Clinical Study Protocol

Drug Substance	Anifrolumab (MEDI-546)
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A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Characterizing the Pharmacokinetics, Pharmacodynamics, and Safety of Anifrolumab following subcutaneous administration in Adult Systemic Lupus Erythematosus Subjects with Type I Interferon test high result and active skin manifestations

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 1.0, 20 Sep 2016
Initial creation

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.

PROTOCOL SYNOPSIS

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

Study site(s) and number of subjects planned

Approximately 32 subjects are planned to be randomized from approximately 15 sites in 4-5 countries.

Study period		Phase of development
Estimated date of first subject enrolled	Q4 2016	Phase 2
Estimated date of last subject completed	Q4 2018	Phase 2

Study design

This is a Phase 2, multicentre, double-blind, randomized, placebo-controlled study characterizing the pharmacokinetics, pharmacodynamics, and safety of two fixed doses of anifrolumab administered as Subcutaneous (SC) injections in adult type I Interferon (IFN) test -high Systemic Lupus Erythematosus (SLE) subjects with active skin manifestations while receiving Standard of Care (SOC) treatment. The study will be double-blind until primary analysis performed after all subjects have completed Week 12. Thereafter, the sponsor will be unblinded while investigators and subjects will remain blinded throughout the remainder of the study.

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

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

- placebo as added to SOC, given Q2W as two SC injections in a volume of 1mL each (4 subjects).

The study is blinded with respect to anifrolumab or placebo but not for dose since treatments will be given as one or two SC injections depending on dose level.

Objectives

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

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

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

Target subject population

Adult SLE subjects with active skin manifestations defined as CLASI activity score ≥ 10 while receiving SOC treatment at a stable dose will be recruited for the study. Only type I IFN test-high subjects will be eligible to allow evaluation of changes in the 21-gene type I IFN PD signature.

Duration of treatment

The study includes:

- A screening period of up to 30 days;
- A treatment period of 52 weeks;
- A follow-up period of 8 weeks

Investigational product (IP) will be administered at study visits from Week 0 to Week 50 (a total of 26 doses) during the treatment period and the last follow-up visit will be 10 weeks after the last IP dose. The approximate total study length will be 15 months. The treatment period will be double-blind up until the data base lock for the primary analysis performed after all subjects have completed Week 12. At this time point Sponsor will be unblinded whereas investigators and subjects will remain blinded throughout the entire study.

Investigational product, dosage and mode of administration

Anifrolumab in two fixed doses or placebo will be added to SOC treatment and administered as SC injections Q2W.

- Anifrolumab 150 mg Q2W given as one SC injection (=1 mL)
- Anifrolumab 300 mg Q2W given as two SC injections (=2 × 1 mL)
- Placebo Q2W given as one SC injection (=1 mL)
- Placebo Q2W given as two SC injections (=2 × 1 mL)

Statistical methods

There is no formal power calculation as there will be no hypothesis testing, and the data collected in this study will be used to inform the design of further development. Subjects will be randomized at a ratio of 3:1 to receive active:placebo treatment (12 subjects on active and 4 subjects on placebo) for the two dosing levels. This gives a total study population of 32 subjects. CCI

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Two data base locks and analyses are planned for the study, i.e., the main analysis after all randomized subjects complete Week 12 or discontinue the study prior to Week 12, and the "end of extension"-analysis that take place once all subjects have completed Week 60 or discontinued the study prior to Week 60.

The full analysis set will be used as the primary population for reporting PD, efficacy and safety data. This comprises of all subjects randomized into the study who receive at least 1 dose of IP and did not discontinue IP, and will be analyzed according to randomized treatment (modified Intention-To-Treat). 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.

Descriptive statistics (number, mean, standard deviation [SD], median, minimum, maximum, and coefficient of variance [%CV]) will be provided by dose level for continuous variables, and counts and percentages will be presented for categorical variables.

The primary characterization of the effect of anifrolumab on the 21-gene type I IFN PD signature will be carried out through the individual and median 21-gene type 1 IFN signature scores and neutralization ratios at Week 12. The PD gene signature will also be explored over time. The primary characterization of anifrolumab PK will be done by descriptive statistics of the derived PK parameters.

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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
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIS	Adenocarcinoma In Situ
ALP	Alkaline Phosphatise
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
anti-dsDNA	Anti-Double Stranded Deoxyribonucleic Acid
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCG	Bacillus Calmette-Guerin
BICLA	British Isles Combined Lupus Assessment
BP	Blood Pressure
C3	Third Component of Complement
C4	Fourth Component of Complement
CDC	Centers for Disease Control and Prevention
CH50	Total Haemolytic Complement
CHMP	Committee for Medicinal Products for Human Use
CIS	Carcinoma In Situ
CK	Creatine Kinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
C_{trough}	Trough concentration
CNS	Central Nervous System
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report

Abbreviation or special term	Explanation
C-SSRS	Colombia Suicidality Severity Rating Scale
CV-EAC	Cardiovascular Event Adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
EOT	End of Treatment
EULAR	European League Against Rheumatism
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFA	Immunofluorescent Assay
IFIGx	Interferon-Inducible Gene Expression
IFN	Interferon
IFNAR1	Type I Interferon Receptor
Ig	Immunoglobulin
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous Immunoglobulins
IXRS	Interactive Voice/Web Response System
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantitation
mAb	Monoclonal Antibody
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
mRNA	Messenger Ribonucleic Acid
NSAID	Nonsteroidal anti-Inflammatory Drugs
OCS	Oral Corticosteroids
PA	Posterior-Anterior
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetics
PGA	Physician Global Assessment
PI	Principal Investigator
PP	Per-Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
QFT-G	QuantiFERON-TB Gold
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	Standard of Care
SRI[4]	Systemic Lupus Erythematosus Responder Index of ≥4
SSc	Systemic Sclerosis
TB	Tuberculosis
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Systemic Lupus Erythematosus (SLE) is a chronic, multisystemic, disabling autoimmune rheumatic disease of unknown aetiology. The disease predominantly affects women of childbearing years (Cooper et al, 1998; Lahita, 1999) with a female-to-male ratio in the childbearing years of 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. SLE has a broad range of clinical manifestations including constitutional symptoms, alopecia, skin rashes, serositis, arthritis, nephritis, vasculitis, lymphadenopathy, splenomegaly, haemolytic anaemia, cognitive dysfunction and other nervous system involvement. Skin is the second most commonly involved organ and even though the reported prevalence varies among different studies more than 80% of SLE patients have skin symptoms at some stage of their disease (Rothfield N et al, 2006, Kapadia N et al, 1996, Wysenbeek AJ et al, 1992, Grönhagen CM et al, 2010). Both the disease manifestations as well as the currently used SOC treatment, commonly oral corticosteroids (OCS) and other immunosuppressive agents, cause a significant disease burden (Doria and Briani, 2008; Petri, 2001; Zonana-Nanach et al, 2000). All currently used SLE therapies have well known adverse effects and there is a medical need to identify new targeted therapies, particularly agents that may reduce the requirement for corticosteroids and cytotoxic agents.

There is growing evidence that type I IFNs play an important role in autoimmune diseases including SLE. Subjects with high anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody titers, progressive skin rashes, and lupus nephritis (LN), have high serum levels of type I IFN (Bengtsson et al, 2000). Overexpression of type I IFN activated genes, the so called “interferon signature”, has been shown in blood and skin biopsies from SLE subjects with acute skin involvement (Dall’era et al, 2005, Blomberg S et al, 2001, Farkas et al, 2001, Yao et al, 2009).

Anifrolumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against subunit 1 of the type I IFN receptor (IFNAR1). Anifrolumab inhibits binding of type I IFN to IFNAR and inhibits the biologic activity of all type I IFNs. The growing evidence that type I IFNs play an important role in SLE, suggests that inhibition of the biological activity of type I IFNs with anifrolumab may be a novel therapy for the treatment of SLE patients with significant unmet medical need.

Anifrolumab as administered as intravenous (IV) infusions is currently being investigated by the Sponsor for treatment of moderate to severe active SLE in the following ongoing studies; one global open-label extension phase 2 study, one phase 2 study in adult Japanese subjects, two global phase 3 studies and a long-term extension study of these, and in proliferative LN (one global phase 2 study).

Development of a SC route of administration for anifrolumab is expected to offer increased flexibility in meeting patients’ dosing needs and to improve treatment accessibility and

compliance. The PK/PD, bioavailability and safety of SC administered anifrolumab in healthy volunteers is being evaluated in a phase 1 study (D3461C00006).

The purpose of this study is to better understand the PK and PD of SC administered anifrolumab in SLE with the goal to identify dose and dosing regimen to be further evaluated in future development of the SC route of administration.

1.2 Rationale for study population, study design, and dosing

1.2.1 Rationale for study population and study design

The overall aim of this Phase 2, multicentre, double-blind, randomized, placebo-controlled study is to provide PK/PD, safety and efficacy data to facilitate identification of dose and dosing regimen for future development of the SC route of administration of anifrolumab in SLE. To allow optimal evaluation of the PD marker, i.e., changes of the 21-gene type 1 IFN PD signature, only subjects with type I IFN test-high results will be eligible for the study. In addition to evaluate the effects on the 21-gene type I IFN PD signature, anifrolumab efficacy on active skin manifestations will be characterized by recruitment of subjects with CLASI activity score ≥10.

Data from phase 2b study (CD-IA-MEDI-546-1013) shows that anifrolumab administered IV Q4W, demonstrated a clinically relevant benefit in patients with moderate to severe SLE when added to SOC. The proportion of patients achieving a SLE responder index (SRI) 4 response with a sustained reduction in corticosteroids at Day 169, was greater in both the 300 mg (34.3%) and 1000 mg (28.8%) anifrolumab groups than in the placebo group (17.6%). Similar response rates were seen in the type I IFN test-high subpopulation (approximately 75% of the overall population): 13.2% in the placebo group, 36.0% in the 300 mg anifrolumab group, and 28.2% in the 1000 mg anifrolumab group.

Anifrolumab showed efficacy across multiple efficacy measures including improvement of skin symptoms. The proportion of subjects with a CLASI activity score ≥ 10 at baseline who achieved at least a 50% decrease from baseline was numerically higher for anifrolumab than placebo group and the difference was observed from Day 29 and was sustained during the 52 week treatment period. Furthermore, data showed that the majority of subjects with active skin manifestations exhibited high IFN test scores.

To ensure adequate treatment, subjects will remain on stable doses of SOC treatment with at least one of the following; oral corticosteroids, antimalarials, or immunosuppressants. This is consistent with both the European League Against Rheumatism (EULAR) (Bertsias et al, 2008) and American College of Rheumatology (ACR) (ACR ad hoc committee, September 1999) management guidelines of moderate to severe SLE, including treatment of skin manifestations.

The study will be randomized, placebo-controlled, and double-blind until primary analysis after all subjects have completed Week 12 to ensure a robust design and minimise bias. The study is blinded with respect to anifrolumab and placebo, but not blinded at dose level. 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 LN (CHMP, February 2015). After Week 12, and unblinding of the sponsor, treatment will continue with investigators and subjects kept blinded throughout the remainder of the study. A treatment period of 52 weeks will allow further characterization of PK/PD, safety, and efficacy of SC administered anifrolumab.

1.2.2 Rationale for primary endpoint selection

The 21-gene type I IFN PD signature was chosen as a PD biomarker as an increase in type I IFN inducible mRNAs is a direct molecular consequence of increased expression of type I IFN proteins. Furthermore, measurement of mRNA via reverse transcription-polymerase chain reaction (RT-PCR) is a comprehensive and reliable technique. A robust panel of 21 type I IFN-inducible genes were selected based on the magnitude of their overexpression in whole blood of patients with SLE, providing a sensitive and specific PD marker where mRNA expression can be measured quantitatively.

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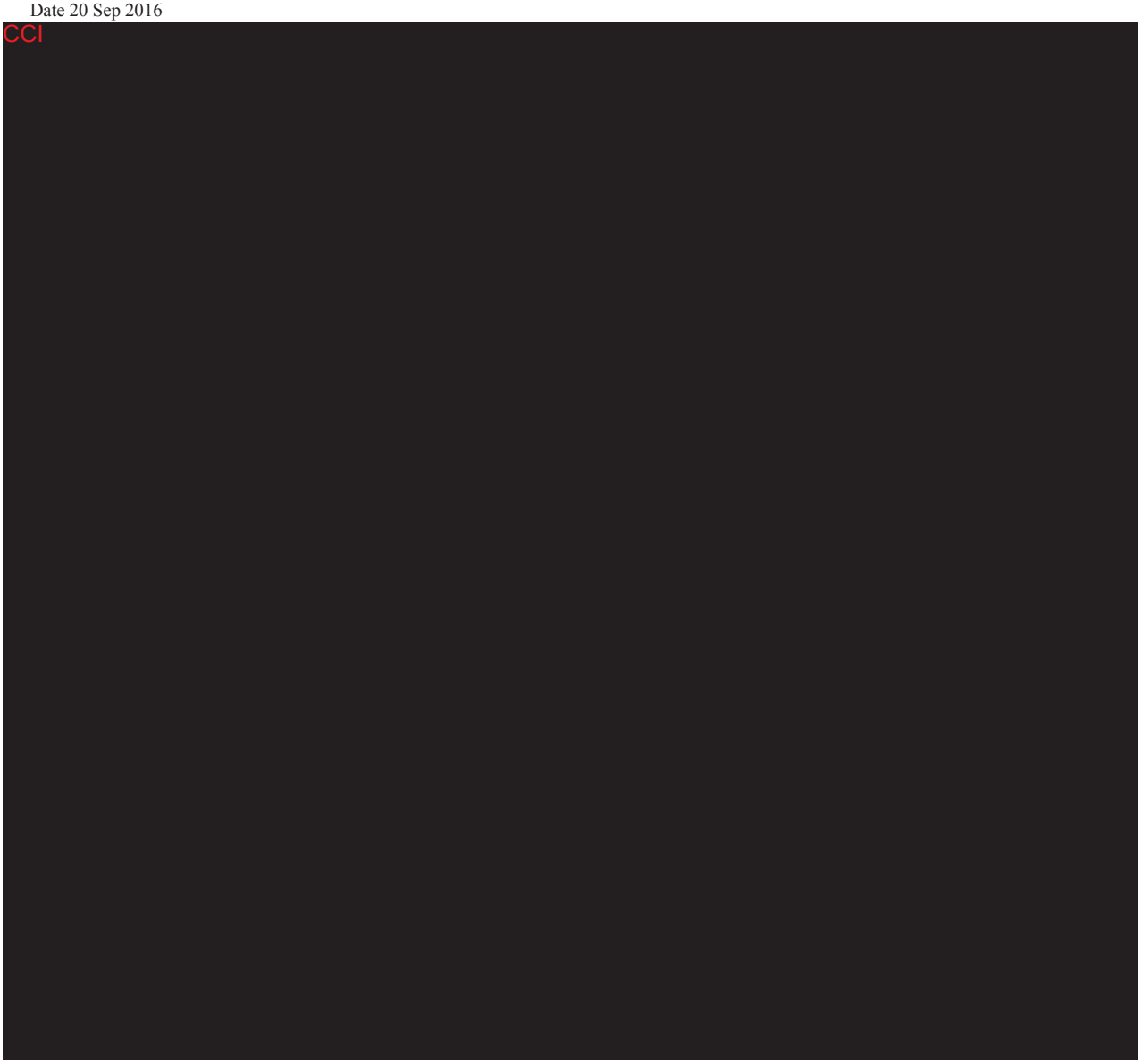
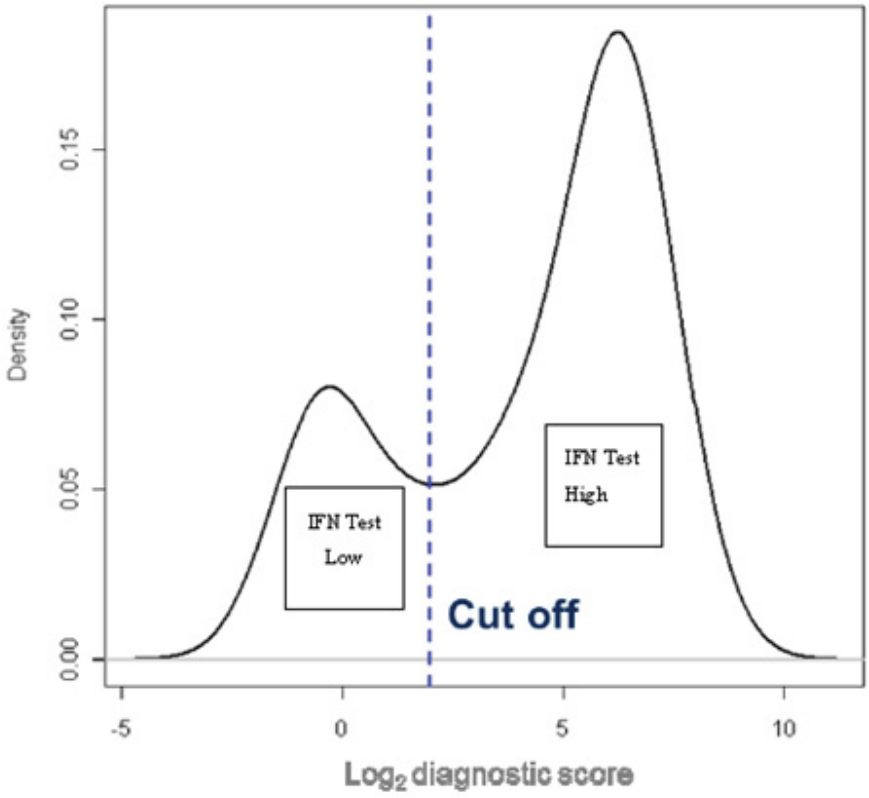


1.2.4 IFN test background

Type I IFN has long been considered to be important in the pathogenesis of SLE and inhibition of this pathway is an attractive goal, 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 specific patient's disease is driven by type I IFN activation. Direct measurement of the IFN is challenging, so a transcript-based marker, measuring the effect of IFN, was developed to evaluate the effect of over-expression of the target protein on a specific set of messenger ribonucleic acid (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 patients, as shown in the Figure 2 below, supports defining an IFN test-high and IFN test-low subpopulation.

Figure 2 Distribution of IFN transcript scores



1.3 Benefit/risk and ethical assessment

A detailed assessment of the overall benefit/risk of anifrolumab is discussed in the Investigator's Brochure.

There is significant unmet medical need for the treatment of patients with moderate to severe SLE. Since type I IFNs seem very likely to have a role in SLE, a therapy such as anifrolumab, that targets type I IFN receptors, may be beneficial.

Anifrolumab has been, or is being, investigated in the following MedImmune/AstraZeneca-sponsored clinical studies in adult subjects with systemic sclerosis (SSc) or SLE:

- Study MI-CP180 was a Phase 1, open-label, dose escalation study of single and multiple IV doses of anifrolumab in adult subjects with SSc (completed study).
- Study CD-IA-MEDI-546-1013 was a Phase 2b, randomized, double-blind, placebo-controlled study of anifrolumab (300 mg and 1000 mg IV Q4W) in adult subjects with moderately to severely active SLE (completed study).

- Study CD-IA-MEDI-546-1145 is the open-label extension for subjects completing Study CD-IA-MEDI-546-1013 (ongoing at the time of writing this protocol).

- Study D3461C00002 is an open-label study in Japanese adult subjects with moderately to severely active SLE (ongoing at the time of writing this protocol).

- Study D3461C00004 and study D3461C00005 are phase 3 randomized, double-blind, placebo-controlled studies evaluating safety and efficacy in adult subjects with moderately to severely active SLE (ongoing at the time of writing this protocol).

- Study D3461C0007 is a Phase 2 randomized, double-blind, placebo-controlled study characterizing the safety and efficacy of anifrolumab in adult subjects with LN (ongoing at the time of writing this protocol).

- Study D3461C009 is randomized, double-blind, placebo-controlled phase 3 extension study characterizing the long-term safety and tolerability of anifrolumab in adult subjects with moderately to severely active SLE enrolling subjects who have completed studies D3461C00004 and D3461C00005 (ongoing at the time of writing this protocol).

- Study D3461C00006 is a Phase 1 study evaluating two dose levels (300 and 600 mg) of SC administered and one dose level (300 mg) of IV administered anifrolumab in healthy volunteers.

Study CD-IA-MEDI-546-1013

This was a Phase 2b, randomized, double-blind, placebo-controlled, parallel group study to characterize the efficacy and safety of anifrolumab in adult subjects with moderately to severely active SLE with an inadequate response to SOC treatment. In total 305 subjects were randomized and received placebo (n=102), anifrolumab 300 mg (n=99), or anifrolumab 1000 mg (n=104) IV Q4W while continuing SOC treatment. The study has been completed.

Efficacy findings

Anifrolumab demonstrated a clinically relevant benefit with the proportion of patients achieving the primary endpoint, an SRI (4) response with a sustained reduction in corticosteroids at Day 169, being greater in both the 300 mg (34.3%) and 1000 mg (28.8%) anifrolumab groups than in the placebo group (17.6%). The response rates in the IFN test-high population (approximately 75% of the overall population) were 13.2% in the placebo group, 36.0% in the 300 mg anifrolumab group, and 28.2% in the 1000 mg anifrolumab group. Compared with the placebo group, a numerically higher proportion of patients in the anifrolumab groups achieved SRI (4) response with sustained reduction of OCS at Day 365 (placebo, 25.5%; 300 mg, 51.5%; and 1000 mg, 38.5%). The 300mg anifrolumab group saw a numerically higher proportion of patients have a reduction of background OCS dose to ≤7.5

mg/day at Day 365 in those taking ≥10 mg/day at baseline compared to placebo, whilst no apparent differences were seen when comparing the 1000 mg anifrolumab and placebo groups (placebo, 26.6%; 300 mg, 56.4%; and 1000 mg, 31.7%). Similar results were observed for the secondary endpoints in the IFN test-high population.

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 (4) 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)[8] 2004 based combined lupus assessment (BICLA) response. Higher response rates were also observed in organ specific measures for anifrolumab-treated subjects compared with placebo. The proportion of subjects with a CLASI activity score ≥10 at baseline who achieved a 50% decrease from baseline was numerically higher for the 300 mg and 1000 mg anifrolumab groups than for the placebo group CCI [redacted]. The difference compared to placebo was observed at Day 29 and was sustained throughout the treatment period. 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. The mean changes from baseline to Day 365 in anti-dsDNA for subjects with abnormal baseline values were numerically greater for the 300 mg and 1000 mg anifrolumab groups than placebo groups. Among subjects with C3, C4, and CH50 levels below lower normal limit at baseline no clear difference in improvement of complement levels were seen between treatment groups.

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Expression of type I IFN-inducible genes in whole blood using the 21-gene type I IFN PD signature decreased following anifrolumab administration for all dose groups in subjects with a baseline IFN test-high result in whole blood. For both the 300 mg and 1000 mg anifrolumab groups, > 85% median neutralization of the 21-gene type I IFN PD signature was observed through Day 365, with numerically greater neutralization observed in the 1000 mg group. In the placebo group (N = 70 at baseline), no neutralization of the 21-gene type I IFN PD signature was observed at any time point. Because subjects who were PD signature negative do not have significant type I IFN signature expression at baseline, the level of signature neutralization could not be robustly determined in this population.

Safety findings

The 300 and 1000 mg doses of anifrolumab were generally safe and well tolerated compared to placebo. After the review of all adverse events (AEs) as well as pre-specified safety topics of interest, the review revealed a favourable safety profile for anifrolumab. The overall number of patients with treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and AESIs; new or reactivated tuberculosis; malignancy; and infusion, hypersensitivity, or anaphylactic reactions, and non SLE related vasculitis) were similar between the placebo and anifrolumab groups. TESAEs classified by the investigator as related to the study drug were observed in 5.9% of the patients in the placebo group, 3.0% in the 300 mg anifrolumab group, and 1.0% in the 1000 mg anifrolumab group. AEs leading to discontinuation of the study drug were observed in 7.9% in the placebo group, 3.0% in the 300 mg anifrolumab group, 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 frequency of patients 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%). An event of special interest, *herpes zoster*, was reported more frequently in the anifrolumab-treated patients (300 mg anifrolumab group [5.1%]; 1000-mg anifrolumab group [9.5%]) compared with placebo-treated patients (2.0%). Importantly, patients with herpes zoster infection responded well to standard antiviral treatment. One TESAE of transverse myelitis with a positive *varicella zoster* virus polymerase chain reaction in cerebrospinal fluid was reported. The patient fully recovered following treatment with pulsed steroid and standard antiviral medication.

Herpes zoster reactivation, including cutaneous events, has been confirmed as an identified risk associated with administration of anifrolumab.

There was a higher number of patients with infections reported as influenza in the anifrolumab groups (300 mg [6.1%]; 1000 mg [7.6%]) compared with 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 patients, 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.

No clinically important difference was observed in haematology, chemistry, urinalysis, vital signs, lipid parameters, or electrocardiograms (ECGs) in any of the treatment groups.

Overall benefit/risk assessment

Anifrolumab demonstrated a clinically relevant benefit in subjects with moderate to severe SLE receiving SOC treatment. 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 observed compared with placebo. No apparent difference was observed when comparing the 1000 mg and placebo group. Anifrolumab was generally well tolerated. A dose ordered increase in the proportion of subjects with uncomplicated *herpes zoster* infections was observed in subjects receiving anifrolumab compared with placebo. *Herpes zoster* has been determined to be an identified risk associated with anifrolumab treatment in SLE patients.

To date, in clinical studies of anifrolumab, hypersensitivity events or anaphylaxis/anaphylactoid events have not occurred more frequently in subjects who were treated with anifrolumab IV 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. Reports of infusion-related reactions from clinical studies conducted to date suggest that the frequency, severity and characteristics of these reactions are similar across all treatment groups after IV administration. In the Phase 1 SC study (Study D3461C00006), anifrolumab 300 mg or placebo were administered SC to healthy volunteers. Both anifrolumab and placebo were administered as 2 injections into the SC tissue of the anterior thigh or abdomen. Subjects experienced minimal to mild and very transient pain immediately after the injections with no difference between the placebo and anifrolumab group. Similarily, injection-site pruritus was minimal and transient and showed no difference between anifrolumab and placebo groups.

Even though anifrolumab is a human monoclonal antibody, subjects can develop ADA 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 order to minimise the risk associated with anifrolumab treatment, subjects with risk factors for serious infections, recurrent *herpes zoster*, 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, and vasculitis (non-SLE) are designated as AESIs in this study. An external independent adjudication committee will assess all deaths and cardiovascular SAEs to determine if they meet criteria for MACE (stroke, acute coronary syndrome, myocardial infarction, or cardiovascular death). Specific details will be addressed in a cardiovascular event adjudication charter. There have been no imbalances in reported 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 case identification and categorisation for signal detection activity across treatment arms. Compared to the general population, patients with lupus have a higher rate of depression and suicide. Therefore, subjects will be screened for suicidality and those who are at high risk as assessed at screening and baseline will be excluded from participation in the study.

In conclusion, AstraZeneca believes that the available non-clinical and clinical data indicate an acceptable safety profile for anifrolumab when administered via the IV route. A similar safety and tolerability profile has been seen in a Phase 1 SC study in healthy volunteers. The proposed dosing regimens for this study 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 clinical evaluation in subjects with moderate to severe SLE and development of a SC administration route.

1.4 Study Design

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

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

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

Subjects must be taking either 1 or any combination of the followings: OCS, antimalarial, or immunosuppressants at stable doses. Specific medication restriction are contained in the eligibility criteria as described in Sections 3.1 and 3.2.2. OCS doses should remain stable

through Week 12, unless there is a clinical, safety or ethical reason for not to taper in which case reduction of OCS dose may be permitted from Week 4. Starting at Week 12 a mandatory steroid tapering attempt will be required for all subjects with an OCS dose ≥10.0 mg per day of prednisone or equivalent at randomization as described in Section 7.7.2.1.

See Figure 3 for outline of the study design.

This study includes:

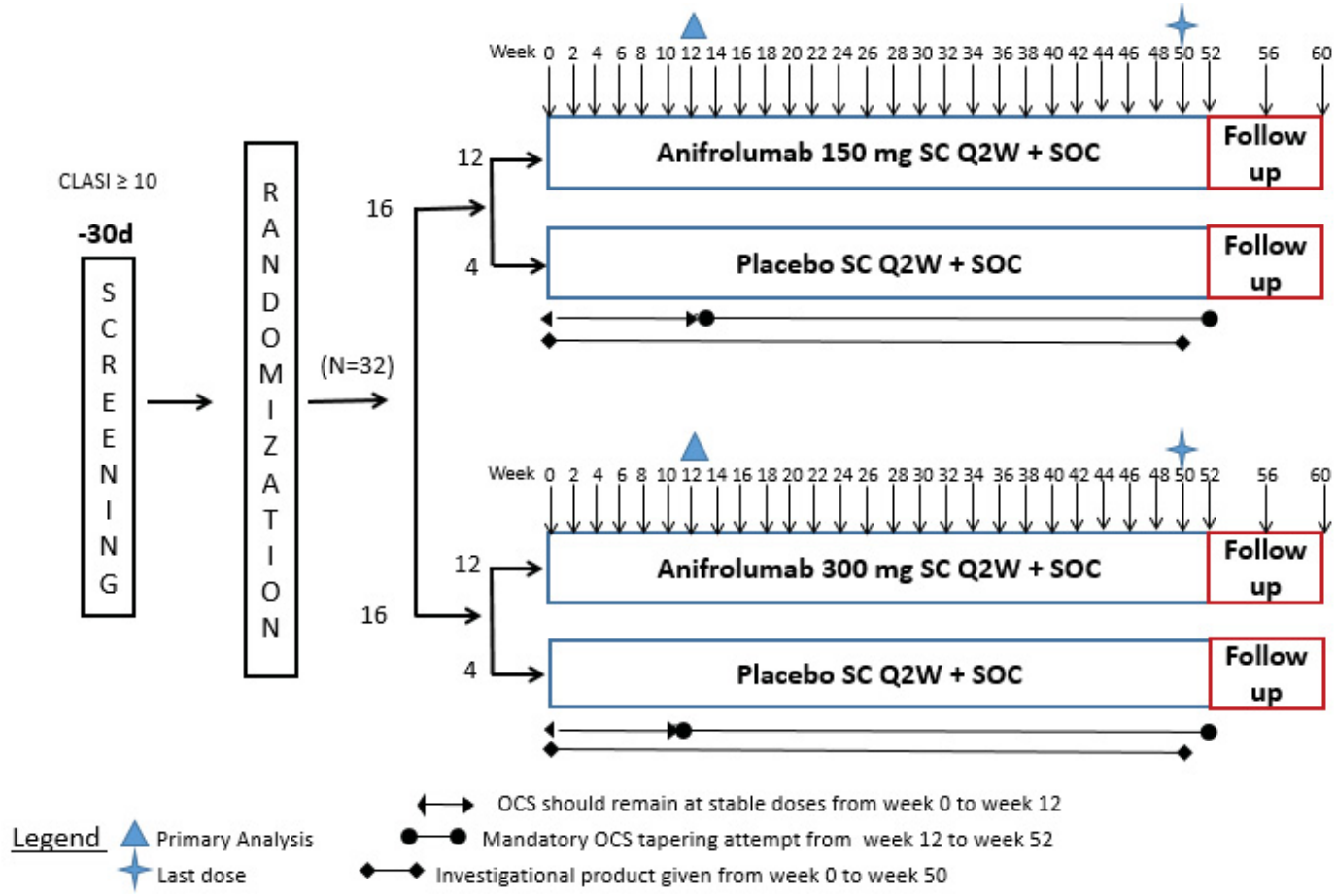
A screening period of up to 30 days;

A treatment period of 52 weeks;

A follow-up period of 8 weeks.

IP will be administered at study visits for a total of 26 doses (Week 0 to Week 50) during the treatment period and the last follow-up visit will be 10 weeks after the last IP dose.

Figure 3 Study flow chart



Abbrev: Q2W= once every second week; SOC= standard of care; OCS=oral corticosteroids

2. STUDY OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objectives

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

2.3 Safety objectives

Safety Objective:	Outcome Measure :
See above.	

2.4 Exploratory objectives

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

3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, 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

1. In the opinion of the investigator, the subject must be able to understand the informed consent form (ICF), and all protocol-related assessments

2. Written informed consent and any locally required authorisation (e.g., Health Insurance Portability and Accountability Act [HIPAA] in the US, Data Privacy Directive in the European Union [EU]) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations

3. Completion of all screening procedures within 30 days of signing the ICF

4. Aged 18 through 70 years at the time of screening

5. Diagnosis of paediatric or adult SLE for ≥24 weeks prior to signing the ICF and fulfilling at least 4 of the 11 ACR classification criteria for SLE with at least one of which being:

    - Positive antinuclear antibody (ANA) test at screening by immunofluorescent assay (IFA) at the central laboratory with titer ≥1:40; *or*

    - anti-dsDNA antibodies at screening elevated to above normal (i.e., indeterminate or positive results) as per central laboratory *or*

- anti-Smith (anti-Sm) antibodies at screening elevated to above normal (i.e., positive or equivocal results), as per central laboratory

Clinical criteria may have been present by history if documented in the medical record. Historical laboratory values can be counted for SLE criteria but at least one of the values specified above must be met during screening for eligibility.

6. Weight ≥40.0 kg at screening

7. Type I IFN test-high result

8. Having a CLASI activity score ≥ 10 at screening

9. Currently receiving at least 1 of the following for treatment of SLE*:

   - A dose of oral prednisone or equivalent of ≤40 mg/day for a minimum of 2 weeks prior to signing the ICF. The dose of oral prednisone or equivalent must be stable for a minimum of 2 weeks prior to randomization at Day 1

   - Any of the following medications administered for a minimum of 12 weeks prior to signing the ICF, and at a stable dose for a minimum of 8 weeks prior to randomization at Day 1:

   (i) Azathioprine ≤200 mg/day

   (ii) Antimalarials (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) combined with another agent listed above, the dose duration for both must be met. If subject´s immunosuppressive treatment consists of oral prednisone or other oral corticosteroid alone the minimal dose must be ≥7.5 mg/day or equivalent.

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

11. Females of childbearing potential must use effective methods (Table 1) of avoiding pregnancy, only one of which is a barrier method and the other is a highly effective intrauterine device or hormonal method described in Table 1 below, from Screening until 12 weeks after the final dose of IP unless the subject is surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a

sterile male partner, is 1 year post-menopausal, or practices sustained abstinence. Cessation of birth control after the specified period for IP 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.
- Post-menopausal is defined as at least 1 year since last menses and the subject having an elevated follicle-stimulating hormone (FSH) level greater than the central laboratory value of post-menopausal at screening if <55 years of age at the time of signing the ICF.

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

Table 1 Highly effective intrauterine device and hormonal methods and effective barrier methods of birth control (2 methods are required, one being a barrier method and one being a intrauterine device/hormonal method)

Contraceptive methods		
Barrier Methods (choose only one)	**Intrauterine Device/Hormonal Methods (choose only one)**	
	Intrauterine Device Methods	**Hormonal Methods**
Male condom (with spermicide*)	Progesterone T	Contraceptive implants
Cap (with spermicide cream or jelly*)	Copper T	Hormone shot or injection
Diaphragm (with spermicide cream or jelly*)		Combined pill (progesterone and estrogen)
		Minipill (progesterone only)
		Contraceptive patch

*where commercially available

12. All males (sterilised or non-sterilised) who are sexually active must use condom (with spermicide where commercially available for contraception if sexually active with a woman of child bearing potential) from Day 1 until at least 12 weeks after receipt of the final dose of IP. It is strongly recommended that female partners of child bearing potential of male subjects also use a highly effective method of contraception from Table 1 (other than a barrier method) throughout this period.

13. Male subjects must not donate sperm during the course of the study and for 12 weeks after the last dose of the IP.

14. Females with an intact cervix must have documentation of a normal Pap smear with no documented malignancy (e.g., cervical intraepithelial neoplasia grade III [CIN III], carcinoma in situ [CIS], or adenocarcinoma in situ [AIS]) within 2 years prior to randomization. (See Appendix J for guidance on abnormal Pap smear results). Any abnormal Pap smear result documented within 2 years prior to randomization must be repeated to confirm patient eligibility.

15. Meets all 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 or currently receiving prophylactic treatment for latent TB and the subject commits to completing the full duration of prophylaxis

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

(c) No recent close 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 randomization (documented appropriately in source), and, if warranted, receipt of appropriate treatment for latent TB at or before the first administration of IP

(d) Meet one of the following criteria:

- Negative QuantiFERON-TB Gold [QFT-G] test result for TB obtained from central laboratory within 30 days prior to randomization **or**
- Positive QFT-G test result for TB obtained during the screening period from central laboratory for which active TB has been ruled out and appropriate treatment for latent TB has been initiated prior to the first IP administration and the subject commits to completing the full duration of prophylaxis, which may mean completing prophylaxis during the study **or**
- Indeterminate (confirmed as indeterminate on retest during screening) QFT-G test for TB obtained during the screening period from central laboratory with ongoing QFT-G testing for TB to the Study Plan (Table 2)
- A chest radiograph with no evidence of current active TB or other infection, 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 ICF

3.2 Exclusion criteria

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

3.2.1 General exclusion criteria

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

2. Concurrent enrolment in another clinical study with an IP.

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 IP. If serum or urine β-hCG is positive at randomization the subject must be excluded.

5. Current alcohol, drug or chemical abuse, or a history of such abuse within 1 year prior to randomization.

6. Major surgery within 8 weeks prior to signing the ICF or elective major surgery planned during the study period.

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:

    - Aspartate aminotransferase (AST) >2.0 × upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) >2.0 × ULN
    - Total bilirubin >ULN (unless due to Gilbert's syndrome)
    - Serum creatinine >2.0 mg/dL (or >181 μmol/L)
    - Urine protein/creatinine ratio >2.0 mg/mg (or >226.30 mg/mmol)
    - Neutrophil count <1000/μL (or $<1.0 \times 10^9$/L)
    - Platelet count <25000/μL (or $<25 \times 10^9$/L)
    - 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
    - Glycosylated haemoglobin (HbA1c) >8% (or >0.08) at screening (diabetes 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 IP (small molecule or biologic agent) within 4 weeks or 5 half-lives prior to signing of the ICF, whichever is greater.

10. Prior receipt of anifrolumab

11. Receipt of any commercially available biologic agent (as indicated in Section 7.8) within 5 half-lives prior to randomization

12. Receipt of B cell-depleting therapy (including but not limited to ocrelizumab, ofatumumab, obinutuzumab, or rituximab) ≤26 weeks prior to signing the ICF. If B-cell depleting therapy was administered >26 weeks ago an absolute B cell count (CD19+ cells determined during screening by the central laboratory) less than the lower limit of normal or baseline value prior to receipt of B cell-depleting therapy (whichever is lower) will be exclusionary prior to signing the ICF.

13. Receipt of epratuzumab, belimumab, or tabalumab ≤12 weeks prior to signing the ICF or atacicept ≤40 weeks prior to signing the ICF

14. A known history of allergy or reaction to any component of the IP formulation or history of anaphylaxis to any human gamma globulin therapy

15. Receipt of any of the following:

    - Intra-articular, intramuscular or IV glucocorticosteroids within 2 weeks prior to signing the ICF.
    - 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);
    - Bacillus Calmette-Guerin (BCG) vaccine within 1 year of signing the ICF;
    - Any prohibited medication listed in Section 7.8, if the washout period is not met;
    - Blood transfusion within 4 weeks prior to signing the ICF

3.2.3 Exclusion criteria related to systemic lupus erythematosus and other diseases

16. History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome. Vasculitis due to SLE is allowed in the study;

17. 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;

18. 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:

    - That would make the subject unable to fully understand the ICF OR
    - Where, in the opinion of the Principal Investigator (PI), protocolspecified SOC is insufficient and utilisation of a more aggressivetherapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, is indicated;

19. Active severe SLE-driven renal disease where, in the opinion of the investigator, 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

20. 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

21. 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 assessment

22. 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

23. Known history of a primary immunodeficiency (e.g., common variable immunodeficiency syndrome), splenectomy, or any underlying condition that predisposes the subject to infection

24. Opportunistic infection requiring hospitalisation or parenteral antimicrobial treatment within 3 years of randomization

25. Any of the following:
    - Clinically significant chronic infection (i.e., osteomyelitis, bronchiectasis, etc.) within 8 weeks prior to randomization (chronic nail infections not causing open skin lesions are allowed)
    - Any infection requiring hospitalisation or treatment with IV anti-infectives not completed at least 4 weeks prior to randomization
    - Any infection requiring IV or oral anti-infectives (including antivirals) within 2 weeks prior to randomization

26. Confirmed positive HIV test at screening

27. Confirmed positive test for hepatitis B serology for
    - Hepatitis B surface antigen, or
    - Hepatitis B core antibody (HBcAb) and hepatitis B virus (HBV) DNA with a quantifiable level 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 level of quantitation (LLOQ) as per the central laboratory.

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

29. Any severe *herpes zoster* infection at any time prior to randomization, 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)

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

31. History of cancer, apart from:
    - Squamous or basal cell carcinoma of the skin treated with documented success of curative therapy ≥3 months prior to randomization

- Cervical cancer in situ treated with apparent success with curative therapy ≥1 year prior to randomization

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomization

If a subject does not meet eligibility criteria on the basis of a laboratory value at screening, then the laboratory parameter may be repeated once within the screening period; this will be considered as re-testing and re-screening is not required. Please refer Section 4.1.1 for details on re-screening and re-testing.

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

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. See Section 3.

4. At randomization the IXRS will assign eligible subjects to one of the four treatment groups, and assign eligible subjects a unique randomization code and blinded IP kit number(s) to the subject.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization.

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

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria, other than laboratory parameter as described in section 3.2, should not, under any circumstances, be enrolled or receive IP. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Block randomization using an IXRS will be used to randomize subjects and the AstraZeneca Biometrics and Information Sciences group is responsible for generating the randomization scheme for this study using the AZRand.

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

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

3.6 Methods for ensuring blinding

This is a double-blind study in which anifrolumab and placebo are distinguishable during preparation of the suspension for injection by syringe. Given that the treatments will be given as one or two SC injections depending on dose level, the study is double-blinded with respect to anifrolumab or placebo, but not to dose level. The double-blind period will last up until analyses of primary endpoints at Week 12. Thereafter investigators and subjects will remain blinded throughout the remainder of the study. All packaging and labelling of IP is done in such way as to ensure blinding for all Sponsor and investigational site staff other than the unblinded person responsible for final preparation steps and for injections of IP and placebo. The kits on the shelf look identical. Preparation of IP and placebo and injections must be done by an unblinded, qualified person (e.g., pharmacist or nurse) who is otherwise not involved in the study.

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 if the subjects has received anifrolumab or placebo. 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.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists from the IXRS. Routines for this will be described in the IXRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the randomized treatment allocation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP 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.

3.8 Restrictions

3.8.1 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 Study Plan (Table 2 and Table 3). If the subject has not fasted, he/she should fast before the next visit, and the test can be done at that visit.

3.8.2 Perioperative management of investigational product

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

Pre-operative management of investigational product:

If a non-urgent major surgery becomes necessary during the study, it should be scheduled at least 4 weeks after the last administration of investigational product, if clinically feasible. The determination of whether or not a surgery is "urgent" will be at the discretion of the investigator, preferably in consultation with the AstraZeneca study physician. 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 post-operative antibiotic course is completed and
- All acute surgical complications have resolved

Blood donation

Subjects must not donate blood from date of randomization until 12 weeks after the last dose of IP.

3.9 Discontinuation of investigational product

At any time, subjects are free to discontinue IP or withdraw from the study without prejudice to further treatment. A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events. Discontinuation of IP does not mean withdrawal from study participation.

Subjects may be discontinued from IP in the following situations;

1. Subject decision. The primary reason should be documented as one of the following:
    - Subject is unable to comply with protocol-specified visits and/or procedures due to conflicts not related to clinical trial
    - An AE or laboratory abnormality is of concern to the subject, but not clinically significant to physician
    - The subject perceives the IP to be ineffective
    - Subject wishes to participate in another clinical trial
    - Subject is interested in taking a treatment that is not allowed in this study
    - Subject perceives logistics at the clinical site to be unacceptable
    - Other reason
2. Adverse event that, in the opinion of the Investigator or AstraZeneca Study physician contradicts further dosing with IP.
3. Severe non-compliance with the study protocol.
4. The Investigator or AstraZeneca Study Physician deems withdrawal as being in the subject's best interest.
5. Pregnancy, positive pregnancy test, or subject expresses an interest to become pregnant.
6. Isolated HBc positivity with HBV DNA above LLQ confirmed by the central laboratory.
7. Receipt of any medications identified in Section 7.8.

8. The use of SOC medications listed in Section 7.7.1 in doses exceeding the maximal allowed doses, if the AstraZeneca study physician, determines the subject must be discontinued.

9. A diagnosis of active TB, premature discontinuation of treatment for latent TB, or noncompliance with latent TB therapy. Note: Duration of treatment for latent TB should follow the local practice. If local practice is not defined, then CDC guidance for immunocompromised patients should be used.

10. Subjects who develop worsening of SLE as described in Section 3.9.1.

11. IP is unblinded by the Investigator.

If a subject is withdrawn from study, see Section 3.10 for details.

3.9.1 Discontinuation of investigational product due to worsening of SLE

IP will be discontinued at any time during the study in subjects who develop active severe SLE disease manifestations that in the opinion of the Investigator, require treatment with cyclophosphamide, high dose corticosteroids, plasmapheresis, or intravenous immunoglobulins (IVIG) or other treatments not permitted in the protocol.

3.9.2 Procedures for discontinuation of a subject from investigational product

In order to support safety analysis (see Section 8) for anifrolumab subjects who are discontinued from the IP should continue to undergo study visits 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 (as applicable). All visit-related procedures except those associated with IP administration should be completed, (Table 3). Protocol-specified OCS tapering will not be required for these subjects. All subjects should complete an observation period of at least 10 weeks after the last IP received. In case this does not occur within the time frame of the visits specified above, a follow-up visit might be required. The approach taken and reason for premature discontinuation of IP should be registered in the CRF. If the subject permanently discontinues IP prior to their completion of the study and wishes to continue with only selected study assessments; prioritised assessments are listed in Section 3.9. For subjects who wish to withdraw from the study completely refer to Section 3.10.2.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are subjects who have provided informed consent but who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as “Screen Failure” (i.e., subject does not meet the required eligibility criteria). This reason for study withdrawal is only valid for screen failures (not randomized subjects). For eligibility for re-screening of a subject refer to Section 4.1.1. Rescreening of a subject will be permitted once.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment. A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

3.10.3 Lost to follow-up

Subjects will be considered lost to follow-up only if no contact has been established, despite several attempts, by the time of study completion." Lost to follow-up" as a reason for study withdrawal must be documented by time and date of last contact and time.

3.11 Discontinuation of the study

The study may be terminated at individual centers 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. The study may be stopped if, in the judgement of the Sponsor, study subjects are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria (see Section 3.9 for reasons for discontinuation of investigational product) or are otherwise considered significant
- Are assessed as causally related to investigational product
- Are not considered to be consistent with continuation of the study

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2, Table 3 and Table 4 below show the procedures for the Screening, Treatment, and Follow-up visits, respectively.

Table 2 Study plan detailing the procedures at screening

Visit	**V1** **Screening**
Study Day	**Day -30 to Day -1**
Week / Procedure	**-4 to 0**
Written informed consent/assignment Ecode via IXRS	X
Medical history	X
ACR classification criteria	X
Concomitant medications	X
General assessments	
Complete physical examination, height, and weight	X
Vital signs	X
12-lead ECG[a]	X
Chest x-ray[b]	X
Disease assessments	
CLASI[c]	X
SLEDAI-2K[c]	X
Physician Global Assessment of Disease Activity (PGA)[c]	X
Type I IFN 4-gene test	X
Autoantibody panel (ANA, anti-dsDNA, anti-Smith, anti-ribonuclear protein)	X
C3, C4, CH50	X
Safety assessments	
Serum chemistry, haematology, and urinalysis	X
Coagulation Tests	X
Lipid profile	X
Hemoglobin A1c (only diabetics)	X
Serum β-hCG pregnancy test[d]	X
Follicle-stimulating hormone[e]	X
Pap smear[f]	X
B cell count (only if prior B cell-depleting treatment)	X
HIV, Hepatitis B and C	X
QuantiFERON-TB Gold test	X

Visit	**V1** **Screening**
Study Day	**Day -30 to Day -1**
Week / Procedure	**-4 to 0**
TB questionnaire	X
Colombia Suicidality Severity Rating Scale (C-SSRS)	X
Assessment of AEs/SAEs/AESIs	X
Verify eligibility criteria	X

[a]Standard 12-lead ECG

[b]PA and lateral chest x-ray will be performed at screening, if not performed within the previous 12 weeks

[c]These assessment must all be completed at same visit (CLASI, SLEDAI-2K, PGA), if applicable.

[d]Female subjects, unless surgically sterile or 1 year postmenopausal

[e]Females < 55 years of age suspected to be post menopausal.

[f]Only in females with an intact cervix who have not had a Pap smear the last 2 years prior to screening that metinclusion criteria

Table 3 Study plan detailing the procedures during the Treatment Period

Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Day Procedure	1	15 ±3	29 ±3	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	127 ±3	141 ±3	155 ±3	169 ±3	183 ±3	197 ±3	211 ±3	225 ±3	239 ±3	253 ±3	267 ±3	281 ±3	295 ±3	309 ±3	323 ±3	337 ±3	351 ±3	365 ±3
Verify eligibility criteria	X																										
Randomization	X																										
IP administration[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCS tapering							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General assessments																											
Targeted physical exam	X	X	X		X		X		X		X		X						X				X				X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight							X																				X
12-lead ECG																											X
PK, PD and immunogenicity																											
PK pre-dose	X	X	X	X	X	X	X						X						X							X	X
PK post-dose[b]	X																										

Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Day Procedure	1	15 ±3	29 ±3	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	127 ±3	141 ±3	155 ±3	169 ±3	183 ±3	197 ±3	211 ±3	225 ±3	239 ±3	253 ±3	267 ±3	281 ±3	295 ±3	309 ±3	323 ±3	337 ±3	351 ±3	365 ±3
21-gene type 1 IFN PD signature	X	X	X	X	X	X	X						X						X							X	X
Immunogenicity	X						X						X						X								X
Disease assessment																											
CLASI	X	X	X	X	X	X	X		X		X		X						X				X				X
SLEDAI-2K	X		X		X		X		X		X		X						X				X				X
PGA	X	X	X	X	X	X	X		X		X		X						X				X				X
Inflammatory marker panel[c]	X						X						X														X
SLEDAI-2K lab tests[d]	X		X		X		X		X		X		X						X				X				X
Safety assessments																											
Serum chemistry, haematology and urinalysis	X	X	X		X		X		X		X		X			X			X				X				X
Lipid panel																											X
Urine pregnancy test[e]	X		X		X		X		X		X		X		X		X		X		X		X		X		X
Pap smear[f]																											X

Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Day Procedure	1	15 ±3	29 ±3	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	127 ±3	141 ±3	155 ±3	169 ±3	183 ±3	197 ±3	211 ±3	225 ±3	239 ±3	253 ±3	267 ±3	281 ±3	295 ±3	309 ±3	323 ±3	337 ±3	351 ±3	365 ±3
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV[g]																											
QuantiFERON-TB Gold test[h]																											
TB questionnaire	X		X		X		X		X		X		X		X		X		X		X		X		X		X
AEs/SAEs/ AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of injection sites	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient survey							X																				
Optional																											
Skin tape test	X						X																				

[a]Please see Sections 7.2.1 and 7.2.2 for details.

[b]PK-post dose: to be collected on Day 5 (or on Day 6, 7, 8). Actual date and time of sample collection should be documented accurately.

[c]ESR, immunoglobulin levels IgM, IgG, IgA

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

[e]Female subjects, unless surgically sterile or 1 year postmenopausal.

[f]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 smearmay vary by country, the Sponsor recommends that local guidelines for obtaining Pap smears in subjects who have received immunomodulators orimmunosuppressive treatment be followed.

[g]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 levelsmust remain below the LLOQ as per the central laboratory

[h]QuantiFERON-TB Gold test will be followed for those subjects with indeterminate levels at screening.

Table 4 Study plan detailing the procedures during Follow-up

Visit	**V29 (6wks post treatment)**	**V30 (10 wks post treatment)**
Study Day	**393 ±7d**	**421 ±7d**
Week / Procedure	Week 56	Week 60
Concomitant medications	X	X
General assessments		
Complete physical examination, weight		X
Vital signs	X	X
PK, PD, and immunogenicity assessments		
PK	X	X
21-gene type 1 IFN PD signature		X
Immunogenicity		X
Disease assessments		
CLASI	X	X
SLEDAI-2K	X	X
PGA	X	X
Inflammatory marker panel (ESR, IgM, IgG, IgA)		X
SLEDAI-2K lab tests[a]		X
Safety assessments		
Serum chemistry, haematology, and urinalysis	X	X
Urine pregnancy test[b]	X	X
HBV (if applicable)[c]		X
QuantiFERON-TB Gold test (if applicable)[d]		X
TB questionnaire	X	X
Colombia Suicidality Severity Rating Scale (C-SSRS)	X	X
Assessment of AEs/SAEs/AESIs	X	X

[a]SLEDAI-2K lab tests are C3, C4, CH50 complement, anti-dsDNA antibodies, urine protein/creatinine ratio
[b]Female subjects, unless surgically sterile or 1 year postmenopausal
[c]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.

[d]QuantiFERON-TB Gold test will be followed for those subjects with indeterminate levels at screening.

4.1 Enrolment/screening period

At screening, consenting 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 eligibility criteria must not be randomized in the study.

Screening assessments will be performed accordingly to the Screening Visit Procedures (Table 2), from Day -30 to Day -1. Screening procedures may take place during more than 1 visit.

Once screening assessments are complete and all necessary laboratory results are obtained, a subject may be randomized. The randomization at Week 0 (Day 1) may occur at any time point within 30 days after screening visit provided that all required assessment results are available.

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 randomization.

4.1.1 Re-testing and re-screening

Re-testing

If a subject does not meet the eligibility criteria on the basis of a laboratory value for liver enzymes, haematological, or disease activity related tests the laboratory parameter *may be repeated once* within the screening period. This re-testing is allowed without requirement for re-screening.

Re-screening

Subjects who fail to meet the inclusion/exclusion criteria (i.e., screening failures) may be eligible to be re-screened *once* and AstraZeneca Study Physician can be contacted for discussion and decision regarding re-screening. Subjects who are re-screened will be required to re-consent and complete/ repeat all applicable study procedures.

4.1.2 Other considerations for screening

4.1.2.1 Medical history

A complete medical history by body system will be completed during screening. This will also include history of allergies and anaphylaxis, concomitant diseases, viral reactivation events, and previous manifestations of SLE. On Day 1, the medical history will be reviewed and any changes since screening will be documented, if applicable.

4.1.2.2 SLE medication history

All prescription medications the subject has ever taken for SLE should be documented in the subject's file (except for only minor dose adjustments if these were done >3 months prior to

the ICF signature date), including prior use of cyclophosphamide, mycophenolate mofetil, mycophenolic acid, oral and parenteral corticosteroids; if these were discontinued, then reasons for discontinuation must be included. Any medications ongoing at the time of informed consent or received following signing the ICF are considered concomitant medications. Any non-prescription medications, e.g., naturopathic or ayurvedic remedies, ever used for SLE or for any other purpose should be documented, as well as continuing use of any non-prescription remedies not excluded from use during the study period.

4.1.2.3 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.

4.1.2.4 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.

4.2 Treatment period

Assessments during the Treatment Period will be performed according to the Schedule of Treatment Visit procedures (Table 3), from Week 0 (Day 1) to Week 52.

On Day 1, upon confirmation that the subject continues to meet eligibility criteria, the subject will be randomized in to the study via the IXRS system.

Subjects will have scheduled visits at 2-week intervals to complete protocol-specified assessments and IP administration according to the Schedule of Treatment Visit Procedures (Table 3).

The last dose of IP will be administered on Week 50. At Week 52, subjects will have End of Treatment (EOT) visit. For subjects who prematurely discontinue IP and are not willing to continue to participate in the study refer to Section 3.9.

4.2.1 Patient survey at week 12

After subjects complete all the assessments/procedures required at week 12, subjects will be asked to complete patient survey for trial experience. See Appendix O. For subjects who are premature discontinued, the patient survey will be completed at the early discontinuation visit.

4.2.2 Follow-up visits after premature discontinuation of investigational product

Subjects who discontinue IP should continue to undergo study visits 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 (as applicable). If the subject is unwilling to complete all regularly scheduled clinic visits, the subject should complete the Early Discontinuation Visit (Week 52 procedures) within 2 weeks of the last dose of IP, as well as Follow-up Visits (Week 56 and Week 60 procedures) unless consent is withdrawn. If the subject is unwilling to continue with any study visits, including EOT, at the minimum, the following assessment should be completed:

- PK/PD blood sample
- CLASI
- SLEDAI-2K
- PGA

In addition the following safety assessments must be performed:

- C-SSRS
- Assessment of AEs/SAEs (including AESIs)
- Concomitant medications
- Targeted physical exam
- Vital Signs (BP, HR, RR and body temperature)
- Weight
- Safety lab tests
- ADA test
- TB questionnaire

4.3 Follow-up period

All subjects will be followed for 10 weeks after the last IP dose. Table 4 shows all procedures to be conducted during the follow-up period.

4.4 Unscheduled visits

If a subject needs an unscheduled visit the Investigator should decide the assessments needed to be completed based on the reason for the visit and for subject´s safety. Concomitant

medications and AEs should be collected at all unscheduled visits. Efficacy assessments should not be completed at unscheduled visit.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms 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 of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

Efficacy measurements will be made at the times indicated in the Study Plan (Table 2, Table 3 and Table 4).

5.1.1 Training and certification for Systemic Lupus Erythematosus assessments

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

- CLASI
- SLEDAI-2K
- PGA

The CLASI, SLEDAI-2K, PGA 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 and training. Training will include printed training materials, digital video disks (DVDs) and formal presentations, web-based training modules, as well as training sessions during investigator's meeting if applicable.

After attending study presentations (i.e., Investigator Meeting) or after completion of online training module, all Investigators and designed site physicians must pass an online examination in order to obtain certification for all disease evaluation assessments. Investigators and designated site personnel must be trained and certified prior to subjects entering screening at their respective sites. If there is a change in site personnel over the course of the study, new Investigators or physicians must be certified prior to perform the CLASI, SLEDAI-2K and PGA assessments.

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.

5.1.2 Cutaneous Lupus Erythematosus Disease Area and Severity Index

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 F). 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 is each area is measured.

5.1.3 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 assessments and decide whether each manifestation is "present" or "absent" in the last 2 weeks. The assessment also include 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 descriptor are multiplied by 4 and central nervous descriptor 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 score are valid, reliable and sensitive clinical assessments of lupus disease activity.

5.1.4 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. 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 global assessment, factoring in all aspects of subject's lupus disease activity. It should not reflect non-lupus medical conditions.

5.1.5 Oral corticosteroid tapering

Please refer to Section 7.7.2 for all information regarding steroid tapering.

5.2 Safety assessments

5.2.1 Clinical Laboratory assessments

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

A serum pregnancy test (or serum FSH in postmenopausal females of age < 55 years 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.

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 following laboratory variables will be measured:

Table 5 Clinical Laboratory Variables

Haematology (whole blood)	**Clinical Chemistry (serum)**
B-Haemoglobin (Hb)	Calcium
B-Leukocyte count	Chloride
B-Leukocyte differential count (absolute count)	Potassium
B-Platelet count	Sodium
B-Haematocrit	AST*
B-MCV, MCH, MCHC	ALT*
B cell count (only if prior B cell-depleting treatment)	ALP*
Urinalysis	GGT

Colour	BUN
Appearance	Creatinine
Specific gravity	Total bilirubin* (reflexively fractionated if elevated)
pH	Glucose
Protein dipstick	Albumin
Glucose	CK
Ketones	**Fasting lipid profile**:
Blood	Total Cholesterol
Bilirubin	High density lipoprotein (HDL)
Microscopy including WBC/HPF, RBC/HPF, casts	Low density lipoprotein (LDL)
Urine creatinine and protein, Urine protein/creatinine ratio	Triglycerides
Inflammatory marker panel	**Infection related test**
ESR, IgM, IgG, IgA	Human immunodeficiency virus (HIV)
	Hepatitis B surface antigen (HbsAg)
SLEDAI-2K lab tests	Hepatitis B core antibody (HbcAb) (reflex DNA testing if isolated HBc positive)
C3, C4, CH50, anti-dsDNA, Urine protein/creatinine ratio,	Hepatitis C antibody
Autoantibody Panel	**Coagulation test**
ANA, anti-dsDNA, anti-Smith, anti-ribonuclear protein	Prothrombin time (PT)
	Partial Thromboplastin time (PTT)
Pregnancy	**Other**
Serum β-HCG pregnancy test	Type I IFN 4-gee test
Serum FSH	Hemoglobin A1c (only diabetics)
Urine pregnancy test	QuantiFERON-TB Gold test

*Note for serum chemistry: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

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 centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. 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.

5.2.1.1 Haematology, clinical chemistry, and urinalysis testing

Haematology, chemistry, and urinalysis, will be taken throughout the study as described in Sections 4.1, 4.2 and 4.3. Table 5 provides a complete list of the tests included in the Safety Laboratory Variables.

5.2.1.2 Coagulation Testing

Prothrombin time (PT) and partial thromboplastin time (PTT) will be performed as part of the screening tests.

5.2.1.3 Infectious Disease Panel

All subjects will be required to undergo infectious disease testing as part of the screening assessments. The Infectious Disease panel includes testing for human immunodeficiency virus, Hepatitis B and C virus.

Subjects with a confirmed positive HIV test, Hepatitis B surface antigen, or Hepatitis C antibody will not be eligible to participate.

Subjects with an isolated positive test for Hepatitis B core antibody at enrolment/screening, will be tested for Hepatitis B DNA at the central laboratory. Subjects with HBV DNA test above LLQ the will not be eligible to participate and subjects with undetectable HBV DNA, defined as below the LLQ, will be eligible to participate and must be tested every 3 months for HBV DNA. If, at any time during the Active Treatment period, HBV DNA is detected, the subject must be discontinued according to Section 3.9.2.

5.2.1.4 Fasting lipid profile

Subjects will have a fasting lipid profile (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) completed at times indicated in Table 2 and Table 3. Subjects will be required to fast for at least 8 hours prior to this assessment (see Section 3.8.1).

5.2.1.5 Tuberculosis Testing

Subjects will be tested for TB at screening and at various additional time points throughout the study, if required. Please refer to Section 5.2.6.2 for details of TB screening and monitoring.

5.2.1.6 Pregnancy Testing

Females of child-bearing potential will be required to have a negative serum β-hCG test during the enrolment/screening period; please refer to Section 4.1 A negative urine dipstick pregnancy testing is required prior to administration of IP and pregnancy testing is also required at follow-up visits; please refer to Sections 4.2 and 4.3.

Follicle-stimulating hormone (FSH) testing is required at screening for all post-menopausal female subjects of an age of < 55 years, defined as at least 12 months since last menses. FSH level must be greater than the central laboratory value of post-menopausal. If the FSH level is not above the central laboratory value of post-menopausal, two effective methods of contraception (see Table 1) must be used.

5.2.2 Physical examination

Complete physical examination

A complete physical examination will be performed at the visits specified in Table 2, Table 3, and Table 4. The examination includes assessments of; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

Targeted physical examination

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

5.2.3 ECG

Standard 12-lead ECGs will be performed on all patients at specific time points as described in the Study Plan (Table 2, Table 3, and Table 4), as to local routines. A single ECG will be taken after the patient has been resting for 5 minutes in the supine position. Clinically significant abnormalities according to the Investigators´ discretion registered after screening visit should be reported as AEs.

5.2.4 Vital signs

Vital signs (body temperature, blood pressure [BP], pulse rate and respiratory rate) will be obtained at each visit and before and after IP administration as described in Section 7.2.2. 7.2.2

5.2.5 Assessment of Injection Sites

Injection sites will be visually inspected before (except at Day 1) and after IP administration at every visit from Week 0 through Week 50.

5.2.6 Other safety assessments

5.2.6.1 Chest x-ray

A posterioranterior (or anteriorposterior) and lateral view chest x-ray will be obtained during the screening period or can be substituted with documentation of a previous chest x-ray performed anytime within 12 weeks of the expected date of randomization. A chest x-ray that

has no evidence of current active infection (e.g., TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to SLE) is required to meet inclusion criteria.

A formal radiologic report of the chest x-ray should be available at the site. The report should allow the assessment of the following:

- No evidence of any active infection including TB
- No evidence of old active TB
- No evidence of malignancy
- No evidence of other clinically significant abnormalities unless felt secondary to SLE (these should be specified [e.g., pleural effusion])

5.2.6.2 Tuberculosis screening and monitoring

Screening evaluation

A blood test for TB will be done at screening using QFT-G. This is an IFN gamma release assay (IGRAs) test. Evaluation of all subjects by QFT-G test will be performed by the central clinical laboratory, and chest x-rays within 12 weeks prior to Week 0 (Day 1) will be completed. Compared to culture confirmed TB, overall, 87.6% of patients have a positive QFT-G result (Cellestis, 2005). The false negative rate in this setting appears to be over 12%. Further, the performance of the test in the setting of immunosuppressant drugs has not been evaluated. Nor has it been evaluated in individuals with medical conditions other than, or in addition to, latent TB or TB 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 this study, false negative tests are possible, so a chest x-ray, both PA and lateral views, is a relevant and warranted technique (unless limited by local practice) for detecting active pulmonary disease and minimising potential risk to study subjects.

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 randomized without prophylaxis.
- If the screening QFT-G test is newly positive (can be preceded by an indeterminate or negative result) and chest x-ray shows no evidence of active TB, and the subject has no symptoms or medical history consistent with active TB, treatment for latent TB must be initiated prior to the first investigational product administration and the subject must commit to

completing the full duration of prophylaxis, which may mean completing prophylaxis during the study.

- If the screening QFT-G test is positive at screening but the subject is not newly positive, the subject may be randomized if:

  - Previous or current active TB infection was ruled out and

  - The subject was previously diagnosed with latent TB and has documentation confirming completion of appropriate latent TB treatment or

  - The subject was previously diagnosed with latent TB and is currently receiving prophylactic treatment for latent TB and commits to completing the full duration of prophylaxis.

- If the screening QFT-G test is indeterminate, the test must be repeated at least once by the central laboratory as soon as possible. The subject may be randomized if:

  - The QFT-G test result remains indeterminate or becomes negative and

  - There are no signs or symptoms of active TB and

  - There is no known recent close contact with anyone with active TB and

  - There is no history of latent TB (unless diagnosed with documentation of completion of appropriate treatment or active TB.

Additionally, an expert specialising in TB may be consulted prior to randomization, if deemed necessary in the opinion of the Investigator, after discussion with AstraZeneca study physician. If the subject is randomized, additional QFT-G testing will be performed according to Table 3 and Table 4.

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 CDC guidelines may be followed. This should also be reported as an AESI. Once a latent TB is confirmed, treatment must be instituted immediately and no investigational product may be administered until treatment of latent TB has begun.

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

- Indeterminate QFT-G test result, the subject will continue in the study and TB testing will be performed as outlined for subjects with indeterminate results at screening.

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

- Week 52 QFT-G negative: no further testing

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

- QFT-G positive at Week 52 or later. Confirm positive QFT-G 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 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 patients may present as disseminated disease or with extrapulmonary features and should be referred for appropriate treatment.

5.2.6.3 Cervical cancer screening

Most cases of cervical cancer appear to be related to infection with human papilloma virus (HPV), usually HPV types 16 and 18. Because of the potential for viral reactivation due to blockade of the IFN pathway, cervical dysplasia is being assessed in this study, although to date there has been no signal in the anifrolumab studies. A Pap smear is required at screening in women who have not had their cervix surgically removed. If a Pap smear was preformed within 2 years prior to screening with no documented malignancy (e.g., 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 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 see Appendix J for guidance). The Pap smear will be repeated during the last 4 weeks of the study to ensure that there is no evidence of new cervical dysplasia. Since the access to a Pap smear may vary by country, AstraZeneca recommends that local guidelines for obtaining Pap

smears in subjects who have received immunomodulators or immunosuppressive treatment be followed.

If the Pap smear performed at Week 52 is not normal but shows no evidence of malignancy (e.g., CIN III, CIS, or AIS), it should be repeated as per the subject´s gynecologist´s recommendations. If the subject´s gynaecologist has recommended a specified interval, the Pap smear should be obtained as recommended and the report provided in the source document.

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

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. The C-SSRS will be administered at study visits by a trained assessor and the procedure is described in the Study Reference Manual. The assessor will record the clinical observation on the scale, which will be used as the source document. If possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary assessor is not available, a designated back-up assessor who meets the same qualifications may perform the C-SSRS. 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 an assessor other than the Investigator, it is recommended that the Investigator confirms suicidal ideation before making a referral to mental health services; however this should not delay the referral.

5.3 Pharmacokinetics

5.3.1 Collection of samples

Blood samples for the determination of anifrolumab in serum will be taken at the times presented in the study plan (Table 3, Table 4). A post-dose sample after should be collected 4 days (Day 5 or Day 6, 7, 8) after the first dose of investigational product administration to access anifrolumab concentration after dosing. For all pharmacokinetic samples, it is very important that the date, time of anifrolumab administration, and the sample collection are recorded.

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

5.3.2 Determination of drug concentration

Samples for determination of anifrolumab concentration will be analysed using a validated bioanalytical method. Placebo samples will be analysed. Full details of the analytical method used will be described in the methods section of the pharmacokinetic subreport or study report.

5.3.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the study report finalization or six months after issuance of the draft study report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling.

5.4 Immunogenicity

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

5.4.1 Anti-drug antibodies

The pre-dose and follow-up serum samples to measure presence of ADA will be collected according to the Study Plan (Table 3, Table 4). The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

5.4.2 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 neutralizing ADA will be determined using a validated bioanalytical method.

5.5 Pharmacodynamics

5.5.1 21-gene type I IFN PD signature in whole blood (PD marker)

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 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.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the study centers.

Pharmacodynamic samples are exhausted in the isolation process. Any remaining back up whole blood samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed.

5.5.2 4-gene type I IFN test

At screening the IFN test will be used for assessment of 4 type I IFN inducible transcripts in whole blood. The primary intent is to prospectively identify subjects as IFN "test-high" or "test-low" for the purpose of randomization of subjects into the study. Only subjects with a "test-high" result will be eligible for participation in the study. The kit uses the expression of

the transcripts IFI27, IFI44, IFI44L and RSAD2 compared with 3 reference transcripts; 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 transcript expression. The results of the test will not be shared with the investigative site (i.e., all site personnel will remain blinded to IFN test results). The IFN test will be conducted at a designated central laboratory and a detailed description of the test procedure will be included in the laboratory manual. The data will be evaluated for development of a companion diagnostic.

The IFN test utilizes the analysis of mRNA and does not include the assessment of any DNA sequences. There are no pharmacogenetic analyses planned in this study.

5.5.3 Exploratory Transcriptome Analysis (optional)

Whole transcriptome and specific inflammatory pathway RNA transcript analyses using RNA isolated from whole blood and skin tape strip samples will be performed as an optional part of study. The purpose of these analyses will be to retrospectively evaluate whole blood transcript biomarkers predictive of subject response at baseline, prior to investigational product administration, as well as to potentially identify additional PD biomarkers in whole blood and skin.

Whole blood

RNA isolated from whole blood samples collected for 21-gene type I IFN analysis according to Study Plan in Table 3 and Table 4 as described in Section 5.5.1 will be used for transcriptome analyses.

Skin tape strips

Skin tape strips will be collected at Week 0 and Week 12 from subjects consenting to this optional part of study. The skin tape strips will be collected using non-invasive adhesive patches applied to lesional and non-lesional skin.

Instructions for sample collection, processing, storage, and shipment of skin tape strips can be found in the separate laboratory manual provided to the study centers.

5.6 Pharmacogenetics (Not Applicable)

5.7 Biomarker analysis (Not Applicable)

5.8 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed.

5.9 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials

containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

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

5.10 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

5.11 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). 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 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity 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 jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events and SAEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (10 weeks post final dose).

6.3.2 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 Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca 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.

6.3.3 Variables

The following variables will be collect 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.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
  - Date of hospitalisation
  - Date of discharge
  - Probable cause of death
  - Date of death
  - Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug (e.g., 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 A to the Clinical Study Protocol.

6.3.5 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/the child had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 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. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, 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 uses the clinical, rather than the laboratory term (e.g., 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/SAE.

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.

6.3.7 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.

6.3.8 Disease progression/worsening of SLE

Disease progression can be considered as a worsening of a subject's condition attributable to SLE. It may be an increase in the severity of the existing of 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 captured per PI's judgement.

6.4 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.

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

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

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

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

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

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

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

6.5 Overdose

An overdose in this study is defined as a subject receiving a dose of investigational product that is greater than the dose that was intended to be given

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and pregnancy outcomes should be reported to AstraZeneca.

6.6.1 Maternal exposure

The required methods of contraception are described in Section 3.1. If a subject becomes pregnant during the course of the study IP should be discontinued immediately. Pregnancy is not regarded as an AE unless the IP under study is suspected to have interfered with effectiveness of the contraceptive medication used. 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 should be followed up and documented even if the subject was discontinued from the study.

If a pregnancy occurs during the study, the Investigator or other site personnel must inform the appropriate AstraZeneca representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm as described in Section 3.1. Pregnancy of the subject's partner is not considered as an AE, but the outcome of all pregnancies (or any conception) should if possible 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.

6.7 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 non-serious.

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 non-fatal myocardial infarction, non-fatal stroke, and CV death).

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 non-serious AESI will be categorised as an AE. For reporting of AESIs, see Section 6.8.

6.7.1 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.

6.7.2 Opportunistic serious 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.

6.7.3 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 K is provided as a simple and rapid means to make the diagnosis of anaphylaxis during injection 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).

6.7.4 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.

6.7.5 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.

6.7.6 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 case where a biological specimen is positively 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 dose 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.

6.7.7 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 diarrhea, 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.

6.7.8 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 N for a list of vasculitic syndromes excluded from the study.

6.7.9 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 both the Cardiac and Vascular MedDRA System Organ Classes and all SAEs in the Central Nervous System Vascular Disorders Standard Medical Query for evaluation. The CV-EAC chair may adjudicate some events that do not fall into the above categories.

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 randomization group. Please refer to the adjudication charter for details.

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 non-serious) 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 IP related toxicities

6.9.1 Anaphylaxis, hypersensitivity, and injection-related reactions

Hypersensitivity reactions including anaphylaxis have been reported with the subcutaneous administration of 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 recognize and treat anaphylaxis.

Subjects should not be premedicated unless they have had a prior hypersensitivity reaction to anifrolumab. However, if a prior hypersensitivity reaction has been documented, the Investigator may elect to administer an appropriate medication prophylactically potentially including an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the subject prior to subsequent investigational product administration. Prophylactic use of glucocorticosteroids prior to subsequent injection 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 (e.g., 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. For any active infection (e.g., *varicella zoster* infection/chickenpox) or significant exposure to any infection (e.g., *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 (e.g., 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 (i.e., 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. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Anifrolumab (MEDI-546)	150 mg/mL solution of anifrolumab intended for SC administration	MedImmune, LLC
Placebo	Solution intended for SC administration	MedImmune, LLC

Each vial of investigational product or placebo contains 1.3mL fill volume. Investigational product and placebo will be supplied to the site as follows:

For the 150 mg anifrolumab and matched placebo groups = one kit will be dispensed per visit from the IXRS

- Sixteen subjects will be randomized at a 3:1 ratio to receive anifrolumab at a fixed dose of 150 mg (12 subjects) as added to SOC or placebo (4 subjects) plus SOC, given Q2W as one SC injection (= 1 mL)

For the 300 mg anifrolumab and matched placebo groups = two kits will be dispensed per visit from the IXRS

- Sixteen subjects will be randomized at a 3:1 ratio to receive anifrolumab at a fixed dose of 300 mg (12 subjects) as added to SOC or placebo (4 subjects) plus SOC, given Q2W as two SC injections (=2 x 1 mL).

Each kit will have a unique number that will be printed on all labels within the kit (i.e., the outer carton label and the label on the vial within the carton).

Preparation of investigational product and placebo must be performed by a trained unblinded team member (e.g., pharmacist, study nurse) at the site.

AstraZeneca will provide detailed preparation, storage and handling instructions for each product and treatment.

7.2 Dose and treatment regimens

Anifrolumab or placebo, will be administered as SC injections Q2W. Anifrolumab 150 mg and corresponding placebo will be given as one injection in a total volume of 1 mL and anifrolumab 300 mg and corresponding placebo will be given as two injections of a volume of 1 mL each. IP dosing must be at least 10 days apart.

All investigational products will be labelled in a double-blind fashion. AstraZeneca will provide anifrolumab (MEDI-546) 150 mg and Placebo kits containing 1 vial/kit. 1 vial of 150 mg anifrolumab or 1 vial of placebo. The vial will be labelled with a blinded booklet label.

7.2.1 Investigational product administration procedures

An unblinded qualified study site personel, who will not be involved in the management of the subjects, will inject the IP into the SC tissue of the anterior thigh or abdomen. Two injections (150 mg per injection) are required in order to administer anifrolumab at the 300 mg dose and for the corresponding placebo. Therefore at each administration of anifrolumab 300 mg, and corresponding placebo, two separate injection sites on the anterior thigh or abdomen at least 3 cm apart and on the same side for both injections should be used. Injection sites should be rotated at each visit. The time of the first SC injection will be recorded for each subject.

The IP will be administered via a 27-gauge 1/2-inch needle. The person administering the dose will wipe the skin surface of the anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissue. The IP will be slowly injected (at least 5-second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection.

7.2.2 Monitoring of investigational product administration

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before IP administration on all treatment visits. After IP administration, subjects will be monitored for immediate drug reactions; vital signs will be taken immediately after administration of IP and at least every 30 minutes (± 5 minutes) thereafter. In addition, injection sites will be visually inspected.. For the first 3 doses of IP (Weeks 0, 2, and 4), subjects will remain at site for a minimum of 2 hours or until stable, whichever is later. If no safety concerns subjects will remain at site for a minimum of 1 hour or until stable, whichever is later, for the subsequent IP doses, i.e., from dose 4 (Week 6) and onwards. Discharge from site will be determined by the investigator.

7.3 Labelling

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

Before the kit is dispensed to the subject, the investigator must fill in the required information on the empty lines on the front cover page, locate the page with local label text, and demonstrate to the subject. Booklet labels must be opened to find full label text in 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 products) should be recorded in the appropriate sections of the Case Report Form. The investigator product will be administered by study 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 drugs 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. The investigator will either return any unused IP to AstraZeneca or its designate, or destroy IP at the site depending on local regulations. If the IP is destroyed at site, the site personnel will count for all unused IP or appropriated destruction. If the IP is returned to AstraZeneca or its designate, the study site personnel or the AstraZeneca monitor will account for all received IP received at the site, unused IP and for appropriated destruction.

7.7 Concomitant treatment

As anifrolumab is an investigational immunomodulatory agent, non-protocol permitted changes to immune modifiers or immunosuppressants during the study are not allowed. If a subject receives any of the prohibited medications the administration of IP must be immediately discontinued and AstraZeneca study physician notified immediately. If a subject is given any of the allowed, but restricted, medications in unpermitted doses or time periods the Investigator must notify AstraZeneca Study Physician immediately. The subject will be considered as a non-responder for exploratory efficacy assessments and AstraZeneca Study Physician will determine if the subject may continue to receive IP or not.

From 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.

7.7.1 Standard of Care treatment for SLE

Permitted medications for **SOC treatment for SLE** are listed below and **must be kept at stable doses within the dose ranges described below** from indicated time points and throughout the treatment period.

Concomitant medications should only be administered after all visit assessments, including IP administration and, if applicable, post-injection PK blood tests.

Antimalarials, oral corticosteroids and other immunosuppressants (azathioprine, methotrexate, and mycophenolate mofetil/mycophenolic acid, and mizoribine) are permitted, and at least 1 is required, as part of SLE therapy on Day 1. 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.

Permitted SLE SOC treatment	Maximal dose allowed	Stable dose prior to randomization
Methotrexate (oral, sc, or im)	25 mg per week[a]	8 weeks
Hydroxychloroquine,	400 mg per day	8 weeks
Chloroquine, quinacrine	200 mg per day	8 weeks
Azathioprine	200 mg per day	8 weeks
Mycophenolate mofetil	2000 mg per day	8 weeks
Mycophenolic acid	1440 mg per day	8 weeks
OCS	<40 mg per day prednisone or equivalent	2 weeks
Topical treatment for skin symptoms	According to recommended maximal dosing	2 weeks

[a]Route of administration must remain stable.

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

7.7.2 Corticosteroid treatment

7.7.2.1 Protocol-specified corticosteroid tapering

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

- Persistent moderately to severely active skin manifestations 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

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

7.7.2.2 Corticosteroid bursts

Week 0 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. After Week 12 additional steroid bursts may be given as per investigators judgement of clinical need.

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.; *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 AZ study physician should be contacted.

From Week 12 until end of study

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

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

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

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

Steroid bursts for non-SLE causes (e.g., asthma or COPD exacerbation) are allowed throughout the study but the AstraZeneca study physician should be informed. A burst may include OCS up to ≤20 mg/day of prednisone (or equivalent) for up to a total of 14 days and must be tapered to less than or equal to the Day 1 dose within 14 days. The non-SLE reason for the burst must be clearly indicated in the source documents. 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 AstraZeneca study physician, whom will determine if the subject may continue to receive IP.

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 52.

7.7.2.4 Topical therapy

Concurrent use of topical therapy for cutaneous lupus erythematosus (e.g., topical corticosteroids, topical immunosuppressants) is permitted. 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 at same dose as was being used at the time of randomization. It is encouraged that no new dermatologic preparations be initiated for the duration of the study. Subjects should use sunscreen (list as concomitant medication for SLE) and avoid sun exposure for the duration of the study.

7.7.3 Anti-hypertensive agents and statins

Anti-hypertensive agents including; Angiotensin-Converting-Enzyme Inhibitor (ACEI), Angiotensin II Receptor Blockers (ARB), calcium channel blockers, beta blockers, α receptor blockers, are allowed and doses may be adjusted as clinically indicated.

Statins must be kept at stable doses after Day 1. Decreases in the dose are allowed only to reduce statin-related side effects.

Cholestyramine must be discontinued prior to the day of randomization.

7.7.4 NSAIDs

Prescription NSAIDs may be used within label-approved dose ranges. Prescription NSAIDs cannot be administered with other NSAIDs (including over-the-counter non-steroidals) except for low-dose aspirin (≤325 mg/day). On a given visit day, prescription NSAIDs should not be taken until after all assessments have been completed.

7.7.5 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 (e.g., paracetamol) may be used for pain as required.

7.7.6 Low-dose aspirin

Low-dose aspirin (maximum of 325 mg/day) for cardiovascular disease is permitted.

7.7.7 Narcotic analgesics

These can be used during the study as clinically indicated.

7.7.8 Other concomitant treatment

Other 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 CRF.

7.8 Prohibited medications

The prohibited medications listed below are **not allowed at any time point after enrolment** and **must be discontinued prior to signing ICF** in accordance with the time periods below.

Prohibited Medication	**Discontinuation prior to signing ICF**
Abatacept (CTLA 4 Ig)	24 weeks
Acthar gel	6 weeks
Adalimumab	12 weeks
Anakinra	12 weeks
Alefacept	12 weeks
Apremilast	4 weeks
Atacicept (TACI-Ig)	40 weeks

Prohibited Medication	Discontinuation prior to signing ICF
Baricitinib	4 weeks
Belimumab	12 weeks
Blisibimod (AMG 623)	12 weeks
Certolizumab pegol	24 weeks
Chlorambucil	24 weeks
Corticosteroid pulse treatment (oral or IV) with doses >500 mg methylprednisolone or equivalent	24 weeks
Cyclophosphamide (or any other alkylating agent)	24 weeks
Cyclosporine (oral)	8 weeks
Cytokines (eg IFN)	Wash out time
Dapsone	4 weeks
Danazol	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	12 weeks
Etanercept	4 weeks
Golimumab	12 weeks
Infliximab	12 weeks
Intravenous immunoglobulins	4 weeks
Lenalidomide	8 weeks
Lupuzor (IPP-201101)	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Obinutuzumab	26 weeks
Ocrelizumab	26 weeks
Ofatumumab	26 weeks
Pimecrolimus	4 weeks
Plasmapheresis or plasma exchange	24 weeks
Retinoids	4 weeks
Rituximab	26 weeks
Sirolimus	4 weeks

Prohibited Medication	Discontinuation prior to signing ICF
Tabalumab	12 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks
Tofacitinib	4 weeks
MEDI-545 (sifalimumab)	26 weeks
Sirolimus	4 weeks

NOTE: If any of the medications listed above is started at any time after ICF is signed, it will lead to immediate discontinuation of the IP as per Section 3.9.

7.9 Post Study Access to Study Treatment

At the end of the study, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC treatment for the condition under study.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

Summary data will be presented in tabular format. Continuous variables will be summarised by descriptive statistics, including number, mean, standard deviation, median, minimum, maximum and coefficient of variance [%CV]. Confidence intervals (CIs) will be two-sided, unless otherwise stated. Categorical data will be summarized by the number and percentage of subjects in each category.

The study will be double-blind until the database lock, performed after all subjects complete Week 12. Thereafter, the sponsor will be unblinded, whilst the investigators and subjects will remain blinded throughout the remainder of study, including the treatment period up to Week 52 and the follow-up period up to Week 60. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject enrolled and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data at Week 12. Details of endpoint analyses will be described in the SAP.

8.2 Sample size estimate

There is no formal power calculation as there will be no hypothesis testing, and the data collected in this study will be used to inform further study design and development. Subjects will be randomized at a ratio of 3:1 to receive active:placebo (12 subjects on active and 4 subjects on placebo) for the two dosing levels. This gives a total study population of 32 subjects. CCI

CCI

8.3 Definitions of analysis sets

8.3.1 All subjects analysis set

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

8.3.2 Full analysis set

The full analysis set will be used as the primary population for reporting PD, efficacy and safety data. This comprises of all subjects randomized into the study who receive at least 1 dose of investigational product and will be analyzed according to randomized treatment (modified Intention-To-Treat). Any major deviations from randomized treatment will be listed and considered when interpreting the safety data.

8.3.3 PK 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

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

Week 12 is the time point at which outcome measures for PD, safety, efficacy and some PK parameters will first be characterized (primary time point for analysis). A second characterization of all PK, PD, safety and efficacy outcomes will be completed for up to Week 52, study end. Further details will be presented in the SAP.

8.4.1 Primary outcome measures

8.4.1.1 Pharmacodynamics (PD)

The 21-gene type 1 IFN signature score and neutralization ratio (relative to baseline) will be used to characterize PD over time, with the primary time point at Week 12.

8.4.1.2 Pharmacokinetics (PK)

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 concentration after the first dose will also be evaluated. Additional PK parameters may be determined where appropriate.

8.4.2 Secondary outcome measures

8.4.2.1 Immunogenicity

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

8.4.2.2 Safety

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, chest x-ray, haematology, serum chemistry, urinalysis, reported AEs and SAEs (including AEs of special interest, see Section 6.7) and C-SSRS. 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. Other safety assessments: Coagulation Tests, Hemoglobin A1c (only diabetics), Serum β-hCG pregnancy test, Follicle-stimulating hormone, Pap smear, B cell count (only if prior B cell-depleting treatment), HIV, Hepatitis B and C, QuantiFERON-TB Gold test, TB questionnaire.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. Adverse events will be summarised by means of descriptive statistics and qualitative summaries.

Other significant adverse events: During the evaluation of the AE data, a medically qualified expert from Sponsor/Designee team will review:

- AESI: The AESI are listed in Section 6.7. These will be reported in the CSR.
- A list of AEs that were not reported as SAEs, or AEs leading to discontinuations: significant AEs of particular clinical importance may, after consultation with the Astra Zeneca Global Patient Safety Physician, be considered as 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.

8.4.3 Exploratory outcome measures

8.4.3.1 Efficacy

The efficacy outcomes for anifrolumab groups and placebo will be explored using the following outcome measures.

CLASI activity score

The effect of anifrolumab on skin will primarily be characterized by a ≥ 50% improvement in CLASI activity score from baseline.

Additionally, the absolute levels, as well as the change from baseline in CLASI activity scores will be characterized over time.

SLEDAI-2K score and Physician global assessment of disease activity (PGA)

The SLE disease activity will be characterized by SLEDAI and PGA.

SLEDAI will be characterized longitudinally over time by the absolute levels and changes from baseline in SLEDAI-2K.

Physician global assessment (PGA) will be characterized longitudinally over time using the change from baseline in PGA (VAS scale 0-100 mm).

Autoantibodies and inflammatory markers

The outcome variables for disease-related autoantibodies including; anti-nuclear antibody (ANA), parameters of the biological domain (complements C3, C4 and CH50), and the inflammatory marker ESR, will be measured by change from baseline, longitudinally over time.

8.4.3.2 Oral corticosteroid management

OCS management will be characterized over time.

8.4.3.3 Skin tape test (optional)

The skin tape test will be characterized by the 21-gene type 1 IFN signature scores. Further details will be presented in the SAP.

8.5 Methods for statistical analyses

No formal comparisons will be made between treatment groups, and all results will be presented by treatment. The two placebo arms will be pooled for the analyses. In addition, if

deemed appropriate, data from the two anifrolumab arms may be pooled for the exploratory analyses of efficacy, and details for when to do this will be presented in the SAP.

Missing data

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

Presentation of results

Data will be presented by treatment groups. Descriptive statistics (number, mean, standard deviation [SD], median, minimum, maximum and coefficient of variance [%CV]) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

8.5.1 Analysis of the primary variable (s)

The primary characterization of the effect of anifrolumab on the 21-gene type I IFN PD signature will be carried out through the individual and median 21-gene type 1 IFN signature scores and neutralization ratios at Week 12. The PD gene signature will also be explored over time. A subset of the full analysis set will be used, defined as subjects who are randomized, received at least 1 dose of investigational product (modified Intention-To-Treat) and did not discontinue IP, will be used.

The primary characterization of anifrolumab PK will be done by descriptive statistics of the derived PK parameters. Individual and mean anifrolumab concentrations will also be plotted over time.

8.5.2 Analysis of the secondary variables

8.5.2.1 Safety

Adverse events (including AESIs) will be summarised by means of counts summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term (PT). 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 characterized for urinalysis.

The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarised by treatment group, with placebo pooled.

The proportion of subjects with suicidal behaviour and suicidal ideation throughout the study based on the C-SSRS will be presented for each treatment group. The proportion of subjects within each of the 4 suicidal behaviour categories and within each of the 5 suicidal ideation sub-categories will also be presented for each treatment group. Descriptive statistics on the total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be summarised for each treatment group, with placebo pooled. Other safety variables may be summarised as appropriate. Further details will be provided in the SAP.

8.5.2.2 Immunogenicity

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 endpoints will be assessed. The potential association of ADA with safety and efficacy will be explored.

8.5.3 Interim analysis

The treatment period will be double-blind up until the data base lock performed after all randomized subjects complete Week 12 or discontinue the study prior to Week 12 (the main analysis). At this time point Sponsor personnel will be unblinded whereas investigators and subjects will remain blinded throughout the entire study. An additional data base lock will take place once all subjects have completed Week 60 or discontinued the study prior to Week 60. Further details will be presented in the SAP (end of extension analysis).

8.5.4 Sensitivity analysis

Various missing data assumptions may be explored for the primary PD outcome and exploratory outcomes. Further details will be provided in the SAP.

8.5.5 Analysis methods for exploratory outcome measures

8.5.5.1 Efficacy

The efficacy outcomes for anifrolumab groups and placebo will be explored using the analysis methods stated below. These analyses will be performed on individual and pooled anifrolumab treatment groups, where appropriate. Placebo groups will be pooled for all analyses.

CLASI activity score

CLASI activity will be characterized at Week 12 by the proportion of subjects achieving a ≥ 50% improvement in CLASI activity score from baseline. The proportion of patients achieving a ≥ 50% improvement in CLASI activity score from baseline will also be characterized longitudinally from Week 2 up until Week 52.

Change from baseline and overall CLASI activity scores will be characterized up to Week 12 for subjects using line charts. This will also be characterized longitudinally up to study end.

Shift plots in overall CLASI activity score from baseline to Week 12 and baseline to Week 52 will be created.

Further details will be presented in the SAP.

SLEDAI-2K score

SLEDAI-2K will be characterized by summary statistics for change from baseline and overall score at Week 12. Summary statistics for change from baseline and overall score will also be characterized longitudinally from up until Week 52.

Change from baseline and overall SLEDAI-2K scores will be characterized up to Week 12 for subjects using line charts. This will also be characterized longitudinally up to Week 52.

Physician global assessment of disease activity (PGA)

Physician global assessment (PGA) will be characterized by summary statistics for change from baseline and overall score at Week 12. Summary statistics for change from baseline and overall score will also be characterized longitudinally up until Week 52.

Autoantibodies and inflammatory markers

The outcome variables for disease-related autoantibodies including; anti-nuclear antibody (ANA), parameters of the biological domain (complements C3, C4 and CH50), and the inflammatory marker ESR, will be characterized by summary statistics for change from baseline, longitudinally over time.

Further details will be provided in the SAP.

8.5.5.2 Oral corticosteroid management

Shift tables and plots of the OCS dose at baseline and; Week 12, Week 24, and Week 52, will be produced. The potential association between change in OCS dose and CLASI will also be explored graphically. Further details will be presented in the SAP.

8.5.5.3 Skin tape test

Skin tape test outcome measures will be summarised as appropriate. Further details will be provided in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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

9.2 Monitoring of the study

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

- Provide information and support to 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 (e.g., 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.

9.2.1 Source data

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

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

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

The study is expected to start in Q4 2016 and to end by Q4 2018.

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

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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

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

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

Serious Adverse Event (SAE) Reconciliation

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

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

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/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form 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/IRB, and to the study site staff.

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

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

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

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

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

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

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

10.4 Informed consent

The Principal Investigator(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 Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is 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 informed consent form that is approved by an EC/IRB.

10.5 Changes to the protocol and informed consent form

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

If there are any substantial changes to the study protocol, then a new version of the study protocol will be generated.

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

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

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's EC/IRB are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee 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, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

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Appendix A 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 (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the 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.

- 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

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the 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?

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

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

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

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

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

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

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment

standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

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.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** 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.

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

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 patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient 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 AstraZeneca 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:

- Notify the AstraZeneca representative
- 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 patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient 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 Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

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.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- 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

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

Appendix D American College of Rheumatology Criteria for Systemic Lupus Erythematosus Classification

ACR Criteria for SLE Classification

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

ACR Criteria for SLE Classification

Item	Definition
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies based on: 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; 2) a positive test result for lupus anticoagulant using a standard method; or 3) a false-positive test result for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.
Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug.

Appendix E Systemic Lupus Erythematosus Disease Activity Index 2000

SLEDAI 2K
(Modified for assessment over one month)

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 14 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 cytoside 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¤	Above normal range for testing laboratory (See labs).¤	2¤	¤
Fever¤	>38° C. Exclude infectious cause.¤	1¤	¤
Thrombocytopenia¤	<100,000 platelets / x10^3/L, exclude drug causes.¤	1¤	¤
Leukopenia¤	<3,000 white blood cells / x10^3/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.

Appendix F 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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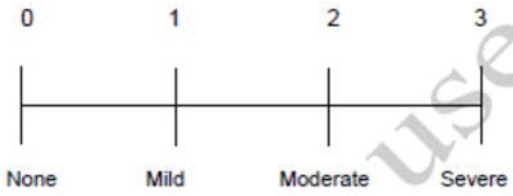
Appendix G Physician global assessment

PHYSICIAN GLOBAL ASSESSMENT (PGA)



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

Appendix H 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	8 mg	8 mg	16 mg	24 mg	32 mg

Example of OCS Tapering Schedule

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

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

Appendix I General guidance for Determination of Major Surgery

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

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

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

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

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

Appendix J 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**

Appendix K 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 patient (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 patient (minutes to several hours); for adults a systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP (taken at or immediately prior to the injection), whichever BP is lower (Sampson et al, 2006).

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 or after the injection of investigational product (but does not meet the definition of anaphylaxis described above).

To assist with the mitigation of these AEs, see Table 6, 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 6 An approach to management of anaphylactic and hypersensitivity

Severity of symptoms	Treatment	Investigational product
Mild reactions (hypersensitivity) Mild 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-injection measurement	Evaluate patient, including close monitoring of vital signs At the discretion of the Investigator, treat patient, 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 injection immediately Option 1: do not resume investigational product injection; Option 2: discontinue any further administration of investigational product; OR at the discretion of the Investigator, continue future investigational product administrations and pretreating patient 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 (hypersensitivity) IP related reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below)	Evaluate patient, including close monitoring of vital signs Treat patient, 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 injection immediately Option 1: do not resume investigational product injection; OR based on risk/benefit evaluation, at the discretion of the Investigator, resume current investigational product injection under observation 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 injections, at the discretion of the Investigator, continue investigational product administration and pretreating patient 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 If moderate event recurs in the same patient, discontinue further investigational product administration
Moderate hypersensitivity reactions IP- 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-injection measurement	Evaluate patient, including close monitoring of vital signs Treat patient, 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 injection immediately DO NOT resume current injection 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-injection 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 patient, including close monitoring of vital signs Maintain airway, oxygen if available Treat patient 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 injection immediately 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

Appendix L Classification criteria for catastrophic anti-phospholipid syndrome

Classification Criteria for Catastrophic Antiphospholipid Syndrome

Criteria

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
4. Laboratory confirmation of the presence of anti-phospholipid antibodies (lupus anticoagulants and/or anticardiolipin antibodies)

Classification

Definite catastrophic antiphospholipid syndrome

Requires all four criteria

Probable catastrophic antiphospholipid syndrome

- All four criteria, except for only two organs, systems, and/or sites of tissue involvement **or**
- All four criteria, except for the laboratory confirmation at least 6 weeks apart due to early death of a patient never tested for antiphospholipid before catastrophic antiphospholipid syndrome **or**
- Criteria 1, 2, and 4 above, **or**
- Criteria 1, 3, and 4, and the development of a third event in more than a week, but less than a month, despite anticoagulation

Adapted from Asherson R, Cervera R, de Groot P, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003;12(7): 530–534.

Appendix M Columbia Suicide Severity Rating Scale (C-SSRS)

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* [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	____	____
© 2008 Research Foundation for Mental Hygiene, Inc.	C-SSRS—Baseline/Screening (Version 1/14/09)	Page 1 of 2

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 - Clinical

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.

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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?
If yes, describe:
Yes ☐ No ☐

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

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

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

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

INTENSITY OF IDEATION

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

Most Severe 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* _____

Appendix N 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

Appendix O Patient Survey at Week 12

Participant Questionnaire on Study Experience

Thank you for your participation in D3461C00008 study. In this questionnaire, we would like to ask you a few questions about your experience of the study with specific focus on study design, the study medication injections, and procedures during the study visits. Your response is very valuable and will allow us to make future trials better tailored to patient´s need. For each question below, please mark the box that best matches your experience and feelings about the study.

1 Did you think the information you received before joining the study was consistent with your experience during the study?

[ ] Yes, it was consistent

[ ] No there was some inconsistency, please specify:

_____

_____

2 Do you believe you received enough information before and during the study?

[ ] Yes

[ ] No

What additional information should we have shared with you before and during the study?

_____

_____

3 You had 25% chance of receiving placebo, rather than the active study medication. Was this a concern and did this affect your willingness to participate in the study?

[ ] No, I had no concern

[ ] Yes, I had some concern but still wanted to participate in the trial

4 You might have had to stop taking medications after joining this study. If you had to do so, how did you feel about that?

[ ] I did not have to stop taking any medication.

[ ] Reasonable

[ ] Unreasonable but acceptable

[ ] Unacceptable, please specify the name of medications.

_____

5 How did you feel about the frequency of visits (every 2 week on-site visit) in this study?

[ ] Comfortable

[ ] Inconvenient but acceptable

[ ] Uncomfortable

6 How did you feel about having the injections once every second week?

[ ] Comfortable

[ ] Inconvenient but acceptable

[ ] Very inconvenient, please give us some advice:

_____

7 How did you feel about having to come to the clinic for the injections?

[ ] Comfortable

[ ] Inconvenient but acceptable

[ ] Very inconvenient

8 Would you prefer to perform the subcutaneous injections yourself at home?

[ ] Yes, I would prefer to inject myself

[ ] No, I prefer injections administered by my doctor or nurse

9 If training were to be provided, would you prefer to give yourself study drug injections?

[ ] Yes

[ ] No

10 Were you comfortable with blood samples being taken during the study?

[ ] Yes

[ ] No

If no, please select reasons below.

[ ] Frequency of blood samples taken

[ ] Volume of blood samples taken

[ ] Pain associated with venous puncture

11 What did you find most challenging in this study?

_____

_____

_____

_____

12 Is there anything we could do to improve your experience during this study? (For example, study design, study procedure and site service, etc.)

_____

_____

_____

_____

13 Do you see any other advantages or disadvantages as a result of participating in the study?

_____

_____

14 If we run another study with similar design, would you want to participate?

[ ] Yes

[ ] No, please specify the reason:

_____