disease and minimising potential risk to study subjects.

5.3.8.2 Tuberculosis results from screening evaluations

- If the screening QFT-G test is negative and there is no known history of recent exposure to individuals with active TB, and chest radiograph shows no evidence of active TB, the subject may be randomised without prophylaxis.
- If the screening QFT-G test is **newly positive** and chest radiograph shows no evidence of active TB, and the subject has no symptoms or medical history consistent with active TB, the subject must have a retest, and if retest is positive, the subject must start on prophylaxis prior to randomisation.
- If the screening QFT-G test is positive at the initial Screening visit, but the subject is **not newly positive as of the initial Screening visit**, the subject must have been diagnosed with latent TB and must have documentation confirming completion of appropriate treatment. Subjects with no history of latent TB prior to the initial Screening visit, but who are diagnosed with latent TB during screening, may be considered eligible if appropriate treatment is initiated prior to randomisation. Such subjects may be re-screened if necessary to allow for local guidelines on latent TB treatment initiation.
- If the screening QFT-G test is indeterminate, the test must be repeated at least once by the central laboratory as soon as possible.
    - If the result remains indeterminate, the chest radiograph shows no evidence of active TB, there are no signs or symptoms of active TB, no recent contact with anyone with active TB, and there is no history of latent (unless diagnosed with documentation of completion of appropriate treatment) or active TB, the subject may be randomised and will have additional QFT-G testing performed according to the Study Plan (Table 2, Table 3, and Table 4). Additionally, in the opinion of the Investigator and after discussion with the medical monitor, an expert specialising in TB may be consulted prior to randomisation.

5.3.8.3 Tuberculosis monitoring during the study

If, during the trial a subject who had an indeterminate TB result at screening is determined to have a:

- Positive QFT-G test result, the subject 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 subject does not need to continue TB testing outlined for subjects with indeterminate results at screening

For subjects with negative QFT at baseline and no symptoms of active TB:

- Week 52 QFT negative: no further testing
- Week 52 QFT indeterminate: repeat at Week 56. If negative no further testing, however if indeterminate repeat again at Week 60.

- QFT positive at Week 52 or later. Confirm positive QFT on another blood sample. 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 subjects for signs and symptoms of TB at every visit prior to receiving investigational product. If the evaluation raises suspicion that a subject 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 subjects may present as disseminated disease or with extrapulmonary features and should be referred for appropriate treatment.

5.3.9 Modified flare index

A modified SELENA flare index, using the SLEDAI-2K instead of the SELENA SLEDAI (see [redacted]), will be completed every 3 months as an exploratory outcome to further characterise flares as safety events.

The modified flare assessment should be completed by the Investigator or delegated/qualified physician as per protocol schedule of assessments. Assessment of flare should be scored in comparison to the subject's previous visit (ie, over the past 28 days) and should only include findings which, in the option of the Investigator, are due to SLE disease activity within that timeframe. Flare will be defined as any 1 criterion present in either the Mild/Moderate Flare or Severe Flare categories. New or worsened manifestations should only be reported for manifestations of SLE.

5.3.10 Clinical laboratory tests

All clinical laboratory tests will be performed in a central clinical laboratory at the times indicated in the Study Plan (Table 2, Table 3, and Table 4).

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 will be performed at the site using a dipstick. 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 the Investigator.

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

The 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 the

centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.6.6.

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to [redacted] '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 5 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 subjects only
Peripheral blood B lymphocyte count (only for subjects who received B cell-depleting therapy prior to signing the ICF, including but not limited to ocrelizumab, ofatumumab, atacicept, obinutuzumab, or rituximab)
BILAG-2004 associated laboratory tests analysed for all subjects at screening (anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs [Coombs will be performed 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
QFT-G test
Haematology
Haematology/Haemostasis (whole blood)
WBC count with differential
RBC count
Haematocrit
Haemoglobin
Platelet count
MCV
MCHC

Serum Chemistry
Calcium
Chloride
Potassium
Sodium
AST*
ALT*
ALP*
GGT
BUN
Creatinine
Total bilirubin* (reflexively fractionated if elevated)
Glucose
Albumin
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 as applicable per BILAG assessment requirements.*

ALP = Alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibody; Anti-Sm = Anti-Smith; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; BILAG = British Isles Lupus Assessment Group; [redacted]; CK = creatine kinase; DNA = Deoxyribonucleic acid; GGT = gamma glutamyl transferase; HbA1c = Glycosylated haemoglobin; HBc = Hepatitis B core antibody; HPF = high power field; MCHC = Mean corpuscular haemoglobin concentration; MCV = Mean corpuscular volume; QFT-G = QuantiFERON-TB Gold; RBC = red blood cell; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; WBC = white blood cell

*In order to avoid having to bring the subject back for a separate phlebotomy, the anticardiolipin, lupus anticoagulant, and haptoglobin blood specimens will be collected at all specified visits, however the blood will be stored at the central laboratory and the analysis performed only if the Investigator indicates that these tests need to be completed because of clinical suspicion of haemolytic anaemia or anti-phospholipid syndrome. Direct Coombs test samples will only be collected per the Investigator's opinion, measured by local laboratory, and applicable BILAG assessment requirements for determining haemolytic anaemia.
**Subjects within the treatment or follow-up period at the time of amendment 4 approval will undergo HIV testing at the time of amendment 4 ICF signature.

5.3.11 Laboratory assessments for cardiovascular risk assessments

5.3.11.1 Fasting lipid profile

Subjects 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 2, Table 3, and Table 4). Subjects will be required to fast for at least 8 hours prior to this assessment (see Section 3.3.3).

5.3.11.2 Immunology profile

Subjects 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 2, Table 3, and Table 4).

5.4 Clinical pharmacology assessments

Clinical pharmacology assessments will be made at the times indicated in the Study Plan (Table 2, Table 3, and Table 4).

[redacted]

[redacted]

5.4.4 Interferon test in whole blood

Whole blood will be collected at screening in PAXgene tubes to measure the overexpression of mRNA for certain types of type I IFN-inducible genes using a 4-gene test. The IFN test and the data will be evaluated for development of a companion diagnostic. The IFN-4-gene testing will be conducted at a designated central laboratory under a separate device test site protocol provided by the device sponsor (QIAGEN). The QIAGEN therascreen® interferon-inducible gene expression (IFIGx) Rotor-Gene Q (RGQ) reverse transcriptase polymerase chain reaction (RT-PCR) System will be used, it comprises the following:

- PAXgene™ Blood RNA Tubes (sample collection)

- PAXgene™ Blood RNA Kit (RNA sample preparation)
- Therascreen IFIGx RGQ RT-PCR Kit used with the RGQ molecular diagnostic Platform with bespoke IFIGx software (sample testing)

The therascreen IFIGx RGQ RT-PCR Kit will be labelled as per 21 CFR 809 .10 (c)(2)(ii), "For Investigational Use Only." The performance characteristics of this product have not been established.

The primary intent is to prospectively identify subjects as "test-high" or "test-low" for the purpose of randomisation. The results of this test will be used to stratify subjects. The kit uses the expression of the genes IFI27, IFI44, IFI44L and RSAD2 compared with 3 reference genes; 18S, ACTB and GAPDH. The result is expressed as a score that is compared with a pre-established cut-off that classifies subjects into 2 groups with low or high levels of IFN inducible gene expression. The results of the test will not be used to determine eligibility and will not be shared with the investigative site (ie, all site personnel will remain blinded to IFN test results). The assay is not intended for prediction of response to anifrolumab in other diseases.

5.4.5 Storage and destruction of biological samples

Samples will be stored for up to 15 years or as per local regulation from the date of the Last Subject's Last Visit, after which they will be destroyed.

[redacted]

[redacted]

[redacted]

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definition of serious adverse events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 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 or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see [redacted]

6.3 Hy's law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3xULN together with total bilirubin ≥2xULN may need to

be reported as SAEs. Please refer to [redacted] for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4 Other events of special interest

6.4.1 Overdose

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

An overdose without associated symptoms is only reported in the Overdose Report.

If an overdose of investigational product occurs during the study, then the Investigator or other site personnel inform the appropriate AstraZeneca representative or designee immediately or **no later than 24 hours** of when he or she becomes aware of it.

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.7. For other overdoses, reporting must occur within 30 days.

6.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.4.3 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative or designee works with the Investigator to ensure that all relevant information is provided to PRA Safety Management and to AstraZeneca **within 1 or 3 calendar days for SAEs** (see Section 6.6) **and within 30 days for all other pregnancies.**

The same timelines apply when outcome information is available.

Any subject who becomes pregnant during the course of the study will be followed so that pregnancy outcome can be determined and reported to AstraZeneca and the regulatory authorities.

6.4.4 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 12 weeks following the last dose.

Pregnancy of the subject'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 product administration until 12 weeks after the last investigational product administration should be followed up and documented. Information on the pregnancy of a subject's partner must be obtained directly from the subject's partner. Therefore, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner.

6.5 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 the Investigator to the Sponsor/Sponsor's delegate. An AESI may be serious or nonserious.

Adverse Events of Special Interest in this protocol will be assessed at each visit in the CRF. The events of interest are serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, *Herpes zoster*, TB (including latent TB), influenza, vasculitis (non-SLE), and MACE (including stroke, MI, or cardiovascular death). Lupus nephritis (associated with SLE; WHO or ISN/RPS Classification Class III, IV or V) is defined not as an AESI but as a new BILAG-2004 A adjudicated AE.

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 6.8.

6.5.1 Non-opportunistic serious infection

A serious non-opportunistic infection is any non-opportunistic infection that meets the SAE criteria in Section 6.2. Serious non-opportunistic infection adverse events are reported as SAEs and AESIs. It is expected that culture results and all diagnostic or therapeutic procedure results performed on a subject experiencing a serious non-opportunistic infection will be provided as an SAE update. Non-serious non-opportunistic infections will not be captured as AESIs.

6.5.2 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.

Examples of opportunistic infections that may occur in SLE subjects include: *Herpes zoster* meningoencephalitis, *Salmonella* bacteremia, *Pneumocystis jiroveci* pneumonia or progressive multifocal leukoencephalopathy. It is expected that culture results and all diagnostic or therapeutic procedure results performed on a subject experiencing a serious opportunistic infection will be provided as an SAE update. Since anifrolumab is an immunomodulatory agent and the Sponsor needs to understand the safety profile of this investigational product, including assessment of how anifrolumab may affect resistance to different types of infections, investigators are asked to undertake appropriate microbiologic identification including culture and report culture results for all patients who develop serious infections.

6.5.3 Anaphylaxis

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as investigational product. For the purposes of this study, the definition detailed in [redacted] is provided as a simple and rapid means to make the diagnosis of anaphylaxis during infusion with investigational product. This definition was a product of a symposium convened by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (Sampson et al, 2006).

6.5.4 Malignancy

Malignancy is a neoplasm characterised by cells with abnormal features, uncontrolled rapid growth with invasive and/or metastatic tendencies diagnosed based on pathologic and clinical standards. Understanding risk of developing different malignancies is critical to establishing the benefit: risk profile for anifrolumab. Investigators are therefore requested to obtain biopsy results and pertinent biomarker and/or genetic testing results performed and to report these for any malignancies reported during the study.

6.5.5 Herpes zoster

Herpes zoster is a viral infection characterised by a cutaneous vesicular eruption on an erythematous base presenting along dermatome(s) and usually associated with prodromal pain. *Herpes zoster* results from the reactivation of *Varicella-zoster* virus; multiple dermatomes may be involved (>3 indicates disseminated disease) and organ or systemic infection may occur (invasive; therefore an opportunistic infection). Polymerase chain reaction testing of samples from vesicles, biopsy, or other specimens (for example, cerebrospinal fluid) may confirm the presence of *varicella-zoster* virus.

For additional information regarding *Herpes zoster*, refer to the Investigator Brochure. As this is an event of special interest, the Sponsor will collect information including whether or not subjects have received vaccination for *Herpes zoster*. The *Herpes zoster* vaccine will be captured in the appropriate sections of the CRF.

6.5.6 Tuberculosis

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

- **A bacteriologically confirmed** TB case is a case 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 a case where the subject does not fulfil the criteria for bacteriological confirmation, but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the subject a full course of TB treatment. This definition includes cases diagnosed on the basis of x-ray 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 (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, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis. 2014 Jan;73(1):183-90.

World Health Organization, 2014).

Latent TB is a mycobacterial infection without clinical, bacteriological findings, or radiologic findings consistent with active TB and a TB blood test such as an IGRA (QuantiFERON Gold) or purified protein derivative skin test that is positive both at the time of provisional diagnosis and on repeat assessment.

Subjects identified with latent TB will be assessed by a local TB specialist to confirm the diagnosis and local SOC that will be used in treatment. Once latent TB is confirmed, treatment must be instituted immediately and no investigational product may be administered until treatment of latent TB has begun. Additionally, subjects with newly diagnosed latent TB must

agree to complete a locally recommended course of treatment for latent TB in order to continue receiving the investigational product.

6.5.7 Influenza

Influenza is a severe viral infection that includes the following symptoms: temperature greater than 100.8°F (38.2°C), and malaise, headache, or myalgia. It is often accompanied by nausea, vomiting, and diarrhoea, and at least 1 of the following respiratory symptoms: cough, sore throat, or shortness of breath.

Laboratory criteria for influenza include at least 1 of the following: isolation of influenza virus from a clinical specimen, detection of influenza virus nucleic acid in a clinical specimen, identification of influenza virus antigen by direct fluorescent antibody test in a clinical specimen, OR influenza-specific antibody response.

A *confirmed* case of influenza meets the clinical and laboratory criteria for the viral illness. Laboratory confirmation should be done using locally available, rapid, commercial tests approved by Regulatory Agencies and sampling respiratory specimens.

Not all upper respiratory viral infections or gastrointestinal viral infections are influenza. In the case where a subject reports a viral infection severe enough to be considered, in the opinion of the Investigator, influenza, a viral test should be performed (if possible) to confirm the diagnosis. If, in the opinion of the Investigator, the subject has had influenza (the specific viral infection), this should be reported as an AESI, whether or not a test to confirm the diagnosis has been performed. Less severe viral infection should be reported as an AE only.

6.5.8 Vasculitis (non-Systemic Lupus Erythematosus)

Vasculitis (non-SLE) is defined as an inflammatory disorder of blood vessels involving arteries and/or veins and characterised by characteristic clinical signs/symptoms and diagnosed by biopsy, imaging such as angiography or blood tests such as findings of antineutrophil cytoplasmic antibodies consistent with the diagnosis. Underlying causes should be identified, such as medications including study drug, infections or systemic inflammatory syndromes, wherever possible. See [redacted] for a list of vasculitic syndromes excluded from the study.

6.5.9 Major acute cardiovascular events

As a measure of enhanced Pharmacovigilance, an independent Cardiovascular Event Adjudication Committee (CV-EAC) will review deaths (due to any cause) and all SAEs in the cardiovascular SOC for evaluation as to whether to classify as MACE events (stroke, MI, or cardiovascular death).

The CV-EAC will review cases of interest to determine if they meet accepted diagnostic criteria. Causality assessments will not be made by the CV-EAC, nor will the committee possess governance authority. The CV-EAC will be blinded regarding any information relating to the randomisation group.

6.6 Recording of adverse events

6.6.1 Time period for collection of adverse events

Adverse Events and SAEs will be collected from the 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) or Week 52 for the subjects who enrol in the LTE study.

6.6.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the study staff for as long as medically indicated. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.6.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome of AE

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

- Onset Date (Date AE met criteria for serious AE)
- Detection Date (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 hospitalisation
    - Date of hospitalisation
    - Date of discharge

(d) Congenital abnormality or birth defect

(e) Important medical event

(f) Suspected transmission via a medicinal product of an infectious agent

- Description of AE
- Investigator causality assessment to concomitant medications
- Investigator causality assessment to study procedures (yes or no)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria defined above. 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. 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. The Investigator should provide an assessment of the severity of each AE/SAE.

6.6.4 Causality collection

The Investigator will assess causal relationship between investigational product and each AE, 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 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 [redacted]

6.6.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study personnel: *'Have you 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.

6.6.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). 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 fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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 will use the clinical, rather than the laboratory term (eg, anaemia versus 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 (or SAE, as appropriate).

6.6.7 Disease progression/worsening of systemic lupus erythematosus

Disease progression can be considered as a worsening of a subject'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. 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.

6.7 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF. PRA Safety Management is to be sent all safety forms and supporting documentation including laboratory tests, imaging reports, diagnostic test results, biopsy reports and discharge summaries.

If any SAE occurs in the course of the study, then the Investigator or other site personnel inform PRA Safety Management within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

PRA Safety Management works with the Investigator to ensure that all the necessary information is provided to the data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events (if received for instance during a weekend or a public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday) and **within 3 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform PRA Safety Management of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the Datalabs system is not available, then the Investigator or other study site personnel reports the SAE to PRA Safety Management on the study specific paper SAE form by telephone, fax, or email. The SAE report form must be completed in the electronic system as soon as the system is available again.

PRA Safety Management contact information for SAE reporting:

FAX: +44 1792 525 720
E-mail: MHGsafety@prahs.com
Telephone: +49 621 8782 154

PRA, on behalf of AstraZeneca, is responsible for reporting certain SAEs as expedited safety reports to applicable Regulatory Authorities, Ethics Committees (ECs), and participating Investigators, in accordance with International Conference on Harmonisation (ICH) Guidelines and/or local regulatory requirements. PRA may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit additional information requested by AstraZeneca or PRA as soon as it becomes available.

The reference document for definition of expectedness/listedness is the IB.

6.8 Reporting of adverse events of special interest

Adverse Events of Special Interest will be assessed by the Investigator for severity, relationship to the investigational 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 recognised 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 subject 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.

6.9 Management of investigational product-related toxicities

6.9.1 Anaphylaxis, hypersensitivity, and infusion-related reactions

Infusion-related reactions have been reported with the administration of IV Ig and monoclonal antibodies. As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis. For a definition of anaphylaxis, hypersensitivity reactions, and infusion-related reactions, see [redacted]

Subjects should not be premedicated unless they have had a prior infusion-related reaction to anifrolumab. However, if a prior infusion-related reaction has been documented, the

Investigator may elect to administer prophylactically an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the subject prior to subsequent infusions. Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted.

6.9.2 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 (eg, chest x-ray 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.

Subjects who develop a new infection while undergoing treatment with investigational product should receive appropriate medical therapy, as determined by local standards, and be monitored closely until the condition resolves. Investigational product should not be administered to a subject with a clinically significant, active infection as determined by the Investigator (see Section 3.7). For any active infection (eg, *Varicella zoster* infection/chickenpox) or significant exposure to any infection (eg, *Varicella zoster* infection in a naive subject, bacterial pneumonia), the Investigator should consider whether to interrupt investigational product administration and should notify the medical monitor.

Similarly, if a subject presents with signs or symptoms where opportunistic infections are considered (eg, CNS symptoms consistent with progressive multifocal leukoencephalopathy or *Herpes encephalitis* or atypical pneumonia suggesting *Pneumocystis jiroveci* pneumonia), investigational product should be interrupted until the 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 (ie, infection or other AE) the investigational 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

6.10 Study governance and oversight

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

6.10.1 Data and Safety Monitoring Board

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 summarised by treatment group using masked treatment group labels (eg, 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 medical monitor 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 subjects, 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.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
Anifrolumab (MEDI-546)	150 mg/mL solution of anifrolumab (clear colourless to slightly yellow) intended for IV administration following dilution into 0.9% saline	MedImmune, LLC
Placebo	Solution (clear) intended for IV administration following dilution into 0.9% saline	MedImmune, LLC

[redacted]

Each vial of investigational product or placebo contains 1.3 mL fill volume. Investigational product and placebo will be supplied to the site in cartons of 2 vials per kit. Each kit will have a unique number that will be printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton).

Preparation of investigational product and placebo must be performed by an unblinded qualified person (eg, pharmacist or study nurse) at the site. When diluted as directed in the investigational 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 product, anifrolumab 300 mg or placebo, will be administered via controlled IV infusion pump into a peripheral vein over at least 30 minutes Q4W. Each dose must be at least 14 days apart.

7.2.1 Dose preparation steps

From a 100 mL IV infusion bag of 0.9% normal saline, withdraw and discard a volume of saline equal to 2.0 mL. Then add 1.0 mL from each of the 2 vials in the kit into the infusion bag and mix by gentle inversion. Due to approximately 10% overfill of normal saline, the final volume of the dilution will be greater than 100 mL.

7.2.2 Prior to administering the investigational product

- Confirm subject was evaluated for signs and symptoms of TB
- Women of childbearing potential must have a negative urine pregnancy test prior to receiving investigational product.
- Subjects should not have clinically significant, active infection as determined by the Investigator.
- There should be at least 14 days between doses. If the previous investigational product infusion was given within 14 days, delay visit until >14 days has elapsed and contact the PRA medical monitor.
- Pre-dose blood samples will be collected
- Subjects should not be premedicated unless they have had a prior infusion-related reaction to anifrolumab. However, if a prior infusion-related reaction has been documented, the Investigator may elect to administer prophylactically an antihistamine or acetaminophen/paracetamol for the comfort and safety of the subject 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 product administration procedures

- Investigational product must be administered within 4 hours after preparation and may be stored at room temperature until administration. Total in-use storage time from dilution of anifrolumab to start of administration should not exceed 4 hours at room temperature. If refrigerated at 2 to 8°C (36 to 46°F), storage time should not exceed 24 hours. If storage time exceeds these limits, a new dose must be prepared from new vials.
- Investigational 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 product.
- Because compatibility of anifrolumab with IV medications and solutions other than 0.9% sodium chloride for injection, (United States Pharmacopeia), is not known,

the investigational product solution should not be infused through an IV line in which other solutions or medications are being administered.

- Investigational product should be administered over a minimum of 30 minutes.
- Immediately following the initial dosing, up to an additional **25 mL of saline** will be given via infusion pump at the same pump speed utilised at the completion of the initial dosing.
- An emergency cart should be available in the infusion suite.

7.2.4 Subject monitoring/procedures during and after the infusion

Subjects will be monitored during the administration of the investigational 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 subjects will be monitored during administration of the investigational 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 (oral 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 product infusion)
- Every 15 ±5 minutes during infusion
- Immediately after completion of administration of investigational product, including postdose saline flush (within 15 ±5 minutes after completion of investigational product administration)
- Every 30 ±5 minutes after completion of investigational product administration (not including saline flush) for at least 2 hours after the first 4 doses (Week 0 [Day 1] to Week 12) of investigational product are administered, and for at least 1 hour, thereafter (Week 16 to 48)
- [redacted]

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

7.2.5 Discharge

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

7.2.6 Documentation of investigational product administration

Both the duration of the investigational product infusion and the duration of investigational product administration will be recorded. The duration of investigational product infusion and duration of investigational product administration will be 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 product is first infused into the subject. Infusion stop time is defined as the time point where the infusion pump completes infusion of the investigational 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).
- Duration of administration: the amount of time elapsed from the infusion pump start time to the infusion pump stop time PLUS the time required to complete the additional flush of saline. The duration of administration will always be greater than the duration of infusion and will always include the additional flush of saline.

Initial IV bag compatibility studies demonstrate that anifrolumab is compatible with IV bags composed of polyolefin that is latex-free, polyvinyl chloride (PVC)-free, and diethylhexyl phthalate (DEHP)-free, and IV administration lines composed of PVC and polyethylene that are latex free and DEHP-free. Additional studies demonstrate that anifrolumab is compatible with IV bags and ancillaries comprised of materials as described in Table 6 and Table 7.

Table 6 Compatible materials of construction for IV bags

IV Bag Diluent	Materials of Construction
0.9% saline	Glass
0.9% saline	Polyolefin copolymer, ethylene and propylene
0.9% saline	PVC and DEHP
0.9% saline	Polyethylene
0.9% saline	Polypropylene
0.9% saline	Ethylene polyvinyl acetate

Table 7 Compatible materials of construction for ancillaries (eg, infusion tubing)

Materials of Construction
Polyethylene
PVC with DEHP
PVC with 2-ethylhexyltrimellitate
Polybutadiene

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 drugs should be kept in a secure place under appropriate storage conditions. The investigational 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 drugs (including investigational product) should be recorded in the appropriate sections of the CRF. The investigational product will be administered by study site personnel, who will monitor compliance.

7.6 Accountability

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

The study personnel will account for all study drug administered to the subjects.

The Investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to AstraZeneca or designee. All unused investigational 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).

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

7.7 Post study access to study treatment

Upon evaluation at Week 52, subjects will either be followed for a 12-week Follow-up Period, or transition to an LTE study (if eligible) that will continue for approximately 3 years after the completion of the Week 52 visit.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol violations. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared prior to the first subject in to the study. Any subsequent amendments to the SAP will be documented, with final amendments 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 360 subjects receiving SOC treatment will be randomised 1:1 to treatment with anifrolumab or placebo.

An update was made to the primary and 2 key secondary endpoints; therefore, a power analysis was conducted based on the updated primary endpoint. The primary endpoint [redacted] was later updated to the difference in the proportion of subjects achieving BICLA response at Week 52. The intercurrent events of discontinuation of the investigational product and receipt of restricted medications were incorporated into the primary and key secondary endpoints (except flares).

8.2.1 Original sample size and power estimation

The sample size is primarily driven by the need to acquire an adequate safety database size, as well as the ability to assess key secondary endpoints. [redacted]

It is not straightforward to precisely arrive at the power estimate for the assessments of key secondary endpoints due to the multiplicity procedure used to preserve the type I error, as well as uncertainties of the size of subgroups in most assessments. Approximate estimates of power for 2 example endpoints are listed below. These calculations assume that the primary endpoint is met, and the testing of the key secondary endpoints is therefore allowed. Further, for these examples each endpoint is tested using a weighted Holm procedure, and the alpha given by the assigned weight in the first step of the algorithm:

- [redacted]
- Difference in the proportion of subjects who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the subgroup of subjects with baseline OCS ≥10 mg/day: Given 60% of subjects have an OCS dose of at least 10 mg at baseline; proportions of subjects tapering the OCS dose of 32% and 59% in the placebo and anifrolumab treatment groups, respectively; a 2-sided alpha of 0.004 yields 87% power.

The assumptions of the effect sizes and sizes of subgroups used for the calculations above are based on the observed results in the interim analyses of study CD-IA-MEDI 546-1013.

8.2.2 Updated power estimation

An updated power analysis was performed based on the previously planned sample size and amended primary endpoint. There were no changes made to the study sample size. Power calculations were performed solely to justify the update to the primary and key secondary endpoints.

The primary endpoint is the difference in the proportion of subjects achieving BICLA response at Week 52, comparing anifrolumab 300 mg to placebo. With assumed proportions of BICLA responders of 30% and 46% in the placebo and anifrolumab 300 mg groups, respectively, 180 subjects/arm yields approximately 88% power to reject the hypothesis of no difference using a 2-sided alpha of 0.05. The minimal detectable difference in BICLA response between anifrolumab 300 mg versus placebo is approximately 10% with this sample size. Calculations are based on a 2-group chi-squared test of equal proportions (nQuery version 8.1.2.0).

The assumptions for effect sizes used in the above calculations are based on the observed results from study D3461C00005.

8.3 Definitions of analysis sets

8.3.1 All subjects analysis set

This analysis set will comprise all subjects 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 and safety data. This comprises all subjects randomised into the study who receive at least 1 dose of investigational product and will be analysed according to randomised treatment (modified Intention-To-Treat). Any major deviations from randomised treatment will be listed and considered when interpreting the safety data.

[redacted]

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 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 used to evaluate the effect of anifrolumab compared to placebo on disease activity is the difference in the proportion of subjects achieving BICLA response at Week 52, where a subject 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 subjects' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment. Restricted medication is defined in Section 3.3 and additional details are given in the SAP.

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 BICLA response at Week 52 in interferon test-high subjects

The key secondary endpoint used to evaluate the effect of anifrolumab compared to placebo on disease activity in the IFN test-high subgroup is the difference in the proportion of subjects achieving BICLA response at Week 52 in subjects classified as IFN test-high. BICLA response is defined in Section 8.4.1.

8.4.2.2 Oral corticosteroid management

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on the ability to reduce the OCS dose in subjects with baseline OCS ≥10 mg/day prednisone or equivalent is the difference in the proportion of subjects 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
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 3.3 and SAP for additional details).

8.4.2.3 Skin lesions

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on inflammatory cutaneous lupus lesions in subjects with baseline CLASI activity score ≥10 is the difference in the proportion of subjects who meet all of the following criteria:

- Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 3.3 and SAP for additional details).

8.4.2.4 Joints

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on swollen and tender joints is the difference in the proportion of subjects 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 criteria are met:

- The percentage reduction from baseline in both the number of swollen joints and the number of tender joints, separately, is ≥50%
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 3.3 and SAP for additional details).

8.4.2.5 Flares

The key secondary endpoint used to evaluate the effect of anifrolumab versus 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 (ie, 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 1 organ system compared to the previous visit).

[redacted]

[redacted]

Supportive outcome variables of the Individual components of [redacted] BICLA

The individual components of the composite [redacted] BICLA endpoints as defined in Section 8.4.1 and above will be assessed by treatment.

Further, the effect of anifrolumab versus placebo on PGA will be evaluated using the difference in mean change in PGA from baseline longitudinally over time to Week 52. [redacted]

[redacted]

Supportive outcome variables for the assessment of skin lesions

In addition to the endpoint described in Section 8.4.2.3, the maintenance of effect in the CLASI activity score will be evaluated using the proportion of subjects 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.

Supportive outcome variables for the assessment of joints

In addition to the endpoint in Section 8.4.2.4, secondary endpoints to evaluate the effect of anifrolumab versus placebo on joints are:

- Difference in change from baseline to Week 52 in the number of active, swollen, and tender joints
- Difference in proportion of subjects with at least 6 swollen and at least 6 tender joints at baseline who achieve at least a 20% reduction from baseline in both the number of swollen and tender joints at Week 52
- Difference in proportion of subjects with at least 8 swollen and at least 8 tender joints at baseline who achieve at least a 20% reduction and at least a 50% reduction from baseline in both the number of swollen and tender joints at Week 52

An active joint is defined as a joint with both swelling and tenderness.

The change from baseline in the number of active, swollen, and tender joints will be explored longitudinally over time up to Week 52.

Supportive outcome variables for the assessment of flares

In addition to the endpoint in Section 8.4.2.5, the annualised rate of flares will also be evaluated where a flare is defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to *baseline*. The endpoint in Section 8.4.2.5 will also be evaluated where the modified BILAG will be used instead of BILAG-2004.

In addition, time to flare, ie, time from first exposure of investigational product to the first flare will be assessed. Both definitions of flares will be used for the assessment: either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items *compared to previous visit* (as introduced in Section 8.4.2.5); and the definition described above comparing to baseline.

[redacted]

[redacted]

8.4.5 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, haematology, clinical chemistry, urinalysis, C-SSRS, PHQ-8, flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K, and reported AEs (including AEs of special interest, see Section 6.5).

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. The number and proportion of subjects with flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K and the number of such flares will be explored. Marked abnormal ECG values or changes from baseline will be identified based on pre-determined criteria. Occurrence of suicidal behaviour and ideation, based on the C-SSRS, from baseline up to Week 52 will be explored. AEs will be summarised by means of descriptive statistics and qualitative summaries.

8.4.5.1 Other significant adverse events

During the evaluation of the AE data, a PRA 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 Astra Zeneca Global Patient Safety Physician, be considered other significant AEs (OAEs) 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.

[redacted]

[redacted]

8.5 Methods for statistical analyses

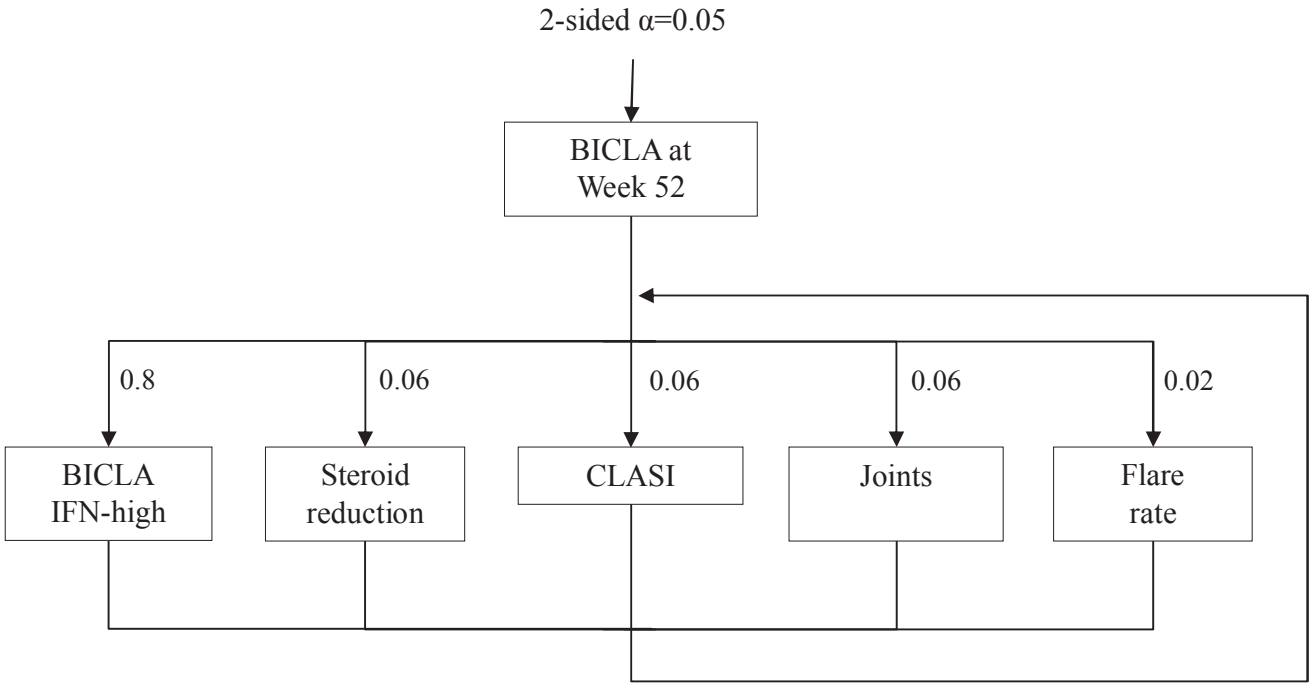
The analysis of the primary and secondary endpoints will include all data captured during the 52-week treatment period, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence.

Testing strategy to account for multiplicity considerations

To account for multiplicity to test the primary and 5 key secondary endpoints, a testing strategy will be followed to control the overall type I error rate in the strong sense. The primary endpoint, ie, the difference in the proportion of subjects achieving BICLA response at Week 52 comparing anifrolumab 300 mg to placebo, will be tested at an alpha level of 0.05. If the observed p-value is ≤ 0.05, a statistically significant difference in BICLA response between the treatment groups at Week 52 will be concluded, and the alpha of 0.05 will be preserved for testing of the key secondary endpoints. If the observed p-value is >0.05, no statistically significant difference between anifrolumab and placebo will be declared, and no formal testing of the key secondary endpoints will be carried out.

If the primary endpoint is statistically significant, then the 5 key secondary endpoints will be tested and a weighted procedure, eg, the weighted Holm procedure (Burman, 2009), will be used in order to strongly control the family-wise error rate at the 2-sided 5% level. The procedure applies alpha recycling according to pre-specified weights (Figure 3) and will be clearly outlined in the SAP.

Figure 3 Alpha recycling



Missing data

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

- From Week 0 (Day 1) to Week 12, the study design allows for 1 burst and taper of OCS in order to allow adequate time for investigational 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.
- Subjects who require additional bursts of OCS will still be encouraged to remain in the study, but will be considered a non-responder for subsequent assessments of disease activity.

Subjects who discontinue investigational 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 endpoint includes a criterion that corresponds to non-response for subjects who prematurely discontinue from investigational product, or who receive restricted medications beyond the protocol-allowed threshold. Sensitivity analyses, excluding this criterion from the definition of BICLA response, where missing data is handled in a different way, (eg, a multiple imputations method) 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. Nominal p-values may be presented for secondary endpoints not included in the strategy for preserving the type I error rate. Statistical significance cannot be interpreted from these p-values.

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

8.5.1 Analysis of the primary variable

The primary endpoint used to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity is the difference in the proportion of subjects achieving BICLA response at Week 52.

The estimand of primary interest is the difference in the proportions of response between anifrolumab and placebo at Week 52 in the full analysis set, where the response is captured with a composite binary endpoint and is defined by improvement from baseline in disease activity as measured by BILAG, no worsening in SLEDAI-2K and PGA and ability to adhere to the planned course of the treatment. The intercurrent events: discontinuation of investigational product and receipt of restricted medications are unfavourable outcomes. Therefore, subjects treated with restricted medications beyond protocol-allowed threshold, and those who discontinued the investigational product for any reasons, will be non-responders. This estimand answers a clinically relevant question comparing the number of subjects able to both complete the study treatment and to achieve adequate response without further medication being required. The response is measured by the primary efficacy endpoint, defined as the difference in the proportion of subjects achieving BICLA response at Week 52, comparing the anifrolumab to the placebo groups.

The null hypothesis is that the proportion of subjects achieving BICLA response on anifrolumab is equal to that of placebo. The alternative hypothesis is that the proportion of subjects achieving BICLA response on anifrolumab is not equal to that on placebo, ie,

H0: difference in proportion achieving BICLA response (anifrolumab vs Placebo) = 0
Ha: difference in proportion achieving BICLA response (anifrolumab vs Placebo) ≠ 0

The proportion of subjects achieving BICLA response in the anifrolumab treatment group will be compared to that in the placebo group using a Cochran-Mantel-Haenszel (CMH) approach (Clowse et al, 2017

Clowse ME, Wallace DJ, Furie RA, Petri MA, Pike MC, Leszczyński P, et al. Efficacy and safety of epratuzumab in moderately to severely active systemic lupus erythematosus: Results from two phase III randomized, double-blind, placebo-controlled trials. Arthritis Rheumatol 2017 Feb;69(2): 362–75.

Cochran, 1954) stratified by:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
- Results of a type 1 IFN test (high versus low)

Strata with low counts will be collapsed prior to the analysis. Details for collapsing of strata will be pre-specified in the SAP.

The estimated treatment effect (ie, the difference in response rate for anifrolumab versus placebo), corresponding 95% CI, and 2-sided p-value for the difference at Week 52 will be presented. In addition, the response rate and the corresponding 95% CI within each treatment group will be presented.

The time to BICLA response sustained up to Week 52 will be analysed 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 analysis, with the corresponding 95% CI, will be created. In addition, the individual components of the composite BICLA endpoints will be summarised by treatment group, and a sensitivity analysis using modified BILAG will be conducted.

8.5.2 Analysis of the secondary variables

8.5.2.1 Analysis methods for key secondary efficacy variables

All key secondary endpoints, with the exception of the difference in annualised flare rate through Week 52 (which will be analysed using a negative binomial regression model), will be analysed and presented similarly to the primary endpoint as described in Section 8.5.1. 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. 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 subjects having different exposure times. The estimated treatment effect and the corresponding 95% CI as well as the 2-sided 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.

[redacted]

8.5.2.3 Analysis methods for safety variables

AEs (including AESIs) will be summarised by means of counts summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term (PT) separately for the study periods (treatment period and follow-up period). All AEs will be listed.

Laboratory data for haematology and clinical chemistry will be summarised. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point 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 each 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 summarised by treatment group.

The proportion of subjects with suicidal behaviour and suicidal ideation throughout the study based on the C-SSRS will be presented for each treatment group. The proportion of subjects within each of the 4 suicidal behaviour categories and within each of the 5 suicidal ideation sub-categories 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 summarised for each treatment group.

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

- [redacted]

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

8.5.4 Interim analysis

No interim analysis is planned.

8.5.5 Pooled analysis

Details of pooled analyses will be presented in the SAP for the Integrated Summary of Efficacy.

9. STUDY AND DATA MANAGEMENT

9.1 Monitoring of the study

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

- Provide information and support to the 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 drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

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

9.1.1 Source data

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

9.1.2 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the Clinical Study Protocol shall prevail with

respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between PRA, on behalf of AstraZeneca, and the PI must be in place before any study-related procedures can take place, or subjects are enrolled.

9.1.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.2 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 is expected to start in Quarter 2, 2015 and to end by Quarter 3, 2018.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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.

9.3 Data management

Data management will be performed by PRA, according to the Clinical Informatics Plan.

The PRA Datalabs system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the CRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and the provision of answers to data queries according to the CSA. The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the PRA coding group. 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 Clinical Informatics Plan and Edit Specifications Document. 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 Clinical Informatics 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 reconciliation

Serious adverse event reconciliation reports are produced and reconciled with the subject safety database and/or the investigational site. SAE reconciliation between safety data and clinical data will be performed by PRA. The frequency depends on the expected volume of SAE reports and will be defined in the AE/SAE Reconciliation Plan.

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 Subject 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 EC 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 subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca or designee before enrolment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca or designee 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 EC annually.

Before enrolment of any subject 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 or designee will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or designee will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca or designee will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each centre will:

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

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International coordinating Investigator and AstraZeneca or designee.

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 EC and if applicable, the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca or designee will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to the ECs, see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca or designee and the centre's EC 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 EC.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, 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, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca or designee immediately if contacted by a regulatory agency about an inspection at the centre.

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