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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT number: 2014-004633-96

AstraZeneca Research and Development site representative

[redacted]

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Date

[redacted]

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	03 June 2015
02	01 February 2016		
03	23 March 2016		
04	18 May 2016		
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 Two Doses of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

International Coordinating Investigator

[redacted]

Study site(s) and number of subjects planned

Approximately 450 subjects are planned at approximately 173 sites.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2015	3
Estimated date of last subject completed	Q2 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 treatment regimen of anifrolumab (150 mg or 300 mg) 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 450 subjects receiving SOC treatment will be randomised in a 1:2:2 ratio to receive a fixed intravenous dose of 150 mg anifrolumab, 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 intravenous (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 300 mg compared to placebo on disease activity as measured by the difference in the proportion of subjects who achieve an SLE Responder Index of ≥4 (SRI[4]) at Week 52	Composite endpoint SRI(4), defined by the following criteria: - Reduction from baseline of ≥4 points in the SLEDAI-2K and - No new organ system affected as defined by 1 or more British Isles Lupus Assessment Group (BILAG)-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004 and - No worsening from baseline in subjects' lupus disease activity defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS) and - No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold[a] before assessment
Key Secondary Objectives:	**Outcome Measures:**
To evaluate the effect of anifrolumab 300 mg compared to placebo on:	
The proportion of subjects with SRI(4) at Week 52 in the IFN test-high sub-group	SRI(4) (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 sub-group of subjects with baseline OCS ≥10 mg/day	Maintained OCS reduction defined by the following criteria: - Achieve an OCS dose of ≤7.5 mg/day prednisone or equivalent by Week 40 and - Maintain an OCS dose ≤7.5 mg/day prednisone or equivalent from Week 40 to Week 52 and - No discontinuation of investigational product or 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 sub-group of subjects with baseline CLASI activity score ≥10	50% reduction in CLASI activity score compared to baseline defined by the following criteria: - Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline and - No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with SRI(4) at Week 24	SRI(4) (see outcome measure for primary objective)
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
Other Secondary Objectives:	**Outcome Measures:**
To evaluate the effect of anifrolumab 150 mg compared to placebo on disease activity as measured by the difference in the proportion of subjects who achieve SRI(4) at Week 52	SRI(4) (see endpoint for primary objective)
To assess the difference between anifrolumab 300 mg and placebo on measures of disease activity including levels of SRI response other than 4, British Isles Lupus Assessment Group - based Composite Lupus Assessment (BICLA), the individual components of SRI, and the number of swollen and tender joints at Week 52, as well as SRI and BICLA over time	SRI(4), SRI(5), SRI(6), SRI(7), SRI(8), BICLA response, BILAG-2004, SLEDAI-2K, PGA, Major Clinical Response, Partial Clinical Response, and joint count
To assess the difference between anifrolumab 300 mg and placebo on measures of organ damage, ie, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) at Week 52	SDI

To assess the difference between anifrolumab 300 mg and placebo on subject-reported health status, health-related quality of life (QoL), and other subject-reported outcome measures of fatigue, pain, patient global assessment, and work productivity at Week 52	Short Form 36 version 2 (acute recall) (SF-36v2 [acute]), Pain numeric rating scale (NRS), Functional Assessment of Chronic Illness Therapy-FATIGUE (FACIT-F), Patient Global Assessment (PtGA), Lupus QoL, EuroQoL 5 dimensions (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI)-Lupus, and Medical Resource Use Questionnaire
To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamics of anifrolumab	Anifrolumab concentration and PK parameters, anti-drug antibodies (ADA), 21-gene type I IFN gene signature, anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, third component (C3), fourth component (C4), and total haemolytic (CH50) complement levels
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
[redacted]	[redacted]
[redacted]	[redacted]

[a] Allowed medication is described in Section 3.3.

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 450 subjects receiving SOC treatment will be randomised in a 1:2:2 ratio to receive a fixed IV dose of anifrolumab or placebo, as follows:

- Anifrolumab (MEDI-546) 150 mg IV administration Q4W OR
- Anifrolumab (MEDI-546) 300 mg IV administration Q4W OR
- Placebo IV administration Q4W

Statistical methods

The primary estimand of interest is the difference in change from baseline in disease activity between anifrolumab 300 mg and placebo, to reflect the effect of the initially assigned and dosed investigational product. This is measured by the primary efficacy endpoint, defined as the difference in the proportion of subjects achieving SRI(4) at Week 52. 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).

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. The primary endpoint is the difference in proportions of subjects achieving SRI(4) at Week 52 comparing anifrolumab 300 mg to placebo. With assumed proportions of SRI(4) of 39% and 63% in the placebo and anifrolumab 300 mg groups, respectively (based on the observed results in the interim analyses of study CD-IA-MEDI-546-1013), 180 subjects/arm yields more than 99% power to reject the hypothesis of no difference using a 2-sided alpha of 0.05. The minimal detectable difference in SRI(4) between anifrolumab 300 mg versus placebo is approximately 10% with this sample size. With half of the sample size (ie, 90 subjects) for the anifrolumab 150 mg treatment group, a 12.5% difference in SRI(4) between anifrolumab 150 mg versus placebo would be associated with a nominal p-value of 0.05.

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.

A non-responder imputation method will be used for the handling of missing data and is incorporated into the definition of the primary endpoint. Subjects who discontinue from treatment and/or the study for any reason, as well as subjects who require restricted medications beyond the protocol-allowed threshold, will be imputed as failures.

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.

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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
EQ-5D-5L	EuroQoL 5 dimensions
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-FATIGUE
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
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
nAb	Neutralising antibodies
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCS	Oral corticosteroids
PD	Pharmacodynamic
PGA	Physician’s Global Assessment
PHQ-8	Personal Health Questionnaire Depression Scale-8
PI	Principal Investigator
PIP	Proximal interphalangeal
PK	Pharmacokinetic(s)
PtGA	Patient Global Assessment
PVC	Polyvinyl chloride
Q4W	Every 4 weeks

Abbreviation or special term	Explanation
QFT-G	QuantiFERON-TB Gold
QoL	Quality of life
RGQ	Rotor-Gene Q
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SF-36v2 (acute)	Short Form 36 version 2 (acute recall)
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SMR	Standardised mortality ratio
SOC	Standard of care
SRI(4)	Systemic Lupus Erythematosus Responder Index of ≥4
TB	Tuberculosis
ULN	Upper limit of normal
VAS	Visual analogue scale
WPAI	Work productivity and Activity Impairment

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 anifrolumab (150 mg or 300 mg) 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 doses 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 Appendix E) 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 who achieve Systemic Lupus Erythematosus Responder Index of ≥4 (SRI[4]) at Week 52. This endpoint was employed as the primary endpoint in both pivotal studies of a large phase 3 program (Furie et al, 2009, Navarra et al, 2011, Wallace et al, 2009) in SLE and provided the basis for regulatory approvals of belimumab.

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. A dose of 150 mg is evaluated in this study to provide supportive evidence that 300 mg is the minimum effective dose of anifrolumab.

1.2.4 Rationale for duration of infusion

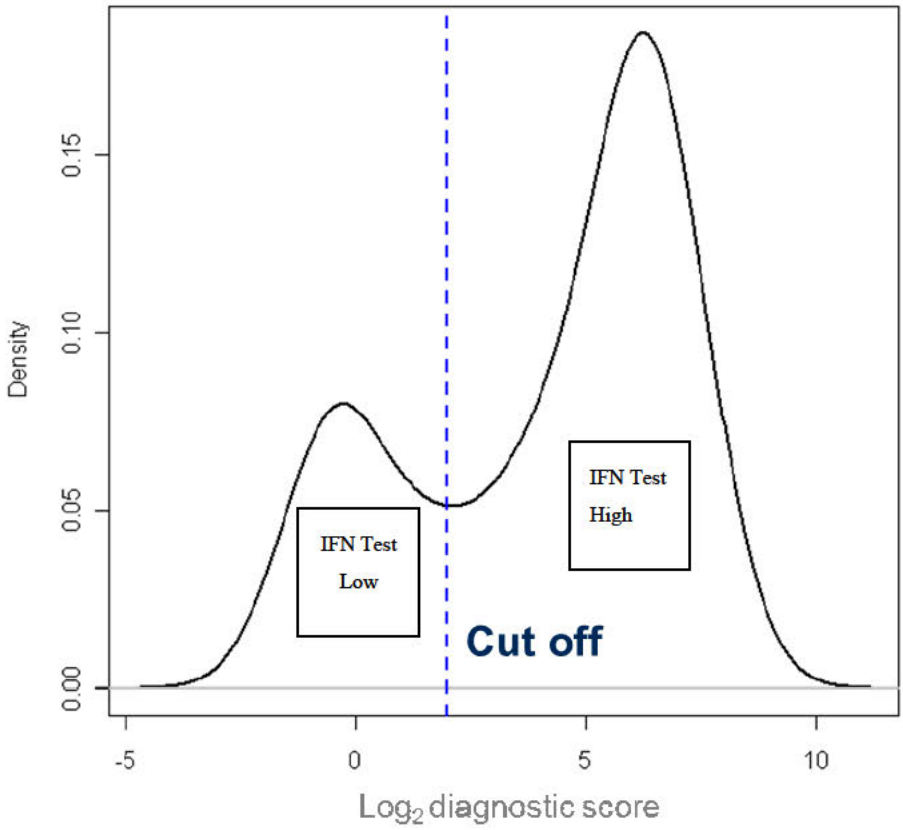
In a Phase 2b study where 2 doses of anifrolumab in combination with SOC (300 mg and 1000 mg) were compared to placebo, combined with SOC, all doses were administered over approximately 60 minutes. The frequency of infusion-related reactions did not differ substantially between the 300 mg (2.0%) and 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 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 D3461C00001 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

a British Isles Lupus Assessment Group (BILAG)-2004 based combined lupus assessment (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 ([redacted]) 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 150 mg or 300 mg Q4W for 52 weeks. The 300 mg dose is 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 D3461C0005 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 anifrolumab (150 mg or 300 mg) 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 450 subjects receiving SOC treatment will be randomised in a 1:2:2 ratio to receive a fixed IV dose of 150 mg anifrolumab, 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, 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:

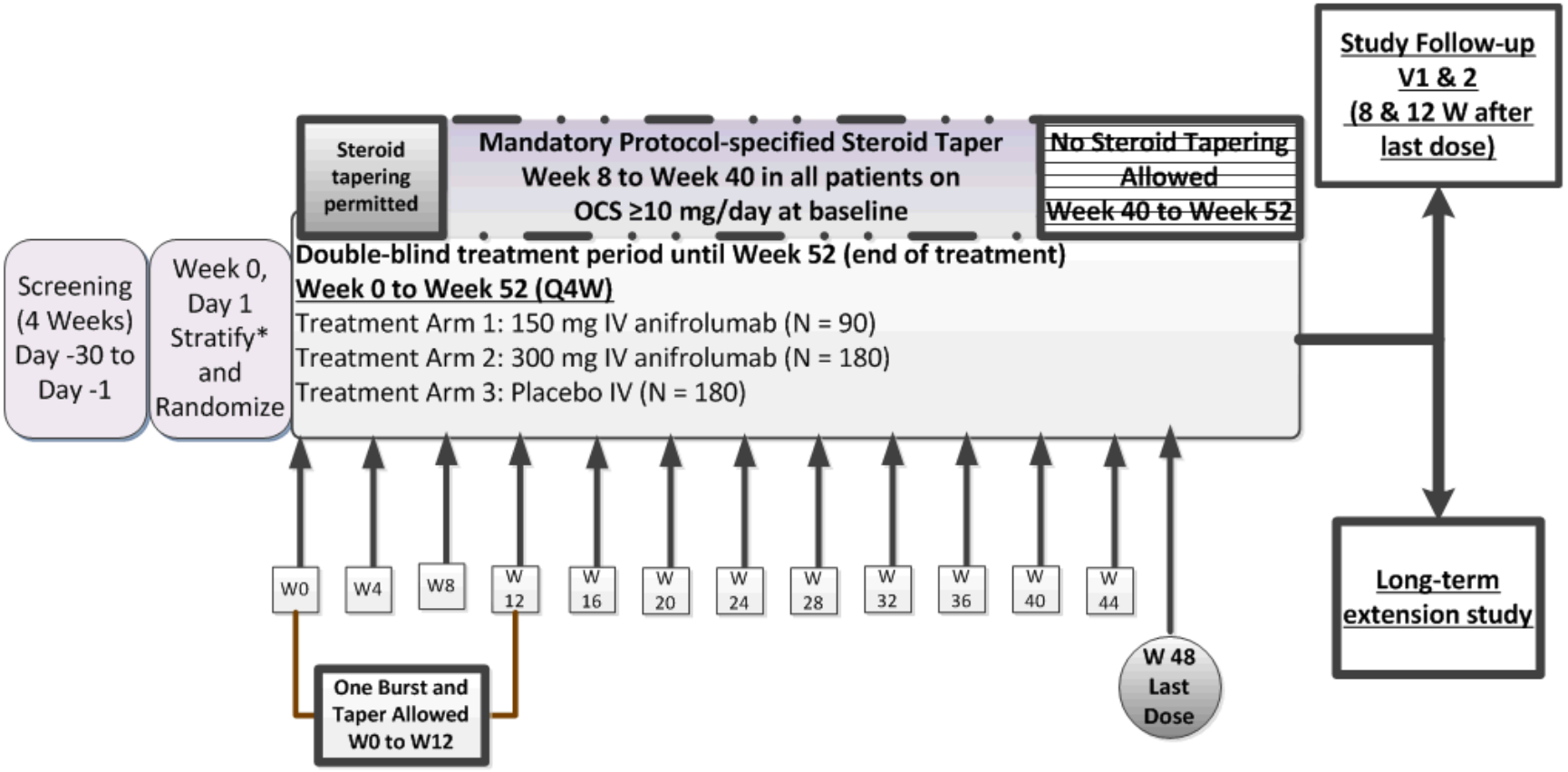
- SLEDAI-2K activity which is worsened compared to baseline in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever, thrombocytopenia, or haemolytic anaemia, or gastrointestinal activity)
- Newly-affected organ system(s) based on the SLEDAI-2K, excluding serological abnormalities (dsDNA 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 Appendix V, 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. Subjects who require OCS dose above their baseline level may continue in the study but will be considered non-responders for subsequent assessments of disease activity.

Steroid tapering will not be permitted after Week 40.

Figure 2 Study flow chart



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 300 mg compared to placebo on disease activity as measured by the difference in the proportion of subjects who achieve an SLE Responder Index of ≥4 (SRI[4]) at Week 52	Composite endpoint SRI(4), defined by the following criteria: - Reduction from baseline of ≥4 points in the SLEDAI-2K and - No new organ system affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004 and - No worsening from baseline in subjects' lupus disease activity defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS) and - No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold[a] before assessment

[a] Allowed medication is described in Section 3.3.

2.2 Secondary objectives

Key Secondary Objectives:	Outcome Measures:
To evaluate the effect of anifrolumab 300 mg compared to placebo on:	
The proportion of subjects with SRI(4) at Week 52 in the IFN test-high sub-group	SRI(4) (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 sub-group of subjects with baseline OCS ≥10 mg/day	Maintained OCS reduction defined by the following criteria: - Achieve an OCS dose of ≤7.5 mg/day prednisone or equivalent by Week 40 and - Maintain an OCS dose ≤7.5 mg/day prednisone or equivalent from Week 40 to Week 52 and - No discontinuation of investigational product or 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 sub-group of subjects with baseline CLASI activity score ≥10	50% reduction in CLASI activity score compared to baseline defined by the following criteria: - Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline and - No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with SRI(4) at Week 24	SRI(4) (see outcome measure for primary objective)
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
Other Secondary Objectives:	**Outcome Measures:**
To evaluate the effect of anifrolumab 150 mg compared to placebo on disease activity as measured by the difference in the proportion of subjects who achieve SRI(4) at Week 52	SRI(4) (see endpoint for primary objective)
To assess the difference between anifrolumab 300 mg and placebo on measures of disease activity including levels of SRI response other than 4, British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA), the individual components of SRI, and the number of swollen and tender joints at Week 52, as well as SRI and BICLA over time	SRI(4), SRI(5), SRI(6), SRI(7), SRI(8), BICLA response, BILAG-2004, SLEDAI-2K, PGA, Major Clinical Response, Partial Clinical Response, and joint count
To assess the difference between anifrolumab 300 mg and placebo on measures of organ damage, ie, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) at Week 52	SDI
To assess the difference between anifrolumab 300 mg and placebo on subject-reported health status, health-related QoL, and other subject-reported outcome measures of fatigue, pain, patient global assessment, and work productivity at Week 52	Short Form 36 version 2 (acute recall) (SF-36v2 [acute]), Pain numeric rating scale (NRS), Functional Assessment of Chronic Illness Therapy-FATIGUE (FACIT-F), Patient Global Assessment (PtGA), Lupus QoL, EuroQoL 5 dimensions (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI)-Lupus, and Medical Resource Use Questionnaire
To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamics of anifrolumab	Anifrolumab concentration and PK parameters, anti-drug antibodies (ADA), 21-gene type I interferon (IFN) gene signature, anti-dsDNA antibodies, C3, fourth component (C4), and total haemolytic (CH50) complement levels

[a] Allowed medication is described in Section 3.3

2.3 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of anifrolumab	Adverse events (including adverse events of special interest [AESI]), 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)

2.4 Exploratory objective

Exploratory Objective:	Outcome Measures:
[redacted]	[redacted]

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 standard of care 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 standard of care 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 Appendix V for examples of prednisone equivalency

8. Fulfils at least 4 of the 11 ACR modified 1982 classification criteria for SLE (see Appendix D), 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 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 greater than the central laboratory value of post-menopausal 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 Appendix X 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 child-bearing 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 Appendix W)

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 standard of care 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 Appendix V for examples of prednisone equivalency)

(b) Where prednisone is not the single standard of care 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 informed consent form through Day 1, OR any change in/ discontinuation of current oral prednisone dose (or equivalent) anytime within the 2 weeks prior to randomisation (see Appendix V 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 Appendix U)

12. Prior receipt of anifrolumab

13. Receipt of any commercially available biologic agent within 5 half-lives (see Appendix U) 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 Appendix U)
- 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 Appendix U 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 Appendix T). 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 intravenous 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 Appendix U (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 [redacted] Medical Monitor immediately. The [redacted] Medical Monitor will determine with the Sponsor if the subject may continue to receive investigational product, however, the subject would be considered a non-responder.

(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 standard of care 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 minimized. 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)
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, 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.

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. 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 [redacted] Medical Monitor. The [redacted] 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 Appendix V, 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 will be considered non-responders for subsequent assessments of disease activity.

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.

Post-operative 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 '[redacted]'.

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 1:2:2 ratio to receive a fixed IV dose of 150 mg anifrolumab, 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 [redacted] 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 non-compliance 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 [redacted] 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), 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; prioritized 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 [redacted]	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]
Joint count	X [i]
TB questionnaire	X

Study Period	Screening
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 Appendix U]) 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] Coombs will be performed as applicable per BILAG assessment requirements.

[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**
PtGA, FACIT-F, Pain NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-8	X			X			X			X				X
SF-36v2 (acute)	X		X		X		X		X		X		X	X
LupusQoL, EQ-5D-5L	X			X			X			X				X
WPAI-Lupus	X			X			X			X				X
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
PK blood sample (predose)	X			X			X			X			X	X
PK blood sample (postdose) [i]	X												X	
Immunogenicity blood sample (predose) [j]	X			X			X			X			X	X
Proteomics/ biomarker blood and urine sample	X			X			X			X				X
SLEDAI-2K associated laboratory tests [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Type I IFN signature with 21-gene signature (PD marker)	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**
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
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	
SDI	X						X							X
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			
Medical Resource Use Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X
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

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**
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X													
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); dsDNA = double stranded deoxyribonucleic acid; ECG = electrocardiogram; EDV = Early Discontinuation Visit; FACIT-F = Functional Assessment of Chronic Illness Therapy-FATIGUE; IFN = interferon; NRS = numeric rating scale; PD = pharmacodynamic; PGA = Physician's Global Assessment; PHQ-8: Personal Health Questionnaire Depression Scale-8; PK = pharmacokinetic; SAE = serious adverse event; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis

[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] Post-dose PK samples should be drawn 15 minutes ±5 minutes after the completion of investigational product administration.

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

[k] SLEDAI-2K associated laboratory tests are C3, C4, CH50 complement, anti-dsDNA antibodies, urine protein/creatinine ratio.

[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 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		
EQ-5D-5L, Pain NRS,SF-36v2 (acute), FACIT-F, WPAI		X
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
PK blood sample	X	X
Immunogenicity blood sample		X
Proteomics/biomarkers blood and urine sample		X
TB questionnaire	X	X
Type I IFN signature with 21-gene assay (PD marker)		X
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

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		
Joint count	X	X
Medical Resource Use Questionnaire	X	X
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; EQ-5D-5L = EuroQoL 5 dimensions; FACIT-F = Functional Assessment of Chronic Illness Therapy-FATIGUE; IFN = interferon; NRS = numeric rating scale; PD = pharmacodynamic; PGA = Physician's Global Assessment; PHQ-8 = Personal Health Questionnaire Depression Scale-8; PK = pharmacokinetic; SAE = serious adverse event; SF-36v2 (acute) = Short Form 36 version 2 (acute recall); SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis; VAS = visual analogue scale; WPAI = Work productivity and Activity Impairment

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

[c] BILAG-2004 laboratory tests to include 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 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 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

[redacted] 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 Appendix E) consists of a list of organ manifestations, each with a definition. A certified Investigator or designated physician will complete the SLEDAI-2K assessment and decide whether each manifestation is "present" or

"absent" in the last 4 weeks. The assessment also includes the collection of blood and urine for assessment of the laboratory categories of the SLEDAI-2K.

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

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

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

5.2.4 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 Appendix F). It has ordinal scales by design and does not have a global score; rather it records disease activity across the different organ systems at a glance by comparing the immediate past 4 weeks to the 4 weeks preceding them. It is based on the principle of physicians' intention to treat and 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.

5.2.5 Physician Global Assessment

A trained and certified Investigator will complete the PGA (see Appendix G). The PGA represents the physician's overall assessment of average SLE disease severity on a VAS scale

with 0 (no disease) to 3 (severe) disease activity over the last 4 weeks. The PGA for a given 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.

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

The SDI has been developed to assess irreversible damage in SLE subjects independently of its cause (SLE activity, therapy, comorbidities) but occurring after disease onset (see Appendix H). Damage, ie, irreversible impairment since onset of SLE is usually defined as a clinical feature that has to be continuously present for at least 6 months to score. In addition some irreversible events such as MI or a cerebrovascular accident score as damage on their occurrence. Briefly, damage is defined for 12 organ systems; peripheral vascular, ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, endocrine (diabetes), gonadal, and malignancies. Damage over time can be stable or increase, to a maximum of 47 points, however there should be no decrease in the number of points (Schwartz et al, 2009).

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 Appendix I). 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.

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 Appendix X 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 Appendix J).

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 Appendix K). 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 standard of care) 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 1 time 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.

[redacted]

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 Appendix C, 'Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

The following laboratory variables will be measured:

Table 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; C3 = third component of complement; C4 = fourth component of complement; CH50 = total haemolytic complement; 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 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).

5.4.1 Pharmacokinetics

For the PK analysis it is important that the date, start and stop time for the IV infusion, and the sample collection time are recorded. Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centres. Serum will be collected according to the Study Plan (Table 3 and Table 4). Post-dose samples should be collected 15 minutes ±5 minutes after completion of investigational product administration after dosing on Week 0 (Day 1) and Week 48. Post-dose specimens should not be drawn through the IV line used to administer the investigational product.

Samples for determination of anifrolumab concentration in serum will be analysed by a central laboratory on behalf of the Sponsor, using a validated bioanalytical method.

5.4.2 Immunogenicity

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

5.4.2.1 Anti-drug antibodies

The pre-dose serum samples to measure presence of ADA will be collected according to the Study Plan (Table 3 and Table 4). The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. In order to help understand the potential drug-relatedness of any hypersensitivity or anaphylaxis reaction, possible additional ADA testing (if not already scheduled for a visit) may be collected and analysed.

5.4.2.2 Neutralising antibodies

Neutralising antibodies testing will only occur on samples that are ADA positive. Samples that are ADA negative will not be tested for nAb. The presence or absence of neutralising ADA will be determined using a validated bioanalytical method.

5.4.3 Pharmacodynamics

Type I IFN inducible signature in whole blood will be assessed by a 21-gene assay to be used as a PD marker to follow the biologic effect of anifrolumab on its target throughout the study. Whole blood will be collected for RNA isolation at the visits indicated in the Study Plan (Table 2, Table 3, and Table 4) in order to evaluate the mRNA expression levels of 21 type I IFN-inducible genes. The remaining mRNA from the PD sample may be utilised for additional biomarker work to further characterise the effects of anifrolumab on its target.

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 Proteomics/biomarkers

Renal disease develops in more than half of SLE subjects. However, the onset of lupus nephritis is commonly insidious and thus, early diagnosis and treatment of lupus nephritis are difficult. Many studies have shown the presence of inflammatory proteins in the urine of lupus nephritis subjects and the correlation of such proteins with disease severity/activity and/or histological results. However, there are very few studies that have evaluated the differences in urine proteomics between subjects with active lupus nephritis requiring treatment and subjects with either minimal or inactive renal disease. Understanding how anifrolumab impacts on urine proteomics should expand our insights regarding the effects of anifrolumab on the kidney in subjects with SLE.

Urine samples will be collected according to the time points outlined in the Study Plan (Table 3 and Table 4). Approximately 30 to 40 mL of urine will be collected from each subject at the specified visits. Baseline urine samples will be used to assess differences in protein analytes from control healthy donor samples by a variety of technical methodologies that may include: immunoassays, protein arrays, and biochemical approaches. Longitudinal alterations in SLE dysregulated proteins will be assessed in association with clinical characteristics and/or

response to treatment. Additionally, the results from the proteomic analyses will be compared to those obtained from urine samples of lupus nephritis subjects.

Plasma will be collected for correlative studies during visits specified in the Study Plan (Table 3 and Table 4). These studies will include proteins, peptides and immune complexes and will be conducted using immunoassays, in vitro assays, and/or biochemical approaches. The data from these studies will be reported in separate research reports.

5.4.6 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.

5.5 Quality of life/pharmacoeconomic assessments

Quality of life and pharmacoeconomic assessments will be made at the times indicated in the Study Plan (Table 2, Table 3, and Table 4). Subject-reported outcome assessments should be completed by the subject, unassisted by spouse, family members or friends.

Subjects will be completing the following subject-reported questionnaires to assess treatment effects.

5.5.1 Short Form 36 version 2 (acute recall)

The SF-36-v2 (acute) is a multipurpose, 36-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health (see Appendix L). It yields scale scores for each of these 8 health domains, and 2 summary measures of physical and mental health: the Physical Component Summary and Mental Component Summary.

5.5.2 Functional Assessment of Chronic Illness Therapy–FATIGUE

The FACIT-F is a 13-item subject-completed questionnaire to assess the impact of fatigue over the previous 7 days (see Appendix M). The responses range from 0 (Not at All) to 4 (Very Much). Final scores are the sum of the responses and range from 0 to 52; higher scores indicate better QoL (Yellen et al, 1997). Changes in scores >3 points are considered to be clinically meaningful (Cella et al, 2002).

5.5.3 EuroQoL 5 dimensions

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

5.5.4 Lupus Quality of Life

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

5.5.5 Patient Global Assessment

Subjects will be asked to complete the PtGA (see Appendix P). The PtGA is a single-item question that takes into account all the ways in which illness and health conditions may affect the patient at this time. The patient should consider the previous week when answering this question. Responses range from very well to very poor on a 100 mm VAS. The physician and subject must complete the PGA and PtGA, respectively, independently of each other.

5.5.6 Work productivity and Activity Impairment

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

5.5.7 Medical Resource Use Questionnaire

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

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

5.5.8 Pain numerical rating scale

Overall subject-reported pain will be captured with an 11-point NRS (0 no pain; worst imaginable) with a 1 week recall period (see Appendix R).

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 Appendix B.

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 Appendix C 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 [redacted] 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 [redacted] 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 Appendix Y 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 characterized 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 (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 IP.

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 characterized 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 Appendix T 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 Appendix B.

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. [redacted] 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 [redacted] Safety Management within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

[redacted] 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 [redacted] 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 [redacted] an automated email alert is sent to the designated [redacted] and AstraZeneca representative(s).

If the [redacted] is not available, then the Investigator or other study site personnel reports the SAE to [redacted] 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.

[redacted] **Safety Management contact information for SAE reporting:**

[redacted]

[redacted], 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. [redacted] 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 [redacted] 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 recognized medical term or diagnosis that accurately reflects the event).

The reporting period for AESIs is the period immediately following the time that written informed consent is obtained through the end of 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 Appendix Y.

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 on-going basis by AstraZeneca representatives in consultation with [redacted] 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, B, and C). 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

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

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 150 mg, 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 [redacted] 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 post-dose 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)
- Samples for PK laboratory assessments should be collected 15 ±5 minutes after completion of investigational product administration after dosing on Week 0 (Day 1) and Week 48

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 Statistical Analysis Plan (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 450 subjects receiving SOC treatment will be randomised 1:2:2 to treatment with 150 mg anifrolumab, 300 mg anifrolumab, or placebo.

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. The primary endpoint is the difference in proportions of subjects achieving SRI(4) at Week 52 comparing anifrolumab 300 mg to placebo. With assumed proportions of SRI(4) of 39% and 63% in the placebo and anifrolumab 300 mg groups, respectively, 180 subjects/arm yields more than 99% power to reject the hypothesis of no difference using a 2-sided alpha of 0.05. The minimal detectable difference in SRI(4) between anifrolumab 300 mg versus placebo is approximately 10% with this sample size.

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 sub-groups 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:

- Difference in proportions of subjects achieving SRI(4) at Week 52 in the IFN test high sub group: Given 75% of subjects are IFN test-high; proportions of SRI(4) in the IFN test-high subgroup of 35% and 61% in the placebo and anifrolumab treatment groups, respectively; a 2-sided alpha of 0.04 yields 98% power.
- Difference in proportion of subjects who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the sub-group 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 anifrolumab 150 mg treatment group will be subject to a secondary analysis to inform the benefit:risk profile for anifrolumab. With half of the sample size (ie, 90 subjects) for the anifrolumab 150 mg treatment group, a 12.5% difference in SRI(4) between anifrolumab 150 mg versus placebo would be associated with a nominal p-value of 0.05. The evaluation of anifrolumab 150 mg is outside of the formal multiplicity testing strategy.

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.

8.3 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.

8.3.3 Pharmacokinetic analysis set

All subjects who received anifrolumab and who had at least 1 quantifiable serum PK observation post first dose, will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

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 300 mg compared to placebo on disease activity is the difference in proportion of subjects achieving SRI(4) at Week 52, where a subject achieves SRI(4) if all of the following criteria are met:

- Reduction from baseline of ≥4 points in the SLEDAI-2K;
- No new organ system affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004;
- No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold before assessment. Allowed medication is defined in Section 3.3.

8.4.2 Key secondary outcome variables

8.4.2.1 Systemic Lupus Erythematosus Responder Index of ≥4 at Week 52 in interferon test-high subjects

The key secondary endpoint used to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity in the IFN test-high subgroup is the difference in proportions of subjects achieving SRI(4) at Week 52 in subjects classified as IFN test-high. SRI(4) 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 300 mg 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 proportions 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 or use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 3.3).

8.4.2.3 Skin lesions

The key secondary endpoint used to evaluate the effect of anifrolumab 300 mg versus placebo on inflammatory cutaneous lupus lesions in subjects with baseline CLASI activity score ≥10 is the difference in proportions of subjects who meet the following criteria:

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

8.4.2.4 Systemic Lupus Erythematosus Responder Index of ≥4 at Week 24

The key secondary endpoint used to evaluate the early effect of anifrolumab 300 mg compared to placebo on disease activity is the difference in proportions of subjects achieving SRI(4) at Week 24. SRI(4) is defined in Section 8.4.1.

8.4.2.5 Flares

The key secondary endpoint used to evaluate the effect of anifrolumab 300 mg 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).

8.4.3 Other secondary outcome variables

8.4.3.1 Assessment of disease activity

SRI(4) of anifrolumab 150 mg treatment group

The effect of anifrolumab 150 mg compared to placebo on disease activity will be assessed by the difference in proportions of subjects achieving SRI(4) at Week 52. SRI(4) is defined in Section 8.4.1.

Supportive SRI endpoints

In addition to the endpoint described in Section 8.4.1, the difference between anifrolumab 300 mg and placebo in SRI at Week 52 will be assessed using levels other than 4, ie, SRI(5), SRI(6), SRI(7), and SRI(8), where SRI(X) (X=5, 6, 7, or 8) is defined by the proportion of subjects who meet the following criteria:

- Reduction from baseline of ≥X points in the SLEDAI-2K;
- No new organ systems affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004;
- No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 3.3).

The difference between anifrolumab and placebo in the proportion of subjects achieving SRI(X), X=4, 5, 6, 7, or 8 will also be assessed longitudinally over time up to Week 52.

BICLA

The effect of anifrolumab 300 mg versus placebo on disease activity will also be assessed using the difference in proportion of subjects meeting the criteria for BICLA response at Week 52, where a subject is a BICLA responder if 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 more than 1 new BILAG-2004 B item;
- No worsening from baseline in SLEDAI-2K as defined as an increase from baseline of >0 points in SLEDAI-2K;
- No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 3.3).

The difference between anifrolumab 300 mg and placebo in the proportion of subjects achieving BICLA will also be assessed longitudinally over time up to Week 52.

Supportive outcome variables of the Individual components of SRI and BICLA

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

Further, the effect of anifrolumab 300 mg versus placebo on PGA will be evaluated using the difference in mean change in PGA from baseline longitudinally over time to Week 52. In addition, the effect of anifrolumab 300 mg versus placebo on Major Clinical Response and Partial Clinical Response will be evaluated where these endpoints are defined as:

- Difference in proportion of subjects who achieve Major Clinical Response, ie, a subject with BILAG-2004 C scores or better at Week 24 with no new BILAG-2004 A or BILAG-2004 B scores and maintenance of response with no new BILAG-2004 A or B scores between Week 24 and Week 52.
- Difference in proportion of subjects who achieve Partial Clinical Response, ie, a subject with a maximum of 1 BILAG-2004 B score or better at Week 24 and maintenance of response without a new BILAG-2004 A or more than 1 new BILAG-2004 B item out to Week 52.

Active, swollen and tender joints

The endpoints used to evaluate the effect of anifrolumab 300 mg versus placebo on active, swollen, and tender 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 8 swollen and at least 8 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 50% reduction from baseline in both the number of swollen and tender joints at Week 52.

Change in SDI

The endpoint used to evaluate the effect of anifrolumab 300 mg versus placebo on irreversible damage in SLE subjects is the difference in mean change in SDI global score from baseline to Week 52.

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 300 mg 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 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*.

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.

8.4.4 Subject reported outcome variables

8.4.4.1 Short Form 36 version 2 (acute recall)

The difference between anifrolumab 300 mg and placebo in the mean change from baseline in SF-36v2 (acute) Physical Component Score and Mental Component Score to Week 52 will be assessed.

8.4.4.2 Pain Numerical Rating Scale

The difference between anifrolumab 300 mg and placebo in the mean change from baseline in pain NRS to Week 52 will be assessed.

8.4.4.3 Functional Assessment of Chronic Illness Therapy-FATIGUE

The difference between anifrolumab 300 mg and placebo in the mean change from baseline in FACIT-F total score to Week 52 will be assessed.

8.4.4.4 Patient Global Assessment

The difference between anifrolumab 300 mg and placebo in the mean change from baseline in PtGA (measured on a VAS ranging from 0 to 100mm) to Week 52 will be assessed.

8.4.4.5 LUPUS quality of life scale

The difference between anifrolumab 300 mg and placebo in the mean change from baseline in LUPUS QoL score to Week 52 will be assessed.

8.4.4.6 EuroQoL 5 dimensions

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

8.4.4.7 Work productivity and Activity Impairment - Lupus

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

8.4.4.8 Medical Resource Use Questionnaire

The following endpoints will be explored:

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

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 [redacted] 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.

8.4.6 Immunogenicity variables

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

8.4.7 Pharmacokinetic variables

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed steady-state serum trough (predose) concentrations, C_{trough}. Maximum concentrations after the first and last dose will also be evaluated.

8.4.8 Pharmacodynamic outcome variables

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

The outcome variable for the suppression of the IFN 21 gene PD signature is the percent suppression of fold change, relative to a pooled normal control, from baseline levels.

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.

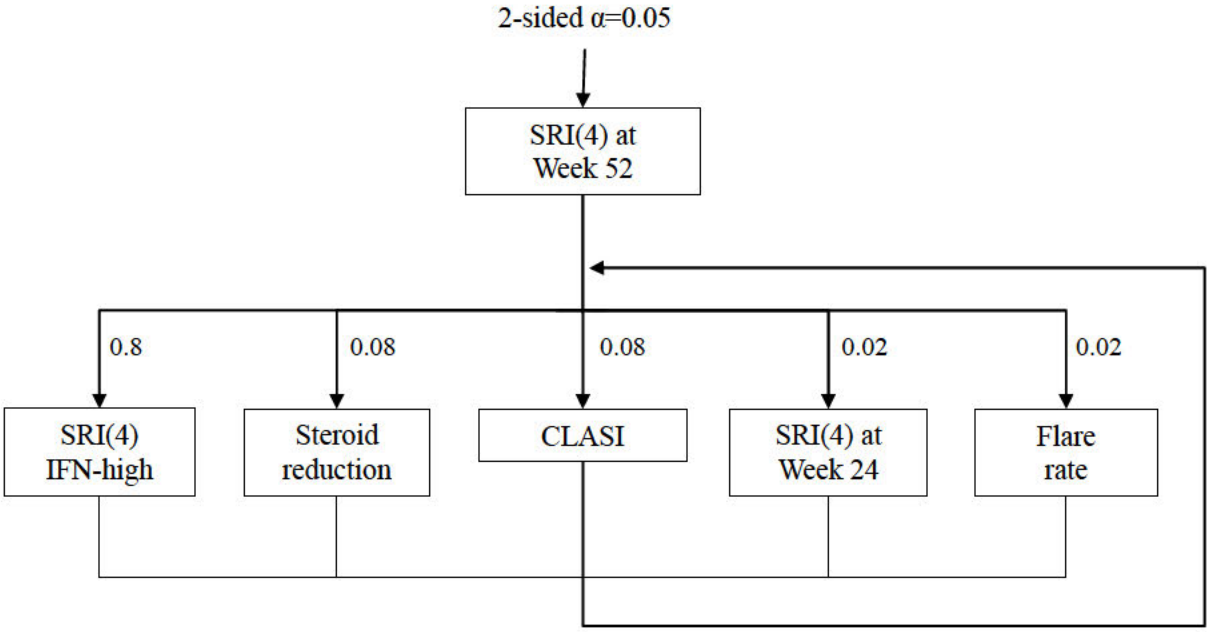
The comparison between the anifrolumab 300 mg and placebo treatment groups will be the main comparison for all outcome variables. In addition, the anifrolumab 150 mg data will be summarized.

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 proportion of subjects achieving SRI(4) 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 SRI(4) 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 a non-responder imputation 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 SRI-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 estimand of primary interest in this study is the difference in change from baseline in disease activity between anifrolumab 300 mg and placebo, to reflect the effect of the initially assigned and dosed investigational product (full analysis set). This is measured by the primary efficacy endpoint, defined as the difference in the proportion of subjects achieving SRI(4) at Week 52 comparing the anifrolumab 300 mg to the placebo group. The null hypothesis is that the proportion of subjects achieving SRI(4) on anifrolumab 300 mg is equal to that of placebo. The alternative hypothesis is that the proportion of subjects achieving SRI(4) on anifrolumab 300 mg is not equal to that on placebo, ie,

H0: difference in proportion achieving SRI(4) (anifrolumab vs Placebo) = 0
Ha: difference in proportion achieving SRI(4) (anifrolumab vs Placebo) ≠ 0

The proportion of subjects achieving SRI(4) in the anifrolumab 300 mg treatment group will be compared to that in the placebo group using a Cochran-Mantel-Haenszel (CMH) approach (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 300 mg 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.

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 SRI(4) endpoints will be summarised by treatment group.

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. Non-responder imputation will be used when applicable to handle missing data.

The flare rate in the anifrolumab 300 mg 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.

8.5.2.2 Analysis methods for other secondary efficacy variables

The difference between anifrolumab 150 mg and placebo in the proportion of subjects who achieve SRI(4) at Week 52 will be assessed and presented similarly to the primary endpoint as described in Section 8.5.1. The difference between anifrolumab 300 mg and placebo in other secondary binary responder endpoints will be assessed in the same way. In addition, the

individual components of the composite SRI and BICLA endpoints will be summarised by treatment group.

The time to first flare will be analysed as a supportive analysis to the assessment of reduction of flares to explore the extent to which treatment with anifrolumab 300 mg delays the time to first flare compared with placebo. A Cox proportional hazard model will be fitted to data including the covariates of treatment, and the stratification factors. Details will be presented in the SAP.

Continuous endpoints (including SLEDAI-2K, PGA, joint counts (active, swollen and tender), activity and damage CLASI scores, FACIT-F, PtGA, and LUPUS QoL Scale) will be analysed using linear mixed effect models with fixed effects for treatment group, visit, and stratification factors and subject as random effect. Results will be presented in terms of the adjusted means for each treatment group, estimates of treatment differences, and associated CIs. Model assumptions will be checked and, if not met, appropriate data transformations may be applied or non-parametric approaches will be considered. Details will be presented in the SAP.

The EQ-5D-5L health states (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems) will be summarised by visit and treatment group for each dimension. The VAS Score and single summary utility index as well as their change from baseline will also be summarised by visit and treatment group. The WPAI scores will be summarised as percentages by visit and treatment. Also, the improvements in these scores from baseline to Week 24 and Week 52 will be summarised. The medical resource use, as described in Section 8.4.4.8, will be summarised by visit and treatment.

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 summarized 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 summarized for each treatment group.

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

8.5.2.4 Analysis method for immunogenicity variables

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

8.5.2.5 Analysis methods for pharmacokinetic variables

Anifrolumab serum concentrations will be summarised using descriptive statistics at each visit by treatment group. Serum concentration-time profiles of anifrolumab by treatment group will be generated. The potential influence of demographic covariates such as body weight, race, gender and age will be explored. Impact of ADA on PK will also be explored. Serum concentrations of anifrolumab, summary statistics, empirical covariate analysis results and PK profiles will be provided in the CSR or as an addendum to the CSR.

8.5.2.6 Analysis methods for pharmacodynamic variables

Pharmacodynamic variables will be summarised as appropriate.

8.5.3 Subgroup analysis

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

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- OCS dose at baseline (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
- IFN test (IFN test [high versus low])
- Gender
- Age (≥18 to 65 and ≥65 years)
- Geographic region
- Onset of disease (adult versus paediatric onset)
- BMI (≤35, >35 kg/m^2)
- Race

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

A pre-planned pooled analysis of SRI(4) at Week 52 in the IFN test-low subjects, pooling data from this study and its sister study, D3461C00004, will be carried out to characterise the disease activity in this population.

Similarly, pre-planned pooled analyses will be carried out to further support the evaluation of the key secondary endpoints assessing the effect of anifrolumab 300 mg on skin lesions, ability to reduce the OCS dose, and flares.

Details of these 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 [redacted] 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 2, 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 [redacted], according to the Clinical Informatics Plan.

The [redacted] 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 [redacted] 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 [redacted] 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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Clinical Study Protocol Appendix B

Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
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Appendix C
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with [redacted] clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥2xULN irrespective of an increase in alkaline phosphatase (ALP), at any point during the study following the start of study medication. The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3x ULN **and** TBL ≥2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3xULN

- AST ≥3xULN
- TBL ≥2xULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to [redacted] representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section 2 of this appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the subject meets PHL criteria (see Section 2 of this appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Immediately notify the [redacted] Medical Monitor representative who will then inform the AstraZeneca Medical and Safety Study Team within 1 business day.

Within 1 business day, the [redacted] Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data. Subsequent to this initial contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the [redacted] Medical Monitor
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the [redacted] Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

The [redacted] Medical Monitor will contact the Investigator to carry out actions as described in Section 4. The [redacted] Medical Monitor should contact the Investigator within 1 business day of seeing the PHL laboratory criteria in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate and should be notified within 1 business day of the [redacted] Medical Monitor having discussed data with the Investigator.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term ‘Hy’s Law’) according to AstraZeneca standard processes.

  – The ‘Medically Important’ serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of ‘related’ should be assigned.

If the [redacted] medical monitor cannot contact the site within 2 weeks of the PHL laboratory values being available to clarify details of the case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix D	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
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Appendix D
American College of Rheumatology Criteria for Systemic Lupus Erythematosus Classification

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis or pericarditis	a. Pleuritis--convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion **OR** b. Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria > 0.5 gm per day or > 3+ if quantitation not performed OR b. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	a. Seizures--in the absence of offending drugs or known metabolic derangement, eg, uremia, ketoacidosis, or electrolyte imbalance OR b. Psychosis--in the absence of offending drugs or known metabolic derangement, eg, uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	a. Hemolytic anemia with reticulocytosis OR b. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions OR c. Lymphopenia--< 1,500/mm^3 on ≥ 2 occasions OR d. Thrombocytopenia--< 100,000/mm^3 in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies based on: 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; 2) a positive test result for lupus anticoagulant using a standard method; or 3) a false-positive test result for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Item	Definition
Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug.

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Clinical Study Protocol Appendix E	
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Appendix E
Systemic Lupus Erythematosus Disease Activity Index 2000

Guidelines for Use of the SLEDAI 2K to Assess Disease Activity (Modified for assessment over one month)

Table 2. SLEDAI-2K data collection form

Study No.: _____ **Patient Name:** _____ **Visit Date:** _____

(Enter weight in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 28 days.)

Descriptor	Definition	Weight	Score
Seizure	Recent onset, exclude metabolic, infectious or drug causes.	8	
Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.	8	
Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.	8	
Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.	8	
Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.	8	
Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.	8	
CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.	8	
Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.	8	
Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).	4	
Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.	4	
Urinary casts	Heme-granular or red blood cell casts.	4	
Hematuria	> 5 red blood cells/high power field. Exclude stone, infection or other cause.	4	
Proteinuria	>0.5 gram/24 hours	4	
Pyuria	>5 white blood cells/high power field. Exclude infection.	4	
Rash	Inflammatory type rash.	2	
Alopecia	Abnormal, patchy or diffuse loss of hair.	2	
Mucosal ulcers	Oral or nasal ulcerations.	2	
Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.	2	
Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion or electrocardiogram or echocardiogram confirmation.	2	
Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory. Increased	2	
Increased DNA binding	DNA binding by Farr assay above normal range for testing laboratory.	2	
Fever	>38° C. Exclude infectious cause.	1	
Thrombocytopenia	<100,000 platelets / x10^9/L, exclude drug causes.	1	
Leukopenia	<3,000 white blood cells / x10^9/L, exclude drug causes.	1	
TOTAL SLEDAI SCORE			

Gladman, et al: J. Rheumatol. 29:288-291, 2002 with 28 day modification in Tourma et al: Lupus 19:49-50.

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Clinical Study Protocol Appendix F

Drug Substance	Anifrolumab (MEDI-546)
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Date	09 April 2015
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Appendix F
British Isles Lupus Assessment Group-2004

BILAG-2004 INDEX

Centre:_____ Date:_____ Initials/Hosp No:_____

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND** Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
***Y/N** Confirm this is due to SLE activity (Yes/No)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) **Y/N***
79. Diastolic blood pressure (mm Hg) value ( ) **Y/N***
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) **Y/N***
82. Urine albumin-creatinine ratio mg/mmol ( ) **Y/N***
83. Urine protein-creatinine ratio mg/mmol ( ) **Y/N***
84. 24 hour urine protein (g) value ( ) **Y/N***
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) **Y/N***
87. GFR (calculated) ml/min/1.73 m^2 ( ) **Y/N***
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) **Y/N***
91. Total white cell count (x 10^9/l) value ( ) **Y/N***
92. Neutrophils (x 10^9/l) value ( ) **Y/N***
93. Lymphocytes (x 10^9/l) value ( ) **Y/N***
94. Platelets (x 10^9/l) value ( ) **Y/N***
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 1/Sep/2009

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Revised Clinical Study Protocol Appendix G	
Drug Substance	Anifrolumab (MEDI-546)
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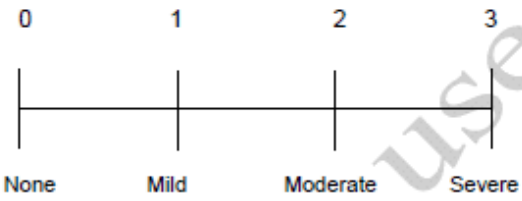
Appendix G
Physician Global Assessment

PHYSICIAN GLOBAL ASSESSMENT (PGA)



PGA Visual Analogue Scale Measurement = ____.____ inches (measure to the nearest 1/10 of an inch

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Revised Clinical Study Protocol Appendix H	
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Appendix H
System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

SLICC/ACR Damage Index

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

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

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)
Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996,39(3):363

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Clinical Study Protocol Appendix I

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Appendix I
Cutaneous Lupus Erythematosus Disease Area and Severity Index

Cutaneous LE Disease Area and Severity Index (CLASI)

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

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

Mucous membrane

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

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

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

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

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

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

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

Figure 1. The Cutaneous Lupus Erythematosus (LE) Disease Area and Severity Index instrument. Post indicates posterior; incl, includes.

study reflected a broad group of patients with CLE in terms of disease type, skin type, and therapy. To reflect different skin types, we decided to have at least 3 patients, but not more than 7 patients, with Fitzpatrick skin type V or VI, and at least 3 patients with Fitzpatrick skin type I, II, or III. A major inclusion criterion was a biopsy-proven CLE, with or without systemic involve-

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Clinical Study Protocol Appendix J	
Drug Substance	Anifrolumab (MEDI-546)
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Appendix J
Columbia Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted]*, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

AstraZeneca

Clinical Study Protocol Appendix K	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix K
Personal Health Questionnaire Depression Scale-8

STANFORD
PATIENT EDUCATION
RESEARCH CENTER

Personal Health Questionnaire Depression Scale (PHQ-8)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
*(circle **one** number on each line)*

How often during the past 2 weeks were you bothered by...	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Scoring

If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

Characteristics

Tested on 1165 subjects with chronic conditions.

No. of items	Observed Range	Mean	Standard Deviation	Internal Consistency Reliability	Test-Retest Reliability
8	0-24	6.63	5.52	.86	NA

Source of Psychometric Data

U.S. National Chronic Disease Self-Management Study. Study described in Ory MG, Ahn S, Jiang L, et al. National study of chronic disease self-management: six month outcome findings. Journal of Aging and Health. 2013 [in press].

Comments

This is an adaptation of the PHQ-9 scale. Since this scale is self-administered in our studies, question #9, "How often during the past 2 weeks were you bothered by thoughts that you would be better off dead, or of hurting yourself in some way?", was deleted. This scale available in Spanish.

References

Kroenke K, Strine TW, Spritzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009; 114(1-3):163-73.

Razykov I, Ziegelstein RC, Whooley MA, Thombs BD. The PHQ-9 versus the PHQ-8--is item 9 useful for assessing suicide risk in coronary artery disease patients? Data from the Heart and Soul Study. J Psychosom Res. 2012; 73(3):163-168.

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Stanford Patient Education Research Center
1000 Welch Road, Suite 204
Palo Alto CA 94304
(650) 723-7935
(650) 725-9422 Fax
self-management@stanford.edu
http://patienteducation.stanford.edu

Funded by the National Institute of Nursing Research (NINR)

AstraZeneca

Clinical Study Protocol Appendix L	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix L
Short Form 36 Version 2 (Acute Recall)

SF-36v2 Health Survey Single-Item Presentation Text Acute, United States (English)

Note: Item SF36v2_BP1 (Item #21) has 6 answers, not 5 answers; see entry for item at end of sheet for more detail.

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	Your Health and Well-Being						
		This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one box that best describes your answer.					
SF36v2_GH1	None	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
SF36v2_HT	None	Compared to one week ago, how would you rate your health in general now?	Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
SF36v2_PF01	The following question is about activities you might do during a typical day.	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF02	The following question is about activities you might do during a typical day.	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF03	The following question is about activities you might do during a typical day.	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF04	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF05	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF06	The following question is about activities you might do during a typical day.	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_PF07	The following question is about activities you might do during a typical day.	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF08	The following question is about activities you might do during a typical day.	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF09	The following question is about activities you might do during a typical day.	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF10	The following question is about activities you might do during a typical day.	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_RP1	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Cut down on the amount of time you spent on work or other activities as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP2	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Accomplished less than you would like as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP3	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Were limited in the kind of work or other activities as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP4	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE1	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE2	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE3	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_SF1	None	During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely
SF36v2_BP1	None	How much bodily pain have you had during the past week?	See end of document for answers #1-#6				

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_BP2	None	During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely
SF36v2_VT1	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week did you feel full of life?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH1	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you been very nervous?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH2	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you felt so down in the dumps that nothing could cheer you up?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH3	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT2	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH4	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT3	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week did you feel worn out?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH5	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you been happy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT4	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been	How much of the time during the past week did you feel tired?	All of the time	Most of the time	Some of the time	A little of the time	None of the time

(SF-36v2® Health Survey Single-Item Presentation Text Acute, United States (English))

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	feeling.						
SF36v2_SF2	None	During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_GH2	How TRUE or FALSE is the following statement for you?	I seem to get sick a little easier than other people.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH3	How TRUE or FALSE is the following statement for you?	I am as healthy as anybody I know.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH4	How TRUE or FALSE is the following statement for you?	I expect my health to get worse.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH5	How TRUE or FALSE is the following statement for you?	My health is excellent.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
		SF-36v2® Health Survey © 1992, 2000, 2010 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-36® is a registered trademark of Medical Outcomes Trust. (SF-36v2® Health Survey Acute, United States (English))					

Data for item SF36v2_BP1 (item #21 in the survey template)

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_BP1	None	How much bodily pain have you had during the past week?	None	Very mild	Mild	Moderate	Severe	Very severe

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Clinical Study Protocol Appendix M	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix M
Functional Assessment of Chronic Illness Therapy-FATIGUE

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

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Clinical Study Protocol Appendix N	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix N
EuroQoL 5 Dimensions

EQ-5D-5L	
EQ-5D-5L Tablet version	
English (USA)	Country (Language)
Health Questionnaire	Health Questionnaire
English version for the USA	Version (Target Language)
	Version (English)
Please tap the ONE box that best describes your health TODAY.	Instruction
MOBILITY	**Mobility**
I have no problems walking	MB1
I have slight problems walking	MB2
I have moderate problems walking	MB3
I have severe problems walking	MB4
I am unable to walk	MB5
SELF-CARE	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
PAIN / DISCOMFORT	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5
ANXIETY / DEPRESSION	**Anxiety / Depression**
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
This scale is numbered from 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health
Next	button.next
Previous	button.previous

Clinical Study Protocol Appendix O

Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix O
LupusQoL Questionnaire

The following questionnaire is designed to find out how SLE affects your life. **Read** each statement and then circle the response, which is **closest to how you feel**. Please try to answer all the questions as honestly as you can.

How often over the last 4 weeks

1. Because of my Lupus I need help to do heavy physical jobs such as digging the garden, painting and/or decorating, moving furniture
All of the time most of the time a good bit of the time occasionally never

2. Because of my Lupus I need help to do moderate physical jobs such as vacuuming, ironing, shopping, cleaning the bathroom
All of the time most of the time a good bit of the time occasionally never

3. Because of my Lupus I need help to do light physical jobs such as cooking/preparing meals, opening jars, dusting, combing my hair or attending to personal hygiene
All of the time most of the time a good bit of the time occasionally never

4. Because of my Lupus I am unable to perform everyday tasks such as my job, childcare, housework as well as I would like to
All of the time most of the time a good bit of the time occasionally never

5. Because of my Lupus I have difficulty climbing stairs
All of the time most of the time a good bit of the time occasionally never

6. Because of my Lupus I have lost some independence and am reliant on others
All of the time most of the time a good bit of the time occasionally never

7. I have to do things at a slower pace because of my Lupus
All of the time most of the time a good bit of the time occasionally never

8. Because of my Lupus my sleep pattern is disturbed
All of the time most of the time a good bit of the time occasionally never

How often over the last 4 weeks

9. I am prevented from performing activities the way I would like to because of pain due to Lupus
All of the time most of the time a good bit of the time occasionally never

10. Because of my Lupus, the pain I experience interferes with the quality of my sleep
All of the time most of the time a good bit of the time occasionally never

11. The pain due to my Lupus is so severe that it limits my mobility
All of the time most of the time a good bit of the time occasionally never

12. Because of my Lupus I avoid planning to attend events in the future
All of the time most of the time a good bit of the time occasionally never

13. Because of the unpredictability of my Lupus I am unable to organise my life efficiently
All of the time most of the time a good bit of the time occasionally never

14. My Lupus varies from day to day which makes it difficult for me to commit myself to social arrangements
All of the time most of the time a good bit of the time occasionally never

15. Because of the pain I experience due to Lupus I am less interested in a sexual relationship
All of the time most of the time a good bit of the time occasionally never not applicable

16. Because of my Lupus I am not interested in sex
All of the time most of the time a good bit of the time occasionally never not applicable

17. I am concerned that my Lupus is stressful for those who are close to me
All of the time most of the time a good bit of the time occasionally never

18. Because of my Lupus I am concerned that I cause worry to those who are close to me
All of the time most of the time a good bit of the time occasionally never

19. Because of my Lupus I feel that I am a burden to my friends and/or family
All of the time most of the time a good bit of the time occasionally never

Over the past 4 weeks I have found my Lupus makes me

20. Resentful
All of the time most of the time a good bit of the time occasionally never

21. So fed up nothing can cheer me up
All of the time most of the time a good bit of the time occasionally never

22. Sad
All of the time most of the time a good bit of the time occasionally never

23. Anxious
All of the time most of the time a good bit of the time occasionally never

24. Worried
All of the time most of the time a good bit of the time occasionally never

25. Lacking in self-confidence
All of the time most of the time a good bit of the time occasionally never

How often over the past 4 weeks

26. My physical appearance due to Lupus interferes with my enjoyment of life
All of the time most of the time a good bit of the time occasionally never

(continued)

e2

The following questionnaire is designed to find out how SLE affects your life. **Read** each statement and then circle the response, which is **closest to how you feel**. Please try to answer all the questions as honestly as you can.

27. Because of my Lupus, my appearance (e.g. rash, weight gain/loss) makes me avoid social situations
All of the time | most of the time | a good bit of the time | occasionally | never | not applicable

28. Lupus related skin rashes make me feel less attractive
All of the time | most of the time | a good bit of the time | occasionally | never | not applicable

How often over the past 4 weeks

29. The hair loss I have experienced because of my Lupus makes me feel less attractive
All of the time | most of the time | a good bit of the time | occasionally | never | not applicable

30. The weight gain I have experienced because of my Lupus treatment makes me feel less attractive
All of the time | most of the time | a good bit of the time | occasionally | never | not applicable

31. Because of my Lupus I cannot concentrate for long periods of time
All of the time | most of the time | a good bit of the time | occasionally | never

32. Because of my Lupus I feel worn out and sluggish
All of the time | most of the time | a good bit of the time | occasionally | never

33. Because of my Lupus I need to have early nights
All of the time | most of the time | a good bit of the time | occasionally | never

34. Because of my Lupus I am often exhausted in the morning
All of the time | most of the time | a good bit of the time | occasionally | never

Please feel free to make any additional comments.

Please check that you have answered each question
Thank you, for completing this questionnaire

Clinical Study Protocol Appendix P

Drug Substance	Anifrolumab (MEDI-546)
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Appendix P
Patient Global Assessment

AMERICAN COLLEGE OF RHEUMATOLOGY

Patient Assessment

Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:

Very Well ——————————————— Very Poorly

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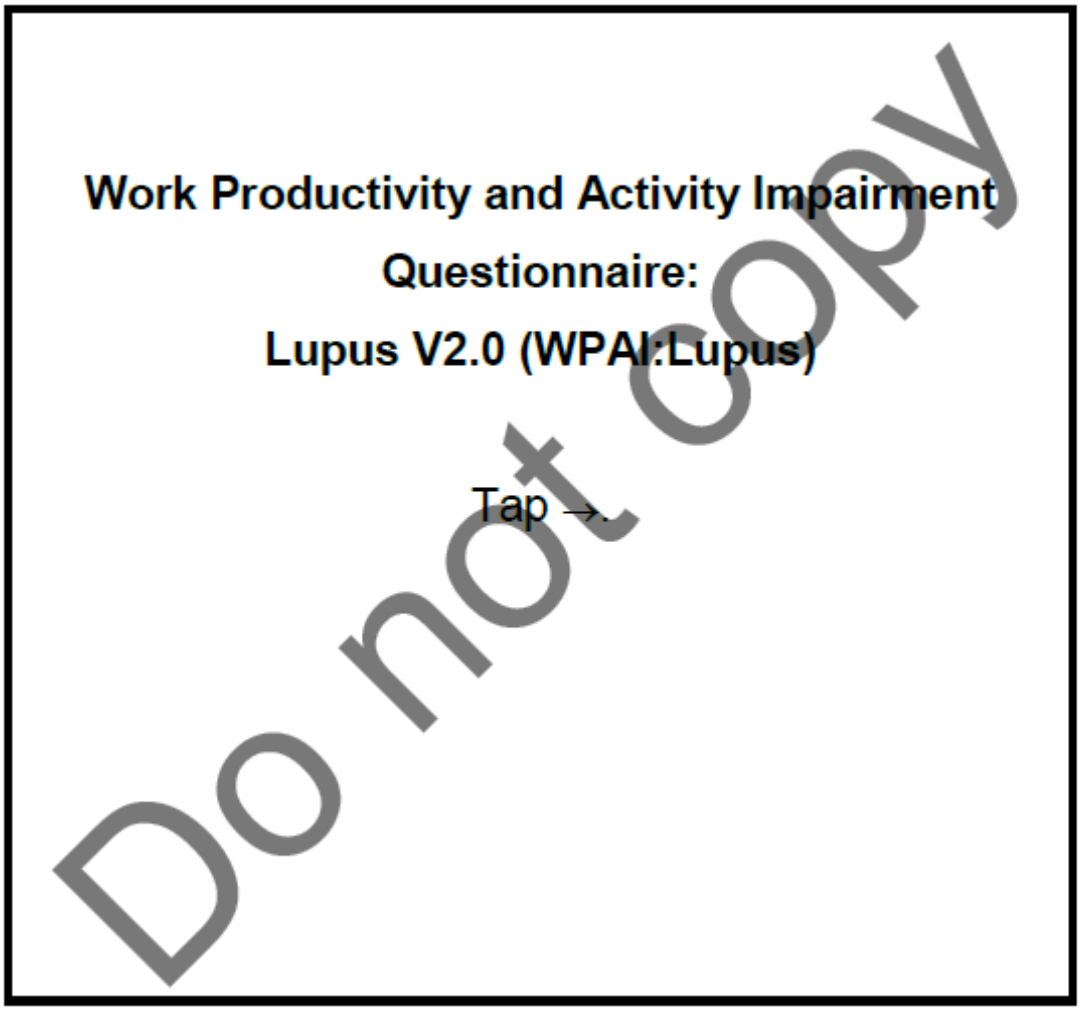
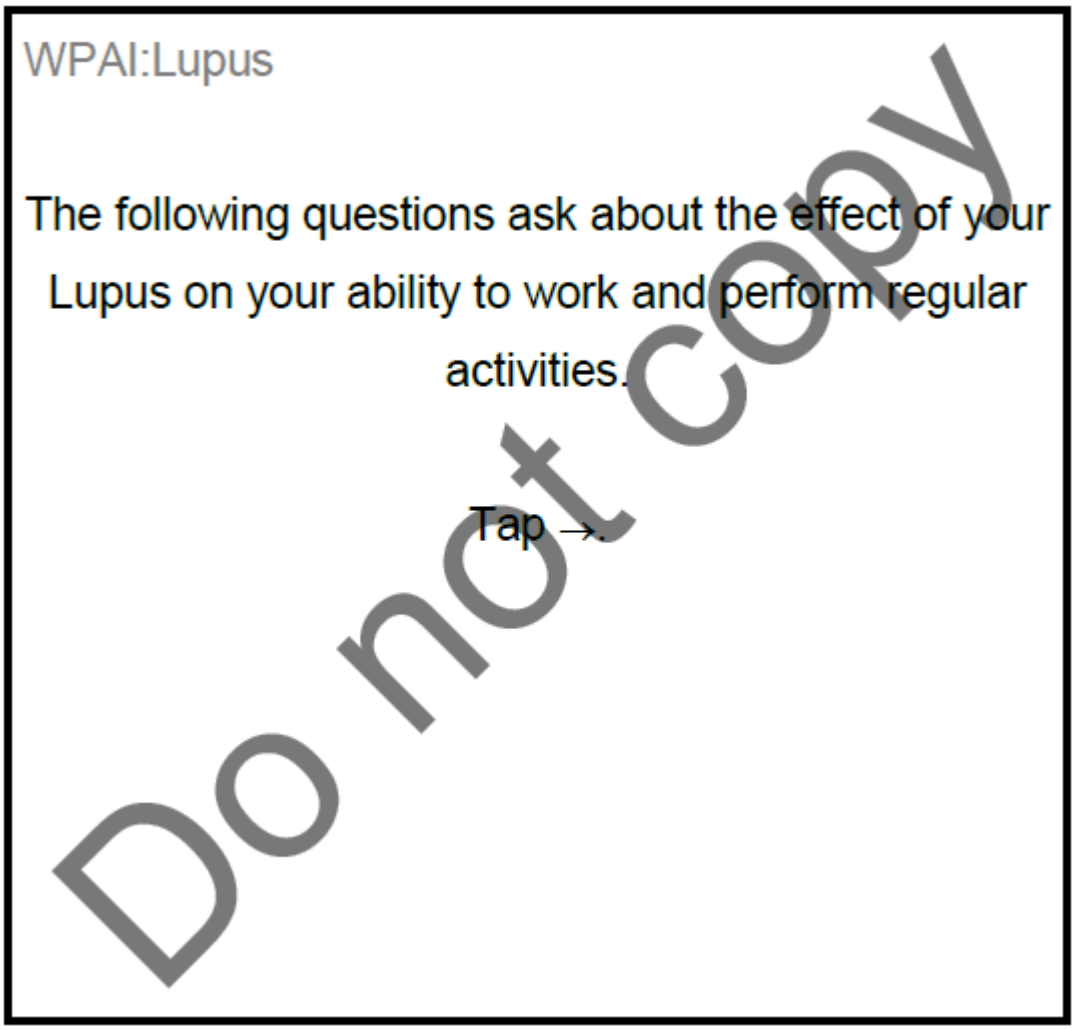
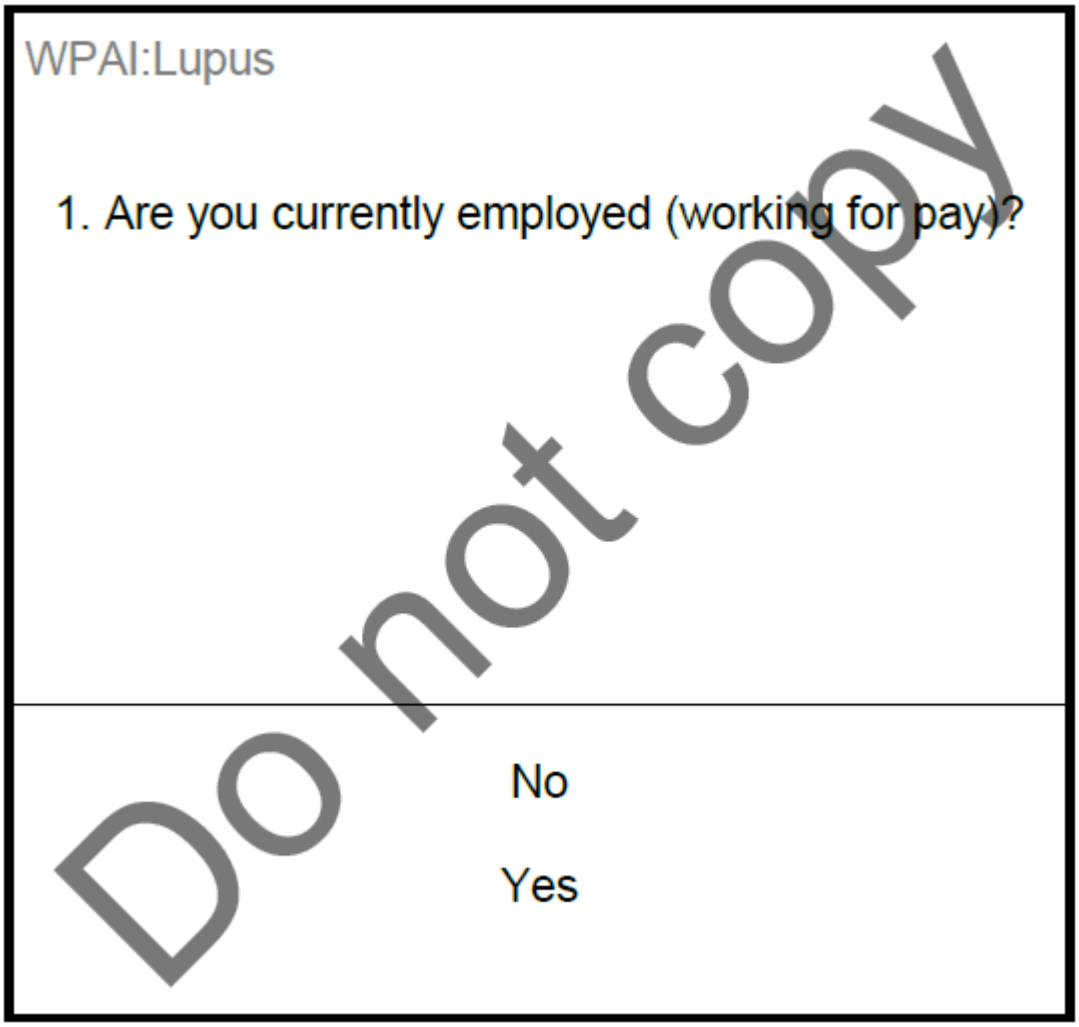
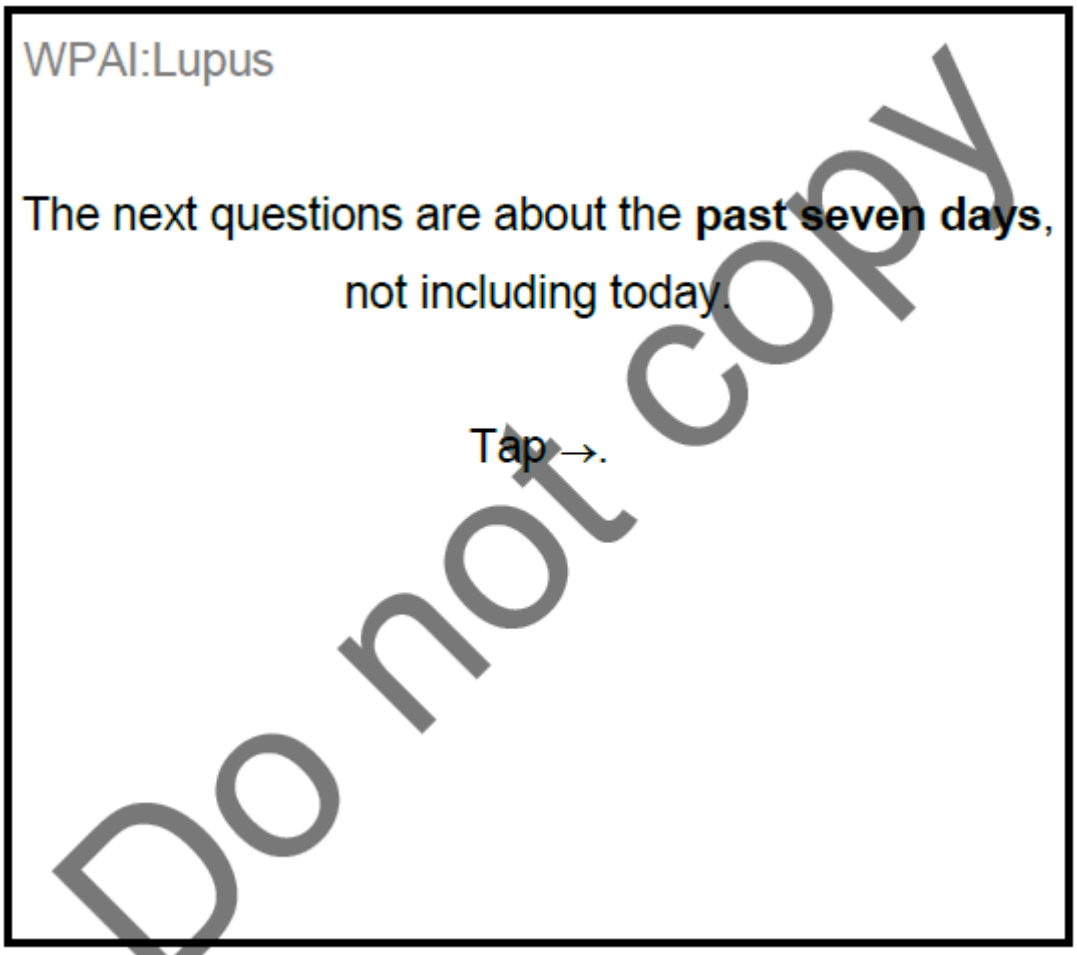
Clinical Study Protocol Appendix Q	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix Q
Work Productivity and Activity Impairment


Work Productivity and Activity Impairment
Questionnaire:
Lupus V2.0 (WPAI:Lupus)
Tap →.
Do not copy


WPAI:Lupus
The following questions ask about the effect of your Lupus on your ability to work and perform regular activities.
Tap →.
Do not copy


WPAI:Lupus
1. Are you currently employed (working for pay)?
No
Yes
Do not copy


WPAI:Lupus
The next questions are about the **past seven days**, not including today.
Tap →.

WPAI:Lupus

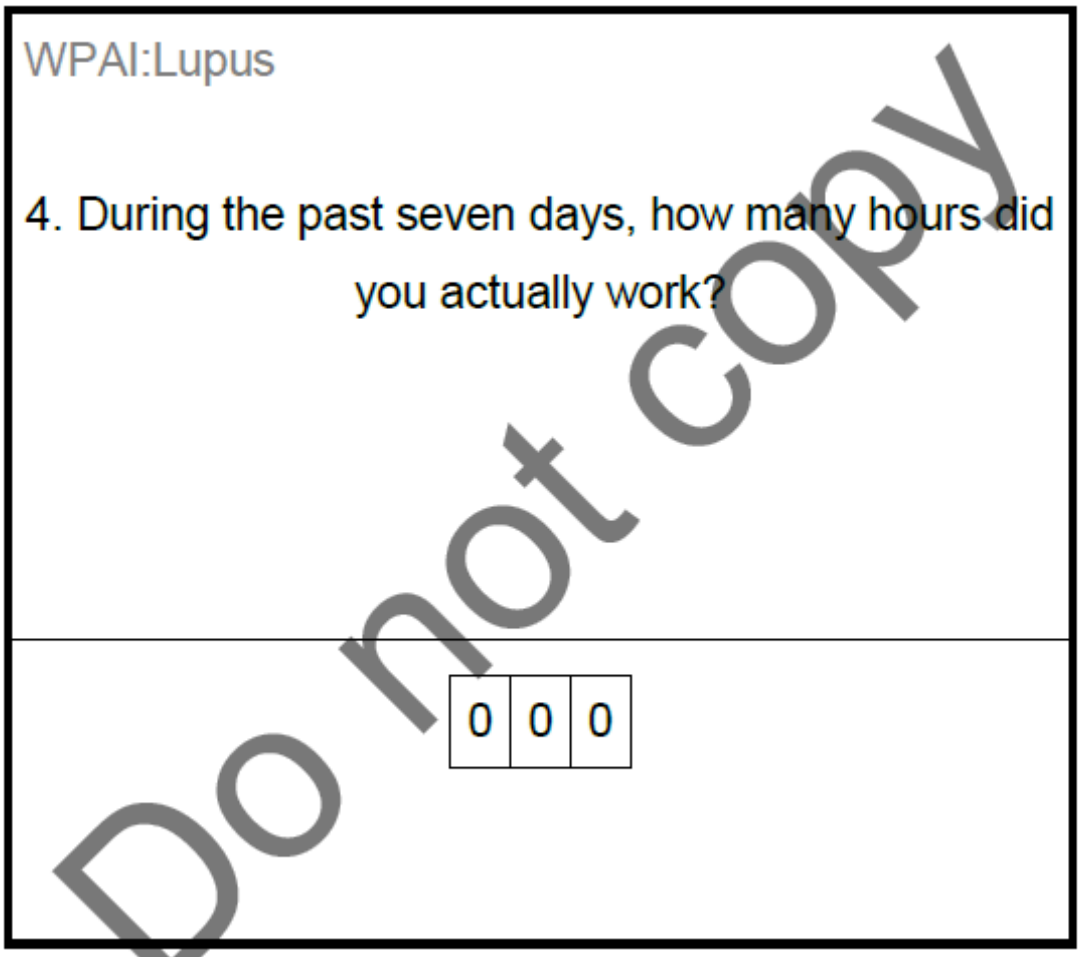
2. During the past seven days, how many hours did you miss from work because of problems associated with your LUPUS? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Lupus. Do not include time you missed to participate in this study.*

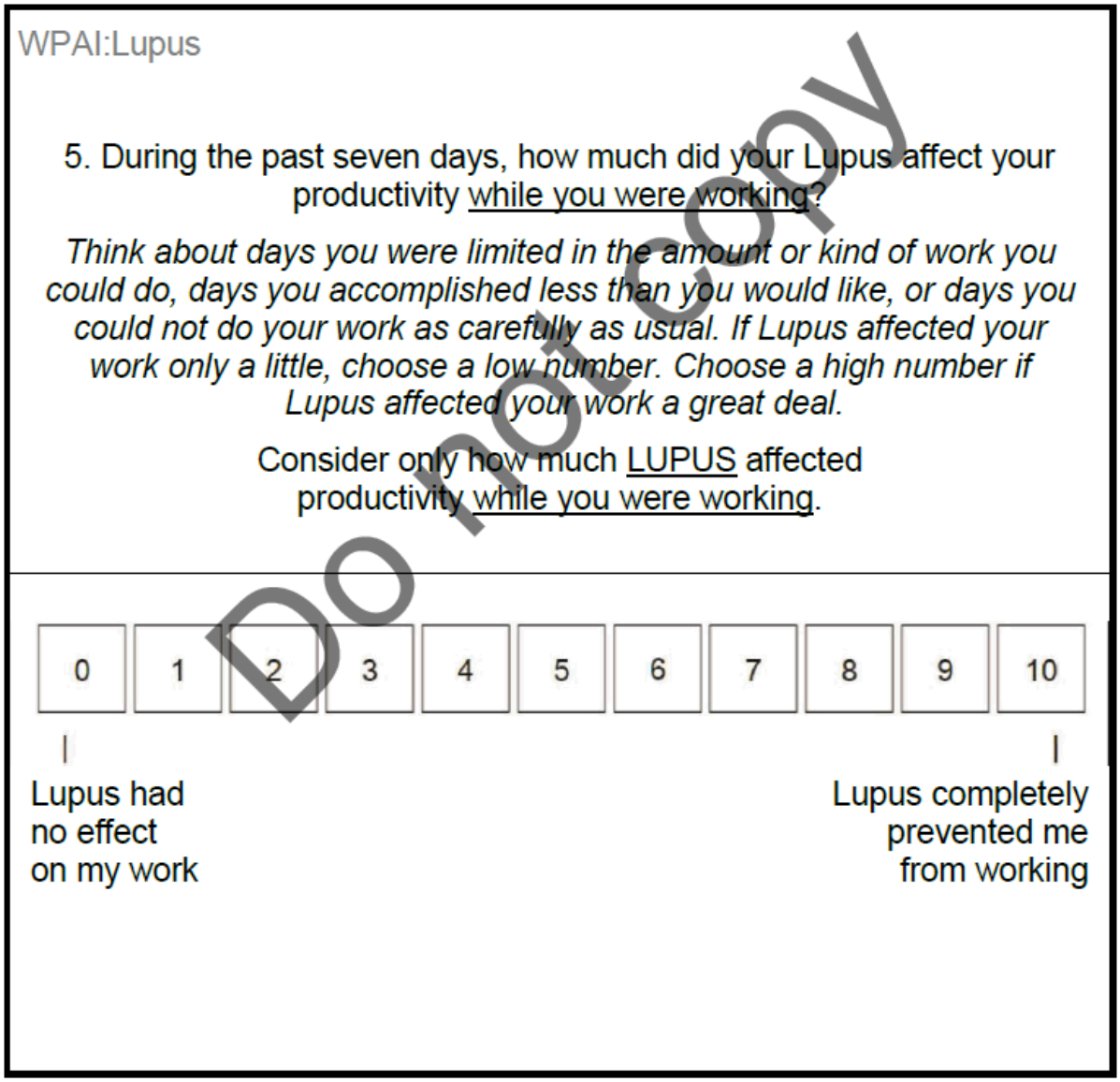
0	0	0

WPAI:Lupus

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

0	0	0


WPAI:Lupus
4. During the past seven days, how many hours did you actually work?
0 0 0


WPAI:Lupus
5. During the past seven days, how much did your Lupus affect your productivity while you were working?
Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Lupus affected your work only a little, choose a low number. Choose a high number if Lupus affected your work a great deal.
Consider only how much LUPUS affected productivity while you were working.
0
1
2
3
4
5
6
7
8
9
10
Lupus had no effect on my work
Lupus completely prevented me from working

WPAI:Lupus

6. During the past seven days, how much did your Lupus affect your ability to do your regular daily activities, other than work at a job?

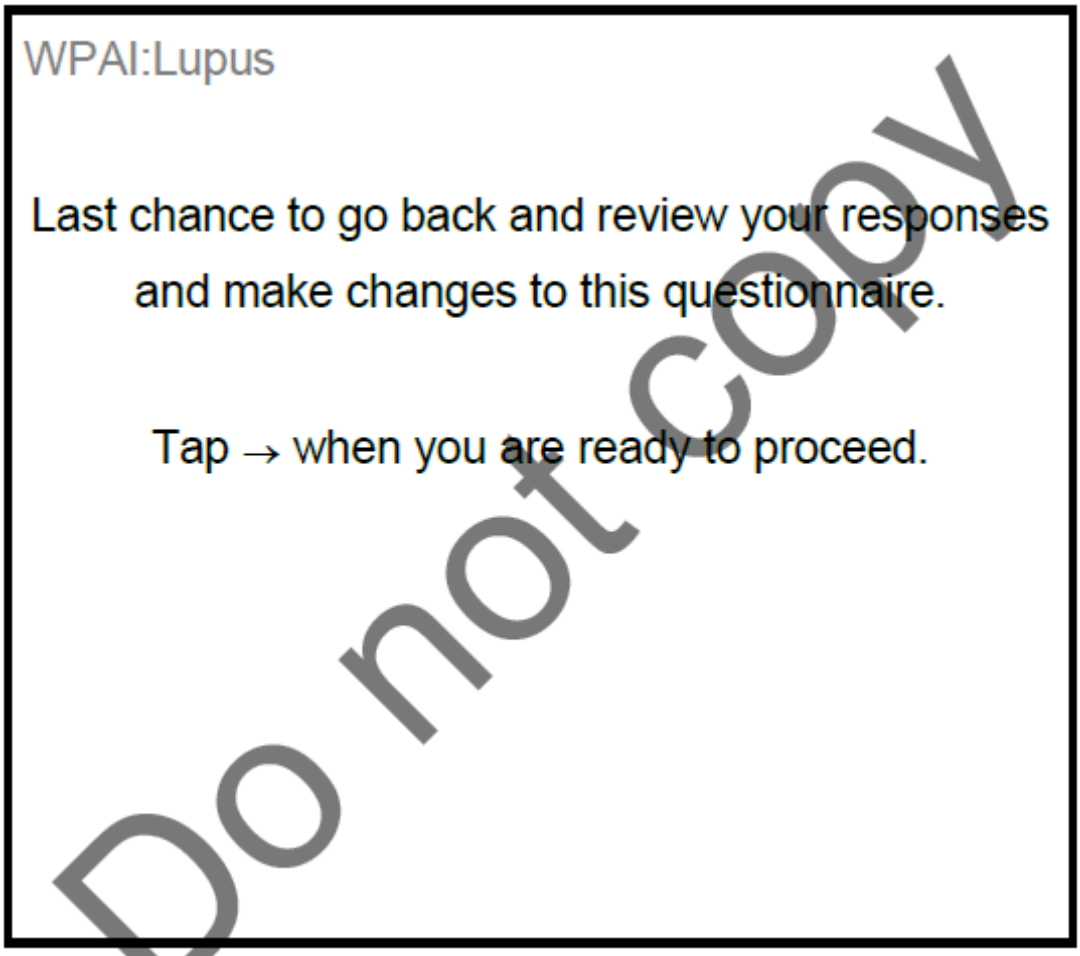
By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Lupus affected your activities only a little, choose a low number. Choose a high number if Lupus affected your activities a great deal.

Consider only how much LUPUS affected your ability to do your regular daily activities, other than work at a job.

0	1	2	3	4	5	6	7	8	9	10

Lupus had no effect on my daily activities

Lupus completely prevented me from doing my daily activities


WPAI:Lupus
Last chance to go back and review your responses and make changes to this questionnaire.
Tap → when you are ready to proceed.

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Clinical Study Protocol Appendix R	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix R
Pain Numerical Rating Scale

How much pain have you had because of your illness OVER THE LAST WEEK?

0	1	2	3	4	5	6	7	8	9	10

No Pain — Worst pain imaginable

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Revised Clinical Study Protocol Appendix S	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	3
Date	01 February 2016
Protocol Dated	01 February 2016

Appendix S
Medical Resource Use Questionnaire

Protocol Number _____ SID _____
Visit Number _____ CONFIDENTIAL Date_____
Subj Initials _____ Language code : 015-00 (DD/ MON/ YYYY)

This form requires information on health care visits which were not a part of the schedule of events as per protocol

MEDICAL RESOURCE USE QUESTIONNAIRE, Edition 3

1. Since the last visit, has the subject had other health care visits (Specialist/General Practice/Family Practice/Nurse practitioner/other): ☐ Yes ☐ No ☐ NA

   a. If Yes, total number of specialist visits: ___
   If Yes, total number of primary care visits (General practice/Family practice/nurse practitioner/other): ___

2. Since the last visit, has the subject had an Emergency Department (ED) visit (defined as <24 hour observation period)
   ☐ Yes ☐ No ☐ NA

   a. If Yes, total number of ED visits: ___
   b. For each visit, enter the following information:

Visit #	Date: mm/dd/yyyy	Was this related to increase in lupus related symptoms?	Cause of ED visit	Data confirmed using medical record	Was this related to an AE
1		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
2		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
3		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
4		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
5		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form

Visit #	Date: mm/dd/yyyy	Was this related to increase in lupus related symptoms?	Cause of ED visit	Data confirmed using medical record	Was this related to an AE
6		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
7		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
8		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
9		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form
10		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others	☐ Yes ☐ No	☐ Yes ☐ No If yes, complete AE form

3. Since the last visit, has the subject had a hospital stay (defined as ≥24 hour observation period)
☐ Yes ☐ No ☐ NA

a. If Yes, total number of hospital visits: ___
b. For each visit, enter the following information:

Visit #	Date: mm/dd/yyyy	Was this related to increase in lupus related symptoms?	Cause of hospitalization	Total length of hospital stay: enter #	Did it include an ICU stay:	Total number of days in ICU: enter #	Data confirmed using medical record	Completed SAE form
1		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
2		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete

Visit #	Date: mm/dd/yyyy	Was this related to increase in lupus related symptoms?	Cause of hospitalization	Total length of hospital stay: enter #	Did it include an ICU stay:	Total number of days in ICU: enter #	Data confirmed using medical record	Completed SAE form
3		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
4		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
5		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
6		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
7		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
8		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
9		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete
10		☐ Yes ☐ No ☐ NA	☐ Cardiovascular ☐ Central Nervous ☐ Renal ☐ Infections ☐ Others		☐ Yes ☐ No ☐ NA		☐ Yes ☐ No	☐ Yes ☐ No If no, please complete

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Clinical Study Protocol Appendix T	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
Protocol Dated	09 April 2015

Appendix T
Vasculitic Syndromes Excluded from the Study

Subjects with a history or current diagnosis of the following vasculitis syndromes are excluded from participating in the study. Vasculitis due to SLE is allowed in the study.

- Behçet's Disease
- Buerger's Disease
- Central Nervous System Vasculitis
- Churg Strauss Syndrome
- Cryoglobulinemia
- Giant Cell Arteritis
- Henoch-Schönlein Purpura
- Kawasaki Disease
- Microscopic Polyangiitis
- Polyarteritis Nodosa
- Polymyalgia Rheumatica
- Takayasu's Arteritis
- Wegener's Granulomatosis

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Revised Clinical Study Protocol Appendix U	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	5
Date	18 May 2016
Protocol Dated	18 May 2016

Appendix U
Restricted Medications

Medications to be Discontinued Prior to signing ICF

Restricted medication	Discontinuation prior to signing ICF	Restricted medication	Discontinuation prior to signing ICF
Abatacept (CTLA 4 Ig)	24 weeks	Intravenous Globulin	4 weeks
Acthar® gel	6 weeks	Leflunomide	36 weeks
Adalimumab	12 weeks	Lenalidomide	8 weeks
Alefacept	12 weeks	Lupuzor (IPP-201101)	12 weeks
Anakinra	12 weeks	Memantine	4 weeks
Apremilast	4 weeks	Natalizumab	24 weeks
Atacicept (TACI-Ig)*	40 weeks	Obinutuzumab*	26 weeks
B cell depleter*	26 weeks	Ocrelizumab*	26 weeks
Belimumab	12 weeks	Ofatumumab*	26 weeks
Blisibimod (AMG 623)	8 weeks	Plasmapheresis	24 weeks
Certolizumab pegol	24 weeks	Retinoids	4 weeks
Cyclophosphamide	24 weeks	Rituximab*	26 weeks
Cyclosporine**	4 weeks	Sifalimumab (MEDI-545)	26 weeks
Cytokines (eg, IFN)	Washout Time	Similar to Study drug	26 weeks
Danazol	4 weeks	Sirolimus	4 weeks
Dapsone	4 weeks	Sulfasalazine	4 weeks
Eculizumab	12 weeks	Tabalumab	26 weeks
Efalizumab	12 weeks	Tacrolimus***	4 weeks
Epratuzumab	26 weeks	Thalidomide	8 weeks
Etanercept	4 weeks	Tocilizumab	12 weeks
Golimumab	12 weeks	Tofacitinib	4 weeks
Immunosuppressants	Washout Time	Topical Pimecrolimus	4 weeks
Infliximab	12 weeks		

* provided B cell count is normal at screening
** cyclosporine eye drops are acceptable for use in the study
*** oral tacrolimus has a 4 week washout period and topical tacrolimus has a 2 week washout period

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Clinical Study Protocol Appendix V	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
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Appendix V
Oral Corticosteroid Guidance

Examples of Equivalent Doses of Oral Prednisone

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

Example of OCS Tapering Schedule

Time point	**Initial Dose of Oral Prednisone or Equivalent**			
	40 mg	**30 mg**	**20 mg**	**10 mg***
Week 8	35 mg	27.5 mg	17.5 mg	10 mg
Week 12	30 mg	25 mg	15 mg	10 mg
Week 16	25 mg	20 mg	10 mg	10 mg
Week 20	15 mg	15 mg	10 mg	7.5 mg
Week 24	10 mg	10 mg	7.5 mg	≤7.5 mg
Week 28	7.5 mg	7.5 mg	≤7.5 mg	≤7.5 mg

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

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Clinical Study Protocol Appendix W	
Drug Substance	Anifrolumab (MEDI-546)
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Date	09 April 2015
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Appendix W
General Guidance for Determination of Major Surgery

The goal of this guidance is to maximize the benefit/risk for each subject entering this study. An important aspect to this goal is taking into account all relevant history, including recent surgeries and/or injuries that could influence the safety of the subject potentially being exposed to an additional immunomodulatory medication or could bias the efficacy endpoints of the trial.

Given the advancement and availability of surgical techniques, major surgery is in the judgment of the Investigator and his/her evaluation of the following criteria, regardless of the specific surgical procedure:

1. Has the subject completely recovered (mentally, emotionally, and physically) from the surgery and is not receiving additional medications related to the prior surgery (ie, antibiotics)?

2. Has the subject completed all follow-up visits related to the surgery, including ancillary services such as physical and/or occupational therapy?

3. Has the subject resumed all of their prior activities?

4. Has the subject returned to his/her baseline medications for SLE and non-SLE indications?

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Clinical Study Protocol Appendix X	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
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Appendix X
Guidance for Abnormal Pap Smear Results

Pap Smear Result	Abbreviation	Also Known As	Suggested Action
Atypical squamous cells–undetermined significance	ASC–US	—	Permitted to enter study
Atypical squamous cells–cannot exclude HSIL	ASC–H	—	Permitted to enter study
Atypical glandular cells	AGC	—	Permitted to enter study
Low-grade squamous intraepithelial lesion	LSIL	Mild dysplasia Cervical intraepithelial neoplasia–1 (CIN–1)	Permitted to enter study
High-grade squamous intraepithelial lesion	HSIL	Moderate dysplasia CIN-2 / CIN II	Permitted to enter study
High-grade squamous intraepithelial lesion	HSIL	CIN–3 / CIN III Carcinoma in situ (CIS)	**Exclude/discontinue subject**
Endocervical adenocarcinoma in situ	AIS	—	**Exclude/discontinue subject**

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Clinical Study Protocol Appendix Y

Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	2
Date	09 April 2015
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Appendix Y
Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalised hives, pruritus or flushing, swollen lips, tongue and/or uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
- Reduced BP (see number 3 below for definition) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalised hives, itch, flush, swollen lips, tongue and/or uvula)
- Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
- Reduced BP (see number 3 below for definition) or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that subject (minutes to several hours); for adults a systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP (taken at or immediately prior to start of the infusion), whichever BP is lower.

The following definitions are provided for the purposes of this study:

Hypersensitivity reaction: an acute onset of an illness with involvement of the skin, mucosal tissue, or both during infusion of investigational product (but does not meet the definition of anaphylaxis described above).

Infusion-related reaction: any other reaction occurring during infusion of investigational product or felt to be temporally related to the infusion within 24 hours of investigational product administration.

To assist with the mitigation of these AEs, see Table 1, which categorizes reactions by severity of symptoms, proposes severity-specific treatment and offers guidance on management of investigational product. Final treatment is at the discretion of the Investigator and should reflect local SOC.

Table 1 An approach to management of anaphylactic, hypersensitivity, and infusion-related reactions

Severity of symptoms	Treatment	Investigational product
Mild reactions (infusion and hypersensitivity) Mild infusion-related reactions such as headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localised cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤20 mmHg change in systolic BP from pre-infusion measurement	Evaluate subject, including close monitoring of vital signs At the discretion of the Investigator, treat subject, for example, with: - Normal saline (~500 to 1000 mL/hour IV) and/or - Diphenhydramine 50 mg IV or equivalent and/or - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or - Topical antihistamines and/or low-potency topical corticosteroid preparations and/or - Anti-nausea medication, as needed	Stop investigational product infusion immediately Option 1: do not resume investigational product infusion; OR at the discretion of the Investigator, resume current investigational product infusion under observation and complete investigational product infusion at no more than half the planned infusion rate Option 2: discontinue any further administration of investigational product; OR at the discretion of the Investigator, continue future investigational product administrations and consider slowing infusion rate and pretreating subject 1.5 to 0.5 hours prior to investigational product administration, for example with: - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol
Moderate reactions (infusion) Infusion-related reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below)	Evaluate subject, including close monitoring of vital signs Treat subject, for example, with: - Normal saline (~500 to 1000 mL/hour IV) and/or - Diphenhydramine 50 mg IV or equivalent and/or - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or - Anti-nausea and/or antiemetic intramuscular, as needed	Stop investigational product infusion immediately Option 1: do not resume investigational product infusion; OR based on risk/benefit evaluation, at the discretion of the Investigator, resume current investigational product infusion under observation and at no more than half the planned infusion rate after treatment of current signs and symptoms as suggested (eg, normal saline and/or Tylenol and/or topical antihistamines)

Severity of symptoms	Treatment	Investigational product
		Additional Options for Future Administration of investigational product Discontinue any further administrations of investigational product; OR Further investigational product infusions, at the discretion of the Investigator, continue investigational product administration and consider slowing infusion rate and pretreating subject 0.5 to 1.5 hours prior to investigational product administration, for example with: - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol - Anti-nausea and/or antiemetic by mouth Prior to next administration of investigational product administration, consider initiating at a slower infusion rate and pretreating subject 0.5 to 1.5 hours prior to next administration of investigational product, for example, with - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol If moderate event recurs in the same subject, discontinue further investigational product administration

Severity of symptoms	Treatment	Investigational product
Moderate hypersensitivity reactions Infusion related reactions which may include generalised rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with >20 mmHg change in systolic BP from pre-infusion measurement	Evaluate subject, including close monitoring of vital signs Treat subject, for example, with: - Normal saline (~500 to 1000 mL/hour IV) and/or - Diphenhydramine 50 mg IV or equivalent and/or - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or - IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg	Stop investigational product infusion immediately DO NOT resume current infusion Discontinue any further administrations of investigational product Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days

Severity of symptoms	Treatment	Investigational product
Severe Above plus fever with rigors, hypo- or hypertension with ≥40 mmHg change in systolic BP, signs of end organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope, incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor OR **Life-threatening** Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	Evaluate subject, including close monitoring of vital signs Maintain airway, oxygen if available Treat subject immediately, for example with: - Normal saline (~500 to 1000 mL/hour IV) - Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases - IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg - Diphenhydramine 50 mg IV or equivalent - Acetaminophen 500 to 650 mg or equivalent dose of paracetamol Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine Grade 4 event At the discretion of the Investigator	Stop investigational product infusion immediately Do not resume current infusion Permanently discontinue investigational product administration Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days

Revised Clinical Study Protocol Appendix Z	
Drug Substance	Anifrolumab (MEDI-546)
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Appendix Z
Modified Flare Index

Modified Flare Index

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 (i.e., 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 one criterion present in either the Mild/Moderate Flare or Severe Flare categories. New or worsened manifestation should only be reported for manifestations of SLE.

Mild or Moderate Flare

☐ Change in SLEDAI 2K instrument score of ≥ (greater than or equal to) 3 but < (less than) 7 points compared to previous visit

☐ New/Worse (check all that apply):

- Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus
- ☐ Nasopharyngeal ulcers
- ☐ Pleuritis
- ☐ Pericarditis
- ☐ Arthritis
- ☐ Fever (SLE)

☐ ≥ (greater than or equal to) 1.0 increase in PGA score, but not to more than 2.5

Severe Flare

☐ Change in SLEDAI 2K instrument score of ≥ (greater than or equal to) 7 points compared to previous visit

☐ New/worse (check all that apply):

- ☐ CNS-SLE
- ☐ Vasculitis
- ☐ Nephritis
- ☐ Myositis
- ☐ Hemolytic anemia: Hb <70g/L or decrease in Hb >30 g/L with positive Coombs AND at least one of the following: decreased haptoglobin, increased total bilirubin not due to Gilbert's disease, increased reticulocyte count.

☐ Hospitalization which, as per investigator assessment of causality, is due to SLE Activity

☐ Increase in Physician's Global Assessment to > (greater than) 2.5

Clinical Study Protocol Amendment	
Amendment Number	04
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Date	18 May 2016
Protocol Dated	18 May 2016

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

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

All sites participating in the study.

Note: in addition to the changes listed below, minor text/style changes were made.

Sections of protocol affected:

3.1 Inclusion criteria; 3.3.2 Concomitant medications for Systemic Lupus Erythematosus standard of care during the study

Previous text:

3.1 Inclusion criteria

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

   (a) A dose of oral prednisone (≤40 mg/day) or prednisone equivalent dose for a minimum of 2 weeks prior to signing of the ICF. The dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to Week 0 (Day 1)

   (b) 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 and until 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 another agent, the dose duration for both (a) and (b) must be met

15. Meets all of the following TB criteria:

(a) No history of latent or active TB prior to Screening, with the exception of latent TB with documented completion of appropriate treatment

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

(c) 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

(d) 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

(e) 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

17. OCS dose stable for at least 2 weeks at Randomisation (Day 1)

18. Stable SLE SOC treatment at Randomisation (Day 1) (see Section 3.3.2)

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

Permitted SOC SLE	**Limitations of Use**
OCS	- Oral prednisone or equivalent up to ≤40 mg/day is permitted from at **least 2 weeks prior to signing of the informed consent**. The dose of oral prednisone must remain stable **at least 2 weeks prior to Day 1** - 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

Revised text:

3.1 Inclusion criteria

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

(a) Where prednisone is the single standard of care 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 standard of care 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 Appendix V for examples of prednisone equivalency**

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

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

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

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 standard of care 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

Reason for Amendment:

The criteria for inclusion based on concomitant medication and tuberculosis status were clarified. These changes were made to provide further guidance to the Investigator.

Persons who initiated the Amendment:

AstraZeneca

Section of protocol affected:

3.2.2 Exclusion criteria related to concomitant medications; 3.3.1.2 Restricted medications; 4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening

Previous text:

3.2.2 Exclusion criteria related to concomitant medications

9. Receipt of any of the following:

   (a) Any new oral prednisone therapy (or equivalent) anytime from 2 weeks prior to signing of the ICF through Day 1 or any change in current oral prednisone dose (or equivalent) any time from 2 weeks prior to Day 1 (see Appendix V for examples of prednisone equivalency)

   (b) Any new dose of the following anytime in the 12 weeks prior to signing the ICF or change in the current dose anytime in the 8 weeks prior to signing the ICF through Day 1: azathioprine; any antimalarial (eg,

chloroquine, hydroxychloroquine, quinacrine); mycophenolate mofetil/mycophenolic acid; oral, SC, or intramuscular methotrexate

13. 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 Appendix U)
- 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)

14. Receipt of epratuzumab, belimumab, or tabalumab ≤12 weeks prior to signing the ICF

3.3.1.2 Restricted medications

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

4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening

Footnote '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 Appendix U]) 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).

Revised text:

3.2.2 Exclusion criteria related to concomitant medications

9. Receipt of any of the following:

(a) **Where prednisone is the single standard of care 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 Appendix V for examples of prednisone equivalency)

(b) Where prednisone is not the single standard of care 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 informed consent form through Day 1, OR any change in/ discontinuation of current oral prednisone dose (or equivalent) anytime within the 2 weeks prior to randomisation (see Appendix V 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**

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 Appendix U)
- 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

3.3.1.2 Restricted medications

(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.

4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening

Footnote '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 Appendix U]) 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).

Reason for Amendment:

The criteria for exclusion based on concomitant medications were clarified, and a minor addition was made allowing the concomitant use of cyclosporine eye drops (to match with Appendix U). These changes were made to provide further guidance to the Investigator.

Persons who initiated the Amendment:

AstraZeneca

Sections of protocol affected:

List of abbreviations and definition of terms; 3.2.4 Exclusion criteria related to infection and malignancy risk factors; 4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening; 4 Study plan and timing of procedures, Table 3 Study plan detailing the procedures during the Treatment Period (double-blind period); 5.3.10 Clinical laboratory tests, Table 5 Clinical laboratory tests

Previous text:

3.2.4 Exclusion criteria related to infection and malignancy risk factors

26. 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

27. Confirmed positive test for hepatitis B serology for:

(a) Hepatitis B surface antigen, OR

(b) Hepatitis B core antibody (HBcAb) AND hepatitis B virus (HBV) DNA detected by reflex testing by the central laboratory at screening

Note: Subjects with HBcAb positivity at screening will be tested every 3 months for HBV DNA. To remain eligible in the study, subject HBV DNA levels must remain below the lower limit of quantitation (LLOQ) as per the central laboratory.

31. Opportunistic infection requiring hospitalisation or parenteral antimicrobial treatment within 3 years of randomisation

4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening

Footnote 'b':

Redraw for ANA/anti-dsDNA, or IFN test can be done within the 30-day screening window, however, results must be available within the 30-day screening window for subjects to be randomised.

4 Study plan and timing of procedures, Table 3 Study plan detailing the procedures during the Treatment Period (double-blind period)

Footnote 'f':

Subjects with HBcAb positivity at screening will be tested every 3 months for HBV DNA. To remain eligible in the study, subject HBV DNA levels must remain below the LLOQ as per the central laboratory.

Revised text:

List of abbreviations and definition of terms

A new abbreviation was added:

HBsAg Hepatitis B surface antigen

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.

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

4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening

Footnote '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.

4 Study plan and timing of procedures, Table 2 Study plan detailing the procedures at screening

A new footnote 'g' was added:

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.

4 Study plan and timing of procedures, Table 3 Study plan detailing the procedures during the Treatment Period (double-blind period)

Footnote '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.

5.3.10 Clinical laboratory tests, Table 5 Clinical laboratory tests

A new footnote '**' was added:

** **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.**

Reason for Amendment:

The criteria for performing HIV testing at screening were clarified, along with exclusion based on antimicrobial treatment and hepatitis B serology. It was also further clarified that ANA/anti-dsDNA, or IFN test results needed to determine eligibility and stratification must be available within the 30-day screening window for subjects to be randomised. These changes were made to provide further guidance to the Investigator.

Persons who initiated the Amendment:

AstraZeneca

Section of protocol affected:

4.4 Follow-up Period

Previous text:

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), and be followed 8 and 12 weeks after the last administration of investigational product by completing the Follow up Visit 1 and 2 assessments (see Section 3.7).

Revised text:

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).

Reason for Amendment:

The timing of the early discontinuation visit was clarified. This change was made to provide further guidance to the Investigator.

Persons who initiated the Amendment:

AstraZeneca

Section of protocol affected:

5.3.8.2 Tuberculosis results from screening evaluations

Previous text:

- If the screening QFT-G test is positive at screening but the subject is **not newly positive**, the subject must have been diagnosed with latent TB and must have documentation confirming completion of appropriate treatment.

Revised text:

- 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.**

Reason for Amendment:

The screening requirements for a positive QFT-G test at screening were clarified. This change was made to provide further guidance to the Investigator.

Persons who initiated the Amendment:

AstraZeneca

Section of protocol affected:

7.7 Post study access to study treatment

Previous text:

Following evaluation at Week 52, subjects will either be followed for a 12-week Follow-up Period or continue in a LTE study that will continue until anifrolumab has been approved for use on the market or until development has been discontinued by the Sponsor.

Revised text:

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.**

Reason for Amendment:

The duration of the long-term extension (LTE) study was clarified. This change was made to provide further guidance to the Investigator.

Persons who initiated the Amendment:

AstraZeneca

Section of protocol affected:

Appendix U Restricted Medications

Previous Text:

Medications to be Discontinued Prior to signing ICF

Restricted medication	Discontinuation prior to signing ICF	Restricted medication	Discontinuation prior to signing ICF
Abatacept (CTLA 4 Ig)	24 weeks	Intravenous Globulin	4 weeks
Acthar® gel	6 weeks	Leflunomide	36 weeks
Adalimumab	12 weeks	Lenalidomide	8 weeks
Alefacept	12 weeks	Lupuzor (IPP-201101)	12 weeks
Anakinra	12 weeks	Memantine	4 weeks
Apremilast	4 weeks	Natalizumab	24 weeks
Atacicept (TACI-Ig)*	40 weeks	Obinutuzumab*	26 weeks
B cell depleter*	26 weeks	Ocrelizumab*	26 weeks
Belimumab	12 weeks	Ofatumumab*	26 weeks
Blisibimod (AMG 623)	8 weeks	Plasmapheresis	24 weeks
Certolizumab pegol	24 weeks	Retinoids	4 weeks
Cyclophosphamide	24 weeks	Rituximab*	26 weeks
Cyclosporine**	4 weeks	Sifalimumab (MEDI-545)	26 weeks
Cytokines (eg, IFN)	Washout Time	Similar to Study drug	26 weeks
Danazol	4 weeks	Sirolimus	4 weeks
Dapsone	4 weeks	Sulfasalazine	4 weeks
Eculizumab	12 weeks	Tabalumab	12 weeks
Efalizumab	12 weeks	Tacrolimus***	4 weeks
Epratuzumab	12 weeks	Thalidomide	8 weeks
Etanercept	4 weeks	Tocilizumab	12 weeks
Golimumab	12 weeks	Tofacitinib	4 weeks
Immunosuppressants	Washout Time	Topical Pimecrolimus	4 weeks
Infliximab	12 weeks		

* provided B cell count is normal at screening
** cyclosporine eye drops are acceptable for use in the study
*** oral tacrolimus has a 4 week washout period and topical tacrolimus has a 2 week washout period

Revised text:

Medications to be Discontinued Prior to signing ICF

Restricted medication	Discontinuation prior to signing ICF	Restricted medication	Discontinuation prior to signing ICF
Abatacept (CTLA 4 Ig)	24 weeks	Intravenous Globulin	4 weeks
Acthar® gel	6 weeks	Leflunomide	36 weeks
Adalimumab	12 weeks	Lenalidomide	8 weeks
Alefacept	12 weeks	Lupuzor (IPP-201101)	12 weeks
Anakinra	12 weeks	Memantine	4 weeks
Apremilast	4 weeks	Natalizumab	24 weeks
Atacicept (TACI-Ig)*	40 weeks	Obinutuzumab*	26 weeks
B cell depleter*	26 weeks	Ocrelizumab*	26 weeks
Belimumab	12 weeks	Ofatumumab*	26 weeks
Blisibimod (AMG 623)	8 weeks	Plasmapheresis	24 weeks
Certolizumab pegol	24 weeks	Retinoids	4 weeks
Cyclophosphamide	24 weeks	Rituximab*	26 weeks
Cyclosporine**	4 weeks	Sifalimumab (MEDI-545)	26 weeks
Cytokines (eg, IFN)	Washout Time	Similar to Study drug	26 weeks
Danazol	4 weeks	Sirolimus	4 weeks
Dapsone	4 weeks	Sulfasalazine	4 weeks
Eculizumab	12 weeks	Tabalumab	**26 weeks**
Efalizumab	12 weeks	Tacrolimus***	4 weeks
Epratuzumab	**26 weeks**	Thalidomide	8 weeks
Etanercept	4 weeks	Tocilizumab	12 weeks
Golimumab	12 weeks	Tofacitinib	4 weeks
Immunosuppressants	Washout Time	Topical Pimecrolimus	4 weeks
Infliximab	12 weeks		

* provided B cell count is normal at screening
** cyclosporine eye drops are acceptable for use in the study
*** oral tacrolimus has a 4 week washout period and topical tacrolimus has a 2 week washout period

Reason for Amendment:

Appendix U was modified to provide further guidance to the Investigator. The washout periods for Epratuzumab and Tabalumab were corrected.

Persons who initiated the Amendment:

AstraZeneca

Section of protocol affected:

Appendix Z Modified Flare Index

Previous Text:

Hemolytic anemia: Hb <70g/L or decrease in Hb >30 g/L with positive Coombs AND at least one of the following: decreased haptoglobin, increased total bilirubin due not due to Gilbert's disease, increased reticulocyte count.

Revised text:

Hemolytic anemia: Hb <70g/L or decrease in Hb >30 g/L with positive Coombs AND at least one of the following: decreased haptoglobin, increased total bilirubin **not due** to Gilbert's disease, increased reticulocyte count.

Reason for Amendment:

Incorrect text was amended.

Persons who initiated the Amendment:

AstraZeneca

AstraZeneca

Clinical Study Protocol Amendment 04 Appendix A	
Drug Substance	Anifrolumab (MEDI-546)
Study Code	D3461C00005
Edition Number	5
Date	18 May 2016
Protocol Dated	18 May 2016

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

19 MAY 2016
Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

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

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

18-May-2016
Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

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

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representativ [redacted]

19 May 2016
Date
(Day Month Year)

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

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

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.:

Signature: [redacted]

18 MAY 2016
Date
(Day Month Year)