Protocol Number: D3461C00009

Official Title: A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

NCT Number: NCT02794285

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AstraZeneca

Clinical Study Protocol

Drug Substance	Anifrolumab (MEDI 546)
Study Code	D3461C00009
Version	3.0
Date	10 August 2017

A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

EudraCT number: *2016-000625-39*

[redacted]

VERSION HISTORY

Version 3.0, 10 August 2017

The following changes were incorporated into Version 3.0 of the Clinical Study Protocol:

- The requirement that females with an intact cervix must have a Pap smear without documented malignancy (eg, no cervical intraepithelial neoplasia grade III [CIN III], carcinoma in situ [CIS], or adenocarcinoma in situ [AIS]) obtained within 90 days prior to randomization or up to 30 days post-randomisation, ie, before dosing with Investigational Product (IP) at V2 was added. Also, it was added that all female subjects with an intact cervix should have a Pap smear performed within 3 months of the last IP dose, eg, at the end of study or at the early discontinuation visit. (Sections affected: Section 3.1 Inclusion criteria – Inclusion criterion #6; Section 4 Study plan and timing of procedures – Table 2 footnote c and Table 3 footnote b; Section 4.2.1 Premature discontinuation of investigational product; Section 5.2.4 Pap smear).
- The permitted exclusion time for sperm donation by male subjects participating in the study was changed from 85 to 90 days after the last dose. (Section affected: Section 3.3.3.3 Blood and sperm donation).
- The exclusion criteria were updated to clarify that while concurrent enrolment in another clinical study with an investigational product is prohibited, patients who were previously enrolled in studies D3461C00004 and D3461C00005 are permitted to enrol into this study (D3461C00009). (Section affected: Section 3.2.1 General exclusion criteria).
- [redacted]
- [redacted]
- The wording describing the packaging of the investigational product was revised to allow for the use of commercial material in the study in the future and to ensure consistency with the Investigational Medicinal Product Dossier. (Section affected: Section 7.1 Identity of investigational product(s)).
- The requirement for QuantiFERON® (QFT) testing for cases where newly indeterminate QFT test results are obtained were added. The QFT testing for tuberculosis was added to the list of assessments to be performed at the EDV, in

order to correspond with the study schedule assessments. (Sections affected: Section 3.1 Inclusion criteria – 8(d); Section 4.2.1 Premature discontinuation of the investigational product; Section 5.2.7.1 Tuberculosis results at time of randomisation/Week 52 of the Phase 3 Study D3461C00004 or D3461C00005; Section 5.2.7.3 Tuberculosis monitoring at Week 156).

- Clarifications were made to the permitted doses of azathioprine, mycophenolate mofetil, mycophenolic acid, methotrexate, and mizoribine during the study. (Sections affected: Section 3.2.2 Exclusion criteria related to concomitant medications; Section 3.3.1.2 Restricted medications; Background Systemic Lupus Erythematosus standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants)).

- The wording of the instructions for tacrolimus monitoring during the study was revised to remove references to serum levels as the central laboratory requires plasma for tacrolimus testing. In addition, references to absolute tacrolimus levels were deleted. (Sections affected: 3.3.2.1 Background Systemic Lupus Erythematosus standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants); Section 4 Study plan and timing of procedures – Table 2 footnote o, Table 3 footnote m; Section 5.2.9 Clinical laboratory tests – Table 5).

- Mizoribine was added to the list of permitted immunosuppressants. (Section affected: 3.3.2.1 Background Systemic Lupus Erythematosus standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants).

- Mycophenolic acid was added to the list of permitted immunosuppressants in the Protocol synopsis and the dose of mycophenolic acid not to be exceeded was updated to >1.44 g/day. (Sections affected: Protocol synopsis – Target subject population; Section 3.2.2 Exclusion criteria related to concomitant medications; Section 3.3.1.2 Restricted medications; Section 3.3.2.1 Background Systemic Lupus Erythematosus Standard of Care medications (oral corticosteroids, antimalarials, and immunosuppressants)).

- The description of the sample size estimate was amended to ensure consistency with the Statistical Analysis Plan (SAP). (Sections affected: Protocol synopsis – Statistical methods; Section 8.2 Sample size estimate).

- The range for postmenopausal follicle-stimulating hormone (FSH) levels was amended. (Section affected: Section 3.1 Inclusion criteria).

- The wording of the text and table describing acceptable contraception for female and male subjects during the study was updated. (Section affected: Section 3.1 Inclusion criteria – Table 1).

- Instructions were added regarding safety testing requirements if the standard of care (SOC) is changed during the study. (Sections affected: Section 3.3.2.1 Background

Systemic Lupus Erythematosus standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants); Section 4 Study plan and timing of procedures – Table 2 footnote g added and Table 3 footnote f added; Section 5.2 Safety assessments).

- Baricitnib, tofacitinib, or other Janus kinase inhibitors were added to the list of prohibited concomitant medications. [redacted].
- Updates were made to the permitted and prohibited medications. [redacted]
- Serum chemistry, haematology and urinalysis sampling were added to Visit 3/Week 8 and Visit 10/Week 36. (Section affected: Section 4 Study plan and timing of procedures - Table 2).
- Text was added to clarify that additional safety laboratory tests, eg, haematology, liver function tests, and serum creatinine may be required in the judgement of the PRA/AZ medical monitor if the Day 1/Visit 1/Week 0 visit occurs >60 days after the Week 52 final visit of the pivotal studies. (Section affected: Section 4.1 Randomisation).

[redacted]

- The treatment group "All Placebo" was changed to "Randomised Placebo" for the sample size calculation. (Sections affected: Protocol synopsis – Statistical methods; Section 8.2 Sample size estimate; Section 8.5.1 Analysis methods for safety variables).
- Text relating to the unblinding of Sponsor and Clinical Research Organisation (CRO) staff following the database lock of the pivotal studies was amended, in addition to modifications made to the text regarding interim analyses. (Sections affected: Protocol synopsis – Statistical methods; Section 3.8 Methods for unblinding; Section 8.5.3 Interim analysis).
- Other minor changes in wording were made throughout Section 8 Statistical analyses in order to reflect changes made to wording in the SAP, version 1.1 (Sections affected: Section 8.2 Sample size estimate; [redacted] Section 8.3.3 Treatment groups for analysis; Section 8.4 Outcome

measures for analyses; [redacted] Section 8.5 Methods for statistical analyses; Section 8.5.1 Analysis methods for safety variables)

[redacted]

- Other minor edits were made throughout the document for clarification.

Version 2.0, 06 May 2016

The following changes were incorporated into Version 2.0 of the Clinical Study Protocol:

- The requirement that female subjects with an intact cervix must have documentation of a Pap smear with no documented malignancy before Day 1/Visit 1 and yearly thereafter was removed. Access to a Pap smear may vary by country. The Sponsor recommends that local guidelines for obtaining Pap smears in subjects who have received immunomodulators or immunosuppressive treatment are followed. (Sections affected: Section 3.1 Inclusion criteria; Section 4 Study plan and timing of procedures – Tables 2 and 3; Section 5.2.4 Pap smear).

- Previous use (within the last 60 days) of mizoribine >150 mg/day has been added as an exclusion criterion. (Sections affected: Section 3.2.2 Exclusion criteria related to concomitant medications; Section 3.3.2.1 Background Systemic Lupus Erythematosus standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants).

- The requirement that human immunodeficiency virus status must be confirmed by a test performed by the central laboratory if not tested in Studies D3461C00004 or D3461C00005 was added. (Sections affected: 3.2.4 Exclusion criteria related to infection and malignancy risk factors; Section 4 Study plan and timing of procedures – Table 2; Section 5.2.9 Laboratory tests – Table 5).

- Wording in the instructions regarding tuberculosis monitoring was revised to clarify

that in case a subject has a diagnosis of latent tuberculosis, there must be documentation confirming initiation and/or completion of appropriate treatment, depending on the date of diagnosis. In addition, a footnote in the study plan Tables 2 and 3 was reworded to clarify that it is subjects with a newly positive QuantiFERON®-TB Gold test, and not newly indeterminate, who will undergo a chest x-ray. (Sections affected: Section 3.1 Inclusion criteria; Section 4 Study plan and timing of procedures – Tables 2 and 3; Section 5.2.7.1 Tuberculosis results at time of ~~enrolment~~ randomisation/Week 52 of the Phase 3 Study D3461C00004 or D3461C00005; Section 5.2.7.2 Tuberculosis monitoring during the study).

- Wording in the adverse events section was revised to clarify that events will be collected from the time of randomisation in the long-term extension (LTE) study rather than the time of signature of informed consent. Events that occur prior to randomisation in the LTE study should be reported in Studies D3461C00004 or D3461C00005. (Sections affected: Section 6.6.1 Time Period for collection of adverse events; Section 6.8 Reporting of adverse events of special interest).

- Some wording was revised to ensure consistency between Studies D3461C00004, D3461C00005 and D3461C00009 and clarify randomisation process. This includes removal of references to "screening" and "enrolment" to be replaced with "randomisation," and removal of the term "undetectable" to be replaced with "below the lower limit of quantitation." In addition, the Clinical Informatics Plan is renamed as Data Management Plan. (Sections affected: Protocol synopsis – Study period; Protocol synopsis – Study design; Protocol synopsis – Target subject population; Section 1.4 Study design; Section 3 Subject selection, ~~enrolment,~~ randomisation, restrictions, discontinuation, and withdrawal; Section 3.2.1 General exclusion criteria; Section 3.2.4 Exclusion criteria related to infection and malignancy risk factors; Section 3.3.2.1 Background Systemic Lupus Erythematous standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants); Section 3.4 Subject ~~enrolment and~~ randomisation; Section 3.5 Procedures for handling incorrectly ~~enrolled or~~ randomised subjects; Section 3.6 Methods for assigning treatment groups; Section 3.9.2 Withdrawal of the informed consent; Section 4 Study plan and timing of procedures – Tables 2 and 3; Section 4.1 Randomisation ~~Enrolment/screening period~~; Section 4.1.1 Other considerations for ~~enrolment~~ randomisation; Section 5.2.3 Physical examination; Section 5.2.7 Tuberculosis monitoring; Section 5.2.7.1 Tuberculosis results at time of ~~enrolment~~ randomisation/Week 52 of the Phase 3 Study D3461C00004 or D3461C00005; Section 5.2.9 Laboratory tests [including Table 5]; Section 8.3.3 Treatment groups for analysis; Section 9.1 Training of study site personnel; Section 9.2.2 Study agreements; Section 9.4 Data Management; Section 10.3 Ethics and regulatory review; [redacted]

- [redacted]

[redacted] • Other minor edits were made throughout the document for clarification.

Version 1.0, 24 February 2016
Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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.

AstraZeneca

PROTOCOL SYNOPSIS

A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

International Coordinating Investigator

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USA

Study site(s) and number of subjects planned

Approximately 575 subjects are planned at approximately 300 sites.

Study period		Phase of development
Estimated date of first subject randomised	Q3 2016	3
Estimated date of last subject completed	Q3 2021	

Study design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled, extension study characterising the long-term safety and tolerability of an intravenous treatment regimen of anifrolumab (300 mg) versus placebo in subjects with moderately to severely active systemic lupus erythematosus who completed a Phase 3 study (D3461C00004 or D3461C00005) through the 52-week double-blind treatment period.

Approximately 575 subjects from Studies D3461C00004 or D3461C00005 who were previously treated with anifrolumab (150 or 300 mg) or placebo for 52 weeks while receiving standard of care treatment and who are willing to continue treatment may participate in the long-term extension study if all eligibility criteria are met. Subjects will receive either a fixed intravenous dose of 300 mg anifrolumab every 4 weeks for up to 39 doses (Week 0 to Week 152) or placebo. Investigational product will be administered as an intravenous infusion via an infusion pump over a minimum of 30 minutes, every 4 weeks. In order to ensure that subjects with active systemic lupus erythematosus who enter the long-term extension study will have adequate treatment of their disease in this 3-year blinded,

placebo-controlled extension study, Investigators will be allowed to change the background standard of care treatment for systemic lupus erythematosus during the course of the study.

In the long-term extension study, treatment assignment will follow an Interactive Voice/Web Response System algorithm as follows:

- Subjects previously treated with intravenous anifrolumab 300 mg will stay on blinded treatment
- Subjects previously treated with anifrolumab 150 mg will switch to blinded anifrolumab 300 mg
- Subjects previously randomised to placebo will be randomised 1:1 to blinded anifrolumab 300 mg or placebo

Therefore, in the long-term extension study subjects will receive double-blind treatment with either anifrolumab 300mg or placebo in an approximate ratio of 4:1.

Although the study will initially be completely double-blind (ie, blind for subjects, Investigators/site staff, and Sponsor/designated clinical research organisation), at the conclusion of the Phase 3 Studies D3461C00004 or D3461C00005 treatment allocation for most subjects will become known to the Sponsor staff and/or the designated clinical research organisation. The blind will be maintained for the Investigator and investigational site staff, and for the subjects.

In general, the first dose of study drug in the long-term extension study (Day 1/Visit 1/Week 0) should occur on the same day as the final study visit of the prior study (ie, Week 52); however, special circumstances may warrant a delay in subject randomisation of up to 30 days following the final visit of the prior study (ie, Week 52). Administration of study drug in the long-term extension study should not occur until all Pivotal (Visit 14/Week 52) and LTE (Day 1/Visit 1/Week 0) evaluations are completed.

This long-term extension study includes:

- **Treatment Period:** A 156-week treatment period with investigational product administered every 4 weeks from Week 0 to Week 152 for a total of 39 doses. During the treatment period, visits will be scheduled for each administration (every 4 weeks).
- **At Week 156 (or after the last dose of investigational product)** subjects will continue in the study for another 8 weeks to complete a 12-week safety follow-up period after the last dose of investigational product (last dose of investigational product will be given at Week 152).

An independent Data and Safety Monitoring Board will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study.

Objectives

Primary Objective:	Outcome Measure:
To characterise the long-term safety and tolerability of intravenous anifrolumab	- Rates of adverse events of special interest and serious adverse events

[redacted]

Target subject population

The extension study will be performed in adult subjects who completed a Phase 3 study (D3461C00004 or D3461C00005) through the 52-week double-blind treatment period.

Subjects may be taking any of the following: oral corticosteroids, azathioprine, antimalarials (eg, chloroquine, hydroxychloroquine, quinacrine), mycophenolate mofetil, mycophenolic

acid, methotrexate or mizoribine at the time they sign informed consent for this long-term extension study. Subjects are not required to have a specific degree of disease activity to be randomised in the long-term extension study.

Duration of treatment

Investigational product or placebo will be administered every 4 weeks from Week 0 to Week 152 for a total of 39 doses. The total study duration will be up to approximately 164 weeks (including a 12-week Follow-up Period after administration of the final dose).

Investigational product, dosage and mode of administration

Subjects will receive blinded anifrolumab (MEDI-546) 300 mg or placebo every 4 weeks. Investigational product will be administered intravenously over a minimum of 30 minutes.

Statistical methods

No formal comparisons are planned in this study; point estimates and confidence intervals will be presented for each treatment group separately. The sample size is not based on statistical considerations, but is defined as all subjects who completed the treatment period in the Phase 3 pivotal Studies D3461C00004 or D3461C00005 (through Week 52) and met all study eligibility criteria. Assuming annual dropout rates of 30% (Randomised Placebo), 30% (Randomized Anifrolumab150 mg) and 20% (Randomized Anifrolumab 300 mg) , and that 90% of the subjects completing the pivotal studies will enter the long-term extension, follow-up times of approximately 893, 517, and 1343 patient-years for the "Randomised Anifrolumab 300 mg," "Randomised Placebo," and "All Anifrolumab" treatment groups are expected. Given this exposure, the 95% CIs for an adverse event of special interest for which the observed incidence rate is 10 events in 1000 subject-years will be 5.21 to 19.21 for "Randomised Anifrolumab 300 mg," and 4.24 to 23.57 for "Randomised Placebo." For an adverse event of special interest for which the observed incidence rate is 1 event in 1000 subject-years, the 95% confidence interval will be 0.18 to 5.42 for "All Anifrolumab" (0.13 to 7.95 for "Randomised Anifrolumab 300 mg"), and 0.07 to 15.25 for "Randomised Placebo," using the Rothman-Greenland Method.

All subjects enrolled in Studies D3461C00004 or D3461C00005 will be included in the main analysis of the long-term extension study, even if they do not enter the long-term extension study. Therefore, the full analysis set will consist of all subjects who were randomised and received at least 1 dose of investigational product in the Phase 3 pivotal Studies D3461C00004 or D3461C00005.

The analyses of long-term safety and tolerability will include data from randomisation in the Phase 3 pivotal Studies D3461C00004 or D3461C00005 until the end of the long-term extension study, including follow-up data. Adverse events of special interest and serious adverse events will be summarised by means of descriptive statistics and qualitative summaries. [redacted]

Interim analyses may be performed at appropriate timepoints during the study, according to regulatory and other requirements. Further details of interim analyses will be provided in the SAP.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
AGC	Atypical glandular cells
AIS	Adenocarcinoma in situ
ALT	Alanine aminotransferase
[redacted]	[redacted]
ASC-H	Atypical squamous cells where HSIL cannot be ruled out
AST	Aspartate aminotransferase
[redacted]	[redacted]
anti-RNP	Anti-ribonucleoprotein
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
CIN I, II, or III	Cervical intraepithelial neoplasia grade I, II, or III
CIS	Carcinoma in situ
CNS	Central nervous system
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CV-EAC	Cardiovascular Event Adjudication Committee
DEHP	Diethylhexyl phthalate
DILI	Drug Induced Liver Injury
DMARD	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDV	Early Discontinuation Visit
[redacted]	[redacted]
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HSIL	High-grade squamous intraepithelial lesion
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IFN	Interferon
IFNAR	Interferon receptor
Ig	Immunoglobulin(s)
IGRA	Interferon-gamma release assay
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the investigators and/or activities internationally.
IV	Intravenous
IXRS	Interactive Voice/Web Response System
LLOQ	Lower limit of quantitation
LTE	Long-term extension
mAb	Monoclonal antibody(ies)
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
mRNA	Messenger ribonucleic acid
[redacted]	[redacted]
OCS	Oral corticosteroid(s)
[redacted]	[redacted]
[redacted]	[redacted]
PHL	Potential Hy's Law
[redacted]	[redacted]
[redacted]	[redacted]
PVC	Polyvinyl chloride
Q4W	Every 4 weeks
QFT-G	QuantiFERON®-TB Gold
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
[redacted]	[redacted]
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	Standard of care
TB	Tuberculosis
TBL	Total bilirubin
ULN	Upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Systemic lupus erythematosus (SLE) is a chronic, multisystemic, disabling autoimmune rheumatic disease of unknown aetiology. Clinical manifestations of SLE include, but are not limited to, constitutional symptoms, alopecia, rashes, serositis, arthritis, nephritis, vasculitis, lymphadenopathy, splenomegaly, haemolytic anaemia, cognitive dysfunction and other nervous system involvement. Systemic lupus erythematosus predominantly affects women of childbearing years (Cooper et al, 1998; Lahita, 1999) with a review reporting the female-to-male ratio in the childbearing years to be about 12:1 (Ramsey-Goldman and Manzi, 2000). There is a substantial unmet medical need in the treatment of SLE, particularly in subjects with moderate or severe disease. Although off-label therapy has improved management options in recent years, long-term prognosis remains poor for many subjects. Compared to the general population, the overall mortality in SLE is increased with a standardised mortality ratio (defined as the ratio of the number of deaths observed to deaths expected) of 2.4, (2.3 to 2.5 95% confidence interval [CI]) in a large international cohort of 9,457 subjects followed for over 70000 subject-years (Bernatsky et al, 2006).

All of the therapies currently used for the treatment of SLE 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.

Multiple lines of evidence indicate a role of type I interferons (IFNs) in the pathogenesis of SLE (Hylton et al, 1986; Bengtsson et al, 2000; Baechler et al, 2003; Bennett et al, 2003; Crow and Wohlgemuth, 2003; Kirou et al, 2004; Okamoto et al, 2004; Dall'era et al, 2005; Kirou et al, 2005; Feng et al, 2006; Criswell, 2008; Huang et al, 2008; Sigurdsson, Göring et al, 2008; Sigurdsson, Nordmark et al, 2008; Yao et al, 2010).

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

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

1.2 Rationale for study design, doses and control groups

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled, long-term extension (LTE) study to characterise the long-term safety and tolerability of an intravenous (IV) treatment regimen of anifrolumab (300 mg) versus placebo in adult subjects

who completed a Phase 3 study (D3461C00004 or D3461C00005) through the 52-week double-blind treatment period.

The LTE will allow subjects to continue with treatment for an extended period of up to 3 years. Subjects who received anifrolumab (150 or 300 mg) in the Phase 3 Pivotal studies will receive anifrolumab (300 mg) and subjects who received placebo in the Phase 3 Pivotal studies will be randomised to receive anifrolumab (300 mg) or placebo in a 1:1 ratio. The expected ratio of subjects receiving anifrolumab (300 mg) vs placebo in the LTE study will be approximately 4:1. Subjects randomised to placebo in the LTE study serve as comparators to support interpretability of the data collected for subjects randomised to anifrolumab. Subjects who were receiving anifrolumab 150 mg in the Phase 3 Pivotal study will switch to 300 mg in the LTE to provide long-term safety data on the higher study dose. This study allows for the addition of new oral immunosuppressants or changing doses of background immunosuppressants, as well as for flexible oral corticosteroids (OCS) use in order for subjects to achieve adequate control of their disease throughout the study.

Although the study will initially be completely double-blind, (ie, blind for subjects, Investigators/site staff, and Sponsor/designated clinical research organisation [CRO]), at the conclusion of the Phase 3 Studies D3461C00004 or D3461C00005 treatment allocation for most subjects will become known to some Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the subjects.

A treatment period of 156 weeks is an appropriate study duration to characterise the investigational product's long-term safety profile.

The primary outcome measure is the assessment of adverse events of special interest (AESIs), and serious adverse events (SAEs) to characterise safety profile.

The selection of a dose of 300 mg anifrolumab every 4 weeks (Q4W) is based on safety and efficacy results from the analysis of a Phase 2b study where 2 doses of anifrolumab (300 mg and 1000 mg) were evaluated relative to placebo, as well as dose-response modelling and simulation that were performed.

1.3 Benefit/risk and ethical assessment

A detailed assessment of the data supporting the overall risk/benefit of anifrolumab is discussed in the Investigator's Brochure (IB).

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

Anifrolumab demonstrated a clinically relevant benefit in subjects with moderate to severe SLE treated with standard of care (SOC). The efficacy was supported by a broad range of clinical measures of global (various levels of SLE Responder Index responses, British Isles

Lupus Assessment Group-based Composite Lupus Assessment) and organ-specific disease activity (Cutaneous Lupus Erythematosus Disease Area and Severity Index, joint count). A clinically relevant increase in the proportion of subjects achieving pre-specified corticosteroid reduction in the 300 mg group was also observed compared with placebo.

In this study, anifrolumab will be administered at a fixed IV dose of 300 mg Q4W for 156 weeks (the last dose of investigational product will be given at Week 152), equivalent to the lower dose in the Phase 2 study (CD-IA-MEDI-546-1013).

Anifrolumab was generally well tolerated. A dose-related increase in the reporting rate of herpes zoster reactivation with cutaneous presentation was observed in patients receiving anifrolumab compared with placebo. Herpes zoster reactivation with cutaneous presentation is an identified risk for anifrolumab. No other infectious risks have been identified; however, this continues to be closely monitored. Although anifrolumab is a human mAb, patients can develop anti-drug antibodies (ADAs) that may neutralize the activity of the drug or may be associated with acute or delayed hypersensitivity reactions, including anaphylaxis. Furthermore, the administration of any foreign protein may be associated with acute allergic or hypersensitivity reactions that may be severe and may result in death. Patients will be monitored for the presence of and the clinical manifestations associated with the formation of specific antibodies to anifrolumab.

As of 18 January 2017, a total of 2 severe hypersensitivity events have occurred in clinical studies of anifrolumab, although these events remain blinded. Careful monitoring for such events will continue.

In addition to the ongoing, blinded review provided by the PRA Medical Monitor, an independent Data and Safety Monitoring Board (DSMB) reviews safety data on a regular basis throughout the study (see Section 6.10.1).

AstraZeneca considers that the available non-clinical and clinical data indicate an acceptable safety profile for anifrolumab. Protocol-defined exclusions are in place to prevent enrolment of patients with infection and malignancy risks that might compromise their safety. AESIs, such as herpes zoster reactivation with cutaneous presentation, as well as other herpes zoster-associated adverse events (AEs), anaphylaxis, opportunistic infections, serious infections, influenza, TB (including latent TB), malignancies, major adverse cardiovascular events (MACE), and vasculitis (non-SLE), are being closely monitored in clinical studies.

The proposed dosing regimens for the Phase 3 studies are supported by positive Phase 2 efficacy data and an acceptable safety profile. The management plan for identified, potential, and important potential risks associated with anifrolumab is designed to minimize risk to patients, and the emerging safety profile supports continued investigations. AstraZeneca considers that anifrolumab continues to demonstrate an overall positive benefit risk balance to support its further clinical evaluation.

1.4 Study Design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled extension study characterising the long-term safety and tolerability of an IV treatment regimen of anifrolumab (300 mg) versus placebo in subjects with moderately to severely active SLE who completed a Phase 3 study (D3461C00004 or D3461C00005) through the 52-week double-blind treatment period.

Approximately 575 subjects from Studies D3461C00004 or D3461C00005 who were previously treated with anifrolumab (150 or 300 mg) or placebo for 52 weeks while receiving standard of care (SOC) treatment and who are willing to continue treatment may participate in the long-term extension (LTE) study if all eligibility criteria are met. Subjects will receive either a fixed IV dose of 300 mg anifrolumab Q4W for up to 39 doses (Week 0 to Week 152) or placebo. Investigational product will be administered as an IV infusion via an infusion pump over a minimum of 30 minutes, Q4W.

In order to ensure that subjects with active SLE who enter the LTE will have adequate treatment of their disease in this 3-year blinded, placebo-controlled extension study, Investigators will be allowed to change the background SOC treatment for SLE during the course of the study. This study allows for the addition of new oral immunosuppressants or changing doses of background immunosuppressants, as well as for flexible OCS use, so that subjects may achieve adequate control of their disease on study. However, it is recommended that subjects receive the lowest possible corticosteroid dose. Concomitant medications for SLE during the study are detailed in Section 3.3.2.

In the LTE study, treatment assignment will follow an Interactive Voice/Web Response System (IXRS) algorithm as follows:

- Subjects previously treated with anifrolumab 300 mg IV will stay on blinded treatment
- Subjects previously treated with anifrolumab 150 mg will switch to blinded anifrolumab 300 mg
- Subjects previously randomised to placebo will be randomised 1:1 to blinded anifrolumab 300 mg or placebo

Therefore, in the LTE study subjects will receive double-blind treatment with either anifrolumab or placebo in an approximate ratio of 4:1.

Although the study will initially be completely double-blind (ie, blind for subjects, Investigators/site staff, and Sponsor/designated CRO), at the conclusion of the Phase 3 Studies D3461C00004 or D3461C00005 treatment allocation for most subjects will become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the subjects.

In general, the first dose of study drug in the LTE study (Day 1/Visit 1/Week 0) should occur on the same day as the final study visit of the prior study (ie, Week 52); however, special circumstances may warrant a delay in subject randomisation of up to 30 days following the final visit of the prior study (ie, Week 52). Administration of study drug in the LTE long-term extension study should not occur until all Pivotal (Visit 14/Week 52) and LTE (Day 1/Visit 1/Week 0) evaluations are completed.

This LTE study includes:

- **Treatment Period:** A 156-week treatment period with investigational product administered Q4W from Week 0 to Week 152 for a total of 39 doses. During the treatment period, visits will be scheduled for each Q4W administration.

- **At Week 156 (or after the last dose of investigational product**) subjects will continue in the study for another 8 weeks to complete a 12-week safety follow-up after the last dose of investigational product (last dose of investigational product will be given at Week 152).

The total study duration will be up to approximately 164 weeks (including a 12-week Follow-up Period after administration of the final dose).

Once subjects have completed Studies D3461C00004 or D3461C00005 (through Week 52), signed the informed consent form (ICF), and met all study eligibility criteria, they may be included in the LTE study.

In the event a site has not obtained the required approval (eg, regulatory authority, local ethics committee [EC]) by the time a subject is eligible to be randomised in the LTE study, the site may be allowed the time to obtain the approval(s).

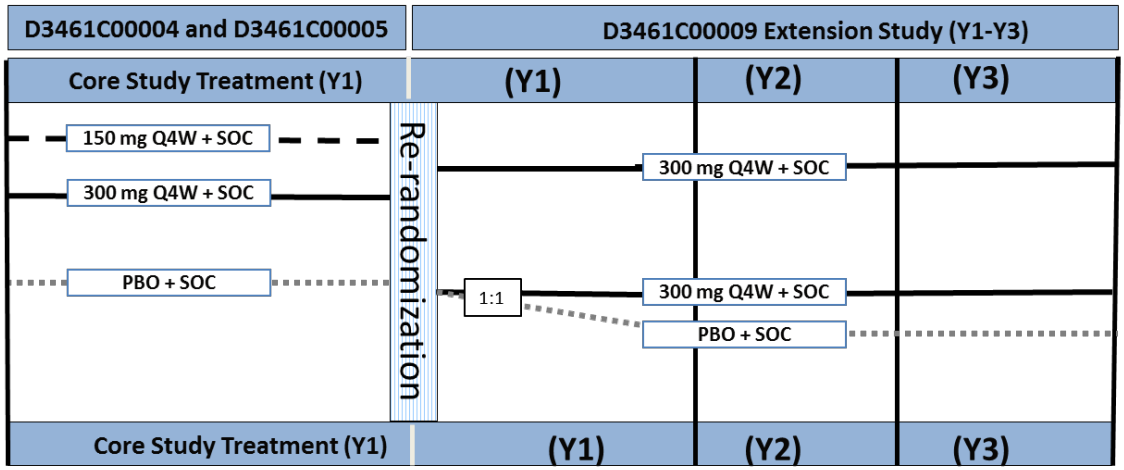
If due to regulatory delays or other exceptional circumstances it is likely that Day 1/Visit 1/Week 0 will occur greater than 30 days after the final visit of the prior study, the PRA Medical Monitor must be contacted to confirm that the subject will be permitted to be randomised. The rationale for the delayed start, date of last dose of study drug, and subject compliance in the prior study will be reviewed to determine whether the subject will be permitted to be randomised. In addition, all Day 1/Visit 1/Week 0 visit procedures listed in Table 2 must be performed.

If dosing occurs on the same day of the final visit of the prior study, it should occur after all Day 1/Visit 1/Week 0 assessments have been completed, the Investigator has determined that the subject can continue dosing, and the subject has been randomised.

An independent DSMB will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study.

See Figure 1 for an outline of the study design.

Figure 1 Study flow chart



- Subjects receiving anifrolumab150 mg in pivotal trial D3461C00005 receive anifrolumab 300 mg in LTE
- Subjects receiving anifrolumab 300 mg in pivotal trials continue on anifrolumab 300 mg in LTE
- Subjects on placebo who complete pivotal studies are re-randomized 1:1 to anifrolumab 300 mg or placebo in LTE

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To characterise the long-term safety and tolerability of intravenous anifrolumab	- Rates of AESIs and SAEs

2.2 Secondary objectives (Not applicable)

2.3 Safety objectives

See Section 2.1 Primary objective.

[redacted]

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

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

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Subjects who have qualified for and received investigational product (anifrolumab or placebo) and completed the treatment period in Studies D3461C00004 or D3461C00005 (through Week 52)

2. Written informed consent and any locally required authorisation (eg, Health Insurance Portability and Accountability Act [HIPAA] in the USA, Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including Day 1 evaluations

3. Adequate peripheral venous access

4. Females of childbearing potential must use 2 effective methods (Table 1) of avoiding pregnancy, only 1 of which is a barrier method and the other is a highly effective intrauterine device or hormonal method described in Table 1 below, from Day 1/Visit 1 until 12 weeks after the final dose of investigational product unless the subject is surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a sterile male partner, is 1 year postmenopausal, or practices sustained abstinence. Cessation of birth control after the 12-week follow-up period should be discussed with a responsible physician.

    - Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
    - Postmenopausal is defined as at least 1 year since last menses and the subject has a follicle-stimulating hormone (FSH) level within postmenopausal range according to central laboratory testing at Day 1/Visit 1.

    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 an intrauterine device/hormonal method and the other a barrier 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

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

6. Females with an intact cervix must have a Pap smear completed and without documented malignancy (eg. no signs of CIN grade III, CIS, or AIS) within 90 days prior to randomization or up until 30 days post-randomization, ie, before IP dosing at V2.
Subjects with abnormal Pap smear results of atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells where high-grade squamous intraepithelial lesion (HSIL) cannot be ruled out (ASC-H), atypical glandular cells (AGC), or CIN grades I and II (CIN I and II) will be allowed to enter the study [redacted].

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

8. Meets the following TB criteria:

(a) **Negative** QuantiFERON®-TB Gold [QFT-G] test result for TB obtained from the study central laboratory at Week 52 of Studies D3461C00004 or D3461C00005

OR

(b) **Newly positive** QFT-G test result for TB obtained at Week 52 of Studies D3461C00004 or D3461C00005 from the study central laboratory. A chest x-ray must be performed. If the chest x-ray shows no evidence of active TB, and the subject has no symptoms or medical history consistent with active TB, the subject must have a retest. If the retest is positive, the subject must initiate treatment for latent TB within 30 days of randomisation, but prior to the second dose of investigational product administration (Visit 2/Week 4). This should be reported as an AESI.

OR

(c) **Positive but not newly positive** QFT-G test at Week 52 of Studies D3461C00004 or D3461C00005 from the study central laboratory. The subject must have been diagnosed with latent TB and must have documentation confirming completion of appropriate treatment OR initiate treatment for latent TB within 30 days of randomisation, but prior to the second dose of investigational product administration (Visit 2/Week 4)

OR

(d) **Newly indeterminate** (as confirmed on retest unless prior positive QFT-G was documented, along with completed treatment for latent TB) or **indeterminate but not newly indeterminate** QFT-G test result at Week 52 of Studies D3461C00004 or D3461C00005 from the study central laboratory with ongoing QFT-G testing for TB according to the Study Plan

The QFT-G test results obtained at Week 52 of Studies D3461C00004 or D3461C00005 should be available within 30 days of randomisation, but prior to the second dose of investigational product administration (Visit 2/Week 4). The PRA Medical Monitor may be contacted for questions.

9. In the opinion of the Investigator, subject must be able to comprehend the ICF and all protocol-related assessments, and be able to complete all study-required documents, procedures, and outcome measures

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 investigational product or interpretation of subject safety or study results

2. Concurrent enrolment in another clinical study (except studies D3461C00004 and D3461C00005) with an investigational product

3. Pregnant females or females who intend to become pregnant anytime from randomisation until the end of the 12-week safety Follow-up Period following last dose of investigational product

4. Current alcohol, drug, or chemical abuse

3.2.2 Exclusion criteria related to concomitant medications

5. Receipt of any of the following within the last 60 days prior to Day 1/Visit 1:

   (a) Azathioprine >200 mg/day

   (b) Mycophenolate mofetil >2.0 g/day /mycophenolic acid >1.44 g/day

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

   (d) Mizoribine >150 mg/day

6. Receipt of any investigational product (small molecule or biologic agent other than anifrolumab) within 4 weeks or 5 half-lives prior to Day 1/Visit 1, whichever is greater

7. Receipt of any commercially available biologic agent within 5 half-lives prior to Day 1/Visit 1

8. Receipt of any of the following:

   (a) Any live or attenuated vaccine within 8 weeks prior to Day 1/Visit 1 (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)

   (b) Bacillus Calmette-Guerin (BCG) vaccine between the end of Studies D3461C00004 or D3461C00005 and Day 1/Visit 1

3.2.3 Exclusion criteria related to systemic lupus erythematosus and other diseases

9. Active severe SLE-driven renal or neuropsychiatric disease where, in the opinion of the Principal 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

3.2.4 Exclusion criteria related to infection and malignancy risk factors

10. Any underlying condition that predisposes the subject to infection, including history of/current human immunodeficiency virus (HIV) infection

    An HIV test confirmed by the central laboratory must be performed if not done in Studies D3461C00004 or D3461C00005. The result should be available within 30 days of randomisation, but prior to the second dose of investigational product administration (Visit 2/Week 4).

11. Subjects with Hepatitis B core antibody (HBcAb) positivity at enrolment of Studies D3461C00004 or D3461C00005 will be tested every 3 months for Hepatitis B virus (HBV) deoxyribonucleic acid (DNA). To remain eligible in the LTE study, subject HBV DNA levels must remain below the lower limit of quantitation (LLOQ) as per the central laboratory.

12. Opportunistic infection requiring hospitalisation or parenteral antimicrobial treatment within 3 years of Day 1/Visit 1

13. Any of the following:

    (a) Clinically significant chronic infection (ie, osteomyelitis, bronchiectasis, etc) within 8 weeks prior to Day 1/Visit 1 (chronic nail infections not causing open skin lesions are allowed)

    (b) Any infection requiring hospitalisation or treatment with IV anti-infectives not completed at least 4 weeks prior to Day 1/Visit 1

14. Any infection requiring IV or oral anti-infectives (including antivirals) within 2 weeks prior to Day 1/Visit 1

Procedures for withdrawal of incorrectly randomised subjects see Section 3.5.

3.3 Restrictions and concomitant medications

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

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

3.3.1.1 Medications that lead to immediate discontinuation of investigational product

(a) Cyclophosphamide

(b) Baricitinib, tofacitinib or other Janus kinase inhibitors

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

(d) Investigational agents

(e) Biologic immunomodulators (including, but not limited to, belimumab, abatacept, or rituximab)

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

(g) Plasmapheresis

(h) BCG vaccine

(i) Any Ig therapy

(j) Intravenous corticosteroids >1 g methylprednisolone or equivalent

[redacted]

Combination therapy of tacrolimus and a second immunosuppressant is not permitted during the study and would lead to discontinuation of the investigational product.

3.3.1.2 Restricted medications

(a) Sulfasalazine

(b) Danazol

(c) Dapsone

(d) Azathioprine >200 mg/day

(e) Mycophenolate mofetil >2.0 g/day or mycophenolic acid >1.44 g/day

(f) Oral, subcutaneous, or intramuscular methotrexate >25 mg/week

(g) Mizoribine >150 mg/day

(h) Intravenous corticosteroids >40 mg/day but ≤1 g/day methylprednisolone or equivalent

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

(j) Adrenocorticotropic hormone agents (eg, Acthar) or corticosteroid precursors

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

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

(m) Other immunosuppressants including but not limited to calcineurin inhibitors (eg, cyclosporine) or leflunomide, except for tacrolimus (see Section 3.3.2.1)

If a subject receives any of the above listed medications, the Investigator will use his/her judgment to consider if the subject may continue to receive investigational product. The Investigator may contact the PRA Medical Monitor to discuss the case.

3.3.1.3 Other concomitant medications

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

3.3.2 Concomitant medications for Systemic Lupus Erythematosus during the study

Concomitant medications should only be administered after all visit assessments, including investigational product administration [redacted], with the exception of a subject with a previous infusion-related reaction who is to receive acetaminophen or equivalent. The acetaminophen or equivalent should be given after all visit assessments have been completed, and prior to starting the infusion.

3.3.2.1 Background Systemic Lupus Erythematosus standard of care medications (oral corticosteroids, antimalarials, and immunosuppressants)

Permitted SOC medications for SLE during the LTE study include OCS (up to 40 mg/day of prednisone or equivalent [redacted]), antimalarials, and immunosuppressants (methotrexate, mycophenolate mofetil/mycophenolic acid, mizoribine, azathioprine, and tacrolimus).

Investigators should apply local practices for safety monitoring, eg, by serum chemistry tests, in case SOC dose is changed, eg, increased, and/or new disease-modifying antirheumatic drug (DMARD) is added.

Subjects may undergo changes in their background SOC medication for SLE (OCS, antimalarials, or immunosuppressants) doses, based on the opinion of the Investigator. On treatment days, changes in doses will commence after all assessments have been completed and the investigational product has been administered. There is no minimum dose requirement for background SOC medications for SLE, and subjects may taper off as permitted by disease activity. Due to variability in subject responses to background SOC medications for SLE and tolerability of taper, Investigators are asked to use their clinical judgment with respect to the taper schedule. If the subject experiences an increase in SLE disease activity, SOC medications for SLE may be adjusted according to the Investigator's clinical judgment, but may not exceed maximally permitted doses as defined by exclusionary criteria.

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

Immunosuppressants

Subjects may change from the immunosuppressant on which they entered the LTE study to another permitted immunosuppressant (methotrexate, mycophenolate mofetil/mycophenolic acid, mizoribine, azathioprine, or tacrolimus) at the discretion of the Investigator. Subjects who were not taking an immunosuppressant at the time they enter the LTE study may add 1 of the permitted immunosuppressants and be escalated up to the protocol-defined doses. Combination therapy of tacrolimus and a second immunosuppressant is not permitted during the study and would lead to discontinuation of the investigational product. Doses of any new immunosuppressants will be limited to the doses defined below. It is recommended that immunosuppressants not be changed more frequently than every 4 months, unless for intolerability reasons.

If subjects are on immunosuppressants, dosing must not exceed the following:

- Azathioprine >200 mg/day
- Mycophenolate mofetil >2.0 g/day or mycophenolic acid >1.44 g/day
- Oral, subcutaneous, or intramuscular methotrexate >25 mg/week
- Mizoribine >150 mg/day
- Tacrolimus >0.2 mg/kg/day (tacrolimus at a starting dose of 0.05 mg/kg/day to be escalated to ≤0.2 mg/kg/day. Subjects must maintain tacrolimus trough levels below the central laboratory upper limit of the therapeutic range based on monthly measurements.)

If the subject plans to use tacrolimus during the study, the subject must not have a history of intolerance to tacrolimus or a past history of reversible posterior leukoencephalopathy, other severe central nervous system (CNS) disorders, past history of renal impairment, or microangiopathic disorders in association with a calcineurin inhibitor, including tacrolimus.

Corticosteroids

Subjects with increased SLE disease activity may receive 1 steroid burst within the first 12 weeks of the LTE study. Subsequently, 1 burst every 6 months is allowed. If additional bursts are needed, the Investigator should contact the PRA Medical Monitor to discuss subject's management. Additionally, subjects may have their background OCS dose titrated

for increased disease activity during the study. However, it is recommended that subjects receive the lowest possible dose of corticosteroids.

A steroid burst is defined as:

- OCS increase up to a daily dose of 40 mg/day prednisone (or equivalent) for up to a total of 14 days, which must be fully administered and tapered to ≤20 mg by the end of the 14th day. Any course of OCS >20 mg dose should be tapered to the Visit 1 dose within 30 days from the first day of the steroid burst;

OR

- Intramuscular methylprednisolone (≤120 mg) or IV methylprednisolone (**≤250 mg**) or equivalent administered as a single dose;

OR

- Two intra-articular/tendon sheath/bursal injections (for a total methylprednisolone ≤160 mg or equivalent) can be given. Subjects who receive any intra-articular/tendon sheath/bursal injections should not receive OCS or intramuscular steroids at the same time.

When OCS treatment is above a total dose >40 mg/day for a dosing period >14 days, dosing with investigational product (anifrolumab or placebo) may be continued, unless there is a safety concern. However, Investigators should carefully consider whether subjects requiring prolonged high corticosteroid use would benefit by a change to another permitted SOC therapy.

3.3.2.2 Use of other medications for increased SLE disease activity

If during the course of the study permitted SOC SLE medications are not adequate for the treatment of increased SLE disease activity, a subject may receive other medications as deemed necessary by the Investigator or the subject's treating physician after notifying the PRA Medical Monitor. [redacted] The subject may only continue to receive investigational product with Sponsor approval.

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

Subjects will be allowed to receive up to an additional 20 mg/day prednisone or equivalent at the discretion of the Investigator for 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 a severe illness, surgery, or symptoms of adrenal insufficiency or corticosteroid withdrawal, if clinically warranted during the Treatment Period (Year 1 through Year 3). Use of corticosteroids should be minimised for subject safety reasons.

3.3.3 Other restrictions

3.3.3.1 Fasting lipid profile

Subjects will be required to fast for at least 8 hours prior to assessment of lipid profile at the visits described in the Treatment Period Study Plan (Table 2 and Table 3). If the subject has not fasted, they should fast before the next visit, and the test can be done at that visit.

3.3.3.2 Perioperative management of investigational product

Surgery should be avoided during the study if clinically feasible, but is permitted. If a surgery becomes necessary during the study, it should be scheduled at least 4 weeks after the previous administration of investigational product.

For non-major surgery, the decision to withhold investigational product administration is at the Investigator's discretion.

For major surgery, investigational product administration can be resumed at the Investigator's discretion after all of the following criteria are met:

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

3.3.3.3 Blood and sperm donations

Subjects should not donate whole blood, blood components or sperm until the completion of the follow-up period or 90 days after the last dose.

3.4 Subject randomisation

Investigator(s) should keep a record of subjects considered for randomisation in the LTE study (ie, those who completed a Phase 3 study [D3461C00004 or D3461C00005] through the 52-week double-blind treatment period and consented, but were not randomised) and those randomised in the study.

The same subject identifier (E-code) used in the Phase 3 study (ie, D3461C00004 or D3461C00005) will be used in the LTE study.

Subjects will be randomised in the LTE and stratified by Phase 3 study (ie, D3461C00004 and D3461C00005) according to the algorithm described in Section 3.6.

A similar pseudo-randomisation will be done for all subjects randomised in the previous Phase 3 Studies (D3461C00004 or D3461C00005) but not randomised in the LTE study, ie, a pseudo-treatment (treatment that would have been administered if the subject would have continued in the LTE study) will be assigned to each of these subjects. The pseudo-treatment will be used for analysis purposes only.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study-specific procedures are performed.

2. Determine subject eligibility for the LTE study.

3. On Day 1, the Investigator will perform an IXRS transaction for all subjects who sign the ICF. The IXRS will assign blinded investigational product kit number(s) to randomised subjects.

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

3.5 Procedures for handling incorrectly randomised subjects

Where a subject does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should immediately inform the PRA Medical Monitor, who will discuss with AstraZeneca study physician, whether the subject should continue or discontinue from treatment. The PRA Medical Monitor must ensure all decisions are appropriately documented.

3.6 Methods for assigning treatment groups

Treatment assignment will follow an IXRS algorithm as follows:

- Subjects previously treated with anifrolumab 300 mg IV will stay on blinded treatment

- Subjects previously treated with anifrolumab 150 mg will switch to blinded anifrolumab 300 mg

- Subjects previously randomised to placebo will be randomised 1:1 to anifrolumab 300 mg or placebo

In general, the first dose of study drug in the LTE study (Day 1/Visit 1/Week 0) should occur the same day as the final study visit of the prior study (ie, Week 52); however, special circumstances may warrant a delay in subject randomisation of up to 30 days following the final visit of the prior study (ie, Week 52). Administration of study drug should not occur until all Pivotal (Visit 14/Week/52) and LTE (Day 1/Visit 1/Week 0 evaluations are completed.

3.7 Methods for ensuring blinding

This is a double-blind study in which anifrolumab and placebo are distinguishable during the final preparation step of the investigational infusion bag. All packaging and labelling of investigational product is done in such a way as to ensure blinding for all Sponsor and investigational site staff other than the unblinded investigational product manager. The kits

on the shelf, and the infusion bags when prepared, look identical. Since anifrolumab and placebo can be distinguished at the preparation step, investigational product will be prepared by an unblinded investigational product manager at the site, who will not be involved in the management of study subjects.

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

3.8 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised 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 treatment randomisation. The Investigator should promptly document and explain any premature unblinding to the Sponsor, without revealing the treatment given to subject. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

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

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

Although the study will initially be completely double-blind (ie, blind for subjects, Investigators/site staff, and Sponsor/designated CRO), at the conclusion of the Phase 3 Studies D3461C00004 or D3461C00005 treatment allocation for most subjects will become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the subject.

3.9 Discontinuation of investigational product

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

1. Subject decision. The subject is at any time free to discontinue study treatment, without prejudice to further disease treatment. The primary reason should be documented as 1 of the following:

   (a) Subject perceives the investigational product to be ineffective

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

   (c) Subject perceives logistics to be unacceptable

   (d) Subject wishes to participate in another clinical trial

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

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

   (g) Other, please specify reason

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

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

4. Severe non-compliance with the study protocol

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

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

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

8. Receipt of any medications identified in Section 3.3.1.1

9. The use of restricted medications listed in Section 3.3.1.2 if the Investigator determines the subject should be discontinued

10. A diagnosis of active TB, premature discontinuation of treatment for latent TB, or non-compliance with TB therapy. Note: duration of treatment for latent TB should

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

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

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (due to an AE, or other), will be identified as having permanently discontinued treatment.

3.9.1 Subject decision to discontinue investigational product

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

3.9.2 Withdrawal of the informed consent

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

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

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

3.9.3 Lost to follow-up

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

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

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

3.9.4 Study completion and end of study

An individual subject will be considered to have completed the study if the subject was followed up until the end of the study (Follow-up Visit 2), regardless of the number of doses of investigational product that were received.

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

3.9.5 Procedures for discontinuation of a subject from investigational product

Discontinuation of investigational product does not necessarily mean discontinuation of follow-up or termination of study participation. Compliant subjects who are discontinued from the investigational product should be encouraged to continue to undergo all study-related visits/procedures for the full treatment period (Table 2 and Table 3) in order to support the final analysis for anifrolumab (see Section 8). The reason for premature discontinuation of investigational product will be documented in the source documents and recorded on the CRF.

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

For subjects who wish to withdraw from the study completely refer to Section 3.9.2.

3.10 Criteria for withdrawal

3.10.1 Ineligible subjects who sign informed consent

Subjects who have provided informed consent and who subsequently do not fulfil eligibility criteria for the study must not be included in the study. These subjects should have the reason for study withdrawal recorded as "Eligibility Criteria Not Fulfilled" (ie, subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for subjects who were never randomised.

3.10.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment. A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

3.11 Discontinuation of the study

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

- Meet individual stopping criteria or are otherwise considered significant (see Section 3.9 for reasons for discontinuation of investigational product)
- Are assessed as causally related to the 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 on the CRF.

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study plan detailing the procedures during the Treatment Period Year 1

Visit Month	**Day 1 V1** [a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7 (M6)**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 (M12)**
Study Week (Year 1)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Procedure/Visit Window		**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**
Written informed consent	X													
Physical examination, weight and height [b]	X													X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X													X
Pap smear [c]	X													X
Laboratory														
Blood test for TB [d,e,f] (QFT-G In-Tube Test)	X			X[f]			X[f]							X
Serum chemistry, haematology, and urinalysis [g]	X	X	X	X			X			X				X
Urine pregnancy test [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B virus DNA [i]	X			X			X			X				X
HIV test [j]	X													
[redacted]														

Table 2 Study plan detailing the procedures during the Treatment Period Year 1

Visit Month	Day 1 V1 [a]	V2	V3	V4	V5	V6	V7 (M6)	V8	V9	V10	V11	V12	V13	V14 (M12)
Study Week (Year 1)	W0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52
Procedure/Visit Window		±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D
[redacted]														

Table 2 Study plan detailing the procedures during the Treatment Period Year 1

Visit Month	Day 1 V1 [a]	V2	V3	V4	V5	V6	V7 (M6)	V8	V9	V10	V11	V12	V13	V14 (M12)
Study Week (Year 1)	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Procedure/Visit Window		**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**
Safety														
Assessment of AEs, AESIs, SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Modified Flare Index	X			X			X			X				X
Concomitant medications, including SLE medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tacrolimus trough levels [o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility														
Verify eligibility criteria	X													
Randomisation	X													
Investigational product														
Investigational product administration [p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted] AE = adverse event; AESI = adverse event of special interest; AIS = adenocarcinoma in situ; [redacted] IN = cervical intraepithelial neoplasia; CIS = carcinoma in situ; D = day; DMARD = disease-modifying antirheumatic drug; DNA = deoxyribonucleic acid; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; [redacted] HIV = human immunodeficiency virus; [redacted] LLOQ = lower limit of quantitation; LTE = long-term extension; M = month; [redacted] SLE = systemic lupus erythematosus; [redacted] SOC = standard of care; TB = tuberculosis; V = Visit; W = week; [redacted]

[a] The Week 52 assessments of the Phase 3 Studies D3461C00004 or D3461C00005 will serve as Day 1/Visit 1/Week 0 assessments of the LTE study; additional procedures that are part of the LTE study will also be performed. If Day 1/Visit 1/Week 0 occurs more than 30 days after the Week 52 final

visit of D3461C00004 or D3461C00005, the PRA Medical Monitor must be contacted. The rationale for waiting, date of last dose of study drug, and subject compliance in the prior study will be reviewed. In addition, all procedures for Day 1/Visit 1/Week 0 must be completed.

[b] Height to be performed only at Day 1/Visit 1.

[c] Females with intact cervix must have a Pap smear completed and without documented malignancy (eg. no signs of CIN grade III, CIS, or AIS) within 90 days before Day 1 or up until 30 days after randomization, ie, before dosing at V2. Pap smears should thereafter be performed yearly and all female subjects with an intact cervix should have a Pap smear performed within 3 months of the last IP dose, eg, at the end of study or at the early discontinuation visit. If the Pap smear is abnormal, but without malignancy, it should be repeated as per the subject's gynaecologist's recommendation. If the subject's gynaecologist has recommended a repeat Pap smear be performed at a specified interval, the Pap smear should be obtained as recommended and the report provided in the source document. Since access to a Pap smear may vary by country, the Sponsor recommends that local guidelines are used for obtaining routine follow-up Pap smears in females who have received immunomodulators or immunosuppressive treatment.

[d] Interferon-gamma release assay (IGRA) using QFT-G In-Tube Test.

[e] If subject has a newly positive QFT-G test at Day 1/Visit 1 or at any time during the study, the subject will undergo a chest x-ray. Posterior-anterior and lateral images are required.

[f] If subject has a newly indeterminate QFT-G test, it must be repeated every 3 months for the first 6 months, and every 6 months thereafter unless it reverts to negative.

[g] Investigators should apply local practices for safety monitoring, eg, by serum chemistry tests, in case SOC dose is changed, eg, increased, and/or new DMARD is added.

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

[i] Only subjects with Hepatitis B core antibody positivity at enrolment of Studies D3461C00004 or D3461C00005. To remain eligible in the LTE study, subject Hepatitis B virus DNA levels must remain below the LLOQ as per the central laboratory.

[j] HIV test only in subjects not tested in Studies D3461C00004 or D3461C00005.

[redacted]

[o] Monthly tacrolimus trough levels in subjects receiving tacrolimus as standard of care SLE therapy. These subjects must maintain tacrolimus trough levels below the central laboratory upper limit of the therapeutic range based on monthly measurements.

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

Table 3 Study plan detailing the procedures during the Treatment Period Year 2 through Year 3 or End of Study

Visit Month (Year 2)	**V15**	**V16**	**V17**	**V18**	**V19**	**V20 (M18)**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27 (M24)**
Study Week (Year 2)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**
Visit Month (Year 3)	**V28**	**V29**	**V30**	**V31**	**V32**	**V33 (M30)**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40 (M36)**
Study Week (Year 3)	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156 (EDV) [a]**
Procedure/Visit Window	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**
Physical examination, weight													X[o]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X[o]
ECG													X
Pap smear [b]													X
Laboratory													
Blood test for TB [c,d,e] (QFT-G In-Tube Test)			X[e]			X[e]							X
Serum chemistry, haematology, and urinalysis [f]						X							X[o]
Urine pregnancy test [g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B virus DNA [h]			X			X			X				X
[redacted]													

Table 3 Study plan detailing the procedures during the Treatment Period Year 2 through Year 3 or End of Study

Visit Month (Year 2)	V15	V16	V17	V18	V19	V20 (M18)	V21	V22	V23	V24	V25	V26	V27 (M24)
Study Week (Year 2)	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104
Visit Month (Year 3)	V28	V29	V30	V31	V32	V33 (M30)	V34	V35	V36	V37	V38	V39	V40 (M36)
Study Week (Year 3)	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	W148	W152	W156 (EDV) [a]
Procedure/Visit Window	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D
[redacted]													

Table 3 Study plan detailing the procedures during the Treatment Period Year 2 through Year 3 or End of Study

Visit Month (Year 2)	**V15**	**V16**	**V17**	**V18**	**V19**	**V20 (M18)**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27 (M24)**
Study Week (Year 2)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**
Visit Month (Year 3)	**V28**	**V29**	**V30**	**V31**	**V32**	**V33 (M30)**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40 (M36)**
Study Week (Year 3)	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156 (EDV) [a]**
Procedure/Visit Window	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**	**±7 D**
[redacted]													
Safety													
Assessment of AEs, AESIs, SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X[o]
Modified Flare Index						X							X
Concomitant medications, including SLE medications	X	X	X	X	X	X	X	X	X	X	X	X	X[o]
Tacrolimus trough levels [m]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3 Study plan detailing the procedures during the Treatment Period Year 2 through Year 3 or End of Study

Visit Month (Year 2)	V15	V16	V17	V18	V19	V20 (M18)	V21	V22	V23	V24	V25	V26	V27 (M24)
Study Week (Year 2)	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104
Visit Month (Year 3)	V28	V29	V30	V31	V32	V33 (M30)	V34	V35	V36	V37	V38	V39	V40 (M36)
Study Week (Year 3)	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	W148	W152	W156 (EDV) [a]
Procedure/Visit Window	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D	±7 D
Investigational product													
Investigational product administration [n]	X	X	X	X	X	X	X	X	X	X	X	X	X[p]

[redacted] AE = adverse event; AESI = adverse event of special interest; AIS = adenocarcinoma in situ; [redacted] CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ; D = day; DMARD = disease-modifying antirheumatic drug; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; EDV = Early Discontinuation Visit; [redacted] LLOQ = lower limit of quantitation; M = month; [redacted] QFT-G = QuantiFERON®-TB Gold; SAE = serious adverse event; [redacted] LE = systemic lupus erythematosus; [redacted] SOC = standard of care; TB = tuberculosis; V = Visit; W = week; [redacted]

[a] Subjects who prematurely discontinue investigational product will have the Early Discontinuation Visit within 4 weeks after the last dose of investigational product.

[b] Females with intact cervix must have a Pap smear completed and without documented malignancy (eg. no signs of CIN grade III, CIS, or AIS) within 90 days before Day 1 or up until 30 days after randomization, ie, before dosing at V2. Pap smears should thereafter be performed yearly and all female subjects with an intact cervix should have a Pap smear performed within 3 months of the last IP dose, eg, at the end of study or at the early discontinuation visit. If the Pap smear is abnormal, but without malignancy, it should be repeated as per the subject's gynaecologist's recommendation. If the subject's gynaecologist has recommended a repeat Pap smear be performed at a specified interval, the Pap smear should be obtained as recommended and the report provided in the source document. Since access to a Pap smear may vary by country, the Sponsor recommends that local guidelines are used for obtaining routine follow-up Pap smears in females who have received immunomodulators or immunosuppressive treatment.

[c] Interferon-gamma release assay (IGRA) using QFT-G In-Tube Test.

[d] If a subject has a newly positive QFT-G test at any time during the study or at Week 156, the subject will undergo a chest x-ray to rule out the presence of active TB or other clinically relevant findings. Posterior-anterior and lateral images are required.

[e] If subject has a newly indeterminate QFT-G test, it must be repeated every 3 months for the first year and every 6 months thereafter unless it reverts to negative.

[f] Investigators should apply local practices for safety monitoring, eg, by serum chemistry tests, in case SOC dose is changed, eg, increased, and/or new DMARD is added.

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

[h] Only subjects with Hepatitis B core antibody positivity at enrolment of Studies D3461C00004 or D3461C00005. To remain eligible in the LTE study, subject Hepatitis B virus DNA levels must remain below the LLOQ as per the central laboratory.

[m] Monthly tacrolimus trough levels in subjects receiving tacrolimus as standard of care SLE therapy. These subjects must maintain tacrolimus trough levels below the central laboratory upper limit of the therapeutic range based on monthly measurements.

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

[o] If the subject is unwilling to continue with any study visits, including EDV, or is willing to continue with only selected study assessments, at a minimum, these assessments should be completed.

[p] No investigational product dosing occurs at Week 156 or EDV.

Table 4 Study plan detailing the procedures during Follow-up

Visit	Follow-up Visit 1 [a]	Follow-up Visit 2 [a]
Study Week	**8 weeks post-final dose**	**12 weeks post-final dose**
Procedure/Visit Window	**±3 D**	**±3 D**
[redacted]		
Physical examination, weight		X
Vital signs	X	X
Serum chemistry, haematology, and urinalysis	X	X
Urine pregnancy test in females of childbearing potential	X	X
[redacted]		
Assessment of AEs, AESIs, SAEs	X	X
Concomitant medications	X	X

AE = adverse event; AESI = adverse event of special interest; [redacted] D = day; dsDNA = double-stranded deoxyribonucleic acid; [redacted] AE = serious adverse event; [redacted]

[a] Follow-up assessments are to be completed when subjects complete the study (eg, early termination or after the treatment period).

[redacted]

4.1 Randomisation

Before randomisation (Day 1/Visit 1/Week 0), subjects will be assessed to ensure that they have signed the ICF and meet eligibility criteria. Once the subject is randomised, relevant data must be captured in the appropriate LTE system. Events that occur prior to randomisation in the LTE study should be reported in Studies D3461C0004 or D3461C00005. Subjects who do not sign the ICF and/or who do not meet the eligibility criteria must not be randomised into the LTE study.

The Week 52 assessments of the Phase 3 Studies D3461C00004 or D3461C00005 will serve as Day 1/Visit 1/Week 0 assessments of the LTE study; additional procedures that are part of the LTE study will also be performed. If Day 1/Visit 1/Week 0 occurs more than 30 days after the Week 52 final visit of the Phase 3 Studies D3461C00004 or D3461C00005, the PRA Medical Monitor must be contacted. In case the Day 1/Visit 1/Week 0 occurs >60 days after the Week 52 final visit of the pivotal studies, additional safety laboratory tests, eg, haematology, liver function tests, and serum creatinine, might be required as judged by the PRA/AZ medical monitor. The rationale for delayed start, date of last dose of study drug, and subject compliance in the prior study will be reviewed. In addition, all procedures for Day 1/Visit 1/Week 0 must be completed.

4.1.1 Other considerations for randomisation

4.1.1.1 Oral examination

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

4.1.1.2 Mammography

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

4.2 Treatment period

During the treatment period, visits will be scheduled for each Q4W administration.

Procedures during the Treatment Period Year 1 will be performed according to the Study Plan detailing the procedures (Table 2). Procedures during the Treatment Period Year 2 through Year 3 will be performed according to the Treatment Period Study Plan detailing the procedures (Table 3). The subject-reported outcome assessments should be completed by the subject (unassisted by spouse, family members, or friends) prior to all other evaluations and prior to the infusion, as disease assessments/clinical evaluations may confound the results.

4.2.1 Premature discontinuation of investigational product

Subjects who prematurely discontinue investigational product (see Section 3.9.1) will be asked to return for all regularly scheduled clinic visits. If the subject is unwilling to complete all regularly scheduled clinic visits, the subject should complete the Early Discontinuation Visit (EDV, Week 156) within 4 weeks after the last administration of investigational product, as well as Follow-up Visit 1 and Follow-up Visit 2 (8 and 12 weeks after the last dose of investigational product) unless consent is withdrawn. If the subject is unwilling to continue with any study visits, including EDV, or is willing to continue with only selected study assessments, at a minimum, the following assessments should be completed:

- AEs including AESIs and SAEs
- [redacted]
- Serum chemistry, haematology, urinalysis
- Urine for protein, creatinine, and urine-protein-creatinine ratio
- Vital signs
- Physical examination, weight
- [redacted]
- [redacted]
- Concomitant medications
- Blood test for TB
- Pap smear test (female subjects with an intact cervix only)

If the subject does not agree to do this, they will be asked if they can be followed on a monthly basis via telephone calls. At these calls, they will be asked about AEs/SAEs, lupus symptoms, and lupus medications.

Adverse events will be followed up per Section 6.6.2.

4.3 Unscheduled visit

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

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

4.4 Follow-up period

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

Subjects who are withdrawn from the study, and do not agree to complete the 156-week study period, and do not agree to complete the 3-year study period, should complete the EDV (Week 156 procedures) and be followed 8 and 12 weeks after the last administration of investigational product by completing the Follow-up Visits 1 and 2 assessments (see Section 3.9).

5. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the CRFs as specified in the study protocol and in accordance with the instructions provided.

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

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

[redacted]

[redacted]

5.2 Safety assessments

Key safety assessments are AESIs and SAEs, which will be assessed at every study visit. All AEs will also be collected at every study visit. Investigators should apply local practices for safety monitoring, eg, by serum chemistry tests, in case SOC dose is changed, eg, increased, and/or new DMARD is added.

In addition, vital signs, physical examination, safety laboratory tests, and electrocardiograms (ECGs) will be assessed at the times indicated in the Study Plan (see Table 2 for assessments to be performed for Treatment Period Year 1, Table 3 for Treatment Period Year 2 to 3, and Table 4 for the Follow-up Period).

5.2.1 Adverse events

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

Recording of AEs is described in Section 6.6, and reporting of SAEs and AESIs is described in Sections 6.7 and 6.8, respectively.

5.2.2 Vital signs

Vital signs (oral temperature, blood pressure, pulse rate, and respiratory rate) will be obtained at each visit. Specific information on vital signs surrounding the infusion is included in Section 7.2.4 (Subject monitoring/procedures during and after infusions).

5.2.3 Physical examination

A physical examination will be performed at the visits specified in the Study Plan (Table 2, Table 3, and Table 4) and will include an assessment of the following: general appearance, head and neck, breast, respiratory, cardiovascular, abdomen, musculoskeletal/extremities, neurological, skin, lymph nodes, and thyroid. Body height will be captured at randomisation only. Subjects will be weighed at each study visit. Medically significant changes from randomisation in the LTE study on physical examination will be recorded as AEs.

5.2.4 Pap smear

Most cases of cervical cancer appear to be related to papilloma virus infection. Because of the potential for viral reactivation due to blockade of the Type 1 IFN pathway, we are assessing cervical dysplasia in this study, although to date there has been no signal in the anifrolumab studies. Females with an intact cervix must have a Pap smear completed and without documented malignancy (eg. no signs of CIN grade III, CIS, or AIS) within 90 days before Day 1 or up until 30 days after randomization, ie before dosing at V2. Pap smears should thereafter be performed yearly and all female subjects with an intact cervix should have a Pap smear performed within 3 months of the last IP dose, eg, at the end of study or at the early discontinuation visit.

Subjects with abnormal Pap smear results of atypical squamous cells of undetermined significance, atypical squamous cells where high-grade squamous intraepithelial lesion (HSIL) cannot be ruled out (ASC-H), atypical glandular cells (AGC), or CIN grades I and II (CIN I and II) will be allowed to enter the study; [redacted]. If the subject's gynaecologist has recommended a repeat Pap smear be performed at a specified interval, the Pap smear should be obtained as recommended and the report provided in the source document. Since access to a Pap smear may vary by country, the Sponsor recommends that local guidelines are used for obtaining routine follow-up Pap smears in females who have received immunomodulators or immunosuppressive treatment.

5.2.5 Assessment of cardiovascular risk

To understand the contribution of the chronic inflammatory response in SLE to dyslipidaemia (as a potential risk for accelerated subclinical arteriosclerotic cardiovascular disease) and the potential effects of anifrolumab treatment, both lipid (including low- and high-density lipoproteins and triglycerides [see Section 5.2.9]) and inflammatory profiles will be obtained during the study. Concomitant medications received for cardiovascular indications should be collected and recorded.

5.2.6 Electrocardiogram

Digital ECGs for all subjects at all centres will be conducted at the centre using a machine provided by the central ECG vendor and will be transmitted to the central ECG laboratory. Digital ECGs will be performed at the visits specified in the Study Plan (Table 2 and Table 3). Digital ECGs will be obtained after the subject has been resting in a supine position for at least 10 minutes. All digital ECGs will be documented by recording the date, time, heart rate, QRS duration, PR interval, RR interval, QT, and corrected QT interval. The corrected QT intervals will be calculated using the Fridericia formula.

The Investigator or qualified designee will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant, and the reason for the abnormality will be recorded on the CRF, if the Investigator considers it clinically significant. Abnormal values shall not be recorded as AEs unless deemed clinically significant.

5.2.7 Tuberculosis monitoring

Blood testing for TB will be done using the interferon-gamma release assay (IGRA) test (ie, QTF-G In-Tube Test). Evaluation of all subjects by QFT-G In-Tube Test will be performed by the central clinical laboratory according to the Study Plan (Table 2 and Table 3). Annual QFT-G testing is required for all study subjects.

Compared to culture-confirmed TB, overall, 87.6% of subjects have a positive QFT-G In-Tube Test 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)."

5.2.7.1 Tuberculosis results at time of randomisation/Week 52 of the Phase 3 Study D3461C00004 or D3461C00005

- If the QFT-G test result was **negative** and there is no known history of recent exposure to individuals with active TB, the subject may be randomised.

- If the QFT-G test result was **newly positive**, a chest x-ray must be performed. If the chest x-ray shows no evidence of active TB, and the subject has no symptoms or medical history consistent with active TB, the subject must have a retest. If the retest is positive, the subject must start on prophylaxis within 30 days of randomisation, but prior to the second dose (Visit 2/Week 4) in the LTE study. The subject should be referred to a TB specialist. If a TB specialist is not available, the local country guidelines should be followed for further diagnostic work up and anti-TB treatment regimens. If no local guidelines exist for immunocompromised

individuals, then USA guidelines may be followed. This should be reported as an AESI. The QFT-G test must be repeated annually.

- If the QFT-G test was **positive but not newly positive**, the subject must have been diagnosed with latent TB and must have documentation confirming completion of appropriate OR initiate treatment for latent TB within 30 days of randomisation, but prior to the second dose (Visit 2/Week 4).

- If the QFT-G test result was newly indeterminate (as confirmed on retest unless prior positive QFT-G was documented, along with completed treatment for latent TB) or indeterminate but not newly indeterminate, further QFT-G testing will be done according to the Study Plan (Table 2 and Table 3).

QFT-G testing is performed at least annually and in some cases more often, depending on the result. Refer to the Study Plan (Table 2 and Table 3).

5.2.7.2 Tuberculosis monitoring during the study

At every visit, sites should ensure that the subject has no signs or symptoms of active TB, no recent contact with anyone with active TB, and there is no history of latent (unless diagnosed with documentation of initiation of appropriate treatment) or active TB.

If during the trial a subject is determined to have a:

- **Negative** QFT-G test result, only the annual TB testing is required.

- **Newly positive** QFT-G test result, a chest x-ray has to be performed, and the subject should be referred to a TB specialist. If a TB specialist is not available, the local country guidelines should be followed for further diagnostic work up and anti-TB treatment regimens. If no local guidelines exist for immunocompromised individuals, then USA guidelines may be followed. This should be reported as an AESI. The QFT-G test must be repeated annually.

- For **indeterminate** QFT-G test result, refer to Section 5.2.7.1.

QFT-G testing is performed at least annually and in some cases more often, depending on the result. Refer to the Study Plan (Table 2 and Table 3).

5.2.7.3 Tuberculosis monitoring at Week 156

- **Negative** QFT-G test result: No further testing is required.

- **Newly positive** QFT-G test result at Week 156 or later: Follow prior recommendations for newly positive QFT-G result during study.

- **Newly indeterminate** QTF-G test result (as confirmed on retest unless prior positive QFT-G was documented, along with completed treatment for latent TB): Repeat at Follow-up Visit 1 (8 weeks post-final dose).
  - If negative, no further testing
  - If indeterminate, repeat again at Follow-up Visit 2 (12 weeks post-final dose).

5.2.8 Modified Flare Index

A modified SELENA flare index, using the SLEDAI-2K instead of the SELENA SLEDAI, will be completed at the times indicated in the Study Plan (Table 2 and Table 3) to characterise flares as safety events [redacted].

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

5.2.9 Clinical laboratory tests

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

Urine pregnancy tests will be performed at the site using a dipstick. A serum FSH will be performed at randomisation at the central laboratory in newly postmenopausal females with menses absent for ≥1 year.

Abnormal safety laboratory results should be repeated as clinically indicated, as soon as possible (preferably within 24 to 48 hours). Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

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

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.6.

In case a subject shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) **and** total bilirubin (TBL) ≥2 × ULN [redacted] 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law' for further instructions.

The following laboratory variables in Table 5 will be measured:

Table 5 Clinical laboratory test

Randomisation
[redacted]
HbA1c in diabetic subjects only
HBV DNA (testing every 3 months for subjects with HBcAb positivity at enrolment of Studies D3461C00004 or D3461C00005. To remain eligible in the LTE study, subject HBV DNA levels must remain below the LLOQ as per the central laboratory.)
HIV test (only in subjects not tested in Studies D3461C00004 or D3461C00005)
CK
[redacted]
Urine protein/creatinine ratio
QFT-G
Haematology
Haematology/Haemostasis (whole blood)
WBC count with differential
RBC count
Haematocrit
Haemoglobin
Platelet count
MCV
MCHC
Serum Chemistry
Calcium
Chloride
Potassium
Sodium
AST*
ALT*
ALP*
GGT
BUN
Creatinine
TBL* (reflexively fractionated if elevated)

Table 5 Clinical laboratory test

Glucose
Albumin
CK
*Note for serum chemistry: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.
Urinalysis
Colour
Appearance
Specific gravity
pH
Protein dipstick
Glucose
Ketones
Blood
Bilirubin
Microscopy including WBC/HPF, RBC/HPF, casts
Urine creatinine and protein, urine protein/creatinine ratio
Pregnancy Test
Urine β-hCG (at every visit, using a dipstick)
Serum FSH (at randomisation only) in newly postmenopausal females with menses absent for ≥1 year
[redacted]
Other Safety Evaluations
Tacrolimus trough levels (in subjects receiving tacrolimus as standard of care SLE therapy. These subjects must maintain tacrolimus trough levels below the central laboratory upper limit of the therapeutic range based on monthly measurements.)

Table 5 Clinical laboratory test

ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] AST = aspartate aminotransferase; β-hCG = β human chorionic gonadotropin; BUN = blood urea nitrogen; [redacted] CK = creatine kinase; DNA = deoxyribonucleic acid dsDNA = double stranded deoxyribonucleic acid; GGT = gamma glutamyl transferase; HbA1c = glycosylated haemoglobin; HBcAb = Hepatitis B core antibody; HBV = Hepatitis B virus; HPF = high power field; HIV = human immunodeficiency virus; LLOQ = lower limit of quantitation; LTE = long-term extension; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; QFT G = QuantiFERON®-TB Gold; RBC = red blood cell; SLE = systemic lupus erythematosus; [redacted] TBL = total bilirubin; WBC = white blood cell

5.2.9.1 Fasting lipid profile

Subjects will have a fasting lipid profile (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) completed at times indicated in the Study Plan (Table 2 and Table 3). Subjects will be required to fast for at least 8 hours prior to this assessment (see Section 3.3.3).

5.2.9.2 Immunology profile

Subjects will have tests to determine Ig profile (anti-nuclear antibody [ANA], anti-Smith [anti-Sm], anti-ribonucleoprotein [anti-RNP], anti-Sjogren's Syndrome-related antigen A [anti-SSA], and anti-Sjogren's Syndrome-related antigen B [anti-SSB]), and quantitative Ig completed at times indicated in the Study Plan (Table 2 and Table 3).

[redacted]

[redacted]

[redacted]

[redacted]

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

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

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

[redacted]

6.3 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with TBL ≥2 × ULN may need to be reported as SAEs. [redacted]

6.4 Other events of special interest

6.4.1 Overdose

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

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

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

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

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

6.4.2 Pregnancy

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

6.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic

pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

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

6.4.2.2 Paternal exposure

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

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

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

6.5 Adverse events of special interest

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

Adverse events of special interest in this protocol will be assessed at each visit on the CRF. The events of interest are medically significant infections (non-opportunistic serious infections and opportunistic infections including viral infection/reactivation), severe hypersensitivity reactions including anaphylaxis and immune complex disease, malignancy, *herpes zoster* with cutaneous presentation, TB (including latent TB), influenza, vasculitis (non SLE), and MACE (including stroke, myocardial infarction, or cardiovascular death). Lupus nephritis (associated with SLE; WHO or ISN/RPS Classification Class III, IV or V) is defined

not as an AESI but as a new SLEDAI AE, and diagnosis will be supported with laboratory results.

An AESI that meets 1 of the seriousness outcomes listed in Section 6.2 will be categorised as an SAE for the purposes of follow-up responsibility and safety reporting. A nonserious AESI will be categorised as an AE. For reporting of AESIs, see Section 6.8.

6.5.1 Medically significant infections (including viral infection/reactivation/opportunistic infections)

Medically significant infections are an important potential risk based on the mechanism of action of anifrolumab. For safety reporting purposes, in this study, infections are classified as either serious non-opportunistic infections or opportunistic infections as described here.

6.5.1.1 Serious non-opportunistic infection

A serious non-opportunistic infection is any non-opportunistic infection that meets the SAE criteria in Section 6.2. Serious non-opportunistic infection AEs 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. Nonserious non-opportunistic infections will not be captured as AESIs.

6.5.1.2 Opportunistic infection

An opportunistic infection is an invasive infection caused by microorganisms that are normally non-pathogenic or rarely pathogenic in individuals with normal immune function or cause an infection of a type or severity not seen in the normal host.

Examples of opportunistic infections that may occur in SLE subjects include: *herpes zoster* meningoencephalitis, *Salmonella* bacteraemia, *Pneumocystis jirovecii* 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 subjects who develop serious infections.

6.5.1.3 Influenza

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

Laboratory criteria for influenza include at least 1 of the following: isolation of influenza virus from a clinical specimen, detection of influenza virus nucleic acid in a clinical specimen,

identification of influenza virus antigen by direct fluorescent antibody test in a clinical specimen, OR influenza-specific antibody response.
A confirmed case of influenza meets the clinical and laboratory criteria for the viral illness. Laboratory confirmation should be done using locally available, rapid, commercial tests approved by regulatory agencies and sampling respiratory specimens. Not all upper respiratory viral infections or gastrointestinal viral infections are influenza. In the case where a subject reports a viral infection severe enough to be considered, in the opinion of the Investigator, influenza, a viral test should be performed (if possible) to confirm the diagnosis. If, in the opinion of the Investigator, the subject has had influenza (the specific viral infection), this should be reported as an AESI, whether or not a test to confirm the diagnosis has been performed. Less severe viral infection should be reported as an AE only.

6.5.2 Severe hypersensitivity reactions including anaphylaxis and immune complex disease

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 [redacted] is provided as a simple and rapid means to make the diagnosis of anaphylaxis during infusion with investigational product. This definition was a product of a symposium convened by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (Sampson et al, 2006).

6.5.3 Malignancy

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

6.5.4 Herpes zoster reactivations (including cutaneous events)

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

. Systemic infections or other medically significant herpes zoster infections are considered important potential risks and classified as *medically significant infections* for adverse event reporting in this study unexpected for regulatory reporting purposes. For additional information regarding *herpes zoster*, refer to the IB. As all herpes zoster events are considered to be an AESI, the Sponsor will collect information including whether or not

subjects have received vaccination for *herpes zoster*. The *herpes zoster* vaccine medical history data will be captured in the appropriate sections of the CRF.

6.5.5 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 (IGRA), radiographic imaging, body fluid and tissue sampling; presentation may include disseminated or latent disease. An infection may be new (at least conversion of a TB test to positive) or reactivation of dormant disease (new active disease in a previously TB test positive subject without prior evidence of active disease).

- **A bacteriologically confirmed TB** case is a case where a biological specimen is positive by smear microscopy, culture or rapid diagnostic, such as polymerase chain reaction or nucleic acid amplification test (Xpert MTB/RIF).

- **A clinically diagnosed TB** case is a case where the subject does not fulfil the criteria for bacteriological confirmation, but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the subject a full course of TB treatment. This definition includes cases diagnosed on the basis of x-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

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

Latent TB is a mycobacterial infection without clinical, bacteriological findings, or radiologic findings consistent with active TB and a TB blood test such as an IGRA (QFT-G) 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 to continue to receive investigational product.

6.5.6 Vasculitis (non-systemic lupus erythematosus)

Vasculitis (non SLE) is defined as an inflammatory disorder of blood vessels involving arteries and/or veins and characterised by characteristic clinical signs/symptoms and diagnosed by biopsy, imaging such as angiography, or blood tests such as findings of antineutrophil cytoplasmic antibodies consistent with the diagnosis. Underlying causes should

be identified, such as medications including study drug, infections, or systemic inflammatory syndromes, wherever possible.

6.5.7 Major adverse cardiovascular events

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

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

6.6 Recording of adverse events

6.6.1 Time period for collection of adverse events

Adverse events and SAEs will be collected from the time of randomisation, throughout the treatment period, and including the follow-up period until Follow-up Visit 2 (12 weeks post-final dose). Events that occur prior to randomisation in the LTE study should be reported in Studies D3461C0004 or D3461C00005.

6.6.2 Follow-up of unresolved adverse events

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

6.6.3 Variables

The following variables will be collected for each AE;

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

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

- Onset Date (Date AE met criteria for serious AE)
- Detection Date (Date Investigator became aware of serious AE)
- AE is serious due to:
  - (a) Death
    - Date of death
    - Autopsy performed
    - Primary/secondary cause of death
  - (b) Life-threatening
  - (c) In-patient hospitalisation or prolongation of existing hospitalisation
    - Date of hospitalisation
    - Date of discharge
  - (d) Congenital abnormality or birth defect
  - (e) Important medical event
  - (f) Suspected transmission via a medicinal product of an infectious agent
- Description of AE
- Investigator causality assessment to concomitant medications
- Investigator causality assessment to study procedures (yes or no)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria defined above. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE. The Investigator should provide an assessment of the severity of each AE/SAE.

6.6.4 Causality collection

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

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

[redacted]

6.6.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded on the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.6.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE (or SAE, as appropriate).

6.6.7 Disease progression/worsening of systemic lupus erythematosus

Disease progression can be considered as a worsening of a subject's condition attributable to SLE. It may be an increase in the activity or severity of the existing manifestations of SLE or the appearance of new manifestations. Worsening of SLE should not be reported as an AE, unless the signs and symptoms meet criteria for an SAE. [redacted]

6.7 Reporting of serious adverse events

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

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

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

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

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

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

PRA Safety Management contact information for SAE reporting:

FAX: [redacted]
Email: [redacted]
Telephone: [redacted]

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

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

6.8 Reporting of adverse events of special interest

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

The reporting period for AESIs is the period immediately following randomisation through the end of subject participation in the study. Adverse events of special interest that occur prior to randomisation in the LTE study should be reported in Studies D3461C0004 or D3461C00005. Following detection of an AESI (nonserious), 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. Nonserious non-opportunistic infections will not be captured as AESIs.

6.9 Management of investigational product-related toxicities

6.9.1 Anaphylaxis, hypersensitivity, and infusion-related reactions

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

Subjects should not be premedicated unless they have had a prior infusion-related reaction to anifrolumab. However, if a prior infusion-related reaction has been documented, the Investigator may elect to administer prophylactically an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the subject prior to subsequent infusions. Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted.

6.9.2 Infections

When an infection is reported as an SAE or AESI, cultures should be obtained and culture results should be reported with the event. Other specific laboratory tests or other investigations (eg, chest x-ray for pneumonia) that confirm or aid in the diagnosis or treatment should be obtained when indicated, and results should be reported with the SAE or AESI. Failure to obtain this information will impair the Sponsor's ability to characterise the benefit:risk profile of anifrolumab.

Subjects who develop a new infection while undergoing treatment with investigational product should receive appropriate medical therapy, as determined by local standards, and be monitored closely until the condition resolves. Investigational product should not be administered to a subject with a clinically significant, active infection as determined by the Investigator (see Section 3.9). For any active infection (eg, *varicella zoster* infection/chickenpox) or significant exposure to any infection (eg, *varicella zoster* infection in

a naive subject, bacterial pneumonia), the Investigator should consider whether to interrupt investigational product administration and should notify the PRA Medical Monitor.

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

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

6.10 Study governance and oversight

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

6.10.1 Data and Safety Monitoring Board

An independent DSMB will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. After reviewing the data, the DSMB may choose to unblind the treatment groups for additional review. The DSMB will not routinely review efficacy data.

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

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

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 (clear colourless to slightly yellow) intended for IV administration following dilution into 0.9% saline	MedImmune, LLC
Placebo	Solution (clear) intended for IV administration following dilution into 0.9% saline	MedImmune, LLC

IV = intravenous

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

Investigational product and placebo will be provided in vials within cartons. Each kit will contain 2 mL nominal volume. Every kit will have a unique number that will be printed on all the labels within the kit (ie, the outer carton label and the vial label).

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

7.2 Dose and treatment regimens

The investigational product, anifrolumab (MEDI-546) 300 mg or placebo, will be administered via controlled IV infusion pump into a peripheral vein over a minimum of 30 minutes Q4W. Each dose must be at least 14 days apart, ie, the next infusion can be scheduled on Day 15 or later.

7.2.1 Dose preparation steps

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

7.2.2 Prior to administering the investigational product

- Confirm subject was evaluated for signs and symptoms of TB.

- Women of childbearing potential must have a negative urine pregnancy test prior to receiving investigational product.
- Subjects should not have clinically significant, active infection as determined by the Investigator.
- There should be at least 14 days between doses. If the previous investigational product infusion was given within 14 days, delay visit until >14 days has elapsed and contact the PRA Medical Monitor.
- Pre-dose blood samples will be collected.
- Subjects should not be premedicated unless they have had a prior infusion-related reaction to anifrolumab. However, if a prior infusion-related reaction has been documented, the Investigator may elect to administer prophylactically an antihistamine or acetaminophen/paracetamol for the comfort and safety of the subject prior to subsequent infusions. The medications should be given after visit assessments have been completed. Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted.

7.2.3 Investigational product administration procedures

- Investigational product must be administered within 4 hours after preparation and may be stored at room temperature until administration. Total in-use storage time from dilution of anifrolumab to start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36 to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.
- Investigational product must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product.
- Because compatibility of anifrolumab with IV medications and solutions other than 0.9% sodium chloride for injection (United States Pharmacopeia) is not known, the investigational product solution should not be infused through an IV line in which other solutions or medications are being administered.
- Investigational product should be administered over a minimum of 30 minutes.
- Immediately following the initial dosing, up to an additional **25 mL of saline** will be given via infusion pump at the same pump speed utilised at the completion of the initial dosing.
- An emergency cart should be available in the infusion suite.

7.2.4 Subject monitoring/procedures during and after the infusion

Subjects will be monitored during the administration of the investigational product and for at least 2 hours after the first 4 infusions (Visits 1 to 4). For subsequent infusions, if there are no safety concerns, subjects will be monitored during administration of the investigational product and for a minimum of 1 hour after completion of the IV infusion thereafter.

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

- Shortly before the IV infusion (within 15 ±5 minutes of the beginning of the investigational product infusion)
- Every 15 ±5 minutes during infusion
- Immediately after completion of administration of investigational product, including post-dose saline flush (within 15 ±5 minutes after completion of investigational product administration)
- Every 30 ±5 minutes after completion of investigational product administration (not including saline flush) for at least 2 hours after the first 4 doses of investigational product are administered (Visits 1 to 4), and for at least 1 hour thereafter

[redacted]

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

7.2.5 Discharge

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

7.2.6 Documentation of investigational product administration

Both the duration of the investigational product infusion and the duration of investigational product administration will be recorded. The duration of investigational product infusion and duration of investigational product administration will be calculated as follows:

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

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

- Duration of administration: the amount of time elapsed from the infusion pump start time to the infusion pump stop time PLUS the time required to complete the additional flush of saline. The duration of administration will always be greater than the duration of infusion and will always include the additional flush of saline.

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

Table 6 Compatible materials of construction for IV bags

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

DEHP = diethylhexyl phthalate; IV = intravenous; PVC = polyvinyl chloride

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

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

DEHP = diethylhexyl phthalate; PVC = polyvinyl chloride

7.3 Labelling

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

7.4 Storage

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

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the CRF. The investigational product will be administered by study site personnel, who will monitor compliance.

7.6 Accountability

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

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

The Investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to AstraZeneca or designee. All unused investigational product will be returned to an AstraZeneca or designee-authorised depot or disposed of upon authorisation by AstraZeneca or designee or other written instructions provided by AstraZeneca or designee (for contact information and specific shipping instructions).

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

7.7 Concomitant and other treatments

See Section 3.3.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to the first subject included into the study. Any subsequent amendments to the SAP will be documented, with final amendments completed prior to unblinding of the data for the analysis. Details of all analyses, including sensitivity analyses, will be fully documented in the SAP.

8.2 Sample size estimate

No formal comparisons are planned in this study; point estimates and CIs will be presented for each treatment group separately. The sample size is not based on statistical considerations, but is defined as all subjects who completed the treatment period in the Phase 3 pivotal

Studies D3461C00004 or D3461C00005 (through Week 52) and met all study eligibility criteria. Assuming annual dropout rates of 30% (Randomised Placebo), 30% (Randomized Anifrolumab 150 mg) and 20% (Randomized Anifrolumab 300 mg), and that 90% of the subjects completing the pivotal studies will enter the extension, follow-up times of approximately 893, 517, and 1343 subject-years for the "Randomised Anifrolumab 300 mg," "Randomised Placebo," and "All Anifrolumab" treatment groups are expected. Given this exposure, the 95% CIs for an adverse event of special interest (AESI) for which the observed incidence rate is 10 events in 1000 subject-years will be 5.21 to 19.21 for "Randomised Anifrolumab 300 mg," and 4.24 to 23.57 for "Randomised Placebo." For an AESI for which the observed incidence rate is 1 event in 1000 subject-years, the 95% CI will be 0.18 to 5.42 for "All Anifrolumab" (0.13 to 7.95 for "Randomised Anifrolumab 300 mg"), and 0.07 to 15.25 for "Randomised Placebo," using the Rothman-Greenland Method (Rothman and Greenland, 1998).

8.3 Definitions of analysis sets

8.3.1 Full analysis set

All subjects enrolled in Studies D3461C00004 or D3461C00005 will be included in the main analysis of the LTE study, even if they do not enter the LTE study. Therefore, the full analysis set will consist of all subjects who were randomised and received at least 1 dose of investigational product in the Phase 3 pivotal Studies D3461C00004 or D3461C00005. Subjects will be analysed according to the Intention-To-Treat principle. Subjects who withdraw consent to participate in the study will be included up to the date of their study termination.

[redacted]

8.3.3 Treatment groups for analysis

Summaries will be presented according to the following overall treatment groups:

Primary:

- ***Randomised Anifrolumab 300 mg:*** Subjects randomised to anifrolumab 300 mg in Studies D3461C00004 or D3461C00005 using all data from randomisation to end of LTE, including follow-up data.
- ***Randomised Placebo:*** Subjects randomised to placebo in Studies D3461C00004 or D3461C00005 using data from randomisation up until switch to anifrolumab 300 mg (ie, up to Week 52 in Phase 3 pivotal studies) or to end of LTE for subjects re-randomised to placebo, respectively, in the LTE.

Supportive:

- ***Placebo Feeder + Placebo LTE:*** Subjects randomised to placebo in Studies D3461C00004 or D3461C00005 and re-randomised to placebo in LTE using all data from randomisation to end of LTE. Data from subjects discontinuing from the investigational product in Studies D3461C00004 or D3461C00005, or who elect not to participate in the LTE, but who would have been re-randomised to placebo are included in this treatment group up to withdrawal.

- ***All Anifrolumab:*** Subjects randomised to anifrolumab in studies D3461C00004 or D3461C00005, regardless of dose, and subjects randomised to placebo in studies D3461C00004 or D3461C00005 and then re-randomised to anifrolumab 300 mg in LTE, using all data from randomisation or switch to anifrolumab, respectively, to end of LTE.

Additional supportive:

- ***Placebo Feeder + Placebo LTE:*** As described above but using data collected during the LTE study only, ie, reduced to subjects enrolled in the LTE study.

- ***Placebo Feeder + Anifrolumab 300 mg LTE***: Subjects randomised to placebo in studies D3461C00004 or D3461C00005 and then re-randomised to anifrolumab 300 mg in LTE using data from switch to end of LTE.

- ***Anifrolumab 150 mg Feeder + Anifrolumab 300 mg***: Subjects randomised to anifrolumab 150 mg in Study D3461C00005 and then switched to anifrolumab 300 mg in LTE using data from switch to end of LTE.

In addition, supplemental summaries with the data collected in the LTE only (excluding the feeder studies) will be provided.

8.4 Outcome measures for analyses

8.4.1 Primary outcome variables: Safety variables

The following primary safety data will be collected: AESIs (see Section 6.5) and SAEs.

Other safety variables include AEs, vital signs, physical examination, ECGs, flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K, haematology, clinical chemistry, and urinalysis.

Adverse events, AESIs, and SAEs will be summarised by means of descriptive statistics and qualitative summaries.

8.4.1.1 Other significant adverse events

During the evaluation of the AE data, a PRA medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Astra Zeneca Global Patient Safety Physician, be considered other significant AEs and reported as such in the Clinical Study Report.

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

[redacted]

[redacted]

8.5 Methods for statistical analyses

Where applicable, the analyses will include data from randomisation in pivotal Phase 3 Studies D3461C00004 or D3461C00005 until the end of the LTE study, regardless of whether

study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence.

Missing data

Data will be analysed as available. Details for handling of missing data will be presented in the SAP.

Presentation of results

All data will be summarised by treatment groups as described in Section 8.3.3. Details will be presented in the SAP. Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

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

Retention rates over time and reasons for discontinuation of the investigational product will be summarised.

8.5.1 Analysis methods for safety variables

Adverse events (AESIs and SAEs) will be summarised using incidence rates (ie, number of events divided by person-time at risk). The main treatment groups for addressing the primary objective will be "Randomised Anifrolumab 300 mg" and "Randomised Placebo". In addition, rates will also be explored over time to describe potential changes in risks with longer exposure. All AEs will be listed.

Laboratory data for haematology and clinical chemistry will be summarised. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis.

The rate of flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K (number of flares divided by person-time at risk) will be explored.

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

[redacted]

8.5.3 Interim analysis

An independent DSMB will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study as described in Section 6.10.1. Interim analyses may be performed at appropriate timepoints during the study, according to regulatory and other requirements. Further details of interim analyses will be provided in the SAP.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first subject is randomised 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 system(s) utilised (see Section 5.1.1).

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

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

of/destroyed accordingly, and that 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 CSA 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 CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The study is expected to start in Quarter 3, 2016, and to end by Quarter 3, 2021.

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

9.4 Data management

Data management will be performed by PRA, according to the Data Management Plan. The PRA Datalabs system will be used for data collection and query handling.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the PRA coding group. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan and Edit Check 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 reconciliation

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

Management of external data

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

10.3 Ethics and regulatory review

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

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

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

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

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

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure that 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 that each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that a copy of the signed ICF 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 ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

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

If there are any changes to the study protocol, then these changes will be documented in a new version of the study protocol.

If applicable, the new version of the protocol is to be approved by the relevant EC and the national regulatory authority before implementation. Local requirements are to be followed for revised protocols.

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

If a protocol amendment requires a change to a centre's ICF, AstraZeneca or designee and the centre's EC are to approve the revised ICF before the revised form is used.

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

10.6 Audits and inspections

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

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