- **Protocol number:** D3461C00007
- **Document title:** A Multicentre, Randomised, Double-blind, Placebo controlled, Phase 2 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Proliferative Lupus Nephritis
- **NCT number:** NCT02547922
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- **Date of the document:** 13 December 2017

Clinical Study Protocol	
Drug Substance	Anifrolumab
Study Code	D3461C00007
Version	4.0
Date	13 December 2017

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Proliferative Lupus Nephritis

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 4.0, 13 December 2017

Changes to the protocol are summarised below.

The renal function and proteinuria components of renal response criteria will be modified by changing the estimated glomerular filtration rate (eGFR) and 24-hour urine protein to creatinine ratio (UPCR) cut-off values.

For complete renal response (CRR), the alternative complete renal response (aCRR), the partial renal response (PRR), graded CRR, and graded aCRR, the cut-off values for the renal function (eGFR) will be changed to:

- eGFR to ≥60 mL/min/1.73m^2 or no confirmed decrease of eGFR from baseline of ≥20%

For CRR and aCRR, the cut-off value for proteinuria (24-hour UPCR) will be changed to:

- 24-hour UPCR to ≤0.7 mg/mg

For graded CRR and graded aCRR, the cut-off values for proteinuria will be changed to:

- For subjects with baseline 24-hour UPCR of >3 mg/mg 24-hour UPCR cut-off will be changed to ≤1 mg/mg
- For subjects with baseline 24-hour UPCR of ≤3 mg/mg 24-hour UPCR cut-off will be changed to ≤0.7 mg/mg

The flare definition for proteinuria (UPCR) will be changed to >1.5 mg/mg.

Changes to objectives

aCRR and 24-hour UPCR will be added as exploratory objectives at Week 104.

It will be clarified that the proportion of subjects achieving PRR or CRR at Week 104 will be used to evaluate the effect of anifrolumab on lupus nephritis (LN) at this timepoint.

Clarification will be added that International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification and National Institute of Health (NIH) indices will also be summarised based on CRR and PRR at Week 104.

Interim analysis

Text will be added that an interim analysis may be performed after approximately 50% of

subjects have completed Week 52 visit.

CCI [redacted] The statistical analysis plan (SAP) v1.0 was completed and the last SAP amendment will be completed prior to unblinding of data. CCI [redacted]

Changes to statistical analysis

Text will be added in Section 8.6 that strong control of the familywise error rate will be performed for the primary and secondary endpoints for the pooled anifrolumab group compared with placebo as well as the respective tests for the individual anifrolumab regimens and the testing strategy to account for multiplicity considerations will be described. The power and minimal detectable difference will be updated based on primary endpoint for the pooled anifrolumab group compared with placebo in Section 8.2. The sample size will provide approximately 86% power with a 2-sided alpha of 0.049.

Relevant sections in the protocol will be updated to be consistent with the SAP.

- Text will be added that the primary and secondary endpoints will be based on the pooled anifrolumab group compared with the placebo group.
- Three additional subgroups; ADA (positive at any time, negative), eGFR at baseline (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2) and oral corticosteroids (OCS) dose at baseline (≤20 mg/day, >20 mg/day) will be added to Section 8.5.10. The geographic region subgroup will be renamed placebo response region.
- The age subgroups in Section 8.5.10 will be changed to ≥18 to 64 and ≥65 years.
- In Section 8.1 it will be clarified that all personnel involved in the conduct of the study would remain blinded until database soft lock.
- In Section 8.5 it will be clarified that nominal p-values could be presented for endpoints not included in the strategy for preserving type 1 error rate.

Other changes

In Section 3.2.1, the exclusion criteria for aspratate transaminase (AST) and alanine transaminase (ALT) were changed to >2.5x upper limit of normal (ULN).

It will be clarified that no increase in oral corticosteroids (OCS), or the use of intravenous (IV) intra-articular, tendon sheath or bursal injections is allowed from Week 40 until Week 52

assessment.

Exclusion criterion No.3 will be updated that subjects concurrently enrolled in another clinical study with an IP within 4 weeks prior to ICF signing will be excluded.

Text for unblinding plan for anti-drug antibodies (ADA) and pharmacokinetic (PK) analysis will be added.

Criteria for discontinuing investigational product (IP) at Week 52, Week 56 or Week 60 will be included.

Pap smear will be clarified as follows:

- In Section 4.2.1.2 that Pap smear results must be found to meet eligibility requirements for Pap smears as defined in Appendix K. Table 2 footnote h will be corrected to state that Pap smear results must be obtained after Week 48 and must be found to meet eligibility requirements for Pap smears as defined in Appendix K and available by Week 60 or IP will be discontinued.
- Text on Pap smear access varying by country and recommendation that local guidelines for obtaining Pap smears in subjects who have received immunomodulators or immunosuppressive treatment be followed will be removed from Section 5.2.3.3 and footnote h in Table 2.
- In Section 5.2.3.3 that the Pap smear will be repeated in female subjects with an intact cervix between Week 48 and Week 52 and Week 100 and Week 104 to ensure there is no evidence of new cervical dysplasia.

Text in Section 4.2.1.1 will be edited to clarify that all Week 52 laboratory samples (blood and urine, including 24-hour UPCR sample) should be collected between Week 50 to Week 52, to allow assessment of PRR requirement for the second year and reference to Table 2 footnote 1 included. Table 2 footnote 1 will be edited to be consistent with new text and footnote 2 deleted.

It will be clarified that Columbia-Suicide Severity Rating Scale (C-SSRS) is only collected until Week 52. It will be clarified that tuberculosis questionnaire, assessment of Cushingoid features, and assessment of cardiovascular risk (fasting lipid profile) will be analysed for safety.

It will be clarified that only C_{trough} will be assessed in the second year.

It will be clarified that subjects would be randomised at approximately 95 sites and estimated date of last subject completed would be Q3 2020.

Reference to UPCR will be removed from renal discontinuation at Week 52 as re-test applies

to all PRR related laboratory tests not to UPCR only.

In Section 3.9.9 it will be clarified that subjects who discontinue IP earlier than 12 weeks and before Week 52 will be followed until Week 52.

Text in Section 4.2.1.3 on 24-hour UPCR and laboratory assessments will be removed as this was not needed for Week 104.

In Section 4.2.2 it will be clarified that assessment for 24-hour UPCR should be completed for subjects who discontinue IP.

In Section 5.1 it will be clarified that 24-hour UPCR will be used to derive CRR at Week 104.

In Section 5.4.2 it will be clarified that drug concentration determination would be in serum not plasma.

It will be clarified in Section 7.7.4.3 and Table 2 footnote v that randomised subjects who receive anti-malarial therapy within 12 months prior to signing ICF must have an eye exam by a qualified professional within 12 months prior to signing the ICF and that subjects starting anti-malarial therapy during the Screening Period must have an eye exam within 12 weeks after signing the ICF.

In Section 7.2.4, it will be clarified that monitoring which include vital signs will be up to 20 minutes before IP infusion starts and also within 20 minutes after completion of post-dose saline flush.

Text on efficacy in anifrolumab Phase 2b study and safety experience in anifrolumab Phase 2b study through November 2015 in Section 1.3 will be deleted as information is already available in Investigator's Brochure (IB). The overall benefit/risk assessment for study D3461C00007 section will be updated to be consistent with the current IB.

Text on the objective of the Lupus Nephritis Steering Committee will be added to Section 9.4.

It will be clarified that the World Health Organisation (WHO) Drug Dictionary not AstraZeneca Drug Dictionary will be used to classify medications.

Typographical and grammatical errors and administrative changes will be corrected as needed throughout the protocol.

Version 3.0, 3rd September 2016

Changes to the protocol are summarised below.

Text was added to clarify the study design of the second year extension period. Eligible subjects enrolled in the original Phase 2 study will continue in their randomised treatment groups. The treatment groups will continue to receive IP infusions (anifrolumab 300 mg or placebo) every 4 weeks (Q4W) starting at Week 52 for an additional 48 weeks in addition to standard of care (SOC) until Week 100. Final efficacy assessment will be made at Week 104. Safety follow-up will continue every 4 weeks until Week 112.

Criteria for discontinuation of IP at Week 52 were added.

Subjects not meeting the criteria to continue for the second year extension period will not receive any IP at Week 52 and will complete the study after completing the required follow-up visits.

Subjects meeting the following criteria may continue to receive blinded IP between Weeks 52 and 100.

(i) Meeting all of the following criteria based on the renal portion of the PRR definition:

- eGFR is:
  - ≥80 mL/min/1.73 m^2, if baseline eGFR was ≥90 mL/min/1.73 m^2 or
  - >85% of baseline eGFR, if baseline eGFR was <90 mL/min/1.73 m^2
- Improvement in 24-hour UPCR:
  - For subjects with a baseline UPCR ≤3 gm/gm: <1.0 gm/gm
  - For subjects with a baseline UPCR >3 gm/gm: >50% improvement from baseline and ≤3.0 gm/gm

Renal discontinuation criteria must be confirmed in two separate samples. The second UPCR measurement should be at least 1 week after the first measurement.

(ii) No discontinuation of IP

(iii) Negative human immunodeficiency virus (HIV) test after signing the Main informed consent form (ICF)

Criteria for discontinuation of IP during the second year extension period were added:

- Week 56:
  - Abnormal Pap smear or failure to obtain a Pap smear after Week 48
  - Failure to obtain Week 52 QuantiFERON test result by Week 56
- At Week 60 and later
  - OCS >7.5 mg/d (except one OCS burst and taper)
  - Mycophenolate mofetil (MMF) >2 gm/day or >Week 52 dose, whichever is lower

The following flow of activities related to the transitioning to the second year extension was added:

- All Week 52 efficacy assessments must be completed prior to initiation of second year extension period dosing
- First dose in second year extension period must be between Week 52 (+14 days) and Week 60
- At Week 52, the 24-hour UPCR may be collected between Weeks 50 and 52 to assess response and eligibility for participation in the second year extension period
- The eGFR measured between Week 50 and Week 52 will be used to assess eligibility for participation in the second year extension period
- Safety assessments:

  The electrocardiogram (ECG) at Week 52 has to be done prior to dosing of IP. Pap smear, hepatitis B virus (HBV), QuantiFERON-tuberculosis (TB) are to be performed as per protocol. Results must be available prior to the Week 56 dosing of IP. The Week 56 dose (or the Week 60 dose if that is the first in the extension) cannot be administered without the results of the Pap smear, HBV and TB assessments

Text was added to explain the treatments during the second year extension period:

Blinded IP administration every 4 weeks (last dose at Week 100)

<u>MMF:</u>

- MMF ≤2 gm/day and ≤Week 52 dose, whichever is lower

- If >2gm at Week 52, taper to ≤2 gm/day required by Week 60. Failure to do so will lead to withdrawal from IP
- Decrease in MMF dose or discontinuation of MMF allowed at investigators discretion between Week 52 to Week 92; no minimum dose during second year
- If MMF is tapered, return to ≤2 gm/day but not exceeding Week 52 dose is allowed
- No change in MMF dose from Week 92 to Week 104

OCS:

- If OCS >7.5 mg/day at Week 52, taper to ≤7.5 mg/day required by Week 60. Failure to do so will lead to withdrawal from IP
- OCS tapering goal ≤5 mg/day at Week 80. Tapering below 5 mg/day allowed until Week 92
- No change in OCS dose from Week 92 to Week 104
- 1 burst and taper allowed between Week 52 and Week 92

Efficacy and safety assessments in the second year extension period were added to Tables 4 and 5 to clarify the time points of the assessments.

Schedule of samplings was added to Tables 4 and 5 to clarify the time points of sampling.

CCI [redacted]

CCI [redacted] The database will be locked and the primary analysis will be performed once all subjects complete Week 52 or discontinue the study prior to Week 52. The Sponsor and Sponsor's delegates will be unblinded to treatment assignments at the time of the primary analysis.

Investigators and subjects who continue in the second year extension phase will continue to be blinded to their treatment. The database will be locked for the final analysis of the second year extension period once the last subject in the second year extension period completes

Week 112, or discontinues the second year extension period prior to Week 112.

Version 2.0, 28th April 2016 **Changes to the protocol are summarised below.**
Text was added to clarify that stratification sample for 24- hour UPCR can be obtained within 14 days prior to the expected date of randomisation. Without the results of this second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days. On rare occasion an extension of the 30-day screening window is allowed if the re collection of the sample is necessary or the results needed for randomisation are delayed. An error noted in relation to the duration of administration (first "12 weeks" instead of first "3 doses of the IP") has been corrected throughout the protocol. Unit of UPCR has been corrected from "gm/gm" to "mg/mg" throughout the protocol. The abbreviation "SFI" has been deleted throughout the protocol and in Appendix L. The term SFI has been replaced by the term " Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) based Flare Assessment Instrument" The outcome measure to evaluate the safety and tolerability of anifrolumab has been updated as "extra-renal flares using SLEDAI-2K based Flare Assessment Instrument". For the exploratory objectives, the criteria to determine improvement in 24-hour UPCR for subjects with a baseline UPCR >3 mg/mg has been updated as >50% improvement from baseline and ≥3.0 mg/mg (previously <3.0). A note has been added to clarify that MMF will be supplied by the Sponsor to the subjects from the day of randomisation onwards until the end of subject's participation in the study. MMF has been updated as "Sponsor provided MMF" in relevant sections of the protocol. The criteria for discontinuing IP at any time have been updated to include: the receipt of methylprednisolone pulse, discontinuation of MMF and initiation of another immunosuppressant. In addition, text was added to clarify that decrease is eGFR is to be based on two independent samples. The criteria for discontinuing IP at Week 12 and Week 24 have been revised to clarify the wording on OCS that decrease is eGFR is to be based on two independent samples. Cut-off values for nephrotic range UPCR have been aligned with that of UPCR values for stratification.

The term "patients" has been replaced with "subjects" where relevant.

Section 1.3 has been updated based on the safety data from the new Investigator's Brochure (version 9.0, dated 18 November 2015).

The minimum dose of MMF has been updated from ≤1.5 gm/day to ≤1.0 gm/day.

Day 1 has been replaced by "the day of randomisation" for clarity in Section 1.4.1.2 and other applicable sections of the protocol, including the inclusion/exclusion criteria.

Section 1.4.1.2 has been updated to clarify that methylprednisolone pulse can be administered on two consecutive days but the cumulative dose must not exceed 500 mg and that OCS burst and taper means one burst and taper of corticosteroids between Week 8 and Week 40 for increased extra renal systemic lupus erythematosus (SLE) disease activity or for non-SLE activity is allowed from randomisation to Week 40.

Inclusion criterion No. 4(b) has been reworded to address indeterminate values and reference to the Laboratory Manual for specifics has been added.

Inclusion criterion No. 7 has been updated to add System International (SI) values of urine protein to creatinine ratio and to clarify that the stratification sample for UPCR can be collected within 14 days of expected date of randomisation.

Inclusion criterion No. 9 has been updated to include a note on "borderline" pregnancy test result.

Inclusion criteria No. 10, 11, 12, and 13 have been updated to be in line with the MMF product information.

Table 1 under inclusion criterion No. 11 has been updated to remove mention of "plus condom or spermicide" and updated to state that one of the two effective methods of avoiding pregnancy should be the barrier method.

Inclusion criterion No. 12 has been updated to provide clarity on the acceptable contraceptive methods. "MMF" has been added to clarify that contraception requirements are applicable for both IP and MMF. "MMF" has also been added in exclusion criterion No. 6, Section 5.4, Section 6.4.3, and Section 6.4.4.

Text has been added in inclusion criterion No. 14 to provide examples of the types of malignancy that should not be noted at screening and to provide clarity on the timing of Pap smear at screening. Reference to exclusion criterion No. 36(b) has been added for clarity.

Exclusion criterion No. 2 was revised to align with the change in the minimum dose of MMF (from ≤1.5 gm/day to ≤1.0 gm/day.

Exclusion criterion No. 6 has been updated to add that the restriction could be 6 weeks after

the last dose of MMF if it is later than 12 weeks after last dose of IP.

Exclusion criterion No. 13(b) has been updated as "Oral or IV pulse methylprednisolone (cumulative dose)" for clarity. For exclusion criterion No. 13(d), equivalent dose of mycophenolate sodium has been added.

Exclusion criterion No. 14(g) has been updated to simplify the haemoglobin eligibility requirements.

Exclusion criterion No. 15 has been updated to include the term 'the subject' for clarity.

Exclusion criterion No. 17 has been updated to clarify the washout period for specific concomitant medications.

Exclusion criterion No. 19 has been updated for clarity.

Exclusion criterion No. 26 has been updated to provide clarity on the criteria related to infection and malignancy risk factors.

Exclusion criterion No. 27 has been updated to clarify that the subject's HBV DNA levels should be "below the lower limit of quantitation (LLOQ)" as per central laboratory to remain eligible for the study. Reference to HBV DNA level of >20 IU/mL has been deleted.

Exclusion criterion No. 32 has been updated to remove the word "systemic" from "systemic opportunistic infection". Text has been added to clarify that vaginal, oral, and skin candidiasis is not an exclusion criterion. Definition of serious non opportunistic infection and reporting procedure in Section 6.5.2 has been updated and reference to Section 6.5.2 has been added in exclusion criterion No. 32.

Exclusion criterion No. 36 has been updated to be consistent with the corresponding footnote in Table 2.

Section 3.3.2.1 heading has been updated to clarify that the exclusionary timeframe for these medications is upon signing of ICF. The bullet point on "corticosteroid pulse" has been updated for clarity.

Danazol, dapsone, sulfasalazine, and prednisolone have been removed from the list of restricted medications in Section 3.3.2.2. Cholestryramine has been added to the list. Reference to these medications in Section 3.3.2.1 has been deleted. Appendix G has been updated to reflect these changes. In Section 3.3.2.2, the term "burst and taper" has been deleted from the last bullet point and text has been added to cross refer to Section 3.3.2.1 for any increase in methylprednisolone pulses for clarity.

Section 3.3.3.1 has been updated to provide clarity to the investigators whether reaching the target MMF dose of 2 gm/day was mandatory or just recommended. Texts have been added to clarify that the requirements for MMF dose escalation have to be met only once and re-testing

is not required. Several other edits have also been made in Section 3.3.3.1 for clarity.

Several edits have been in Section 3.3.3.2 for clarity.

Text in Section 3.3.4.1 has been updated to simplify the protocol.

Text in Section 3.3.4.2 has been updated to clarify that the use of Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blockers (ARB) was allowed if they were started 10 days prior to the second screening 24- hour UPCR.

Text in Section 3.3.4.3 has been updated to provide clarity on the acceptable timeframe of documented ophthalmologic examination in subjects who have been taking anti-malarials for more than 12 months at the time of signing the ICF or, have initiated anti-malarials within 12 months prior to signing the ICF.

In Section 3.3.4.4, the term "enrolment" has been replaced by "signing ICF" to provide clarity on the timeframe.

Section 3.3.4.5: The text has been moved up to the start of Section 3.3 and has been reworded for clarity.

Section 3.4 has been updated to add additional information about instructions for subjects who were enrolled incorrectly.

A new subsection (Section 3.7.3) on "blood donation" has been added to inform restriction on blood donation from date of randomisation until 6 weeks after the last dose of Sponsor provided MMF.

In Section 3.8.2, bullet No. 11 which was erroneously included has been deleted.

In Section 3.9, the heading name "Criteria for withdrawal" was replaced with "Screen failures". A sentence has been added to Section 3.9 to state that rescreening of a subject is permitted once.

The term "study drug" has been replaced by "IP" in Section 3.10 for clarity. Similar changes have been made in all the applicable sections of the protocol.

Following changes have been made in Table 2:

- American College of Rheumatology (ACR) classification criteria at Visit 1 has been unchecked.
- QuantiFERON-TB Gold (QFT-G) test is checked at Visit 14
- New rows for Sponsor-provided MMF and oral corticosteroids have been

added

- Footnotes have been added for Table 2 and the original foot-notes have been edited for better guidance and consistency.

In Table 3, physical examination (PE) has been checked for Visit 15 and "urine pregnancy tests (using dipstick)" has been added for Visit 15 and Visit 16.

Text in Section 4.1.1 has been reworded for clarity.

Text in Section 4.1.3 has been updated to include the exception (minor dose adjustments done >3 months prior to the ICF signature date) to document prescription medications the subject has ever taken for SLE and LN.

Subsections in Section 4.2 have been updated as: Section 4.2.1 End of treatment visit (Week 52) and Section 4.2.2 Follow-up visits after premature discontinuation of IP. Edits have been made throughout this section for clarity and to simplify protocol.

Text in Section 4.4 has been updated for clarity on the follow-up requirements in subjects who discontinue the IP but continue the study schedule and, other early discontinuation subjects.

The term "unless otherwise specified" has been added in parenthesis in Section 5.1 for clarity

Edits have been made throughout Section 5.2 for clarity and to simplify protocol.

In section 5.3.2, text has been added to state that temperature should be measured by the same methodology for a subject throughout the study.

In Section 5.3.3.3, the text on the requirement of Pap smear at screening in women who have not had their cervix surgically removed has been deleted. The text on the requirement of repetition of Pap smear if performed within 2 years prior to screening has been reworded for clarity.

Text in Section 5.3.4 has been updated to provide clarity on the assessment of cardiovascular risk.

Definition of extra-renal flares in Section 5.3.7 has been updated for clarity to clarify the timeframe for assessments related to the SLEDAI 2K. Section 5.3.7 heading has also been updated for clarity.

Text in Section 5.3.9.1 has been reworded to provide clarity on the criteria for the screening QFT-G test and chest X-rays.

Text in Section 5.3.9.3 has been updated to provide clarity around positive QTF-G test result.

Text in Section 5.4 has been reworded to provide clarity on the urine pregnancy tests that are

performed after the screening visit.

Table 4 in Section 5.4 has been updated to reflect the changes made to the other relevant sections of the protocol. Activated partial thromboplastin time and prothrombin time have been grouped under a new subheading "Coagulation panel". International normalised ratio (INR) has been under this subheading as INR is part of the routine coagulation panel as per central laboratory specifications. A note has been added under Table 4 to state that if central laboratory results are not available for SLEDAI-2K associated tests, samples should be redrawn one time within 14 days of the SLEDAI assessment date.

Cholesterol has been added as part of the fasting lipid profile in Section 5.4.1 as cholesterol is part of the routine lipid profile as per central laboratory specifications.

Text has been added in Section 5.4.3 to state that the dose of MMF should be withheld until samples for the Mycophenolic acid (MPA) blood draw test has been collected on that visit day. Corresponding footnote has been added in Table 2.

Text on how long the samples will be stored has been added in Section 5.4.4 and Section 5.4.5.

In Section 5.4.5.4, text has been reworded to clarify that pharmacogenomics is not considered a sub-study but an optional component of the protocol.

Text in Section 5.4.5.5 has been reworded for clarify.

In Section 5.5, text has been added to explain how the samples will be analysed for determination of drug concentration in plasma.

Section 5.6 has been reworded to clarify the period of patient global assessment (PtGA).

Section 6.4.1 have been updated to add the term 'or designee' due to the change in responsibility of unblinding and overdose reporting, respectively. Similar change has also been made in other applicable section of the protocol.

Subsections on Maternal Exposure and Paternal Exposure have been added under Section 6.4.2 (previously labelled as Section 6.4.3 and Section 6.4.4). Text has been updated to clarify that any subject or subject's partner who becomes pregnant during the course of the study should be followed up for pregnancy until the outcome of the pregnancy is known. Texts have also been updated to clarify the timeframe for collection of pregnancy data for both the IP and MMF.

Text in Section 6.5.1 has been reworded to amend the definition of "serious non opportunistic" infection.

Texts in Section 6.5.2, Section 6.5.4, Section 6.5.5, Section 6.5.6, Section 6.9.2, and Section

6.9.3 have been updated to be in line with the Phase 3 SLE protocol.

Text in Section 6.5.9 has been updated to provide further information regarding the criteria for review of events by an independent Cardiovascular Event Adjudication Committee (CV-EAC).

Text in Section 6.6.1 has been updated to provide clarity on the timeframe for collection of adverse events and serious adverse events (SAEs). Text has been added to clarify the timeframe for following up on SAEs and pregnancies occurring within the 12-week post final dose period.

Text in Section 6.6.3 has been updated to be in line with the causality assessment in the Electronic Case Record Form (eCRF).

Text in Section 6.6.4 has been updated to provide clarity that SAEs causal relationship will be assessed for "any" medication.

Section 6.9 heading has been updated to include "MMF-related warnings and precautions". A new subsection (Section 6.9.3) on MMF-related warnings and precautions has been added.

A sentence has been added to Section 7.1: "Study drug" refers to any medication mandated by the protocol.

Text in Section 7.2.3 has been updated for clarity and to make the description of storage conditions in the protocol consistent with the updated Investigator's Brochure. Reference to Appendix K has been added in this section.

Text in Section 7.2.4 has been updated to clarify the monitoring requirements applicable for the first 3 infusions and also to and to make distinction between infusion (not including saline flush) and administration (including saline flush).

Section 7.2.6, Table 5, and Table 6 have been updated to ensure consistency between text and information presented in the tables.

Text has been added in Section 8.2 to clarify that formal hypothesis testing will not be performed.

The ≤ has been corrected to < in the second sub bullet point in Section 8.4.3.2 and Section 8.4.3.3.

Typographical error in the abbreviation PtGA in Section 8.4.4 has been corrected.

Text in Section 8.5.1 and Section 8.5.10 have been updated to ensure consistency of the protocol with the SAP.

Text on evaluation of change from baseline in spot UPCR has been added in Section 8.5.3 to

align the protocol with the SAP. Text on training of study site personnel has been added in Section 9.1. Text has been added in Section 10.3 to clarify that the Investigatory should submit the written approval to AstraZeneca or designee before consenting of any subject into the study. Appendix E, Appendix G, Appendix J, Appendix L, Appendix M, and Appendix P have been updated in line with the updates made to the protocol.

Version 1.0, 22nd May 2015
Initial creation.

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

CLINICAL STUDY PROTOCOL SYNOPSIS

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Proliferative Lupus Nephritis

International Coordinating Investigator

PPD

Cambridge CB2 20Q
United Kingdom

Study site(s) and number of subjects planned

Approximately a total of 150 subjects are planned to be randomised at approximately 95 sites.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2015	2
Estimated date of last subject completed	Q3 2020	

Study design

This is a Phase 2, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of two intravenous (IV) treatment regimens of anifrolumab versus placebo while taking protocol-specified standard of care (SOC) treatment with mycophenolate mofetil (MMF) and corticosteroids (see Section 7.7.3 for details) in adult subjects with active proliferative lupus nephritis (LN). The study will be performed in adult subjects, 18 to 70 years of age.

Approximately 150 subjects will be randomised in a 1:1:1 ratio to receive one of two IV dosing regimens of anifrolumab or placebo every 4 weeks (Q4W) for 48 weeks in addition to SOC which will continue until Week 52. After the primary objective time point at Week 52, eligible subjects will continue with randomised treatment (anifrolumab 300 mg or placebo IV Q4W) until Week 104. Those subjects not eligible to continue with treatment based on the Week 52 assessments will complete the 8 weeks of additional safety follow-up to complete involvement in the study. The regimens for anifrolumab are as follows:

- **Basic Regimen**: Anifrolumab 300 mg IV Q4W (13 doses) plus SOC
- **Intensified Regimen**: Anifrolumab 900 mg IV Q4W for the first 3 doses followed by 300 mg IV Q4W for an additional 10 doses plus SOC

Subjects who meet the criteria at Week 52 (as defined in Section 3.9) to continue in the second year extension will continue to receive blinded IP (anifrolumab 300 mg or placebo IV Q4W) for an additional 13 doses plus SOC for another 52 weeks (second year extension period).

The primary objective in the study is to evaluate the efficacy of anifrolumab plus SOC compared with placebo plus SOC in subjects with active proliferative LN measured by the relative difference in change from baseline to Week 52 in 24-hour urine protein to creatinine ratio (UPCR), comparing the pooled anifrolumab group (Basic and Intensified) to the placebo group.

After all randomised subjects have completed the 52-week double-blind period, the data base will be soft-locked, and the **primary analysis** will be performed, including the assessment of the primary, secondary, and safety objectives. This analysis will also encompass available data collected after the 52 week time point and details will be provided in the Statistical Analysis Plan (SAP). At this stage the Sponsor and Sponsor's delegate who are not directly involved in the management of sites will be unblinded to randomised treatment, but the subjects and Investigators will remain blinded (single-blind). The **end of study analysis** will be performed after all subjects have completed the second year extension period. One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit. CCI [redacted]

Investigational product (IP) will be administered as an IV infusion via an infusion pump over no less than 60 minutes for the first 3 doses of IP (Visits 1, 2, and 3). Starting with Visit 4, IP can be administered as an IV infusion via an infusion pump over no less than 30 minutes.

Randomisation will be stratified using two factors:

- Results of Type I interferon (IFN) test using a 4-gene type I IFN test (IFN test-high versus IFN test-low) at screening

- 24-hour UPCR ≤3.0 mg/mg versus >3.0 mg/mg (based on 24-hour UPCR performed on a sample obtained within 14 days prior to the expected date of randomisation). Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days.

On rare occasions an extension of the 30-day screening window may be allowed if the re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed. Renal biopsy performed within 12 weeks prior to signing informed consent form (ICF) or during the screening period will be considered as the screening biopsy. Biopsies will be evaluated locally and the local classification will be used to confirm the eligibility criteria. The biopsy must reveal Class III (±Class V) or Class IV (±Class V) LN according to the World Health Organisation (WHO) or 2003 International Society of Nephrology/Renal Pathology Society ISN/RPS classification. An external renal biopsy adjudication group will adjudicate renal biopsies post-randomisation.

The overall study duration is approximately 116 weeks:

- **A Screening Period**: Up to 30 days
- **Treatment Period**:
  The total treatment period is up to 100 weeks (26 doses administered every 4 weeks).
  - **52 week double-blind treatment period**: IP will be administered every 4 weeks from Week 0 to Week 48 for a total of 13 doses. The primary endpoint will be evaluated at Week 52.
  - **Second year extension period**: At Week 52, eligible subjects will continue treatment with IP (anifrolumab 300 mg or placebo) administration Q4W from Week 52 to Week 100 for a total of 13 doses. The last efficacy assessments will be performed at Week 104.
- **Follow-up**: After the completion of the last IP treatment (Week 48 for subjects who are not participating in the second year extension period and Week 100 for subjects who participate in the second year extension period) subjects will continue in the study for another 12 weeks of safety follow-up after the last administration of IP.

Objectives

Primary Objective:	Outcome Measure:
To evaluate the efficacy of anifrolumab plus SOC[a] compared with placebo plus SOC[a] in subjects with active proliferative LN measured by the relative difference in change from baseline to Week 52 in 24-hour urine protein to creatinine ratio (UPCR)	24-hour UPCR

[a] Required SOC is described in Section 7.7.3.

Secondary Objective:	Outcome Measures:
To evaluate the effect of anifrolumab plus SOC[a] compared with placebo plus SOC[a] on the proportion of subjects achieving Complete Renal Response (CRR) at Week 52	CRR is defined as meeting all of the following: • Estimated glomerular filtration rate (eGFR) is - ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20% • 24-hour UPCR ≤0.7 mg/mg • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment eGFR is based on Modification of Diet in Renal Disease (MDRD) formula

[a] Required SOC is described in Section 7.7.3.
[b] Allowed medication is described in Section 7.7.

Safety Objective:	**Outcome Measures:**
To characterise the safety and tolerability of anifrolumab	Adverse events (AEs) (including AEs of special interest [AESIs]), vital signs, physical examination, baseline and End of Treatment 12-lead electrocardiograms (ECG), and clinical laboratory tests (haematology, clinical chemistry, urinalysis), Columbia-Suicide Severity Rating Scale (C-SSRS), Personal Health Questionnaire Depression Scale-8, extra-renal flares using Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI 2K) based Flare Assessment Instrument

Exploratory Objective:	**Outcome Measures:**
To evaluate the effect of anifrolumab plus SOC[a] compared with placebo plus SOC[a] on:	
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Exploratory Objective:	**Outcome Measures:**
Proportion of subjects achieving alternative CRR (aCRR) at Week 52 (and Week 104) The difference between the CRR and the aCRR is the addition of a criterion regarding "inactive urine sediment"	aCRR is defined as meeting all of the following: • eGFR is ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20% • 24-hour UPCR ≤0.7 mg/mg • Inactive urine sediment (defined as <10 red blood cells [RBC]/hpf) • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment eGFR is based on MDRD formula
CCI [redacted]	[redacted]

Exploratory Objective:	**Outcome Measures:**
Proportion of subjects meeting Graded aCRR at Week 52 (and Week 104)	Graded aCRR is defined as meeting both the 24-hour UPCR and eGFR criteria: • A decrease in 24-hour UPCR: - For subjects with baseline UPCR >3 mg/mg: UPCR ≤1 mg/mg - For subjects with baseline UPCR ≤3 mg/mg: UPCR ≤0.7 mg/mg • eGFR: ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20% • Inactive urine sediment defined as <10 RBC/hpf • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment
Proportion of subjects able to achieve sustained reduction in oral corticosteroids (OCS) dose at Week 52 or Week 104	**Sustained reduction of OCS dose:** • Week 52: Prednisone-equivalent dose ≤7.5 mg/day by Week 24 and not exceeding this dose through Week 52 • Week 104: Prednisone-equivalent dose ≤5.0 mg/day by Week 80 and not exceeding this dose through Week 104 **and** • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment
Proportion of subjects achieving CRR at Week 52 or Week 104 **and** achieving sustained reduction of OCS dose	CRR (see definition of CRR above) Sustained reduction of OCS dose (see definition above)
CCI [redacted]	[redacted]

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

Exploratory Objective:	**Outcome Measures:**
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
Mean change in scores for overall disease activity from baseline to Week 52 (and to Week 104)	SLEDAI-2K
Mean change in score measures of non-renal disease activity from baseline to Week 52 (and to Week 104)	Non-renal components of SLEDAI-2K
Mean change in scores for overall disease activity from baseline to Week 52 (and to Week 104)	Physician's Global Assessment (PGA)

Exploratory Objective:	Outcome Measures:
Mean change in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) score from baseline to Week 52 (and to Week 104)	SDI
Mean change in scores for patient-reported health status from baseline to Week 52 (and to Week 104)	Patient Global Assessment (PtGA)
To evaluate the immunogenicity of anifrolumab, pharmacokinetics (PK), pharmacodynamics (the PK and immunogenicity results will be reported in the clinical study report)	Anti-drug antibodies (ADA), anifrolumab concentration and PK parameters, 21 gene type I IFN gene signature
To evaluate the pharmacokinetics of mycophenolic acid (MPA)	MPA concentration and PK parameters (if applicable)
Mean change in lupus serology from baseline to Week 52 (and to Week 104)	Anti-dsDNA antibodies, C3 and C4 complement levels
CCI [redacted]	[redacted]

[a] Required SOC is described in Section 7.7.3.
[b] Allowed medication is described in Section 7.7.
[c] Note: Spot UPCR will be used instead of 24-hour UPCR for the PRR and CRR classification, when evaluating time to renal response modified to include OCS tapering requirement as well as for the PRR and CRR classification for flare assessment.

Target subject population

The study will be performed in adult subjects, 18 to 70 years of age with documented active proliferative LN.

Duration of treatment

The overall study duration is approximately 116 weeks. The total treatment period is approximately 100 weeks (26 doses administered every 4 weeks):

- **52 week double-blind treatment period**: IP will be administered every 4 weeks from Week 0 to Week 48 for a total of 13 doses.
- **Second year extension period**: IP will be administered every 4 weeks from Week 52 to Week 100 for a total of 13 doses plus SOC.

Investigational product, dosage and mode of administration

Approximately 150 subjects will be randomised in a 1:1:1 ratio to receive one of the two IV anifrolumab dosing regimens or placebo, as follows:

- **Basic Regimen**: Anifrolumab 300 mg IV Q4W (13 doses) plus SOC or
- **Intensified Regimen**: Anifrolumab 900 mg IV Q4W for the first 3 doses followed by 300 mg IV Q4W for an additional 10 doses plus SOC or
- **Placebo**: IV Q4W plus SOC

Subjects eligible for the second year extension will continue to receive blinded IP (in the treatment arm they were randomised to on Day 1) for another 13 doses plus SOC.

Criteria for discontinuing investigational product for worsening of LN or SLE:

At any time:

- >30% decrease in eGFR compared to baseline due to LN and eGFR <60 mL/min/1.73 m^2 (on two independent samples) or
- Increase in renal or extra-renal lupus activity requiring prohibited systemic immunosuppressive treatment (eg, cyclophosphamide, rituximab, belimumab)
- Receipt of >1 methylprednisolone pulse after the day of randomisation
- Receipt of any methylprednisolone pulse after Week 8
- The IP will be discontinued if MMF is discontinued and another immunosuppressant is initiated

At Week 12 and Week 24:

- eGFR <75% of baseline and <60 mL/min/1.73 m^2 (on two independent samples) or
- Nephrotic range UPCR (confirmed by a second measurement at least two weeks after the first measurement):
  - Subjects with 24-hour UPCR ≤3 mg/mg at baseline will be withdrawn if 24-hour UPCR increases by >50% from baseline to >3.5 mg/mg
  - Subjects with 24-hour UPCR >3 mg/mg at baseline will be withdrawn if 24-hour UPCR at Week 24 >3.5 mg/mg and there is <60% improvement from baseline or

- Inability to adhere to corticosteroids requirements:
  - Inability to reduce OCS to ≤15 mg/day prednisone-equivalent at Week 12
  - Inability to reduce OCS to <15 mg/day by Week 24

Subjects who exceed the maximum daily OCS dose at the Week 12 or Week 24 visits may continue to receive IP if the current dose is part of a temporary increase in OCS dose (eg, protocol-allowed burst and taper). Subjects who cannot be returned to their pre-increase dose within 14 days from the start of increase will have their IP discontinued at the next visit.

Subjects who discontinue the IP before Week 48 will be followed until Week 52 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks of Week 52).

Criteria for discontinuing investigational product at Week 52:

Subjects not meeting the criteria to continue in the second year extension period will not receive any IP at Week 52 and will complete the study after completing the required follow-up visits.

Subjects meeting the following criteria may continue to receive blinded IP between Weeks 52 and 100.

(i) Meeting all of the following criteria based on the renal portion of the PRR definition:

- eGFR is:

  ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20%

- Improvement in 24-hour UPCR:
  - For subjects with a baseline UPCR ≤3 mg/mg: <1.0 mg/mg
  - For subjects with a baseline UPCR >3 mg/mg: >50% improvement from baseline and ≤3.0 mg/mg

Renal discontinuation criteria must be confirmed in two separate samples. The second UPCR measurement should be at least 1 week after the first measurement.

(ii) No discontinuation of IP

(iii) Negative human immunodeficiency virus (HIV) test after signing the Main ICF

The study Medical Monitor/Designee will confirm eligibility criteria based on electronic data capture (EDC) system, and from the central laboratory.

Criteria for discontinuing investigational product at Week 52, Week 56 or Week 60:

- Failure to obtain pap smear after Week 48 with result available at Week 60 at latest
- Pap smear result not meeting the eligibility criteria (see Appendix K) at Week 52, 56, or 60 of a Pap smear obtained after Week 48
- Failure to obtain Week 52 QuantiFERON test result by Week 56

Criteria for discontinuing investigational product at Week 60 and later:

- OCS >7.5 mg/day (except one OCS burst and taper)
- MMF >2 gm/day or >Week 52 dose, whichever is lower

Subjects who discontinue the IP during the second year extension period will be followed until Week 104 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks of Week 104).

Statistical methods

The primary estimand is evaluating the efficacy on disease activity of anifrolumab relative to placebo in subjects with active proliferative LN. This is measured by the relative difference in change from baseline to Week 52 in 24-hour UPCR. The full analysis set, defined as subjects who are randomised and received at least 1 dose of IP (modified Intention-To-Treat) will be used, in order to reflect the effect of the initially assigned and dosed IP.

Analysis Set

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

Analysis method for primary endpoint

The analysis will be performed using a mixed model repeated measures fitted to log-transformed data comparing the pooled anifrolumab group (Basic and Intensified) with the placebo group, with fixed effects for treatment group, visit, stratification factors and log-transformed 24 hour UPCR at baseline. An interaction term for visit and treatment will also be included in the model to allow the relationship to differ across treatment groups. Note that visit will be fitted as a repeated variable in the model. Model assumptions will be checked

and, if not met, appropriate data transformations may be applied or non-parametric approaches will be considered.

Analysis method for safety endpoints

All safety variables will be analysed descriptively. The safety analysis will be based on the full analysis set.

Interim analysis

One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit. CCI [redacted]

Sample size calculations

A total of 150 subjects will be randomised in a 1:1:1 ratio to receive one of the two IV anifrolumab dosing regimens (Basic Regimen or Intensified Regimen) or placebo.

The sample size is based on the following assumptions:

- Reductions from baseline to Week 52 in 24-hour UPCR of 65% and 46% for the anifrolumab and placebo arms, respectively (ie, ratios of 24-hours UPCR from Week 52 to baseline of 0.35 and 0.54, respectively), based on data presented in Furie et al, 2014[1].
- The log-transformed 24-hour UPCR values follow a normal distribution with a standard deviation (SD) of 0.8, based on data from the anifrolumab Phase 2b study (CD1013).

Based on these assumptions, a sample size of 50 subjects per arm would result in an observed relative difference in the change from baseline to Week 52 in 24-hour UPCR of 0.65 (here expressed as the ratio, comparing anifrolumab to placebo), and a corresponding 95% confidence interval (CI) of (0.50, 0.85) comparing the pooled anifrolumab group (Basic and Intensified) with the placebo group. If the interim analysis is performed, a 0.001 two-sided alpha will be spent, and the final analysis will based on a 2-sided alpha of 0.049 (East Version 6.4). This sample size provides approximately 86% power with a 2-sided alpha of 0.049 to reject the hypothesis of no effect (relative difference =1) for comparing the pooled anifrolumab treatment group with placebo. The minimal detectable relative difference in the change from baseline to Week 52 in 24-hour UPCR between the pooled anifrolumab treatment group versus placebo is approximately 0.76, corresponding to a reduction from baseline to Week 52 in 24-hour UPCR of 59% in the pooled anifrolumab group (ratio of 24-hour UPCR from Week 52 to baseline of 0.41).

[1] Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol. 2014;66(2):379-839.

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CCI [redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACEI	Angiotensin-Converting-Enzyme Inhibitor
ACR	American College of Rheumatology
aCRR	Alternative complete renal response
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AIS	Adenocarcinoma in situ
ALP	Alkaline Phosphatase
ALT	Alanine transaminase
ANA	Antinuclear antibody
Anti-dsDNA	Anti-double stranded deoxyribonucleic acid
Anti-RNP	Anti-ribonucleoprotein
APS	Anti-phospholipid syndrome
ARB	Angiotensin II Receptor Blocker
AST	Aspartate transaminase
β-hCG	β human chorionic gonadotropin
BCG	Bacillus Calmette-Guérin
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	Blood pressure

Abbreviation or special term	Explanation
BUN	Blood Urea Nitrogen
C3	Third component of complement
C4	Fourth component of complement
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIN III	Cervical intraepithelial neoplasia grade III
CIS	Carcinoma in situ
CK	Creatine Phosphokinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CRF	Case Report Form (electronic/paper)
CRR	Complete renal response
CSA	Clinical Study Agreement
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV-EAC	Cardiovascular Event Adjudication Committee
DEHP	Diethylhexyl phthalate
DNA	Deoxyribonucleic acid
dsDNA	Double stranded deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee, synonymous with Institutional Review Board (IRB) and Independent Ethics Committee (IEC)

Abbreviation or special term	Explanation
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FWER	Familywise error rate
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
HbA1C	Glycosylated Haemoglobin
HBcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HBV DNA	Hepatitis B virus DNA
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
hpf	High power field
HPV	Human papilloma virus
HSIL	High-grade squamous intraepithelial lesion

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN	Interferon
IFNAR	Type I Interferon receptor
Ig	Immunoglobulin
IGRA	Interferon-gamma release assay
ICI	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
ISN/RPS	International Society of Nephrology (ISN)/Renal Pathology Society (RPS)
IV	Intravenous
IXRS	Interactive voice/web response system
KDIGO	Kidney Disease Improving Global Outcomes
LN	Lupus nephritis
LLOQ	Lower limit of quantitation
LSLV	Last Subject's Last Visit
MACE	Major adverse cardiovascular events
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MMF	Mycophenolate mofetil
MMRM	Mixed model repeated measures
MPA	Mycophenolic acid
MR Team	SLE Data Medical Review Team
mRNA	Messenger ribonucleic acid
nAb	Neutralising antibodies
NIH	National Institutes of Health
NSAIDs	Non-steroidal anti-inflammatory drugs
OCS	Oral corticosteroids
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PHQ-8	Personal Health Questionnaire Depression Scale
PK	Pharmacokinetic(s)
PRR	Partial renal response
PtGA	Patient Global Assessment
PVC	Polyvinyl chloride
Q4W	Every 4 weeks
QFT-G	QuantiFERON-TB Gold
RBC	Red Blood Cell
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SD	Standard deviation
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage index
SLE	Systemic lupus erythematosus
SLEDAI 2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	Standard of care
SRI (4)	Systemic Lupus Erythematosus Responder Index of ≥4
SSc	Systemic sclerosis
TB	Tuberculosis
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US	United States
VAS	Visual Analogue Scale
WBC	White blood cell
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Anifrolumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody 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 interferon (IFN) to IFNAR1 and inhibits the biologic activity of all type I IFN.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown aetiologies. Lupus nephritis (LN) is the most common major organ manifestation of SLE. It affects approximately 35-60% of lupus patients and is more prevalent in certain ethnic groups, such as African Americans, Asians, and Hispanics (Borchers et al, 2010). Although renal outcome has improved with the introduction of immunosuppressive treatment, LN still represents a major risk factor for the long-term outcome of patients with SLE and adversely affects the prognosis, as measured by patient and renal survival rates as well as quality of life and work disability (Furst et al, 2013; Li et al, 2009; Mok et al, 2013; Pelletier et al, 2009). Renal survival rates in recent studies ranged from 83% to 92% at 5 years of follow-up and from 74% to 84% at 10 years of follow-up (summarised in Mok et al, 2013). The risk of end-stage renal disease is particularly high in patients with diffuse proliferative glomerulonephritis (reviewed in Mok et al, 2013). Several studies have shown that the standardised mortality ratio of patients with LN is 6-9 fold higher compared to the general population and about 3 fold higher compared to patients with non-renal SLE (reviewed in Mok et al, 2013). The mortality rate increases with accumulation of renal damage and is highest in LN patients with end-stage renal disease. The life expectancy of SLE patients with renal disease and those with renal damage is reduced by approximately 15 years and 23 years, respectively, compared to the general population (Mok et al, 2013). Lupus nephritis is also a major factor contributing to SLE-related hospitalisations and overall health care costs (Furst et al, 2013; Li et al, 2009; Pelletier et al, 2009).

There is substantial unmet medical need in the treatment of LN, particularly for patients with proliferative LN. There is no approved treatment for LN, but various treatment regimens are widely used as local standards of care. The standard treatment for proliferative LN consists of 6 to 12 months of intensive immunosuppressive therapy (usually cyclophosphamide or mycophenolate mofetil [MMF] with high-dose corticosteroids) followed by a longer period of less intensive maintenance therapy (Bertsias et al, 2012; Hahn et al, 2012). Corticosteroid dosing frequently includes pulse intravenous (IV) methylprednisolone (500 mg to 1,000 mg/day) followed by daily oral glucocorticoids (0.5 to 1 mg/kg/day of prednisone-equivalent) with a goal of reducing the dose to around 10 mg/day of prednisone-equivalent at 6 months. Mycophenolate mofetil is the recommended agent by American College of Rheumatology (ACR) (Hahn et al, 2012) and the European League Against Rheumatism

(EULAR) (Bertsias et al, 2012) with a total daily dose of 2 to 3 gm orally for 6 months, followed by an extended period of treatment with lower doses of MMF.

Two regimens of IV cyclophosphamide are recommended as alternatives: 1) low-dose "Euro-Lupus" cyclophosphamide (500 mg IV once every 2 weeks×3 months), followed by maintenance therapy with daily oral azathioprine or daily oral MMF or 2) high-dose cyclophosphamide (500 to 1000 mg/m^2 IV once a month×6 months), followed by maintenance treatment with MMF or azathioprine.

Maintenance therapy is recommended for a minimum of 12 months with lower intensity immunosuppression with or without low-dose steroids (≤7.5 mg/day). Mycophenolate mofetil (≤2 gm/day) or azathioprine are the most commonly used agents for maintenance (Bertsias et al, 2012; Hahn et al, 2012; Radhakrishnan et al, 2012).

Mycophenolate mofetil was chosen over cyclophosphamide in this study as standard of care (SOC), because the response rates are similar in all races and ethnicities, whereas African Americans and Hispanics respond less well to IV cyclophosphamide than Whites and Asians (Isenberg et al, 2010). The target dose of MMF recommended by various management guidelines (ACR, EULAR, and KDIGO) is 2 to 3 gm/day orally for 6 months, followed by an extended period of treatment with lower doses of MMF. Several studies in Asian and Caucasian LN populations, have shown doses ≤2 gm/day lead to similar renal responses but lower frequency of adverse events (AEs) compared to doses of 3 gm/day (Chan, 2012; Li et al, 2012; Mulic-Bacic et al, 2008; Ong et al, 2005). Consistent with these observations, the ACR guidelines recommend to target 2 gm/day for induction in Caucasian patients with LN (Hahn et al, 2012), which is also the higher end of the range used for induction in Asian countries. Although a higher target dose is frequently used in patients of African descent, there is no evidence to support this distinction.

Multiple lines of evidence indicate a role of type I IFN in the pathogenesis of SLE and LN. For example, overexpression of type I IFN and proteins induced by type I IFN (the "type I IFN signature") have been associated with greater disease activity and organ system involvement in SLE (Dall'Era et al, 2005; Bengtsson et al, 2000). High serum levels of type I IFN have been associated with high anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody titres, LN, and progressive skin rashes (Bengtsson et al, 2000).

The disease pathogenesis of SLE includes activation of innate immunity, with increased production of type I IFN, including IFN-α, and increased number of plasmacytoid dendritic cells and myeloid dendritic cells in involved tissue (Baechler et al, 2003; Crow and Wohlgemuth, 2003; Baechler et al, 2004; Banchereau et al, 2004; Bengtsson et al, 2000; Crow, 2010; Dall'Era et al, 2005; Rönnblom and Alm, 2003). Specific humoral and cellular immune systems are activated. Autoantibodies are universally present and may precede development of clinically apparent disease by many years (Arbuckle et al, 2003). Systemic lupus erythematosus-associated autoantibodies include anti-dsDNA, anti-nucleosomes, anti-ribonucleoprotein (anti-RNP) complex, and anti-Smith antibodies (Rahman and Isenberg,

2008). Immune complexes containing anti-dsDNA or anti-RNP antibodies can activate type I IFN production by plasmacytoid dendritic cells (Bengtsson et al, 2000; Rönnblom and Alm, 2003).

A potential role of IFN in the pathogenesis of LN has been suggested by both animal and human data.

Animal models:

- Interferon-α can induce glomerulonephritis in normal mice and accelerates the onset of the spontaneous autoimmune disease of NZB/W mice (Mathian et al, 2005).
- A murine model of SLE, treated with a synthetic double stranded RNA ligand that induces type I IFN response, showed high titres of anti-dsDNA antibodies, increased immune complex deposition, and increased metalloproteinase activity, which led to accelerated LN and death (Triantafyllopoulou et al, 2010).
- Overexpression of systemic IFN-α accelerated LN in several murine models of LN (Fairhurst et al 2008, Liu et al, 2011). Signalling blocked by deleting the type I IFN receptor (Jørgensen et al, 2007; Nacionales et al, 2007; Santiago-Raber et al, 2003) or an anti-IFN-α antibody (Baccala et al, 2012) prevented or ameliorated LN.

Human data:

A role for IFN-α in the initiation of the autoimmune disease process is suggested more directly by the observation that patients with non-autoimmune disorders who are treated with IFN-α can develop antinuclear antibodies, anti-dsDNA antibodies, and occasionally also SLE (Rönnblom and Alm, 2003).

Although no direct causal evidence has been established for type I IFN in human LN, several observations suggest that IFNs have an important role in the pathogenesis of this disease:

- The formation of endothelial cell tubuloreticular inclusions found in LN is thought to be driven by type I IFN, and other than in LN, they can only be seen in viral and IFN-induced nephropathies (Anders et al, 2014).
- Plasmacytoid dendritic cells, which are the main producers of type I IFN in SLE, are increased in number in the kidneys of LN patients (Tucci et al, 2008).

- Type I gene signature is increased in the glomeruli of a subset of LN patients (Peterson et al, 2004).

- Some cross-sectional studies showed a positive correlation between the blood IFN signature and active LN or a higher risk of renal flare (Feng et al, 2006; Landolt-Marticorena et al, 2009), whereas other studies showed an association between the blood IFN signature and the presence or history of LN (Baechler et al, 2003; Kirou et al, 2005).

- A strong correlation between type I IFN-induced chemokine and LN was demonstrated in several studies (Bauer et al, 2009; Manoharan et al, 2010). Elevated serum IFN-induced chemokine levels were strongly associated with the risk of renal flare (Bauer et al, 2009), whereas urine chemokine levels were proposed as biomarkers for active LN (Manoharan et al, 2010).

Together, these pre-clinical and clinical data strongly support the hypothesis that type I IFN is involved in the immunopathogenesis of LN and therefore suppressing signalling through the type I IFN receptor may have clinical benefit in active LN.

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

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design

This is a Phase 2, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of two IV treatment regimens of anifrolumab versus placebo in adult subjects with active, proliferative LN proven with biopsy while concurrently taking SOC treatment with MMF and corticosteroids.

It is hypothesised that treatment with anifrolumab will neutralise the type I IFN signalling through the human IFNAR that is driving disease activity and thereby will reduce the severity of disease in patients with proliferative LN, and that anifrolumab will be well tolerated when given at the proposed dose for the duration of the study.

To ensure adequate treatment, all subjects will receive SOC treatment with MMF and corticosteroids. This is consistent with both the EULAR (Bertsias et al, 2012) and ACR (Hahn et al, 2012) management guidelines and kidney disease improving global outcomes (KDIGO) recommendations (Radhakrishnan et al, 2012) for the management of proliferative LN.

The study will be randomised, placebo-controlled, and double-blind prior to the primary analysis to ensure a robust design and minimise bias. This is the preferred design as outlined in the United States Food and Drug Administration (US FDA) Guidance for Industry Systemic Lupus Erythematosus-Developing Medical Products for Treatment (US FDA, June 2010) and in the Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products for the treatment of SLE and LN (CHMP, February 2015). After the last subject completes the Week 52 visit, the primary analysis will be conducted, after which the Sponsor and Sponsor's delegates will be unblinded. Site investigators and subjects will remain blinded to treatment assignment throughout the study.

Randomisation will be stratified using two factors:

- Results of IFN test at screening using a 4-gene type I IFN test (IFN test-high versus IFN test-low)
- 24-hour Urine protein to creatinine ratio (UPCR) ≤3.0 mg/mg versus >3.0 mg/mg (based on 24-hour UPCR performed on a sample obtained within 14 days prior to the expected date of randomisation). Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days.

On rare occasion an extension of the 30-day screening window may be allowed if the re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed.

Stratification is implemented in order to minimise the risk of baseline imbalance(s) across treatment arms on potentially confounding variables. Baseline imbalances of these factors could impact efficacy and/or safety assessments of anifrolumab versus placebo.

The duration of renal responses will be assessed in a second year extension period where eligible subjects will continue in their randomised treatment groups. Treatment assignment will remain blinded for the Investigators and subjects. At the time of primary analysis, after the last subject has completed the Week 52 visit, the Sponsor and Sponsor's delegates will be unblinded to treatment assignment.

1.2.2 Rationale for primary endpoint selection

The primary objective is to evaluate the efficacy of anifrolumab plus SOC compared to placebo plus SOC in subjects with active proliferative LN measured by the relative difference in change from baseline to Week 52 in 24-hour UPCR.

The treatment goal in LN is preservation of renal function. With current SOC, end-stage renal disease occurs late and with a relatively low frequency which makes it impractical for use as endpoint in clinical studies. Recent studies used various composite endpoints for renal

response. The core elements of all these criteria are stable or improving renal function and a decrease in or normalisation of proteinuria. Improvement in proteinuria reflects control of inflammation and the subsequent repair of the kidney. Although the ultimate goal is to eliminate proteinuria, several studies have shown that reducing proteinuria (which in itself is toxic to the kidney) during the first year of treatment is associated with good long-term renal prognosis even if the proteinuria cannot be eliminated (Korbet et al, 2013; Dall'Era et al, 2011; Dall'Era et al, 2015) Therefore, showing a benefit in decreasing proteinuria at Week 52 represents a clinically meaningful endpoint for an exploratory proof of concept study. Furthermore, maintaining renal function while decreasing oral corticosteroid (OCS) dose (worsening of renal function or not meeting clinically meaningful decreases in OCS doses are withdrawal criteria in the study) will provide supportive evidence for potential long-term efficacy in LN patients.

1.2.3 Rationale for duration of treatment

Treatment guidelines for proliferative lupus nephritis recommend maintenance therapy for a minimum of 12 months for patients with adequate response to initial immunosuppressive therapy. The 52 week double-blind randomised period will allow the evaluation of the primary endpoint whereas the second year extension will provide additional data to evaluate the exploratory endpoint assessing the duration of renal responses in patients who achieved clinically important improvements in proteinuria, maintained renal function and decreased the dose of corticosteroids during the first year of treatment.

1.2.4 Rationale for dose selection

The study is evaluating the safety and efficacy of anifrolumab across 2 dosing regimens: the Basic Regimen will test 300 mg throughout the treatment period whereas the Intensified Regimen will test a higher dose of 900 mg for the first 3 doses followed by 300 mg for the rest of the treatment period.

The selection of doses of 300 mg and 900 mg anifrolumab every 4 weeks (Q4W) is based on safety and efficacy results from the interim analysis of a Phase 2b study in extra-renal SLE where 2 doses of anifrolumab (300 mg and 1000 mg) were evaluated relative to placebo. At the interim analysis of the Phase 2b study, clinically meaningful benefit was observed with the 300 mg dose, with no incremental benefit at 1000 mg (see Section 1.3 for details). In addition, a higher proportion of subjects reporting herpes zoster reactivations was observed at 1000 mg compared to 300 mg. Based on these data, the 300 mg dose was identified as the dose to test in a Phase 3 study for extra-renal SLE.

For this study, the rationale for selection of the 300 mg dose-level for evaluation in LN subjects is to replicate the dose identified in the Phase 2b study in subjects with extra-renal SLE.

A higher dose of 900 mg will be given at the first 3 doses (Visits 1, 2, and 3) in LN subjects to account for potential IFN overexpression in the kidneys and potential loss of anifrolumab

concentration due to proteinuria. Based on observations in the extra-renal SLE Phase 2b study, faster IFN signature suppression is expected at the 900 mg dose in LN subjects with potential clinical benefit. The dose of 900 mg will only be given for the first 3 doses of treatment (starting with the fourth dose all subjects will be switched to a dose of 300 mg) in order to limit the incidence of potential AEs related to anifrolumab. The 900 mg dose was chosen over 1000 mg for ease of administration (anifrolumab is supplied in 150 mg vials). For these reasons, the selection of doses of 900 mg and 300 mg anifrolumab are justified for this study.

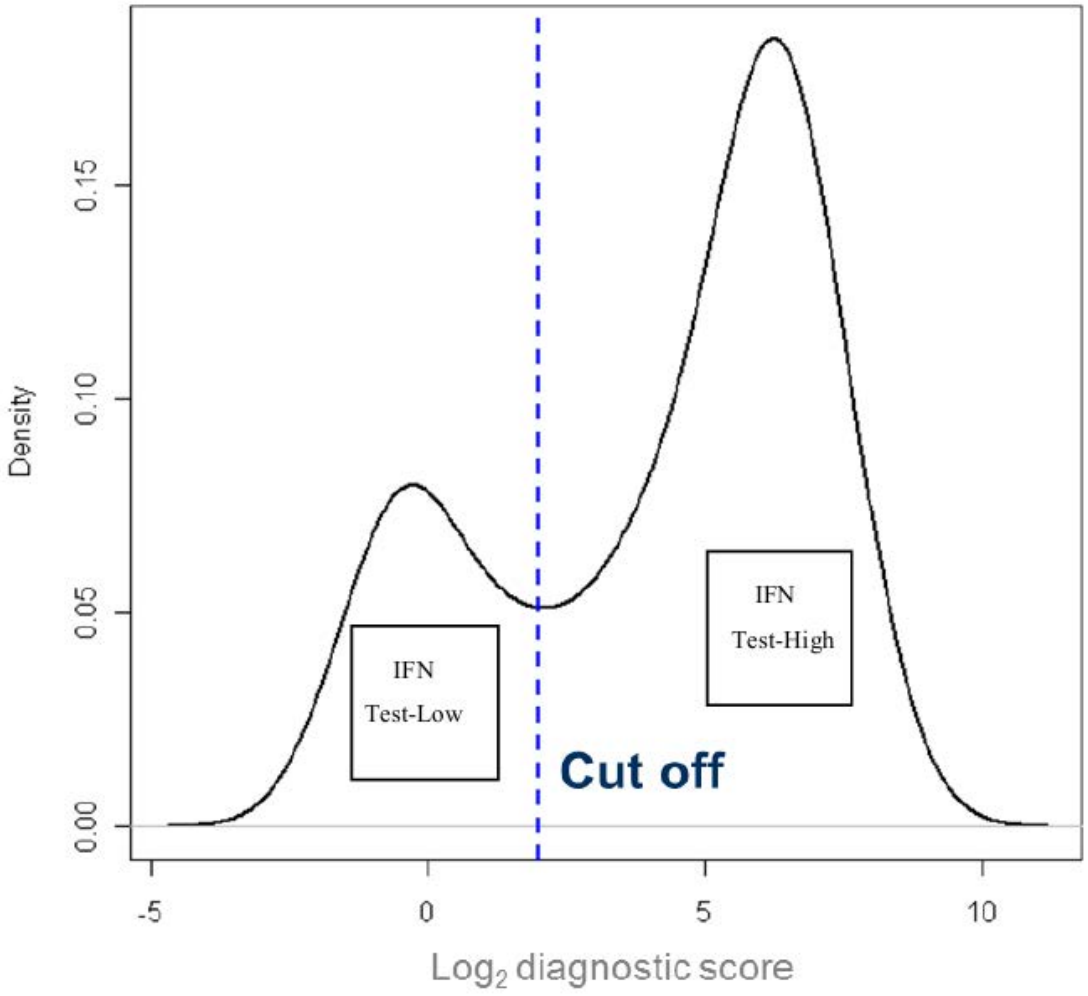
1.2.5 Rationale for duration of infusion

In a Phase 2b study where two doses of anifrolumab (300 mg and 1000 mg) in combination with SOC were compared to placebo combined with SOC, all doses were administered over approximately 60 minutes. Based on the interim analysis, the frequency of infusion-related reactions did not differ substantially between the 300 mg (2.0%) and 1000 mg (3.8%) groups and were lower than that observed in the placebo group (5.9%). Therefore, in this study the infusion time was reduced to a minimum of 30 minutes for the visits (starting with Visit 4), where all the subjects receive 300 mg anifrolumab or placebo. For the first 3 visits (Visits 1 to 3), the time of infusion will be no less than 60 minutes.

1.2.6 Interferon test background

Type I IFN has long been considered to be important in the pathogenesis of SLE and inhibition of this pathway is an attractive goal, targeted by anifrolumab. To understand the relationship between type I IFN expression and response to anti-IFN therapy, it is necessary to know if a specific patient's disease is driven by type I activation. Direct measurement of the IFN is challenging, so a transcript based marker, measuring the effect of IFN, was developed to evaluate the effect of overexpression of the target protein on a specific set of messenger ribonucleic acid (mRNA) markers. The expression of these markers is easily detected in whole blood and demonstrates a correlation with expression in diseased tissue, such as skin, in SLE. The bimodal distribution of the transcript scores for SLE patients, as shown in the Figure 1 below, supports defining an IFN test-high and IFN test-low subpopulation.

Figure 1 Distribution of IFN transcript scores



1.3 Benefit/risk and ethical assessment

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

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

Overall benefit/risk assessment for Study D3461C00007

Clinically relevant benefit has been recognized in subjects with moderately to severely active SLE treated with anifrolumab on a background of SOC. The benefit of anifrolumab was

suggested over a range of efficacy endpoints in a Phase 2b study in SLE, when compared to placebo. The findings included the proportion of subjects achieving response in Systemic Lupus Erythematosus Responder Index (4) (SRI[4]) with sustained reduction of OCS (<10 mg/day and less than or equal to the dose received on Day 1 by Day 85 (Week 12) and maintained between Days 85 and 169 (Week 24)) at Day 169, and the proportions of subjects achieving SRI(4) with sustained reduction of OCS (<10 mg/day and less than or equal to the dose received on Day 1, by Day 281 and maintained between Days 281 [Week 40] and 365 [Week 52]) at Day 365.

The efficacy observed with the primary and secondary endpoints was supported by a wide range of evidence. A higher proportion of subjects receiving anifrolumab met SRI (4) response criteria without the OCS taper requirement at Day 169 and Day 365, compared to placebo. Additionally, compared to the placebo group, a numerically higher proportion of anifrolumab treated subjects achieved SRI(5), SRI(6), SRI(7), and SRI(8) response, as well as a British Isles Lupus Assessment Group (BILAG)‑2004 based combined lupus assessment (BICLA) response.

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

Anifrolumab was generally well tolerated. Herpes zoster reactivation with cutaneous presentation has been determined to be an identified risk for anifrolumab. No other infectious risks have been established; however, this continues to be closely monitored.

SLE and lupus nephritis are thought to impair elements of the human immune system that contribute to the latency of herpes zoster (HZ) virus and prevent reactivation. The addition of a potent immunosuppressant like mycophenolate mofetil (MMF) as standard of care may also diminish the immunologic forces that keep HZV latent, further increasing the likelihood of reactivation. Evidence to date from completed and ongoing studies that included administration of MMF as SOC suggest that HZ reactivations are mostly cutaneous, self-limited and responsive to antiviral medications. Sequelae, such as post-herpetic neuralgia, have been reported infrequently. Overall, risk associated with HZ reactivations in the LN population is anticipated to be acceptable and similar to that reported in the SLE program.

Compared to the general population, patients with SLE and LN have a higher rate of infections including serious and opportunistic infections. In the presence of immunosuppression with MMF and potentially also at the doses of anifrolumab administered in the Basic or Intensified Regimens Q4W in addition to SOC, there is a further theoretically increased likelihood of infections.

Patients receiving immunosuppressants, including MMF are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. These infections may lead to serious, including fatal outcomes.

Immune surveillance related to development and progression of malignancy may be suppressed by standard of care such as MMF, potentially increasing the risk of malignancy, specifically lymphoma. However, at this time, no signal for malignancy risk has been recognized for anifrolumab.

Risk associated with hypersensitivity reactions, including anaphylaxis and development of anti-drug antibodies (ADA) are expected to be unchanged in the LN study. Theoretically, the immunosuppressive effect of MMF may diminish adverse immune responses to anifrolumab.

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

Serious infections including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, TB (including latent TB), influenza, and vasculitis (non-SLE) are designated as AESIs in this study so they are reported and assessed promptly. Careful systematic monitoring and ongoing blinded surveillance for all such events continues.

In order to provide an independent periodic review of safety throughout the study, in addition to the ongoing, blinded review provided by the Sponsor/Designee Medical Monitor for detection of any potential safety signals, an independent Data and Safety Monitoring Board (DSMB) will review blinded and, if needed, unblinded safety data on a regular basis throughout the study (see Section 1.5.1).

In conclusion, AstraZeneca believes there is an unmet medical need in the treatment of LN. Phase 2 clinical findings suggest substantial efficacy in SLE. Available non-clinical and clinical data indicate an acceptable safety profile for anifrolumab for treatment of SLE with some data on ongoing MMF standard of care. Immunosuppression may lead to increased susceptibility to infection MMF treatment has been associated with development of lymphoma. The proposed dosing regimens for Protocol D3461C00007 are adequately justified and the management plan for potential risks associated with anifrolumab is appropriate. The emerging safety profile has not identified any risks that would preclude continued investigation of anifrolumab. AstraZeneca considers that anifrolumab in combination with SOC continues to demonstrate an overall positive benefit/risk balance to support its clinical evaluation in subjects with active proliferative LN.

1.4 Study Design

This is a Phase 2, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of two IV treatment regimens of anifrolumab versus placebo, while taking protocol-specified SOC treatment with MMF and corticosteroids (see

Section 7.7.3 for details), in adult subjects with active biopsy-proven proliferative LN. The study will be performed in adult subjects, 18 to 70 years of age. The study duration is approximately 116 weeks for those subjects who meet the criteria for the second year extension period and approximately 64 weeks for those subjects who do not meet the criteria for the second year extension period.

In this study, approximately 150 subjects will be randomised in a 1:1:1 ratio to receive one of the two IV anifrolumab dosing regimens or placebo, which will continue until Week 52, as follows:

- **Basic Regimen**: Anifrolumab 300 mg IV Q4W for 13 doses plus SOC or
- **Intensified Regimen**: Anifrolumab 900 mg IV Q4W for the first 3 doses followed by 300 mg IV Q4W for 10 doses plus SOC or
- **Placebo**: IV Q4W plus SOC

The primary objective will be evaluated at Week 52. After Week 52, eligible subjects will continue with randomised treatment plus SOC until Week 104. Those subjects not eligible to continue with treatment based on the Week 52 assessments will complete the 8 weeks of additional safety follow-up to complete involvement in the study.

After all randomised subjects have completed the 52 week double-blind period the data base will be soft-locked, and the **primary analysis** will be performed, including the assessment of the primary, secondary, and safety objectives. This analysis will also encompass available data collected after the 52 week time point and details will be provided in the SAP. At this stage the Sponsor and Sponsor's delegate who are not directly involved in the management of sites will be unblinded to randomised treatment, but the subjects and investigators will remain blinded (single-blind). The **end of study analysis** will be performed after all subjects have completed the second year extension period. One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit CCI [redacted]

IP will be administered as an IV infusion via an infusion pump over no less than 60 minutes for the first 3 doses (Visits 1, 2, and 3). Starting with Visit 4, IP can be administered as an IV infusion via an infusion pump over no less than 30 minutes.

Randomisation will be stratified using two factors:

- Results of IFN test at screening using a 4-gene type I IFN test (IFN test-high versus IFN test-low)

- 24-hour UPCR ≤3.0 mg/mg versus >3.0 mg/mg (based on 24-hour UPCR performed on a sample obtained within 14 days prior to the expected date of randomisation). Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days.

On rare occasions, an extension of the 30-day screening window may be allowed if the re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed.

Renal biopsy performed within 12 weeks prior to signing ICF or during the screening period will be considered as the screening biopsy. Biopsies will be evaluated locally and the local classification will be used to confirm the eligibility criteria. The biopsy must reveal Class III (±Class V) or Class IV (±Class V) LN according to the World Health Organisation (WHO) or 2003 International Society of Nephrology/Renal Pathology Society ISN/RPS classification. An external renal biopsy adjudication group will adjudicate renal biopsies post-randomisation.

The overall study duration is approximately 116 weeks:

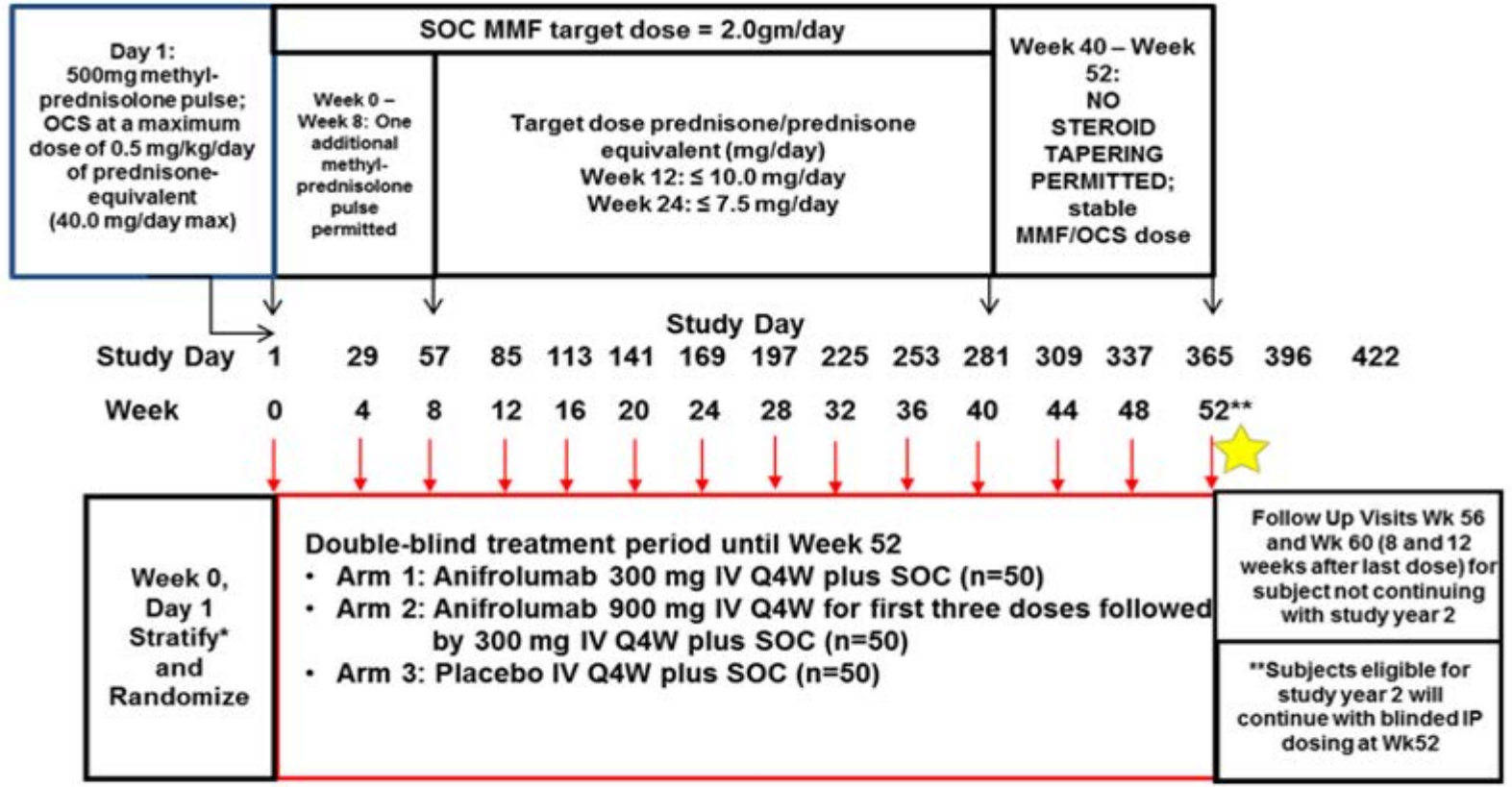
- **A Screening Period**: Up to 30 days
- **Treatment Period**:
  The total treatment period is up to 100 weeks (26 doses administered every 4 weeks).
  - **52 week double-blind treatment period**: IP will be administered every 4 weeks from Week 0 to Week 48 for a total of 13 doses. The primary endpoint will be evaluated at Week 52.
  - **Second year extension period**: At Week 52, eligible subjects will continue treatment with IP (anifrolumab 300 mg or placebo IV Q4W) administration Q4W from Week 52 to Week 100 for a total of 13 doses. The last efficacy assessments will be performed at Week 104.
- **Follow-up**: After the completion of the last IP treatment (Week 48 for subjects who are not participating in the second year extension period and Week 100 for subjects who participate in the second year extension period) subjects will continue in the study for another 12 weeks of safety follow-up after the last administration of IP.

At Week 52, eligible subjects will continue in their randomised treatment group for a second year of IP administration. The treatment groups will continue to receive IP infusions (anifrolumab 300 mg or placebo) Q4W starting at Week 52 for an additional 48 weeks in addition to SOC until Week 100. Final assessments will be performed at Week 104. After

completion of Week 104, subjects will continue for another 8 weeks until Week 112 to complete safety follow-up (every 4 weeks) after the last administration of IP.

See Figure 2 for an outline of the study design. Required SOC specific medication restrictions are contained in the eligibility criteria and Section 7.7.

Figure 2 Study flow chart (52 week double-blind treatment period)

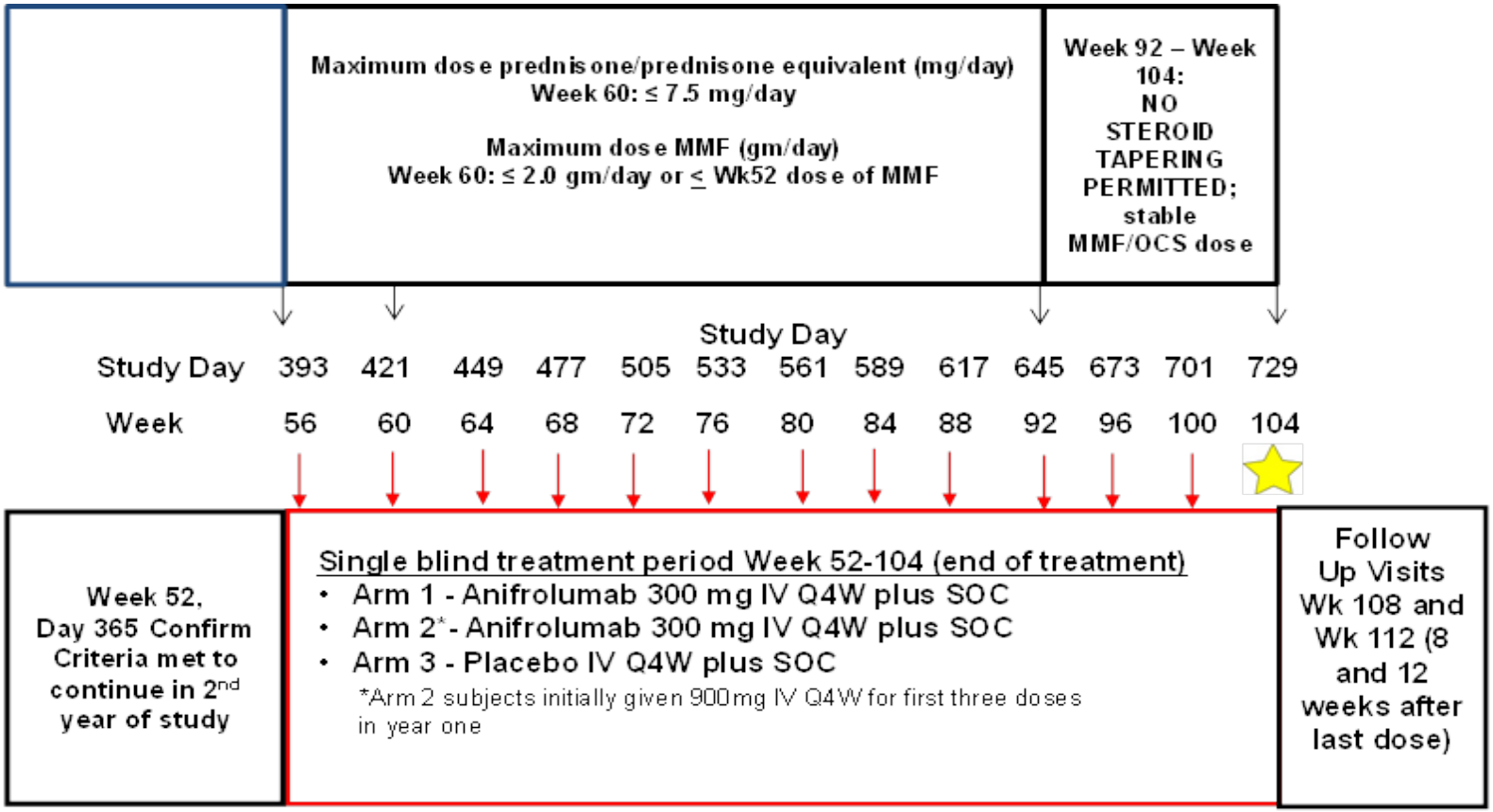


* Stratification:
IFN test (low or high)
Proteinuria (UPCR) ≤3.0 mg/mg or >3.0 mg/mg
IFN=interferon; IV=intravenous; n-number of subjects; OCS=oral corticosteroid; Q4W=every 4 weeks

= Primary Endpoint at Week 52

** For subjects who do not meet study criteria for continued IP dosing in year 2, subject's last IP dose will be at Wk48 and will not receive IP dose at Wk52. These subjects will continue with safety follow-up visits at Wk56 and Wk60, after which point the subject will end study participation.

Study flow chart (second year extension period)



IV=intravenous; n=number of subjects; OCS=oral corticosteroid; Q4W=every 4 weeks

= Year 2 Endpoint at Week 104

1.5 Study governance and oversight

1.5.1 Data and Safety Monitoring Board

An independent DSMB will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. The DSMB will be provided with data that are summarised by treatment group using masked treatment group labels (eg, A and B). After reviewing the data by masked treatment group, the DSMB may choose to unblind the treatment groups for additional review. The DSMB may also ask for unblinded efficacy data, if during the performance of a benefit/risk assessment the Board feels there is a potential safety issue or concern. The DSMB will not routinely review efficacy data (blinded or unblinded).

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

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

1.5.2 Lupus Nephritis Steering Committee

A Lupus Nephritis Steering Committee will ensure the validity and integrity of all of the data (efficacy and safety) as well as the conduct of the trial according to GCP guidelines and to provide guidance for program progression.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To evaluate the efficacy of anifrolumab plus SOC[a] compared with placebo plus SOC[a] in subjects with active proliferative LN measured by the relative difference in change from baseline to Week 52 in 24-hour urine protein to creatinine ratio (UPCR)	24-hour UPCR

[a] Required SOC is described in Section 7.7.3.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To evaluate the effect of anifrolumab plus SOC[a] compared with placebo plus SOC[a] on the proportion of subjects achieving Complete Renal Response (CRR) at Week 52	CRR is defined as meeting all of the following: • Estimated glomerular filtration rate (eGFR) is ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20% • 24-hour UPCR ≤0.7 mg/mg • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment eGFR is based on Modification of Diet in Renal Disease (MDRD) formula

[a] Required SOC is described in Section 7.7.3.
[b] Allowed medication is described in Section 7.7.

2.3 Safety objectives

Safety Objective:	Outcome Measure :
To characterise the safety and tolerability of anifrolumab	Adverse events (AEs) (including AEs of special interest [AESIs]), vital signs, physical examination, baseline and End of Treatment 12-lead electrocardiograms (ECG), and clinical laboratory tests (haematology, clinical chemistry, urinalysis), Columbia-Suicide Severity Rating Scale (C-SSRS), Personal Health Questionnaire Depression Scale-8, extra-renal flares using Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI 2K) based Flare Assessment Instrument

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure :
To evaluate the effect of anifrolumab plus SOC[a] compared with placebo plus SOC[a] on:	
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

Exploratory Objective:	**Outcome Measure :**
Proportion of subjects achieving alternative CRR (aCRR) at Week 52 (and Week 104) The difference between the CRR and the aCRR is the addition of a criterion regarding "inactive urine sediment"	aCRR is defined as meeting all of the following: • eGFR is ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20% • 24-hour UPCR ≤0.7 mg/mg • Inactive urine sediment (defined as <10 red blood cells [RBC]/hpf) • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment eGFR is based on MDRD formula
CCI [redacted]	[redacted]

Exploratory Objective:	**Outcome Measure :**
Proportion of subjects meeting Graded aCRR at Week 52 (and Week 104)	Graded aCRR is defined as meeting both the 24-hour UPCR and eGFR criteria: • A decrease in 24-hour UPCR: - For subjects with baseline UPCR >3 mg/mg: UPCR ≤1 mg/mg - For subjects with baseline UPCR ≤3 mg/mg: UPCR ≤0.7 mg/mg • eGFR: ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20% • Inactive urine sediment defined as <10 RBC/hpf • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment
Proportion of subjects able to achieve sustained reduction in oral corticosteroids (OCS) dose at Week 52 or Week 104	**Sustained reduction of OCS dose:** • Week 52: Prednisone-equivalent dose ≤7.5 mg/day by Week 24 and not exceeding this dose through Week 52 • Week 104: Prednisone-equivalent dose ≤5.0 mg/day by Week 80 and not exceeding this dose through Week 104 **and** • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment
Proportion of subjects achieving CRR at Week 52 or Week 104 **and** achieving sustained reduction of OCS dose	CRR (see definition of CRR above) Sustained reduction of OCS dose (see definition above)
CCI [redacted]	[redacted]

Exploratory Objective:	Outcome Measure :
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

Exploratory Objective:	**Outcome Measure :**
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
Mean change in scores for overall disease activity from baseline to Week 52 (and to Week 104)	SLEDAI-2K
Mean change in score measures of non-renal disease activity from baseline to Week 52 (and to Week 104)	Non-renal components of SLEDAI-2K

Exploratory Objective:	**Outcome Measure :**
Mean change in scores for overall disease activity from baseline to Week 52 (and to Week 104)	Physician's Global Assessment (PGA)
Mean change in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) score from baseline to Week 52 (and to Week 104)	SDI
Mean change in scores for patient-reported health status from baseline to Week 52 (and to Week 104)	Patient Global Assessment (PtGA)
To evaluate the immunogenicity of anifrolumab, pharmacokinetics (PK), pharmacodynamics (the PK and immunogenicity results will be reported in the clinical study report)	Anti-drug antibodies (ADA), anifrolumab concentration and PK parameters, 21 gene type I IFN gene signature
To evaluate the pharmacokinetics of mycophenolic acid (MPA)	MPA concentration and PK parameters (if applicable)
Mean change in lupus serology from baseline to Week 52 (and to Week 104)	Anti-dsDNA antibodies, C3 and C4 complement levels
CCI [redacted]	[redacted]

[a] Required SOC is described in Section 7.7.3.
[b] Allowed medication is described in Section 7.7.
[c] Note: Spot UPCR will be used instead of 24-hour UPCR for the PRR and CRR classification, when evaluating time to achieve renal response modified to include OCS tapering requirement as well as for the PRR and CRR classification for flare assessment.

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

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. If a subject does not meet eligibility criteria on the basis of a laboratory value, then the laboratory parameter may be repeated once within the screening period; this will be re-testing so that re-screening is not required. Please refer Section 4.1.1 for details on re-screening and re-testing.

Note: From the day of randomisation onwards until the end of subject's participation in the study, MMF will be supplied by the Sponsor to the subjects.

3.1 Inclusion criteria

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

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

2. Men and women, age 18 through 70 years at the time of screening

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

4. Fulfils at least 4 of the 11 ACR classification criteria for SLE (see Appendix E), one of which must be:

   (a) Positive antinuclear antibody (ANA) test (1:40 or higher) at screening by immunofluorescence assay at central laboratory; **or**

   (b) Elevated anti-dsDNA antibodies at screening (reported as equivocal or positive results), as per the central laboratory; **or**

   (c) Anti-Smith antibody at screening elevated to above normal (ie, positive or equivocal results) as per the central laboratory

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

5. Weigh ≥40.0 kg at screening

6. Diagnosis of proliferative LN based on a renal biopsy obtained within 12 weeks prior to signing the ICF or during the screening period:

   – Class III (±Class V) or Class IV (±Class V) LN according to the World Health Organisation (WHO) or 2003 ISN/RPS classification (based on local evaluation of renal biopsy)

7. Urine protein to creatinine ratio >1 mg/mg (113.17 mg/mmol), obtained on a 24-hour urine collection at both:

   – The start of screening and

– Within 14 days prior to the expected date of randomisation. Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days.

8. Estimated glomerular filtration rate (as calculated by the MDRD formula, with screening laboratory results for serum creatinine value) ≥35 mL/min/1.73 m^2

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

   Note: If the result of the serum β human chorionic gonadotropin (β-hCG) test is borderline or thought to be false positive the test can be repeated during the screening. The subject can continue if the repeat test is negative.

10. Women of childbearing potential must have a negative urine pregnancy test prior to administration of IP and prior to the first dose of Sponsor-provided MMF

11. Females of childbearing potential must use 2 effective methods (Table 1) of avoiding pregnancy, only one of which is a barrier method, from Screening until 12 weeks after the final dose of IP and from the first dose of Sponsor-provided MMF until 6 weeks after the last dose of Sponsor-provided MMF unless the subject is surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a sterile male partner, is 1 year post-menopausal, or practices sustained abstinence. Cessation of birth control after the specified period for IP or Sponsor-provided MMF should be discussed with a responsible physician.

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

    - Post-menopausal is defined as at least 1 year since last menses and the subject has an elevated follicle-stimulating hormone (FSH) central laboratory value within the post-menopausal range.

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

Table 1 Effective methods of birth control (2 Required)

Barrier Methods (Choose 1)	**Intrauterine Device/Hormonal Methods (Choose 1)**	
	Intrauterine Device Methods	**Hormonal Methods**
Male condom (with spermicide[a])	Progesterone T	Implants
Cap (with spermicide cream or jelly[a])	Copper T	Hormone shot or injection
Diaphragm (with spermicide cream or jelly*)		Combined pill
		Minipill
[a] *where commercially available*		Patch

12. All males (sterilised or non-sterilised) who are sexually active must use condom (with spermicide where commercially available for contraception) from Day 1 until at least 12 weeks after receipt of the final dose of IP and until at least 90 days after the last dose of Sponsor- provided MMF (whichever is later). It is strongly recommended for the female partner of a male subject to also use an effective method of contraception from Table 1 (other than a barrier method) throughout this period.

13. Male subjects must not donate sperm during the course of the study and for 12 weeks after the last dose of the IP and 90 days after the last dose of Sponsor-provided MMF (whichever is later)

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

    Note: Any abnormal Pap smear result documented within 2 years prior to signing the ICF must be repeated to confirm subject eligibility. Refer to exclusion criterion No. 36(b).

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

16. Meets all of the following TB criteria:

(a) No history of latent or active TB prior to screening, with the exception of latent TB with documented completion of appropriate treatment or currently receiving prophylactic treatment for latent TB and the subject commits to completing the full duration of prophylaxis

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

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

(d) Must meet one of the following criteria:

(i) Negative QuantiFERON-TB Gold [QFT-G] test result for TB obtained from central laboratory within 12 weeks prior to randomisation **or**

(ii) Positive QFT-G test result for TB obtained during the screening period from central laboratory for which active TB has been ruled out and appropriate treatment for latent TB has been initiated prior to the first IP administration and the subject commits to completing the full duration of prophylaxis, which may mean completing prophylaxis during the study or

(iii) Indeterminate (confirmed as indeterminate on retest during screening) QFT-G test for TB obtained during the screening period from central laboratory with ongoing QFT-G testing for TB to the Study Plan (Table 2)

(e) A chest radiograph with no evidence of current active TB or other infection, or old active TB, malignancy, or clinically significant abnormalities (unless due to SLE) obtained during the screening period or anytime within 12 weeks prior to signing of the ICF

17. Adequate peripheral venous access

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 interfer with evaluation of the IP or interpretation of subject safety or study results
2. Known intolerance to ≤1.0 gm/day of MMF
3. Concurrent enrolment in another clinical study with an IP within 4 weeks prior to ICF signing or within 5 half-lives of the IP used in that clinical study, whichever is longer
4. Prior participation in an anifrolumab clinical study
5. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at the study site and their immediate family members)
6. Lactating or pregnant females or females who intend to become pregnant or begin breastfeeding anytime from initiation of screening through the 12 week safety follow-up period following last dose of IP and 6 weeks after the last dose of Sponsor-provided MMF (whichever is later)
7. Current alcohol, drug or chemical abuse, or a recent history of such abuse within 1 year before Day 1 (Week 0 visit)
8. Major surgery within 8 weeks before signing the ICF or major surgery planned during the study period (see Appendix J for guidance on major surgery)
9. Spontaneous or induced abortion, still or live birth, or pregnancy ≤4 weeks prior to signing the ICF
10. A diagnosis of pure Class V membranous LN. This will be based on the renal biopsy obtained within 12 weeks prior to signing ICF or during the screening period
11. History of dialysis within 12 months prior to signing the ICF or expected need for renal replacement therapy (dialysis or renal transplant) within a 6 month period after enrolment
12. History of, or current renal diseases (other than LN) that in the opinion of the Investigator could interfere with the LN assessment and confound the disease activity assessment (eg, diabetic nephropathy)
13. Subjects, who at the time of signing the ICF, received any of the following immunosuppressive therapies after their qualifying biopsy:

(a) Oral corticosteroids >0.5 mg/kg/day for more than 8 weeks or

(b) Oral or IV pulse methylprednisolone >3.0 gm (cumulative dose) or

(c) IV cyclophosphamide >2 pulses of high-dose (≥0.5 gm/m^2) or >4 doses of low-dose (500 mg every 2 weeks) or

(d) Average MMF >2.5 gm/day (or >1800 mg/day of enteric coated mycophenolate sodium) for more than 8 weeks or

(e) Tacrolimus >4 mg/day for more than 8 weeks

Note: Any combination of treatments with these therapeutic agents is allowed if none of the components exceeds the above limits

14. During screening (within 30 days before Day 1 [Week 0 visit]), any of the following:

(a) Aspartate transaminase (AST) >2.5×upper limit of normal (ULN)

(b) Alanine transaminase (ALT) >2.5×ULN

(c) Total bilirubin >ULN (unless due to Gilbert's syndrome [based on Investigator's judgement])

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

(e) Neutrophil count <1x10^3/µL (or <1.0 GI/L)

(f) Platelet count <25x10^3/µL (or <25 GI/L)

(g) Haemoglobin <8 g/dL (or <80 g/L)

15. Abnormal ECG findings that in the opinion of the investigator would put the subject at risk, if the subject participated in this study

3.2.2 Exclusion criteria related to concomitant medications

16. Receipt of any experimental agent (small molecule or biologic) or commercially available biologic agent within four weeks or 5 half-lives, whichever is greater (see Appendix H) prior to ICF signing

17. B cell targeted therapy restrictions:

(a) Receipt of epratuzumab, belimumab, or tabalumab ≤12 weeks prior to signing the ICF and atacicept ≤40 weeks prior to signing the ICF

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

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

19. Receipt of any of the following:

(a) Any live or attenuated vaccine within 8 weeks prior to signing the ICF (administration of killed vaccines is acceptable, the Sponsor recommends Investigators ensure all subjects are up to date on required vaccinations prior to study entry) or an anticipated requirement for live vaccine during the treatment period and for 12 weeks following the last dose of the IP

(b) Bacillus of Calmette-Guérin (BCG) vaccine within 1 year (12 months) prior to signing the ICF

(c) Any excluded medication or treatment modality listed in Appendix H

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

(e) The following medications must be discontinued prior to the day of randomisation (because of potential interaction with MMF):

- Methotrexate
- Azathioprine
- Leflunomide
- Tacrolimus
- Cyclosporine
- Mizoribine
- Cholestyramine

3.2.3 Exclusion criteria related to systemic lupus erythematosus and other diseases

20. History of, or current diagnosis of, a clinically significant non-SLE-related vasculitis syndrome (see Appendix G). Subjects who have experienced vasculitis as a feature of their SLE can be recruited to the study

21. History or evidence of suicidal ideation (severity of 4 [active: method and intent, but no plan] or 5 [active: method, intent, and plan]) within the past 6 months; or any suicidal behaviour within the past 12 months based on an assessment with the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or at baseline

22. Active severe or unstable neuropsychiatric SLE including, but not limited to: aseptic meningitis, cerebral vasculitis, myelopathy, demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy), acute confusional state, impaired level of consciousness, psychosis, acute stroke or stroke syndrome, cranial neuropathy, status epilepticus, cerebellar ataxia, and mononeuritis multiplex:

(a) That might cause the subject to be unable to fully understand the ICF or

(b) In the opinion of the Investigator, protocol-specified SOC is insufficient to control neurologic features of SLE 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 or anticipated

23. Documented history of systemic sclerosis or diagnosis of SLE with overlap systemic sclerosis

24. History of, or current diagnosis of, catastrophic anti-phospholipid syndrome (APS), see Appendix P) or APS-related thromboembolic event or pregnancy loss within 1 year prior to signing the ICF. Subjects with APS adequately controlled by anticoagulants or aspirin for at least 12 weeks can be recruited to the study

25. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF

3.2.4 Exclusion criteria related to infection and malignancy risk factors

26. Known history of a primary immunodeficiency (eg, common variable immunodeficiency syndrome), splenectomy, or any underlying condition that predisposes the subject to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at screening

27. Confirmed positive test for hepatitis B serology for:

    (a) Hepatitis B surface antigen (HbsAg), or

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

    Note: Subjects who are HBcAb positive at screening will be tested monthly for HBV DNA. To remain eligible for the study, the subject's HBV DNA levels must remain below the LLOQ as per central laboratory.

    A reflex test is a test that must be performed based on the results of a prior test (pre-set criteria).

28. Positive test for hepatitis C antibody

29. Any severe herpes infection at any time prior to randomisation (Week 0 visit), including but not limited to, disseminated herpes, herpes encephalitis, or ophthalmic herpes

30. Recurrent herpes zoster (defined as 2 episodes within 2 years) within 5 years prior to randomisation

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

32. History of opportunistic infection (see Section 6.4.2 for definition) requiring hospitalisation or parenteral anti-infective treatment with in 3 years prior to randomisation (vaginal, oral and skin candidiasis is not an exclusion reason)

33. Cytomegalovirus and/or Epstein–Barr virus infection that has not been completely resolved within the 12 weeks prior to signing the ICF

34. Either of the following:

    (a) Clinically significant chronic infection (ie, osteomyelitis, bronchiectasis, etc.) which is not resolved within 8 weeks prior to signing the ICF (chronic nail infections are allowed)

    (b) Any infection requiring hospitalisation or treatment with IV anti-infectives not completed at least 8 weeks prior to randomisation

35. Any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to randomisation, except chronic suppressive antiviral treatment for herpes simplex virus in the absence of active lesions within 2 weeks prior to randomisation

36. History of cancer, apart from:

    (a) Squamous or basal cell carcinoma of the skin treated with documented success of curative therapy ≥12 weeks prior to randomisation (Week 0 visit)

    (b) High-grade squamous intraepithelial lesion (CIN III, CIS) treated with apparent success with curative therapy ≥1 year prior to randomisation (Week 0 visit)

For procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

3.3 Subject enrolment and randomisation

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

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

2. IXRS will assign the subject with a unique enrolment number. The subject ID will be pre-fixed with 'E' in IXRS reports and on the screen (sites will have to enter the 7 digit subject ID into the IXRS to retrieve subject data)

3. Determine subject eligibility. During the screening period, the study Medical Monitor/Designee will confirm eligibility criteria based on the data captured in the electronic data capture (EDC) system, and from the central laboratory. Sites will be notified to either randomise the subject or to consider the subject as screen failed, prior to the planned randomisation date.

4. On Day 1, the Investigator will confirm that all eligibility criteria are still fulfilled and will then perform the randomisation transaction in the IXRS.

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

See additional information in Section 3.5.

Randomisation will be stratified using two factors:

- Results of IFN test at screening using a 4-gene type I IFN test (IFN test-high versus IFN test-low)
- 24-hour UPCR ≤3.0 mg/mg versus >3.0 mg/mg (within 14 days prior to the expected date of randomisation). Without the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days. On rare occasion an extension of the 30-day screening window may be allowed if the re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed.

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

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive IP and Sponsor-provided MMF. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Principal Investigator should inform the Sponsor/Designee Medical Monitor immediately, and a discussion should occur between the

Sponsor/Designee Medical Monitor and the Principal Investigator regarding whether to continue or discontinue the subject from treatment. The Sponsor/Designee must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

On Day 1, the Investigator will confirm that all eligibility criteria and will then perform the randomisation transaction in the IXRS. The IXRS will assign eligible subjects a unique randomisation code and blinded IP kit number(s).

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

Block randomisation using an IXRS will be used to randomise subjects in a 1:1:1 ratio to receive one of the two IV dosing regimens of anifrolumab (Basic Regimen/Intensified Regimen) or placebo. AstraZeneca Biostatistics group is responsible for generating the randomisation scheme for this study using the GRand system.

3.6 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. Hence, the IP will be prepared by a trained unblinded team member at the site, who will not be involved in the management of study subjects.

To ensure blinding of the anifrolumab regimens, the duration of infusion is no less than 60 minutes for the first 3 doses of IP (Visits 1, 2, and 3) for all three arms.

All packaging and labelling of IP is done in such way as to ensure blinding for all Sponsor/Designee and investigational site staff, other than the unblinded team member who is assigned to prepare the IP. The kits on the shelf, and the infusion bags when prepared, look identical. Neither the subject nor any of the Investigators or Sponsor/Designees who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. In the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor/Designee must be notified immediately by the Investigator.

Investigators and subjects who continue in the second year extension period will continue to be blinded to their treatment. However, the Sponsor and Sponsor’s delegates who are not directly involved in the management of sites will be unblinded at the time of the primary analysis at Week 52.

3.7 Methods for unblinding

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 must document and report the action to AstraZeneca or designee, without revealing the treatment given to subject to the AstraZeneca staff or the designee. Instructions for unblinding an individual subject's IP allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received IP. In the majority of cases, the management of a medical emergency would be the same whether or not IP was received by the subject. If this was the case, the IP allocation should not be unblinded. Subjects who have been unblinded by the Investigator must be discontinued from IP.

One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit. CCI [redacted]

CCI [redacted] Details of the interim analysis including a description of who will be unblinded will be specified in the interim analysis and communication plans prior to unblinding.

After all randomised subjects have completed the 52 week double-blind period the data base will be soft-locked, and the **primary analysis** will be performed, including the assessment of the primary, secondary, and safety objectives. This analysis will also encompass available data collected after the 52 week time point and details will be provided in the SAP. At this stage the Sponsor and Sponsor's delegate who are not directly involved in the management of sites will be unblinded to randomised treatment, but the subjects and investigators will remain blinded (single-blind). The **end of study analysis** will be performed after all subjects have completed the second year extension period.

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 IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

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

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists at the study site.

Live unblinded randomisation data will be periodically released to an independent PK analyst and an independent immunogenicity samples analyst from PPD, in order to allow them to perform laboratory PK and immunogenicity analysis. The unblinded randomisation data will be only released to specific named personnel for this purpose and will not be made available to any staff from AstraZeneca or Sponsor's delegate.

3.7.1 Unblinding for Data and Safety Monitoring Board

An independent DSMB will review safety data throughout the study. The DSMB will be provided with partially unblinded data (data that are summarised by treatment group using masked treatment group labels). The DSMB may choose to unblind the data for additional review as specified in the DSMB charter. The Sponsor/Sponsor's delegate study team will remain blinded to all data transfers provided to the DSMB. Details about the DSMB will be included in the DSMB charter. For further details on the DSMB, see Section 1.5.1.

3.8 Restrictions

3.8.1 Fasting lipid profile

Subjects will be required to fast for at least 8 hours prior to assessment of lipid profile at the visits described in the Treatment Period Study Plan (Table 2 and Table 4). If the subject has not fasted, he/she should fast before the next visit, and the test can be done at that visit.

3.8.2 Perioperative management of investigational product

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

3.8.2.1 Major surgeries

Pre-operative management of IP: If a non-urgent major surgery becomes necessary during the study, it should be scheduled at least 4 weeks after the last administration of IP, if clinically feasible. The determination of whether or not a surgery is "urgent" will be at the discretion of the investigator, preferably in consultation with the Sponsor/Designee Medical Monitor.

3.8.2.2 Non-major surgeries

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

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

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

3.8.3 Blood donation

Subjects must not donate blood from date of randomisation until 6 weeks after the last dose of Sponsor-provided MMF and within 12 weeks after the last IP dose.

3.9 Discontinuation of investigational product

3.9.1 Criteria for discontinuation of investigational product due to worsening LN or SLE (at any time)

Blinded IP will be discontinued in subjects who meet pre-defined criteria for worsening LN or SLE. Subjects may receive rescue treatment as clinically indicated. Subjects who had their IP discontinued will be followed according to the study schedule. These subjects will be followed until Week 52 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 52). If discontinuation occurs during the second year extension period, subjects will be followed until Week 104 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 104).

- >30% decrease in eGFR compared to baseline due to LN and eGFR <60 mL/min/1.73 m^2 (on two independent samples) or
- Increase in renal or extra-renal lupus activity requiring prohibited systemic immunosuppressive treatment (eg, cyclophosphamide, rituximab, belimumab)
- Receipt of >1 methylprednisolone pulse after the day of randomisation
- Receipt of any methylprednisolone pulse after Week 8
- The IP will be discontinued if MMF is discontinued and another immunosuppressant is initiated

3.9.2 Criteria for discontinuation of investigational product for worsening of LN or SLE at Week 12 and Week 24

- eGFR <75% of baseline and <60 mL/min/1.73 m^2 (on two independent samples) or
- Nephrotic range UPCR (confirmed by a second measurement at least two weeks after the first measurement):
  - Subjects with 24-hour UPCR ≤3 mg/mg at baseline will be withdrawn if 24-hour UPCR increases by >50% from baseline to >3.5 mg/mg

- Subjects with 24-hour UPCR >3 mg/mg at baseline will be withdrawn if 24-hour UPCR at Week 24 >3.5 mg/mg and there is <60% improvement from baseline or

- Inability to adhere to corticosteroids requirements:

  - Inability to reduce OCS to ≤15 mg/day prednisone-equivalent at Week 12

  - Inability to reduce OCS to <15 mg/day by Week 24

Subjects who exceed the maximum daily OCS dose at the Week 12 or Week 24 visits may continue to receive IP if the current dose is part of a temporary increase in OCS dose (eg, protocol-allowed burst and taper). Subjects who cannot be returned to their pre-increase dose within 14 days from the start of the increase will have their IP discontinued at the next visit.

3.9.3 Criteria for discontinuation of investigational product during the second year extension period:

Criteria for discontinuing investigational product at Week 52:

Subjects not meeting the criteria to continue in the second year extension will not receive any IP at Week 52 and will complete the study after completing the required follow-up visits.

Subjects meeting the following criteria may continue to receive blinded IP between Weeks 52 and 100.

(i) Meeting all of the following criteria based on the renal portion of the PRR definition:

- eGFR is:

  ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20%

- Improvement in 24-hour UPCR:

  - For subjects with a baseline UPCR ≤3 mg/mg: <1.0 mg/mg

  - For subjects with a baseline UPCR >3 mg/mg: >50% improvement from baseline and ≤3.0 mg/mg

  Renal discontinuation criteria must be confirmed in two separate samples. The second measurement should be at least 1 week after the first measurement.

(ii) No discontinuation of IP

(iii) Negative HIV test after signing the Main ICF

Criteria for discontinuing investigational product at Week 52, Week 56 or Week 60

- Failure to obtain Pap smear after Week 48 with result available at Week 60 at latest
- Pap smear result not meeting the eligibility criteria (see Appendix K) at Week 52, 56, or 60 of a Pap smear obtained after Week 48
- Failure to obtain Week 52 QuantiFERON test result by Week 56

Criteria for discontinuing investigational product at Week 60 and later

- OCS >7.5 mg/day (except one OCS burst and taper)
- MMF >2 gm/day or >Week 52 dose, if Week 52 dose <2 gm/day

Subjects who discontinue the IP during the second year extension period will be followed until Week 104 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks of Week 104).

3.9.4 Criteria for discontinuation of investigational product for reasons other than lack of efficacy at any time during the study

Subjects may be discontinued from IP in the following situations:

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

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

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

   (c) The subject is concerned about possibility of receiving placebo or ineffective treatment

   (d) Subject wishes to participate in another clinical study

(e) Subject is interested in taking a treatment that is not allowed in this study

(f) Subject perceives logistics at the clinical site to be unacceptable

(g) Other reason

2. Lost to follow-up: must be documented by time and date of telephone calls, e-mails, text messages, numbers called, individuals spoken to if not subject, and at least 2 attempts to contact the subject via certified letter (see Section 3.9.7)

3. Adverse event that, in the opinion of the Investigator or the Sponsor/Designee Medical Monitor, contraindicates further dosing with IP

4. Severe non-compliance with the study protocol

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

6. Pregnancy, positive pregnancy test, or subject expresses an interest in becoming pregnant

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

8. Positive HIV test

9. Receipt of any medications identified in Section 7.7.2.1

10. The use of restricted medications listed in Section 7.7.2.2 if the Sponsor/Designee Medical Monitor, in consultation with the Sponsor, determines the subject must be discontinued

11. A diagnosis of active TB, premature discontinuation of treatment for latent TB, or non-compliance with latent TB therapy. Note: Duration of treatment for latent TB should follow the local practice. If local practice is not defined, then Centers for Disease Control and Prevention (CDC) guidance for immunocompromised patients should be used.

12. Subject is unblinded by the Investigator

Additional restrictions related to concomitant medications are discussed in Section 7.7.

3.9.5 Subject decision to discontinue investigational product

If the subject decides to discontinue IP for any reason including but not limited to those outlined in Section 3.9 above, the subject will not receive any further IP. Subjects who discontinue IP during the 52 week double-blind treatment period will be followed until Week 52 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 52). If discontinuation occurs during the second year extension period, subjects will be followed until Week 104 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 104). The subject may continue to receive Sponsor-provided MMF until the end of the subject's participation in the study.

3.9.6 Withdrawal of the informed consent

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

A subject who withdraws consent will always be asked about the reason(s) (see Section 3.9.2) and the presence of any AEs. The Investigator will follow-up AEs outside of the clinical study.

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

3.9.7 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 e-mails, 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, e-mails, text messages, numbers called, individuals spoken to if not subject, and documentation that 2 certified/registered letters were sent.

3.9.8 Study completion and end of study

An individual subject will be considered to have completed the study if the subject was followed up until the end of the study (Week 112), regardless of the number of doses of IP

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.

A subject will be considered to have completed the double-blind treatment period if they were followed up until Week 60 or if they entered the second year extension period.

A subject will be considered to have completed the second year extension period if the subject was followed up until the end of the study (Week 112).

3.9.9 Procedures for discontinuation of a subject from investigational product

Discontinuation of IP does not necessarily mean discontinuation of follow-up or termination of study participation. Subjects who are discontinued from the IP should be followed up to continue to undergo all study-related visits/procedures for the full treatment period (Table 2) in order to support the final efficacy and safety analysis for anifrolumab (see Section 8). Subjects who discontinue IP earlier than 12 weeks before Week 52 will be followed until Week 52. Those discontinued within 12 weeks prior to Week 52 will need to have follow-up beyond Week 52 to complete a 12 week safety observation period after the last dose of IP administration.

Subjects who discontinue IP in the second year extension period will be followed until Week 104. Those discontinued within 12 weeks prior to Week 104 will need to have follow-up beyond Week 104 to complete a 12-week safety observation period after the last dose of IP administration.

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

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 IP prior to their completion of the study and wishes to continue with only selected study assessments; prioritised assessments are listed in Section 4.2.2.

For subjects who wish to withdraw from the study completely refer to Section 3.9.4.

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

3.10 Criteria for withdrawal

Screening failures are subjects who have provided informed consent but who were subsequently found to not fulfil the eligibility criteria for the study, and therefore must not be randomised. These subjects should have the reason for study withdrawal recorded as 'Screen failure'(the potential subject who does not meet one or more criteria required for participation

in a trial, this reason for study withdrawal is only valid for not randomised subjects). For eligibility for re-screening of a subject refer to Section 4.1.1.

3.11 Discontinuation of the study

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

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

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

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

The Study Plan detailing the procedures from screening through Week 52 is presented in Table 2. The Study Plan detailing the procedures during follow-up is presented in Table 3. The Study Plan detailing the procedures for the second year extension period (Week 56 to Week 104) is presented in Table 4. The Study Plan detailing the procedures during follow-up in the second year extension period is presented in Table 5.

Table 2 Study plan detailing the procedures from screening through Week 52 treatment period (double-blind period)

Study Period	**Sc**	**Treatment Period**														
Days	**-30 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**-**
Visit Number	**SV**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UN[a]**
Study Week	**-**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52/DC[b, 1]**	**-**
Visit Window	**-**		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
Written informed consent/Assignment of Screening ID number	X															
PtGA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS (Screening)	X															
C-SSRS (V1-V16)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PHQ-8		X			X			X			X				X	
Screening renal biopsy[c]																
Local clinical evaluation	X															
Adjudication[d]		X														
Tissue biomarker[e] (optional)	X															
Second renal biopsy (optional)[f]	For eligible subject once after Week 24															
Local clinical evaluation	X															
Adjudication (optional)	X															
Tissue biomarker[e] (optional)	X															
eGFR using MDRD formula	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Sc**	**Treatment Period**														
Days	**-30 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**-**
Visit Number	**SV**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UN[a]**
Study Week	**-**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52/DC[b, 1]**	**-**
Visit Window	**-**		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
Medical history	X	X														
SLE and LN medication history	X															
ACR Classification Criteria	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X	X						X							X	
Focused physical examination			X	X	X	X	X		X	X	X	X	X	X		X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X															
Assessment of Cushingoid features		X						X							X	
ECG	X														X	
Chest X-ray[g]	X															
Tuberculosis Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pap smear[h]	X														X	
Blood collection for:																
Screening labs[i]	X															
FSH in post-menopausal females only	X															
Pregnancy test in females	X															

Study Period	**Sc**	**Treatment Period**														
Days	**-30 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**-**
Visit Number	**SV**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UN[a]**
Study Week	**-**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52/DC[b, 1]**	**-**
Visit Window	**-**		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
QFT-G test (TB testing)[j]	X														X	
QFT-G test (TB testing, only if indeterminate at screening/previous visits)				X				X			X				X	
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology profile[k]	X							X							X	X
IFN test	X															
B cell count[l]	X															
Lipid profile[m]		X						X							X	
Lupus serology tests (C3, C4, anti-dsDNA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-dose ADA		X			X			X			X				X	
Pre-dose PK blood sample		X			X			X			X			X	X[n]	
Post-dose PK blood sample		X												X		
Serum MPA[o]		X			X			X			X				X	X
Serum and Plasma biomarkers		X			X			X			X				X	
Type I IFN signature with 21-gene assay (PD marker)		X			X			X			X				X	

Study Period	**Sc**	**Treatment Period**													
Days	**-30 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**-**
Visit Number	**SV**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UN[a]**
Study Week	**-**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52/DC[b, 1]**	**-**
Visit Window	**-**		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
RNA transcript profiling		X			X			X			X				X	
Pharmacogenomics (optional)		X						X							X	
Cardiovascular risk assessment		X														
Urine collection for:																
24-hour UPCR[p]	X[q]	X[r]			X			X			X				X	X
Spot UPCR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test in females of childbearing potential only[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including microscopic examination)[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local urinalysis (including microscopic examination) for selected sites[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinary biomarkers		X	X	X	X			X			X			X		X
SLEDAI-2K	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLICC/ACR Damage Index (SDI)		X						X							X	
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Sc**	**Treatment Period**														
Days	**-30 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**-**
Visit Number	**SV**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UN[a]**
Study Week	**-**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52/DC[b, 1]**	**-**
Visit Window	**-**		**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
Steroid tapering		X	X	X	X	X	X	X	X	X	X	X				
Extra-renal flare (SLEDAI-2K based Flare Assessment Instrument)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X	X														
Randomisation		X														
Ophthalmologic examination for chloroquine/hydroxychloroquine toxicity (if applicable)[v]	X	X														
IP administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	
Sponsor-provided MMF[w]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

ACR=American College of Rheumatology; ADA=anti-drug antibodies; AE=adverse event; AESI=adverse event of special interest; Anti-dsDNA=anti-double stranded deoxyribonucleic acid; C3=third component of complement; C4=fourth component of complement; C-SSRS=Columbia-Suicide Severity Rating Scale; DC=early discontinuation; dsDNA=double stranded deoxyribonucleic acid; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; IFN=interferon; IP=investigational product; PGA=Physician's Global Assessment; QFT-G=QuantiFERON-TB Gold; MDRD=Modification of Diet in Renal Disease formula; MMF=mycophenolate mofetil; MPA=mycophenolic acid; LN=lupus nephritis; PD=pharmacodynamics; PtGA=patient global assessment; PHQ-8=Personal Health Questionnaire Depression. Scale; PK=pharmacokinetic; PRR=partial renal response; RNA=ribonucleic acid; Sc=screening; SAE=serious adverse event; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR=Systemic Lupus International Collaborating Clinics/American College of Rheumatology; SV= screening visit; TB=tuberculosis; UN=unscheduled; UPCR=urine protein/creatinine ratio

a Not all assessments indicated for the Unscheduled Visit need to be performed. The assessments are to be performed at the discretion of the Investigator, as clinically indicated.

b Subjects with early discontinuation of IP should continue to attend visits according to the Study Plan. However a 24-hour UPCR sample should be collected within 4 weeks of IP discontinuation decision (unless the next scheduled visit is within 4 weeks of this decision, and includes this test already) and before the start of a new treatment for LN. If at any point after IP discontinuation is performed, the subject decides to discontinue from the study

without completing all scheduled visits up to Week 52/Visit 14, an early discontinuation visit needs to be performed as soon as possible after the study discontinuation decision is made.

c Renal biopsy performed within 12 weeks prior to signing the ICF or during the screening period.

d An external renal biopsy adjudication group will adjudicate renal biopsies post-randomisation. The biopsies for adjudication should be sent soon after randomisation.

e Immunostaining, epigenetic and gene expression studies.

f Renal biopsy may be performed at the discretion of the investigator based on clinical indication and local practice for subjects who meet withdrawal criteria for worsening lupus nephritis at Week 24 or later and for subjects not achieving Complete Renal Response at Week 52 (if subject signs the separate ICF).

g Chest X-ray should be performed only in subjects who have not had a chest X-ray within 12 weeks prior to signing the ICF. Posterior-anterior or anterior-posterior and lateral images are required in order to visualize lungs unless limited by local practice.

h At screening, female subjects with an intact cervix must have a Pap smear if they have not had a normal Pap smear within 2 years prior to signing the ICF. Additionally, female subjects with an intact cervix should have a Pap smear at or soon after Week 48 to ensure that there is no evidence of new cervical dysplasia and the results must be found to meet eligibility requirements as described in Appendix K and available by Week 60 or IP administration will be discontinued as described in Appendix K.

i Screening laboratory includes HbA1c (diabetic subjects only), HbsAg, HBcAb (reflex DNA testing if isolated HBcAb positive), hepatitis C antibody, and HIV. A reflex test is a test that must be performed based on the results of a prior test (pre-set criteria). HBV DNA levels in subjects who are HBcAb positive at screening will be tested monthly for HBV DNA. To remain eligible for the study, the subject's HBV DNA levels must remain below the LLOQ as per central laboratory.

j If the test result is indeterminate, the test must be repeated at least one time by the central laboratory as soon as possible.

k Immunology profile includes quantitative immunoglobulins (IgA, IgG, IgM), ANA, and anti-RNP, anti-Smith, anti-SSA (Ro), anti-SSB (La), and anti-cardiolipin antibodies.

l B cell count (CD19+ cells) for those who received rituximab or other B cell-depleting therapy >26 weeks prior to signing ICF. See exclusion criterion No. 17.

m Subjects will be required to fast for at least 8 hours prior to assessment of lipid profile. If the subject has not fasted, he/she should fast before the next visit, and the test can be done at that visit.

n For subjects who do not continue in the second year extension period, there is no dosing at Visit 14, however a PK sample will be collected.

o Mycophenolate mofetil dose should be withheld until samples for the mycophenolic acid blood draw has been collected on that visit day.

p Starting from Week 0 visit, the 24-hour UPCR sample must always be collected before the administration of IP at the marked visits. The collection of the 24-hour UPCR sample should start preferably in the morning of the day before the scheduled visit and end in the morning of the day of the visit. The urine collection can be done within 1 day prior to the visit if the urine sample can be kept refrigerated until the day of the visit. If refrigeration is not possible, subjects should select the coolest possible place to store their urine sample eg, a cool room or use a portable cooler with ice/ice pack. Subjects who prematurely discontinue IP should have the 24-hour UPCR measurement within 4 weeks of the decision to discontinue IP and before the start of a new treatment for LN.

q Two samples of 24-hour urine collection are required during screening period to assess eligibility. One sample is to be collected at the start of the screening process (screening sample). The other sample is to be collected within 14 days prior to the expected date of randomisation. Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days. On rare

occasion an extension of the 30-day screening window may be allowed if the re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed.

r The baseline sample must be provided on Day 1 prior to randomisation and administration of dose.

s This will be done locally from Visit 1 onwards.

t If the subject is menstruating, this must be specified in the eCRF.

u This will be in addition to the central laboratory urinalysis. This will include urine sediment examination for red blood cells (RBC), white blood cells (WBC), and cellular casts (WBC, RBC and mixed) and hematuria on a dipstick test.

v Randomised subjects who receive anti-malarial therapy within 12 months prior to signing the ICF must have an eye exam by a qualified professional either within 12 months prior to signing the ICF or subjects who start on anti-malarial therapy during the Screening Period within 12 weeks after signing ICF.

w Check accountability and dispense Sponsor-provided MMF.

1 All Week 52 laboratory samples (blood and urine, including 24-hour UPCR sample) should be collected between Week 50 to Week 52, to allow assessment of PRR requirement for the second year participation.

2 IP infusion at Week 52 is only for subjects who are continuing in second year extension period.

Table 3 Study plan detailing the procedures during follow-up (for subjects not participating in the second year extension period)

Study Period	**Follow-Up Period**	
Days	**393±7 (8 weeks post final dose)**	**421±7 (12 weeks post final dose)**
Visit Number	**15 (Week 56)**	**16 (Week 60)**
PtGA		X
C-SSRS (V1-V16)	X	X
PHQ-8		X
Vital signs	X	X
Tuberculosis Questionnaire	X	X
Physical examination	X	X
Weight	X	X
Blood collection for:		
Serum chemistry/haematology	X	X
Lupus serology tests (C3, C4, anti-ds DNA)	X	X
Type I IFN signature with 21-gene assay (PD marker)		X
RNA transcript profiling		X
ADA	X	X
PK blood samples[a]	X	X
Serum and plasma biomarkers		X
QFT-G test (TB testing), if applicable[b]	X	

Study Period	**Follow-Up Period**	
Days	**393±7 (8 weeks post final dose)**	**421±7 (12 weeks post final dose)**
Visit Number	**15 (Week 56)**	**16 (Week 60)**
Urine collection for:		
Spot UPCR	X	X
Urinalysis (including microscopic examination)[c]	X	X
Local urinalysis (including microscopic examination) for selected sites[d]	X	X
Urinary biomarkers	X	X
Urine pregnancy tests (using dipstick)	X	X
eGFR using MDRD formula	X	X
SLEDAI-2K	X	X
PGA	X	X
AEs/SAEs/AESIs	X	X
SLEDAI-2K based Flare Assessment Instrument	X	X
Concomitant medications	X	X
Sponsor-provided MMF[e]	X	
Second renal biopsy (optional)[f]	X	
Local clinical evaluation	X	
Adjudication (optional)	X	
Tissue biomarker[g] (optional)	X	

ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; Anti-dsDNA=anti-double stranded deoxyribonucleic acid; C3=third component of complement; C4=fourth component of complement C-SSRS=Columbia-Suicide Severity Rating Scale; eGFR= Estimated Glomerular Filtration Rate; IFN=interferon; MDRD= Modification of Diet in Renal Disease; MMF=mycophenolate mofetil; PGA=Physician's Global Assessment; PtGA=patients global assessment; PHQ-8=Personal Health Questionnaire Depression Scale; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; TB=tuberculosis; UPCR=urine protein/creatinine ratio.

a Although there is no dosing at Weeks 56 and 60, PK sample will be collected.

b For subjects with a negative QFT-G at baseline and no symptoms of active TB: If the Week 52 QFT-G was indeterminate or positive, please refer to Section 5.2.9.3, Tuberculosis monitoring during the study.

c If the subject is menstruating, this must be specified in the eCRF.

d This will be in addition to the central laboratory urinalysis. This will include urine sediment examination for red blood cells (RBC), white blood cells (WBC) and cellular casts (WBC, RBC and mixed) and hematuria on a dipstick test.

e Dispense Sponsor-provided MMF and check accountability. At Week 60, only accountability is to be checked.

f For subjects who meet withdrawal criteria for worsening lupus nephritis at Week 24 or later and for subjects not achieving Complete Renal Response at Week 52 (if subject signs the separate ICF). Renal biopsy may be performed at the discretion of the Investigator based on clinical indication and local practice.

g Immunostaining, epigenetic and gene expression studies.

Table 4 Study plan detailing the procedures from Week 56 to Week 104 during the second year extension period

Study Period														
Days	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**	**-**
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**UN[a]**
Study Week	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104/DC[b]**	**-**
Visit Window	**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
PtGA	X	X	X	X	X	X	X	X	X	X	X	X	X	
Renal biopsy (optional)[c]	If clinically indicated for flare													
Local clinical evaluation	X													
Adjudication (optional)	X													
Tissue biomarker (optional)	X													
eGFR using MDRD formula	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination													X	
Focused physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Cushingoid features						X							X	
ECG													X	
Tuberculosis Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pap smear[d]													X	
Blood collection for:														
QFT-G test (TB testing)													X	

Study Period														
Days	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**	**-**
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**UN[a]**
Study Week	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104/DC[b]**	**-**
Visit Window	**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
QFT-G test (TB testing, only if indeterminate at previous visits)		X				X			X				X	
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology profile[e]					X						X			
Lipid profile[f]						X							X	
Lupus serology tests (C3, C4, anti-dsDNA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-dose ADA				X				X					X	
Pre-dose PK blood sample				X				X					X[g]	
Serum and Plasma biomarkers						X					X			
Type I IFN signature with 21-gene assay (PD marker)				X				X					X	
RNA transcript profiling				X				X					X	
Urine collection for:														
24-hour UPCR[h]			X			X			X				X	X
Spot UPCR	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period														
Days	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**	**-**
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**UN[a]**
Study Week	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104/DC[b]**	**-**
Visit Window	**±7 D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	
Pregnancy test in females of childbearing potential only[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including microscopic examination)[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local urinalysis (including microscopic examination) for selected sites[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLEDAI-2K	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLICC/ACR Damage Index (SDI)						X							X	
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Steroid tapering	X	X	X	X	X	X	X	X	X					
Extra-renal flare (SLEDAI-2K based Flare Assessment Instrument)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP administration[l]	X	X	X	X	X	X	X	X	X	X	X	X		
Sponsor-provided MMF[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	

ACR=American College of Rheumatology; ADA=anti-drug antibodies; AE=adverse event; AESI=adverse event of special interest; Anti-dsDNA=anti-double stranded deoxyribonucleic acid; C3=third component of complement; C4=fourth component of complement; dsDNA=double stranded deoxyribonucleic acid; DC=early discontinuation; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; IFN=interferon;

IP=investigational product; PGA=Physician's Global Assessment; QFT-G=QuantiFERON-TB Gold; MDRD=Modification of Diet in Renal Disease formula; MMF=mycophenolate mofetil; MPA=mycophenolic acid; LN=lupus nephritis; PD=pharmacodynamics; PtGA=patient global assessment; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR=Systemic Lupus International Collaborating Clinics/American College of Rheumatology; TB=tuberculosis; UN=unscheduled; UPCR=urine protein/creatinine ratio

Note: Study period: Transition from the main study to extension period.

a Not all assessments indicated for the Unscheduled Visit need to be performed. The assessments are to be performed at the discretion of the Investigator, as clinically indicated.

b Subjects with early discontinuation of IP should continue to attend visits according to the Study Plan. However a 24-hour UPCR sample should be collected within 4 weeks of IP discontinuation decision (unless the next scheduled visit is within 4 weeks of this decision, and includes this test already) and before the start of a new treatment for LN. If at any point after IP discontinuation is performed, the subject decides to discontinue from the study without completing all scheduled visits up to Week 104/Visit 29, a discontinuation visit needs to be performed as soon as possible after the study discontinuation decision is made.

c Renal biopsy may be performed at the discretion of the investigator based on clinical indication and local practice for subjects who meet withdrawal criteria for worsening lupus nephritis at Week 60 or later and for subjects not achieving Complete Renal Response at Week 52 (if subject signs the separate ICF).

d Female subjects with an intact cervix should have a Pap smear between Week 100 and Week 104 to ensure that there is no evidence of new cervical dysplasia.

e Immunology profile includes quantitative immunoglobulins (IgA, IgG, IgM), ANA, and anti-RNP, anti-Smith, anti-SSA (Ro), anti-SSB (La), anti-cardiolipin antibodies.

f Subjects will be required to fast for at least 8 hours prior to assessment of lipid profile. If the subject has not fasted, he/she should fast before the next visit, and the test can be done at that visit.

g PK sample for Week 104: Although there is no dosing at Visit 29 (Week 104), pre-dose PK sample will be collected.

h The collection of the 24-hour UPCR sample should start preferably in the morning of the day before the scheduled visit and end in the morning of the day of the visit. The urine collection can be done within 1 day prior to the visit if the urine sample can be kept refrigerated until the day of the visit. If refrigeration is not possible, subjects should select the coolest possible place to store their urine sample, eg, a cool room or use a portable cooler with ice/ice pack. Subjects who prematurely discontinue IP should have the 24-hour UPCR measurement within 4 weeks of the decision to discontinue IP and before the start of a new treatment for LN.

i This will be done locally from Visit 17 onwards.

j If the subject is menstruating, this must be specified in the eCRF.

k This will be in addition to the central laboratory urinalysis. This will include urine sediment examination for red blood cells (RBC), white blood cells (WBC) and cellular casts (WBC, RBC and mixed) and hematuria on a dipstick test.

l First dose in extension period must be between Weeks 52 (+14 days) and 60.

m Check accountability and dispense Sponsor-provided MMF.

Table 5 Study plan detailing the procedures during follow-up (second year extension period)

Study Period	**Follow-Up Period**	
Days	**756±7 (8 weeks post final dose)**	**784±7 (12 weeks post final dose)**
Visit Number	**30 (Week 108)**	**31 (Week 112)**
PtGA		X
Vital signs	X	X
Tuberculosis Questionnaire	X	X
Physical examination	X	X
Weight	X	X
Blood collection for:		
Serum chemistry/haematology	X	X
Lupus serology tests (C3, C4, anti-ds DNA)	X	X
Type I IFN signature with 21-gene assay (PD marker)	X	X
RNA transcript profiling	X	X
ADA	X	X
PK blood samples[a]	X	X
Serum and plasma biomarkers		X
QFT-G test (TB testing), if applicable[b]	X	
Urine collection for:		
Spot UPCR	X	X
Urinalysis (including microscopic examination)[c]	X	X

Study Period	**Follow-Up Period**	
Days	**756±7 (8 weeks post final dose)**	**784±7 (12 weeks post final dose)**
Visit Number	**30 (Week 108)**	**31 (Week 112)**
Local urinalysis (including microscopic examination) for selected sites[d]	X	X
Urine pregnancy tests (using dipstick)	X	X
eGFR using MDRD formula	X	X
SLEDAI-2K	X	X
PGA	X	X
AEs/SAEs/AESIs	X	X
SLEDAI-2K based Flare Assessment Instrument	X	X
Concomitant medications	X	X
Sponsor-provided MMF[e]	X	
Renal biopsy (optional)[f]	X	
Local clinical evaluation	X	
Adjudication (optional)	X	
Tissue biomarker[g] (optional)	X	

ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; Anti-dsDNA=anti-double stranded deoxyribonucleic acid; C3=third component of complement; C4=fourth component of complement; eGFR= Estimated Glomerular Filtration Rate; IFN=interferon; MDRD= Modification of Diet in Renal Disease; MMF=mycophenolate mofetil; PGA=Physician's Global Assessment; PtGA=patients global assessment; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; TB=tuberculosis; UPCR=urine protein/creatinine ratio.

a Although there is no dosing at Weeks 108 and 112, PK sample will be collected.

b For subjects with a negative QFT-G at baseline and no symptoms of active TB: If the Week 104 QFT-G was indeterminate or positive, please refer to Section 5.2.9.3, Tuberculosis monitoring during the study.

c If the subject is menstruating, this must be specified in the eCRF.

d This will be in addition to the central laboratory urinalysis. This will include urine sediment examination for red blood cells (RBC), white blood cells (WBC), and cellular casts (WBC, RBC and mixed) and hematuria on a dipstick test.
e Dispense Sponsor-provided MMF and check accountability. At Week 112, only accountability is to be checked.
f For subjects who meet withdrawal criteria for worsening lupus nephritis at Week 60 or later and for subjects not achieving Complete Renal Response at Week 104 (if subject signs the separate ICF). Renal biopsy may be performed at the discretion of the Investigator based on clinical indication and local practice.
g Immunostaining, epigenetic and gene expression studies.

4.1 Screening/Enrolment period

At screening, subjects are assessed to ensure that they meet eligibility criteria. Once the subject signs the ICF, they are considered enrolled in the study. Subjects who do not meet these criteria must not be randomised into the study. These subjects will be considered as screen failures (See Section 3.10).

Screening procedures will be performed according to the Screening Study Plan (Table 2), from Day 30 to Day -1. Screening visit may be conducted as multiple visits, S1, S2, Sx, where laboratory evaluations can be completed initially.

Chest X-rays, renal biopsy, and Pap smears may be completed any time during the screening period as long as all results have been reviewed by the Investigator prior to randomisation.

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

On rare occasion an extension of the 30 day screening window may be allowed if the re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed. Before the Week 0 (Day 1) visit, a notification from the study Sponsor/Designee Medical Monitor should be obtained, confirming that subject meets LN diagnosis related eligibility criteria. The details of eligibility confirmation process will be documented separately for the site (Site Manual), and for the study team (Eligibility Process).

4.1.1 Re-screening subjects who screen fail

If a subject fails screening for reason(s) which, in the opinion of the Investigator, may change to make the subject eligible, the subject may be re-screened one time. In this case, the subject will re-sign the informed consent document and all screening procedures will be performed except those assessments which may be still within the specified periods (eg, chest X-ray, renal biopsy, TB test). If a subject does not meet eligibility criteria on the basis of a laboratory value, then the laboratory parameter may be repeated once within the screening period; this will be re-testing so that re-screening is not required. If the subject fails screening twice, they may not undergo further screening for this study except on a case by case basis, after discussion and approval from the Sponsor/Designee Medical Monitor.

4.1.2 Medical history

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

4.1.3 SLE and LN medication history

All prescription medications the subject has ever taken for SLE and LN should be documented in the subject's file (except for only minor dose adjustments if these were done >3 months prior to the ICF signature date), including prior use of cyclophosphamide, MMF, oral and parenteral corticosteroids; if these were discontinued, then reasons for discontinuation must be included. Any medications ongoing at the time of informed consent or received following signing the ICF are considered concomitant medications. Any non-prescription medications, eg, naturopathic or ayurvedic remedies ever used for SLE or for any other purpose should be documented, as well as continuing use of any non-prescription remedies not excluded from use during the study period.

4.2 Treatment period

Procedures during the treatment period will be performed according to the Treatment Period Study Plan (Table 2 and Table 4), from Week 0 (Day 1) to Week 104. The patient-reported outcome assessments should be completed by the subject prior to all other evaluations, and prior to the infusion, as disease assessments/clinical evaluations may confound the results.

On Day 1, in addition to the eligibility confirmation by study Medical Monitor/Designee, the Principal Investigator must ensure that the subject still meets eligibility criteria, including Day 1 assessments according to the Treatment Period Study Plan (Table 2).

Subjects confirmed to be eligible will be randomised.

Subjects will have scheduled visits at 4-week intervals to complete protocol-specified assessments and IP administration according to the Treatment Period Study Plan (Table 2).

The primary endpoint will be assessed at Week 52. For subjects who prematurely discontinue IP and are not willing to continue to participate in the study refer to Section 3.9.

The SLE Data Medical Review Team (Section 9.2.4) will perform an ongoing review of all SLE and LN data in conjunction with the relevant AE, concomitant medications and central laboratory data.

For subjects who meet withdrawal criteria for worsening LN at Week 24 or later and for subjects not achieving CRR at Week 52, a second renal biopsy may be performed at the discretion of the Principal Investigator based on clinical indication and local practice. A separate consent is required for this second biopsy.

4.2.1 Week 52 visit

Study objectives will be assessed at Visit 14 (Week 52). A 24-hour UPCR must be performed to assess the primary endpoint. Investigational sites should contact subjects prior to this visit in order to ensure the subject is compliant with the protocol to support the study objectives. Laboratory samples, including the 24-hour UPCR may be collected within 14 days prior to the

scheduled Visit 14(Week 50 - Week 52- see Table 2 footnote b), so that results are available for determining if subjects are eligible for continued IP dosing in the second year of the study.

4.2.1.1 Assessment criteria for participation in the second year extension period (Week 52)

The 24-hour UPCR sample collected between Week 50 to Week 52 for the Week 52 response assessment will be used to assess criteria for participation in the second year extension period. The eGFR measured between Week 50 and Week 52 will be used to assess eligibility for participation in the second year extension period.

4.2.1.2 Initiation of dosing in the second year extension period (Week 52 to Week 60)

All efficacy and safety assessments for Week 52 must be completed prior to initiation of dosing in the second year extension period. The first dose in the second year extension period must be administered between Week 52 (+14 days) and Week 60. Prior to administering the first dose in the second year extension period, the Principal Investigator must confirm that all Week 52 safety assessments (including the ECG) are performed and that subject does not meet any withdrawal criteria. The Week 52 QFT-G test results must be available prior to Week 56 and results of the Pap smear must be found to meet eligibility requirements as described in Appendix K and available by Week 60 or IP administration will be discontinued.

4.2.1.3 Week 104 visit

The last dose of IP will be administered at Week 100. At Week 104, a 24-hour UPCR sample must be collected. Investigational sites should contact subjects prior to this visit in order to ensure the subject is compliant with the study procedure to support the study objectives. For subjects who discontinue IP between Week 52 and Week 100, and are not willing to continue to participate in the study refer to Section 3.11.

4.2.2 Follow-up visits after premature discontinuation of investigational product

Subjects who agree to continue scheduled visits until Week 52 (if IP discontinued prior to Week 52) or Week 104 (if IP discontinued after Week 52):

Subjects who prematurely discontinue IP (see Section 3.9) should have a 24-hour UPCR measurement within 4 weeks of the decision to discontinue IP and before the start of a new treatment for LN.

Subjects who discontinue IP will be asked to return for all regular clinic visits. All study assessments will be performed if possible; however, at a minimum, the following assessments should be completed:

- Lupus Serology tests (anti-dsDNA antibodies, C3, C4)
- PGA (Physician's Global Assessment)

- 24-hour urine for protein, creatinine and spot UPCR

The following safety assessments should also be completed:

- Serum chemistry, haematology, urinalysis
- Vital signs
- Physical examination, weight
- Adverse events including AESIs
- TB Questionnaire
- Concomitant medications

Subjects who are unwilling to continue to Week 52 or Week 104:

If during the 52 week double-blind treatment period, the subject is unwilling to continue through Week 52, he/she should complete Week 52 visit and be followed for 12 weeks after the last administration of IP by completing the Follow-up Visits, unless consent is withdrawn. If during the second year extension period, the subject is unwilling to continue through Week 104, he/she should complete Week 104 visit and be followed for 12 weeks after the last administration of IP by completing the Follow-up Visits, unless consent is withdrawn.

If the subject does not agree to return for any clinic visits and perform the laboratory testing requirements of these visits, he/she will be asked if he/she can be followed on a monthly basis via telephone calls for 12 weeks after last dose of IP administration. At these calls, he/she will be asked about AEs/SAEs, lupus symptoms, and lupus medications. Steroid bursts will also be captured.

Subjects who withdraw consent:

If the subject indicates his/her intention to withdraw consent, attempts should be made to complete the Week 52/discontinuation or Week 104/discontinuation visit as applicable before the consent is withdrawn. However, no study procedures or data collection can occur after the subject withdraws consent.

Adverse events will be followed up per Section 6.5.2.

4.3 Unscheduled visit

There may be times a subject needs to have an unscheduled visit. Potential assessments for such a visit are listed on the Treatment Period Study Plan (Table 2 and Table 4). The Investigator should determine and note the reason for the unscheduled visit and the

assessments to be completed based on the reason for the unscheduled visit. Concomitant medications and AEs should be completed whenever a subject has an unscheduled visit.

4.4 Follow-up period

Procedures will be performed according to the Follow-up Period Study Plan (Table 3 and Table 5).

Subjects who complete the double-blind treatment period (Week 52) but do not continue with IP treatment will have follow-up visits at Week 56 and Week 60. Subjects who complete the second year extension will have follow-up visits at Week 108 and Week 112. Subjects who discontinue the IP before Week 52 and are not continuing on the study schedule should complete the Week 52 procedures. Subjects who discontinue the IP between Week 52 and Week 104 and are not continuing on the study schedule should complete Week 104 procedures. All other early discontinuation subjects should be followed until Week 52 or Week 104 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 52 or Week 104) (see Section 3.9).

5. STUDY ASSESSMENTS

The Investigator will ensure that all study assessment data are recorded in the eCRF and also ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

The Site Manual will include a description of specific procedures. All the assessments and laboratory tests (unless otherwise specified) will be done prior to administration of IP.

5.1 Efficacy assessments

Efficacy measurements will be made at the times indicated in the Study Plan (for assessments to be performed at Screening and treatment period, see Table 2 and Table 4, respectively, and for those at Follow-up, see Table 3 and Table 5).

The efficacy assessments based on laboratory tests include:

- Urine protein to creatinine ratio: This consists of:
  - **24-hour UPCR**: The 24-hour UPCR will be determined on a 24-hour UPCR sample.

    This will be performed twice during the screening period, Weeks 0, 12, 24, 36, 52, 64, 76, 88, and 104 and at Early Discontinuation visit.

During the screening period two samples will be required:

- Screening sample at the start of the screening process, after the ICF is signed and
- Stratification sample within 14 days prior to the expected day of randomisation. Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days.

Starting from Week 0, the 24-hour UPCR sample must always be collected before the administration of IP. The sample collected at Week 0 (Day 1) will be the baseline sample which must be provided on Day 1 prior to randomisation and administration of first dose of IP.

The collection of the 24-hour UPCR sample should start preferably in the morning of the day before the scheduled visit and end in the morning of the day of the visit. The urine collection can be done within 1 day prior to the visit if the urine sample can be kept refrigerated until the day of the visit. The sample should be kept refrigerated whenever possible. If refrigeration is not possible, subjects should select the coolest possible place to store their urine sample, eg, a cool room or use a portable cooler with ice/ice pack.

In case subject has a medical reason which would impact the validity of the assessment of proteinuria (eg, urinary tract infection, heavy menstruation), or the sample was not collected appropriately, the collection of the sample may be done/repeated as follows:

- Screening samples: As soon as possible before the next scheduled sampling is due
- Week 0: Prior to IP administration (which may require the Visit 1 to be postponed)
- Weeks 12, 24, 36, 52, 64, 76, 88, and 104: Within 2 weeks of the actual date of visit when the collection was due and if applicable, before any change in SOC or concomitant medications is made (Week 52 sample must be collected before second year extension period dosing)

The 24-hour UPCR will be used only for the primary and secondary endpoints, the PRR, aCRR, graded CRR, and graded aCRR criteria at Week 52 and Week 104, the 24-hour UPCR and CRR at Week 104 and to determine withdrawal criteria at Weeks 12, 24 and 52.

- **Spot UPCR**: Spot UPCR will be performed at all visits and will be used for the calculation of SLEDAI-2K and for the CRR and PRR classification, when evaluating time to achieve renal response modified to include OCS tapering requirement as well as for the CRR and PRR

classification for flare assessments. All assessments except as noted above for the 24-hour UPCR will be based on the spot UPCR. The change in proteinuria will also be assessed based on spot UPCR at Weeks 24, 52 and 104. The spot UPCR sample should be taken prior to administration of IP, on a clean catch urine sampling. The same urine sample can be used for spot UPCR and sediment analysis.

- Urine sediment examination will be performed at all visits: Selected sites will perform local urinalysis including a microscopic examination. The microscopic examination must be assessed by trained personnel, and can be assessed by the site or a local laboratory. This data will be used for exploratory analyses. This will be in addition to the central laboratory urinalysis.

- Estimated glomerular filtration rate based on the MDRD formula calculated by the central laboratory. Refer to the Laboratory Manual for specifics.

The efficacy assessments based on clinical evaluation include SLEDAI-2K (Section 5.1.2, Appendix F), PGA (Section 5.1.4), OCS reduction (Section 5.1.5), and SDI (Section 5.1.3). The assessments for quality of life and patient-reported outcomes are summarised in Section 5.3.1.

5.1.1 Renal biopsy

Renal biopsy is required within 12 weeks prior to screening or during the screening period for inclusion in the study and must meet inclusion criterion number 6 and not meet exclusion criterion number 10. (Note: If renal biopsy is performed during the screening period, adequate time should be allowed before the next scheduled urine sample collection).

Renal biopsy adjudication

Biopsies will be evaluated locally and the local classification will be used to confirm the eligibility criteria. Screening biopsy slides will then be submitted for adjudication by an external adjudication committee consisting of nephropathologists with special expertise in LN. The biopsies will be assessed for all elements of the ISN/RPS classification, the NIH activity, chronicity indices, and the presence of concomitant conditions. The submission of screening biopsies for adjudication is required to participate in the study. The process for adjudication will be defined in a separate document (Renal Biopsy Adjudication Charter). Data obtained during the adjudication will be used for exploratory and sensitivity analyses.

A second renal biopsy is recommended for subjects who meet withdrawal criteria for worsening LN at Week 24 or later and for subjects not achieving CRR at Week 52. This biopsy will be performed at the discretion of the Investigator based on clinical indication and local practice. A separate consent is required for this second biopsy. Second biopsies will be

read locally first and, if the subject agrees, will then be submitted for adjudication to the external adjudication committee. Not agreeing to the review of the second biopsy by the adjudication group will not have any impact on the subject's continuation in the study. If a clinically indicated renal biopsy is performed during the second year extension period, the subject's consent will be required prior to the biopsy slides being submitted for adjudication.

5.1.2 Systemic Lupus Erythematosus Disease Activity Index 2000

The SLEDAI-2K index (see Appendix F) consists of a list of organ manifestations, each with a definition. A certified Investigator or designated physician will complete the SLEDAI 2K assessment and decide whether each manifestation is "present" or "absent" in the last 30 days. The assessment also includes the collection of whole blood for analysis of C3, and C4 complement levels, and anti-dsDNA antibodies.

The proteinuria descriptor should be scored using the spot UPCR.

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

Any missing SLEDAI-2K laboratory assessments should be repeated.

5.1.3 Systemic Lupus International Collaborating Clinics/American College Rheumatology damage index

The SDI (Appendix N) has been developed to assess irreversible damage in SLE subjects independently of its cause (ie, included damage due to SLE activity, SLE-related scarring, therapy, comorbidities) but occurring after disease onset. Damage, ie, irreversible impairment since onset of SLE, is usually defined as a clinical feature that has to be continuously present for at least 6 months to score. In addition some irreversible events such as myocardial infarction or a cerebrovascular accident score as damage on their occurrence. Briefly, damage is defined for 12 organ systems; peripheral vascular, ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, endocrine (diabetes), gonadal, and malignancies. Damage over time can be stable or increase, theoretically to a maximum of 47 points (Schwartz et al, 2009).

5.1.4 Physician's Global Assessment

A trained and certified Investigator will complete the PGA. The PGA represents the physician's overall assessment of average disease severity on a Visual Analogue Scale (VAS)

scale with 0 (none) to 3 (severe) disease activity over the last 30 days. The PGA for a given subject should be completed by the same physician whenever possible.

PGA may be completed after the visit, to allow for laboratory results to be received, as long as this is done prior to the next scheduled visit. Therefore, the date of the associated scheduled visit (Week 0 etc.) will be used to determine baseline (and subsequent visits), and not the actual date of the assessment.

The PGA is a modification of the classic analogue scale in that it is anchored with numbers from 0 to 3 demarcating mild, moderate and severe disease. The number 3 indicates severe disease and is at the very end of the scale. This refers to the most severe possible disease, and does not reflect the most severe ever seen in a particular subject but the most severe disease ever seen in all SLE subjects. Therefore, the line made by the physician along this scale should virtually never get to this edge. The mark made by the physician must be a single line, nearly perpendicular to the axis of the VAS line and not an "X". Any disease rated greater than 2.5 is very severe. The range of moderate disease covers about 1.5 to 2.4. Mild disease falls below 1.5. Clearly, this is a bit like a logarithmic scale with greater distances or demarcations possible among more mild-moderate symptoms. This needs to be kept in mind when scoring the instrument.

When scoring the PGA, always look back at the score from the previous protocol visit and move the mark relative to that previous visit. This is a global assessment, factoring in all aspects of the subject's lupus disease activity. It should not reflect non-lupus medical conditions.

These instructions are quite discrete from those given for other analogue (Likert) scales and are specific for the scoring of the PGA.

5.1.5 Oral corticosteroid reduction

Please refer to Section 7.7.3.2 for all information regarding steroid tapering.

5.2 Safety assessments

Key safety assessments are AEs, AESIs, vital signs, physical examination, safety laboratory tests, ECGs, C-SSRS, PHQ-8, and SLEDAI-2K based Flare Assessment Instrument (Appendix M). Safety assessments will be made at the times indicated in the Study Plan (see Table 2, Table 3, Table 4, and Table 5).

5.2.1 Adverse events

Adverse events, SAEs, and AESIs are defined in Sections 6.1, 6.2, and 6.4, respectively.

Recording of AEs is described in Section 6.5 and reporting of SAEs in Section 6.6.

5.2.2 Vital signs

Vital signs (temperature, blood pressure [BP], pulse rate, and respiratory rate) will be obtained at each visit. Specific information on vital signs surrounding the infusion is included in Section 7.2.4 (Subject Monitoring/Procedures During and After Infusions). Temperature should be measured by the same methodology (eg, oral, tympanic) for a subject throughout the study.

5.2.3 Physical examination

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

5.2.3.1 Complete physical examination

A complete physical examination will be performed at the visits specified in the Study Plan (Table 2, Table 3, Table 4, and Table 5), and will include an assessment of the following: head, eyes, ears, nose and throat, lungs heart, abdomen, joints, muscles and soft tissues, neurologic system, skin, and lymph nodes.

5.2.3.2 Focused physical examination

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

5.2.3.3 Pap smear

Most cases of cervical cancer appear to be related to infection with human papilloma virus. Because of the potential for viral reactivation due to blockade of the interferon pathway, cervical dysplasia will be assessed in this study, although to date there has been no signal in the anifrolumab studies.

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

Female subjects with an intact cervix must have a Pap smear repeated between Week 48 and Week 52 and Week 100 and Week 104 to ensure that there is no evidence of new cervical dysplasia. If a Pap smear was performed between Week 48 and Week 52 and is not normal but

shows no evidence of malignancy (eg, CIN III, CIS, or AIS), it should be repeated as per the subject's gynaecologist's recommendations. 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.

5.2.3.4 Assessment of Cushingoid features

Subjects will be assessed for Cushingoid features at the visits specified in the Treatment Period Study Plan (Table 2 and Table 4). Features, such as moon face, buffalo hump, purple or violaceous striae, central obesity, hirsutism, acne, easy bruising, and fragile skin will be captured separately within the study eCRF to evaluate whether resolution of same can occur overtime with OCS reduction.

5.2.4 Electrocardiogram

A 12-lead ECG tracing will be performed locally at the visits specified in the Study Plan (Table 2 and Table 4). The Investigator or qualified designee must review the ECG for clinically significant changes.

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, lipids (including high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides [see Section 5.2.10.1]) will be measured during the study. Current and previous concomitant medications received for cardiovascular indications and other risk factors for cardiovascular disease such as smoking, hypertension, and diabetes should be collected and recorded. Assessment of cardiovascular risk will be completed as indicated in the Study Plan (Table 2 and Table 4).

5.2.6 Columbia-Suicide Severity Rating Scale

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

The C-SSRS will be administered by a trained rater. The trained rater will record the clinical observation on the scale, which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS. If a subject indicates having a rating of type 4 or 5 suicidal ideation on the C-SSRS suicidal ideation scale at any time since the previous visit when the C-SSRS was administered or indicates having had any suicidal behaviour since the previous visit, the subject should be referred to a mental health professional immediately. If

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

5.2.7 Personal Health Questionnaire Depression Scale–8

The PHQ-8 consists of eight of the nine criteria on which the DSM-IV diagnosis of depressive disorders is based (American Psychiatric Association, 1994). It assesses symptoms of depression over the last 2 weeks. The PHQ-8 is completed by the subject and scored by the investigator at visits specified in the Treatment and Follow-up Study Plans (Table 2 and Table 3). In addition to the 8 questions on depression, there is also a non-scored question to assess how the depressive symptoms affect the subject's level of functioning.

5.2.8 SLEDAI-2K based Flare Assessment Instrument

SLEDAI-2K based Flare Assessment Instrument is modelled after the modified SELENA SLEDAI Flare Assessment Instrument specifically for this study to collect extra-renal flare data.

Extra-renal flares will be assessed over the previous 30 days for the following components:

- Flare assessment based on total score changes of non-renal components of the SLEDAI-2K
- New/worse SLE manifestations (including items that are not included in the SLEDAI-2K instrument)
- Hospitalisation (including hospitalisations due to LN)
- PGA

Please refer to Appendix M for details. Flare will be scored in comparison to the previous protocol visit (ie, over the past 30 days) and will only include findings which, in the opinion of the investigator, are due SLE disease activity within that timeframe.

This assessment should be completed by the investigator or delegated/qualified physician. Training and certification of Investigators and designated site personnel who will be completing this assessment will be conducted. The method of training and training documentation is as described in Section 9.1.1 for the efficacy assessments.

5.2.9 Tuberculosis screening and monitoring

5.2.9.1 Screening evaluation

A blood test for TB will be done at screening using QFT-G. This is an interferon-gamma release assay (IGRAs) test. Evaluation of all subjects by QFT-G test (to be performed by the central clinical laboratory) and chest X-rays must be completed prior to randomisation. Refer

Section 3.1, inclusion criteria 16 (d) (iii) and (e). If an adequate (posterior-anterior or anterior-posterior and lateral posterior-anterior, unless limited by local practice) chest X-ray has been performed within 12 weeks prior to signing the ICF, it does not need to be repeated at the screening visit.

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

Given the population to be enrolled in the LN study, false negative tests are possible, so a chest X-ray, posterior-anterior or posterior-anterior and lateral views is a relevant technique and warranted technique (unless limited by local practice) for detecting active pulmonary disease and minimising potential risk to study subjects.

5.2.9.2 Tuberculosis results from screening evaluations

- If the screening QFT-G test is negative and there is no known history of recent exposure to individuals with active TB, and chest radiograph shows no evidence of active TB, the subject may be randomised without prophylaxis.

- If the screening QFT-G test is **newly positive*** and the chest radiograph shows no evidence of active TB, and the subject has no symptoms or medical history consistent with active TB, treatment for latent TB must be initiated prior to the first IP administration and the subject must commit to completing the full duration of prophylaxis, which may mean completing prophylaxis during the study. Subjects may be re-screened if necessary to allow for local guidelines on latent TB treatment initiation.

  *Note: Newly positive can be a positive result after a previous indeterminate or negative result.

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

  – Previous or current active TB infection was ruled out **and**

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

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

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

  - If the QFT-G test result remains indeterminate or becomes negative and

  - The chest radiograph shows no evidence of active TB and

  - There are no signs or symptoms of active TB and

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

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

Additionally, an expert specialising in TB may be consulted prior to randomisation, if deemed necessary in the opinion of the Investigator, after discussion with the Sponsor/Designee Medical Monitor. If the subject is randomised, additional QFT-G testing will be performed according to the Study Plan (Table 2, Table 3, Table 4, and Table 5).

5.2.9.3 Tuberculosis monitoring during the study

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

- Positive QFT-G test result, confirm positive QFT-G on another blood sample and then the subject should be referred to a TB specialist. If a TB specialist is not available, the local country guidelines should be followed for further diagnostic work up and anti-TB treatment regimens. If no local guidelines exist for immunocompromised individuals, then CDC guidelines may be followed. This should also be reported as an AESI. Once latent TB is confirmed, treatment must be instituted immediately and no IP may be administered until treatment of latent TB has begun

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

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

End of treatment testing for subjects with negative QFT-G at baseline and no symptoms of active TB.

For subjects not continuing in second year extension period:

- Week 52 QFT-G negative: no further testing.
- Week 52 QFT-G indeterminate: repeat at Week 56. If negative no further testing, however if indeterminate repeat again at last visit Week 60.
- QFT-G positive at Week 52 or later. Confirm positive QFT-G on another blood sample. If confirmed follow recommendations for positive QFT-G results during study. If repeat test is indeterminate or negative follow recommendation for indeterminate results above. Consider referral to TB specialist.

For subjects continuing in second year extension period:

- Week 104 QFT-G negative: no further testing.
- Week 104 QFT-G indeterminate: repeat at Week 108. If negative no further testing, however if indeterminate repeat again at last visit Week 112.
- QFT-G positive at Week 104 or later. Confirm positive QFT-G on another blood sample. If confirmed follow recommendations for positive QFT-G results during study. If repeat test is indeterminate or negative follow recommendation for indeterminate results above. Consider referral to TB specialist.

Tuberculosis questionnaire

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

Investigators should be aware that TB in immunocompromised subjects may present as disseminated disease or with extra-pulmonary features and should be referred for appropriate treatment.

5.2.10 Safety laboratory tests

The following are the laboratory-based safety assessments:

- Screening laboratory tests
- Haematology
- Serum chemistry
- Lipid profile
- Urine analysis
- Pregnancy tests

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.

All clinical laboratory tests will be performed in a central clinical laboratory at the times indicated in the Study Plan (Table 2, Table 3, Table 4, and Table 5).

A serum pregnancy test (or serum FSH in post-menopausal females with menses absent for ≥1 year) will be performed at screening at the central laboratory. If the result of the serum β hCG test is borderline or thought to be false positive the test can be repeated during the screening. The subject can continue if the repeat test is negative. At every visit after screening, urine pregnancy tests will be performed at the site using a dipstick. During the treatment period, urine pregnancy tests should be performed at each visit before administering the IP and Sponsor-provided MMF. 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 or efficacy laboratory tests, even if the subject has received the IP.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.5.

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

The laboratory variables that will be measured are summarised in Table 6.

Table 6 Clinical laboratory tests

Screening only test
Haemoglobin A1c (HbA1c; diabetic subjects only)
Peripheral blood B lymphocyte count (CD19+ cells)-Only for subjects who received rituximab or other B cell-depleting therapy >26 weeks prior to signing ICF (see exclusion criterion No. 17)
HbsAg
HBcAb (reflex DNA testing if isolated HBcAb positive)
Hepatitis C antibody
HIV test
TB screening
QFT-G test (repeat test if result is indeterminate, as per Table 2 and Table 4)
Coagulation panel
Activated partial thromboplastin time, Prothrombin Time, INR
Haematology
WBC count with differential
RBC count
Haematocrit
Haemoglobin
Platelet count
MCV

MCHC

Serum chemistry

Calcium

Chloride

Potassium

Sodium

Bicarbonate

AST*

ALT*

ALP*

GGT

BUN

Creatinine

eGFR (calculated)

Total bilirubin* (reflexively fractionated if elevated)

Glucose

Albumin

CK

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

Immunology

Immunology profile: ANA, anti-RNP antibody, anti-Smith antibody, anti-Sjogren's Syndrome A [SSA] and anti-Sjogren's Syndrome B [SSB] antibodies; anti-cardiolipin antibodies (IgA, IgM and IgG), and quantitative total immunoglobulin testing (IgA, IgG, IgM)

Lupus serology tests (C3 and C4 complement, anti-ds DNA)

Urinalysis

Colour

Clarity

Specific gravity

pH

Protein

Glucose

Ketones

Blood

Bilirubin
Microscopy including WBC/HPF, RBC/HPF, cellular casts
Spot urine creatinine and protein, urine protein/creatinine ratio
24-hour urine creatinine and protein, UPCR
Pregnancy test
Serum β-hCG (at screening only)
Urine β-hCG (at every visit after screening, using a dipstick)
Serum FSH (at screening only) in post-menopausal females with menses absent for ≥1 year

ALP=alkaline phosphatase; ALT=alanine transaminase; ANA=antinuclear antibody; anti-RNP=anti-ribonucleoprotein; AST=aspartate transaminase; β-hCG=β-human chorionic gonadotropin; BUN=blood urea nitrogen; C3=third component of complement; C4=fourth component of complement; CK=creatine kinase; DNA=deoxyribonucleic acid; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HbA1c=glycosylated haemoglobin; HBcAb=hepatitis B core antibody; HbsAg=Hepatitis B surface antigen; HPF=high power field; HIV=human immunodeficiency virus; INR=International normalised ratio; MCHC=mean corpuscular haemoglobin concentration; MCV=mean corpuscular volume; QFT-G=QuantiFERON-TB Gold; RBC=red blood cell; WBC=white blood cell
Note: If central laboratory results are not available for SLEDAI-2K associated tests, samples should be redrawn one time within 14 days of the SLEDAI assessment date.
A reflex test is a test that is must be performed based on the results of a prior test (pre-set criteria).

5.2.10.1 Laboratory assessments for cardiovascular risk assessments

Subjects will have a fasting lipid profile (cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) completed at times indicated in the Study Plan (Table 2 and Table 4). Subjects will be required to fast for at least 8 hours prior to this assessment (see Section 3.8).

5.2.11 Immunological tests

5.2.11.1 Immunology profile

Subjects will have tests to determine immunology profile (ANA, anti-Smith, anti-RNP, anti-SSA, anti-SSB, and anti-cardiolipin antibodies), and quantitative immunoglobulins (IgA, IgG, IgM) completed at times indicated in the Study Plan (Table 2 and Table 4).

5.2.11.2 Lupus serology

Anti-dsDNA antibodies and complement C3 and C4 levels are commonly used as markers of SLE and of LN disease activity and comprise the serologic domain of the SLEDAI-2K. Subjects will have these tests performed at the times indicated in the Study Plan (Table 2, Table 3, Table 4, and Table 5).

5.2.11.3 Anti-drug antibodies

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

The pre-dose serum samples to measure the presence of ADA will be collected according to the Study Plan (Table 2, Table 3, Table 4, and Table 5). The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

5.2.11.4 Neutralising antibodies

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

5.2.12 Mycophenolic acid levels

The blood samples will be collected to explore trough MPA concentration in LN subjects. Relationship of MPA concentrations and AEs possibly related to MPA may also be explored. Serum samples for the determination of trough MPA levels will be collected at the times indicated in the Study Plan (Table 2). MPA concentrations will be analysed by a central laboratory on behalf of the Sponsor, using a validated bioanalytical method. The dose of MMF should be withheld until samples for the MPA blood draw test has been collected on that visit day.

5.3 Other assessments

5.3.1 Quality of life/pharmacoeconomic assessments

5.3.1.1 Patient Global Assessment

Subjects will be asked to complete the PtGA at the times indicated in the Study Plan (Table 2, Table 3, Table 4, and Table 5). The PtGA is a single-item question that takes into account "all the ways that your illness affects how you are doing" over the last week. Responses range from 0 (very well) to 100 (very poor) on a 100 mm VAS. The subject must complete the PtGA (see Appendix T).

5.4 Pharmacokinetics

5.4.1 Collection of samples

For the PK analysis it is important that the date, start and stop time for the IV infusion, and the sample collection time are recorded. Instructions for sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual provided to the centres. Serum will be collected according to the Study Plan (Table 2, Table 3, Table 4, and Table 5). Post-dose samples should be collected 15 minutes ± 5 minutes after completion of IP infusion. It must be noted that the duration of the IV infusion for administrating the IP will be no less than

60 minutes for the first 3 doses (Visits 1, 2 and 3) and no less than 30 minutes, starting with Visit 4.

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

5.4.2 Determination of drug concentration

Samples for determination of drug concentration in serum will be analysed by PPD on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.3 Storage and destruction of pharmacokinetic samples

Samples may be stored for up to 15 years or as per local regulation from the date of the last subject last visit (LSLV), after which they will be destroyed.

5.5 Pharmacodynamics

Type I IFN-inducible signature in whole blood, as assessed by a 21-gene assay, will be used as a PD marker to follow the biologic effect of anifrolumab on its target throughout the study.

5.5.1 Collection of samples

Whole blood will be collected for mRNA isolation at the visits indicated in the Study Plan (Table 2, Table 3, Table 4, and Table 5) in order to evaluate the mRNA expression levels of 21 Type I IFN-inducible genes. The remaining mRNA from the PD sample may be utilised for additional biomarker work to further characterise the effects of anifrolumab on its target. For detailed method descriptions refer the reader to the Laboratory Manual.

5.5.2 Storage, re-use and destruction of pharmacodynamic samples

Samples collected for PD analysis may be stored for a maximum of 15 years from the date of the LSLV, or as per the local regulations, after which they will be destroyed.

5.6 Genetics

There will be no mandatory genetic samples collection for this study.

5.6.1 Pharmacogenomics (optional)

DNA from blood for genetic studies will be collected at baseline. DNA from blood for epigenetic studies will be collected at Week 0, Week 24 and Week 52. All genetic analyses will be limited to understanding LN or the efficacy and toxicity of anifrolumab and SOC. Analyses will include but may not be limited to single nucleotide polymorphism profiling, copy number variation analysis and epigenetic profiling by microarray.

The collection of blood for pharmacogenomic analyses is optional. A separate ICF is required for these samples. The results from these investigations will not be reported in the CSR but in

separate reports and in scientific publications as appropriate. Pharmacogenomics will not be included in the second year extension period.

5.7 Biomarker analysis

The subject's consent to the use of donated biological samples has to be taken. Biological samples (blood, urine, and tissue) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

The purpose of these tests is to gain a better understanding of LN, the role of IFNs in LN, the impact of anifrolumab on LN related abnormalities and to identify biomarker candidates with potential clinical applications in LN. The results from these investigations will not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.7.1 Serum and plasma biomarkers

Serum and plasma samples will be collected for mechanistic studies during the visits specified in the Study Plan (Table 2, Table 3, Table 4, and Table 5). These studies may include soluble analytes, such as proteins, antibodies, peptides and immune complexes and will be conducted using a variety of technical approaches such as immunoassays, protein arrays, in vitro assays, and/or biochemical methods. The results from these investigations will not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.7.2 Urine biomarkers

Urine samples will be collected for mechanistic studies during the visits specified in the Study Plan (Table 2 and Table 3). These studies may include soluble analytes such as proteins, peptides, antibodies and immune complexes and will be conducted using a variety of technical approaches such as immunoassays, protein arrays, in vitro assays, and/or biochemical methods. The results from these investigations will not be reported in the CSR but in separate reports and in scientific publications as appropriate. Urine biomarkers will not be assessed in the second year extension period.

5.7.3 RNA transcript profiling

To better understand the impact of Type-1 interferon blockade on systemic immune processes whole blood samples will be collected as indicated in the Study Plan (Table 2, Table 3, Table 4, and Table 5) for retrospective analyses of genome wide transcriptome profiling. Transcriptome profiles will be assessed as potential markers predictive of response or as additional PD response biomarkers. The results from these investigations will not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.7.4 Interferon test in whole blood

Whole blood will be collected at screening in PAXgene tubes to measure the over expression of mRNA for certain types of type I IFN-inducible genes using a 4-gene test. The IFN test and the data will be evaluated for development of a companion diagnostic.

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

5.7.5 Tissue biomarkers: immunostaining, epigenetic and gene expression studies on renal biopsies (optional)

These tests are in addition to the standard evaluation of renal biopsies and require a separate ICF. These studies will be done from existing clinical biopsy material (eg, fixed paraffin embedded tissue tissue). The studies will be limited to gain better understanding about the pathogenesis and the role of IFN in LN. A variety of techniques may be used, such as immunostaining for various inflammatory markers and gene expression and epigenetic analysis. The results from these investigations will not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.7.6 Storage, re-use and destruction of biological samples

Samples may be stored for a maximum of 15 years from the date of the LSLV, or as per local regulation, after which they will be destroyed.

5.7.7 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (see Appendix B, 'IATA 6.2 Guidance Document').

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

5.7.8 Chain of custody of biological samples

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

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

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

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

Samples retained for further use are stored at AstraZeneca R&D Mölndal Biobanken - Pepparedsleden 1 - 431 83 Mölndal - Sweden to be analysed at a facility to be selected by AstraZeneca at a later date, for up to 15 years or as per local regulation from the end of the study, which is expected to be in the third quarter of 2020. The samples will be destroyed after that.

5.7.9 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca and Sponsor's delegate
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section. The Sponsor's delegate Medical Services will provide an out of hours medical management service; contact details will be provided to Investigators and subjects (to be used only by healthcare professionals in case of emergency).

6.1 Definition of adverse events

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

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

6.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- 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.

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

If a subject decides to have surgery to correct a pre-study condition that has not worsened since the ICF was signed or the surgery was planned before the ICF was signed, then the

hospitalisation is not considered an SAE. If however, a new condition occurs or a pre-existing condition worsens and surgery is required, then the hospitalisation is considered an SAE.

6.3 Hy's Law

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

6.4 Definition of Adverse Event of Special Interest

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

Adverse Events of Special Interest will be assessed at each visit in the eCRF. The events of interest are serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, TB (including latent TB), influenza, vasculitis (non-SLE), and MACE (including stroke, acute coronary syndrome, myocardial infarction, or cardiovascular death).

An AESI that meets one 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 6.7.

6.4.1 Non-opportunistic serious infection

A serious non-opportunistic infection is any non-opportunistic infection that meets the SAE criteria in Section 6.2. Serious non-opportunistic infection AEs are reported as SAEs. 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.

6.4.2 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. Opportunistic infections are categorised as serious and reported as an SAE.

Examples of opportunistic infections that may occur in SLE subjects include: *Herpes zoster* meningoencephalitis, *Salmonella* bacteremia, *Pneumocystis jiroveci* pneumonia or progressive multifocal leukoencephalopathy.

It is expected that culture results and all diagnostic or therapeutic procedure results performed on a subject experiencing a serious opportunistic infection will be provided as an SAE update.

Since anifrolumab is an immunomodulatory agent and the Sponsor needs to understand the safety profile of this IP, 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.

6.4.3 Anaphylaxis

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as IP. For the purposes of this study, the definition detailed in Appendix L is provided as a simple and rapid means to make the diagnosis of anaphylaxis during infusion with IP. 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).

6.4.4 Malignancy

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

6.4.5 Herpes zoster

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

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

6.4.6 Tuberculosis

Tuberculosis is a mycobacterial infectious disease generally presenting as cough with systemic symptoms of infection diagnosed by skin test (purified protein derivative), blood test

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

- **A bacteriologically confirmed TB** case is one from whom a biological specimen is positive by smear microscopy, culture or rapid diagnostic such as PCR or nucleic acid amplification test (Xpert MTB/RIF).
- **A clinically diagnosed TB** case is one who 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; and HIV status (World Health Organisation, 2014).

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

Subjects identified with latent TB will be assessed by a local TB specialist to confirm the diagnosis and local SOC that will be used in treatment. If no local guidelines exist for immunocompromised individuals, then CDC guidelines may be followed. Once latent TB is confirmed, treatment must be instituted immediately and no IP may be administered until treatment of latent TB has begun. Additionally, subjects with newly diagnosed latent TB must agree to complete a locally recommended course of treatment for latent TB in order to continue receiving the IP.

6.4.7 Influenza

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

Laboratory criteria for influenza include at least one 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. Whether or not a test to confirm the diagnosis has been performed, if, in the opinion of the investigator, the subject has had influenza (the specific viral infection), this should be reported as an AESI. If the subject has had a viral infection that is less severe, then this should be reported as an AE only.

6.4.8 Vasculitis (non-systemic lupus erythematosus)

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

6.4.9 Major acute cardiovascular events

As a measure of enhanced Pharmacovigilance, an independent Cardiovascular Event Adjudication Committee (CV-EAC) will review deaths (due to any cause) and all SAEs in both the Cardiac and Vascular MedDRA System Organ Classes and all SAEs in the Central Nervous System Vascular Disorders Standard Medical Query for evaluation. The CV-EAC chair may adjudicate some events that do not fall into the above categories.

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

6.5 Recording of adverse events

6.5.1 Time period for collection of adverse events

Adverse events and SAEs will be collected from the time of signature of the ICF until the end of the subject's participation in the study. Serious adverse events occurring within the 12 week post final dose period will be followed to resolution/stabilisation. Pregnancies occurring

within the 12-week post final dose will be followed up until end of subject's participation in the study or until the outcome of pregnancy is known (whichever is later).

6.5.2 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.

6.5.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped. For infusion-related AEs, in addition to date, time when the AE started and stopped must be collected
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- 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

- 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 in Section 6.2. An SAE is an AE that fulfils one or more of the following criteria:

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

For further guidance on the definition of a SAE, see Appendix A.

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

shown in Section 6.2. The Investigator should provide an assessment of the severity of each AE/SAE.

6.5.4 Causality collection

The Investigator will assess causal relationship between IP 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 IP?'

For SAEs causal relationship will also be assessed for any other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A.

6.5.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnosis is preferred (when possible) to 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.

6.5.6 Adverse events based on examinations and tests

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

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/SAE.

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

6.5.7 Disease progression/worsening of systemic lupus erythematosus and lupus nephritis

Disease progression can be considered as a worsening of a subject's condition attributable to SLE or LN. It may be an increase in the activity or severity of the existing manifestations of LN or SLE or the appearance of new manifestations. Disease progression should not be reported as an AE unless it fulfils criteria for SAE (please see Section 6.2 for definition of SAE). However, worsening of SLE or LN will be recorded in the disease assessment tools (SLEDAI-2K, PGA and PtGA).

6.6 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF. All safety forms and supportive documentation include laboratory tests, imaging reports, diagnostic test results, biopsy reports, and discharge summaries is to be sent to the Sponsor's delegate Medical Services.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site or designee **within 1 business day** of initial receipt for all 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 should inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the DataLabs system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the DataLabs system is not available, then the Investigator or other study site personnel reports the SAE to the Sponsor's delegate Medical Services on the study specific paper SAE form by telephone, FAX, or e-mail. The SAE report form must be completed in the electronic system as soon as the system is available again.

SAE information should be sent to the Sponsor's delegate Medical Services.

The Sponsor's delegate Medical Services, on behalf of AstraZeneca, is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, Ethics Committees (ECs), and participating Investigators, in accordance with International Conference on Harmonisation (ICH) Guidelines and/or local regulatory requirements. Sponsor/Designee may be required to report certain SAEs to regulatory authorities within 7

calendar days of being notified about the event; therefore, it is important that Investigators submit additional information requested by Sponsor/Sponsor's delegate as soon as it becomes available.

The reference document for definition of expectedness/listedness is the Investigator's Brochure.

6.7 Reporting of adverse events of special interest

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

The reporting period for AESIs is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study. All serious AESIs and nonserious AESIs are required to be reported within 24 hours and 72 hours of knowledge of the event, respectively, to the appropriate AstraZeneca representative.

6.8 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.6. For other overdoses, reporting must occur within 30 days.

6.9 Pregnancy

All pregnancies occurring during the subjects' participation in the study and the outcomes of pregnancy should be reported to AstraZeneca or designee. In addition, if Investigators become aware of pregnancies occurring after the subject's participation in the study ended they should report them to AstraZeneca or designee in the following cases:

- Female subject: Any conception occurring from the date of randomisation until 12 weeks after the last dose of IP and 6 weeks after the last dose of Sponsor-provided MMF administration (whichever is later).

- Male subject: Any conception of female partner of the subject that occurs from the date randomisation until 12 weeks after the last dose of IP and 90 days after the last dose of Sponsor-provided MMF administration (whichever is later). 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.

The outcome of any conception should be followed up and documented on the pregnancy outcome form and reported within 1 day (no later than 24 hours) of when the Investigator becomes aware of it.

6.9.1 Maternal exposure

If a subject becomes pregnant during the course of the study, IP and Sponsor-provided MMF should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 or designee within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Principal Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.6) 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 up until the outcome of pregnancy is known so that the pregnancy outcome can be determined and reported to AstraZeneca or designee and the regulatory authorities.

6.9.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 12 weeks following the last dose of IP and for 90 days following the last dose of Sponsor-provided MMF (whichever is later).

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 until the outcome of pregnancy is known.

6.10 Medication Error

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

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

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

The designated AstraZeneca representative works with the Principal Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.6) and within 30 days for all other medication errors.

6.11 Management of investigational product-related toxicities and MMF-related warnings and precautions

6.11.1 Anaphylaxis, hypersensitivity, and infusion-related reactions

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

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.

6.11.2 Infections

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

obtained when indicated and results should be reported with the SAE or AESI. 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 IP should receive appropriate medical therapy, as determined by local standards, and be monitored closely until the condition resolves. IP should not be administered to a subject with a clinically significant, active infection as determined by the Investigator (see Section 3.8). 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 IP administration, and should notify the Sponsor/Designee Medical Monitor.

Similarly, if a subject presents with signs or symptoms where opportunistic infections are considered (eg, Central nervous system symptoms consistent with progressive multifocal leukoencephalopathy or herpes encephalitis, or atypical pneumonia suggesting pneumocystis jiroveci pneumonia), IP should be interrupted until the Principal 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 IP must be administered within 14 days of the scheduled time of the missed dose. If this is not possible, dosing should be resumed at the time of the next scheduled dose.

6.11.3 MMF-related warnings and precautions

During the screening period while discussing informed consent, potential study subjects should be informed on the risks of using MMF based on the local prescribing information. The risks of using MMF include, but are not limited to, the following:

- Embryofoetal toxicity/teratogenic potential: Exposure to MMF during pregnancy is associated with increased first-trimester foetal loss and increased risk of congenital malformation. MMF should not be used in lactating females. Due to the risk of male to female transfer of MMF and metabolites in seminal fluid, all male subjects treated with MMF should use condoms. Please refer to Section 3.1 for additional information on contraception requirements for this study.

- Serious infection: The use of immunosuppression, including MMF, is associated with increased risk of infection with bacterial, viral, protozoal, fungal, reactivated viral and/or opportunistic infections. Infections may result in sepsis and may be fatal.

- Malignancy: The use of immunosuppression, including MMF, alone or in combination, poses an increased risk of developing lymphomas and other malignancies, especially of the skin.

- Haematologic abnormalities: Neutropenia may be associated with MMF. Cases of pure red cell aplasia have been reported with MMF in combination with other immunosuppression.

- Gastrointestinal: MMF has been associated with infrequent cases of gastrointestinal ulceration, haemorrhage, pancreatitis, and perforation.

Refer to the locally approved MMF prescribing guide/product characteristics for additional details on risks and AEs associated with MMF.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

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

Each vial of IP or placebo contains 1.3 mL fill volume.

IP and placebo will be supplied to the site as follows:

- Visits 1-3: 6 vials per carton

- Visits 4-28: 2 vials per carton

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

Preparation of IP and placebo must be performed by a trained unblinded team member (eg, pharmacist, study nurse) at the site. When diluted as directed in the IP 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 IP, anifrolumab or placebo, will be administered via controlled IV infusion pump into a peripheral vein over no less than 60 minutes for the first 3 doses (Visits 1, 2 and 3). Starting with Visit 4, IP can be administered as an IV infusion via an infusion pump over no less than 30 minutes.

- **Basic Regimen**: Anifrolumab 300 mg IV Q4W for 13 doses plus SOC or
- **Intensified Regimen**: Anifrolumab 900 mg IV Q4W for the first 3 doses followed by 300 mg IV Q4W for an additional 10 doses plus SOC or
- **Placebo**: IV Q4W plus SOC

Subjects who do not meet withdrawal criteria at Week 52 (as defined in Section 3.9) will continue to receive blinded IP (anifrolumab 300 mg or placebo IV Q4W) for an additional 13 doses plus SOC for another 52 weeks (second year extension period).

7.2.1 Dose preparation steps

Anifrolumab 300 mg, 900 mg or matching placebo: Visits 1-3

From a 100 mL IV infusion bag of 0.9% normal saline, withdraw and discard a volume of saline equal to 6.0 mL. Then add 1.0 mL from each of the 6 vials in the kit into the infusion bag and mix by gentle inversion. Due to approximately 10% overfill of normal saline, the final volume of the dilution will be greater than 100 mL.

Anifrolumab 300 mg or matching placebo: Visits 4-28

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

7.2.2 Prior to administering the investigational product

A separate manual will be provided to the sites that specify the procedures to be followed prior to administering the IP. Please refer to this Study Drug Supply Plan for details.

7.2.3 Investigational product administration procedures

- IP must be administered within 4 hours after preparation and may be stored at room temperature until administration. Total in-use storage time from dilution of anifrolumab to start of administration should not exceed 4 hours at room temperature. If refrigerated at 2 to 8°C (36 to 46°F), storage time should not exceed 24 hours. If storage time exceeds these limits, a new dose must be prepared from new vials.

- IP 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 IP.
- Because compatibility of anifrolumab with IV medications and solutions other than 0.9% sodium chloride for injection, (US Pharmacopeia), is not known, the IP solution should not be infused through an IV line in which other solutions or medications are being administered.
- IP will be administered as an IV infusion via an infusion pump over no less than 60 minutes for the first 3 doses (Visits 1, 2, and 3). Starting with Visit 4, IP can be administered as an IV infusion via an infusion pump over no less than 30 minutes.
- Immediately following the completion of IP 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 IP dosing.
- An emergency cart should be available in the infusion suite. See Appendix L.

7.2.4 Subject monitoring/procedures during and after the infusion

Subjects will be monitored during the administration of the IP and for at least 2 hours after the first 3 infusions (Weeks 0, 4, and 8). If there are no safety concerns, for subsequent infusions subjects will be monitored during administration of the IP and for a minimum of one hour after completion of the IV infusion thereafter (Week 12 to Week 100).

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

- Shortly before the IV infusion (up to 20 minutes before the IP infusion starts)
- Every 15±5 minutes during infusion
- Immediately after completion of administration of IP, including post-dose saline flush (within 20 minutes after completion of post-dose saline flush)
- Every 30±5 minutes after completion of IP infusion (not including saline flush) for at least 2 hours after IP infusion for the first 3 doses (Week 0 [Day 1] to Week 8) and for at least 1 hour, thereafter (Week 12 to Week 100)

- Samples for PK laboratory assessments should be collected 15±5 minutes after completion of IP infusion (not including saline flush) after dosing on Week 0 (Day 1) and Week 48

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

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 IP infusion and the duration of IP administration will be recorded. The duration of IP infusion and duration of IP 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 IP is first infused into the subject. Infusion stop time is defined as the time point where the infusion pump completes infusion of the IP, not including the saline flush.

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

Intravenous bag compatibility studies demonstrate that anifrolumab is compatible with IV bags and ancillaries comprised of materials as described in Table 7 and Table 8.

Table 7 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	Latex-free, PVC-free, and DEHP-free polyolefin
0.9% saline	PVC and DEHP
0.9% saline	Polyethylene
0.9% saline	Polypropylene
0.9% saline	Ethylene polyvinyl acetate

PVC=Polyvinyl chloride; DEHP= diethylhexyl phthalate

Table 8 Compatible materials of construction for ancillaries (eg, infusion tubing)

Materials of Construction
Polyethylene
PVC with DEHP
PVC (latex-free and DEHP-free)
Polyethylene (latex-free and DEHP-free)
Polybutadiene

PVC=Polyvinyl chloride; DEHP=diethylhexyl phthalate

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. Vials and cartons will be labelled with double-blind labels.

The label will include the following information:

- Name of Sponsor (AstraZeneca)
- IP/Sponsor-provided MMF dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code

- Enrolment code or Randomisation code
- Directions for use
- The name of the Principal Investigator, where applicable (this is to be added on the label when the IP/Sponsor-provided MMF is dispensed)
- The period of use eg, expiry date, where required.

The following standard statement will be included: 'for clinical study use only'

Before the kit is dispensed to the subject, the Investigator must fill in the required information on the empty lines on the front cover page, locate the page with local label text, and demonstrate to the subject. Booklet labels must be opened to find the full label text in local language.

7.4 Storage

IP and Sponsor-provided MMF should be kept in a secure place under appropriate storage conditions. The IP should be stored at 2 to 8°C (36 to 46°F) and must not be frozen.

7.5 Compliance

The administration of IP and Sponsor-provided MMF should be recorded in the appropriate sections of the CRF. The IP will be administered by study site personnel, who will monitor compliance.

7.6 Accountability

The IP and Sponsor-provided MMF provided for this study will be used only as directed in the study protocol.

The Investigator's or site's designated unblinded team member trained to prepare the IP is required to maintain accurate IP accountability records. Upon completion of the study, copies of IP accountability records will be returned to AstraZeneca or designee. All unused IP 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 IP will be provided to the sites.

7.7 Concomitant and other treatments

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

Concomitant (including immunosuppressant) medications should be administered consistently and if possible after all visit assessments, including IP administration and post infusion PK blood draws (if applicable), with the exception of subjects with a previous infusion-related reaction who are to receive acetaminophen/paracetamol (which should be given after all visit assessments other than the infusion have been completed, and prior to starting the infusion).

Subjects who are taking concomitant medications must be informed that on the day of the study visit, these medications are to be taken only after the study assessments are completed (if clinically appropriate) or as advised by the Investigator.

7.7.1 Anti-hypertensive agents and statins

Angiotensin-Converting-Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blockers (ARB) may be adjusted to optimise their anti-hypertensive effects up to Week 4. Changes in other classes of anti-hypertensive agents (calcium channel blockers, β-blockers, α-receptor blockers) are allowed as clinically indicated to optimise blood pressure.

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

Cholestyramine must be discontinued prior to the day of randomisation.

7.7.2 Excluded medications

7.7.2.1 Medications that are excluded after signing the ICF

Receipt of any of these medications leads to immediate discontinuation of IP:

- Cyclophosphamide
- IFN therapy (α 2a and 2b, beta 1a and 1b, and pegylated IFNs α 2a and 2b)
- Investigational agents
- Biologic immunomodulators (including belimumab, abatacept, rituximab)
- Tofacitinib
- 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)
- BCG vaccine

- Any immunoglobulin (Ig) therapy
- Exceeding the number or dose of protocol-allowed methylprednisolone pulses (oral or IV)
- Any medications or treatment modality listed in Appendix H

7.7.2.2 Restricted medications

As anifrolumab is an investigative immunomodulatory agent, non-protocol permitted changes to immune modifiers or immunosuppressants during the study are not allowed. If a subject receives one of the following after randomisation, the Investigator must notify the Sponsor/Designee Medical Monitor immediately. The Designee Medical Monitor will determine with the Sponsor if the subject may continue to receive IP, however, the subject would be considered a non-responder for assessments such as CRR.

- Azathioprine
- Methotrexate
- Leflunomide
- Tacrolimus
- Mizoribine
- Cyclosporine
- Cholestyramine
- Increase in corticosteroids (except methylprednisolone pulses) above the protocol-allowed doses or duration. For any increase in methylprednisolone pulses, please see Section 7.7.2.1.
- Corticosteroids with a long biologic half-life (eg, dexamethasone, betamethasone)

7.7.3 Standard of care immunosuppressive treatment during the study

Standard of care treatment for LN will consist of the combination of MMF and corticosteroids.

7.7.3.1 Mycophenolate mofetil

From the day of randomisation onwards until the end of subject's participation in the study, MMF will be supplied by the Sponsor to the subjects.

The target dose of MMF will be 2 gm/day during the 52 week double-blind treatment period, where the dose is titrated to the target dose between randomisation and Week 8. Adjustments of the dose due to suboptimal response, toxicity, or intolerability are allowed if needed according to guidelines described below. A maximum dose of 3.0 gm/day is allowed up to Week 24 for subjects with suboptimal response between Weeks 8 and 24, and needs to be reduced to ≤2.0 gm/day by Week 32. The dose of MMF has to be stable from Week 40 to Week 52.

It is not mandatory for a subject to receive 2 gm/day of MMF if local treatment standards dictate a lower dose to be given (eg, for constitutionally small subjects). During the 52 week double-blind treatment period, the minimum dose of MMF is 1.0 gm/day between Week 8 and Week 52. Subjects who do not tolerate the minimum MMF dose will be considered non-responders for responder analyses (such as CRR), but will be allowed to continue to receive investigational product.

In the second year extension period, MMF dose should be ≤2 gm/day or ≤Week 52 dose, whichever is lower. If MMF dose >2 gm/day at Week 52, taper to ≤2 gm/day will be required by Week 60. Failure to do so will lead to withdrawal from IP. A decrease in MMF dose is allowed at the investigator's discretion between Week 52 to Week 92. The dose of MMF must be stable from Week 92 to Week 104.

During the second year extension period there is no minimum dose requirement for MMF. However, if MMF is discontinued and a different immunosuppressant is started at any time during the study, IP will be discontinued. A decrease below the minimum dose or withholding MMF for 14 days or less for MMF-related side effects, such as gastrointestinal side effects, cytopenias or infection is acceptable at any time throughout the study. (If during the 52 week double-blind treatment period MMF has to be withheld or decreased below the minimum dose for more than 14 days, the subject will be considered a non-responder for responder analyses (such as CRR), but may continue to receive IP. This will not be considered as non-compliance or protocol deviation, because the withdrawal of MMF is for safety reasons).

Subject with premature discontinuation of IP will continue to receive Sponsor-provided MMF (unless subject is pregnant) at the investigator's discretion until subject's participation ends.

Initial adjustment of MMF dose to achieve or maintain the target dose (Randomisation through Week 8)

- Subjects who are receiving MMF at a dose of 2 gm/day at Week 0 (Day 1) will continue this dose
- Subjects who are not taking MMF at Week 0 (Day 1), or subjects who are taking less than 2 gm/day, the dose will be titrated up with the goal of achieving a dose of 2 gm/day (or the therapeutic target dose if local

treatment standards dictate a lower dose) by Week 2 (but not later than Week 8, if dose escalation is limited by intolerability).

Titration of MMF should follow accepted local practice guidelines, including appropriate laboratory monitoring for toxicity.

- Subjects, who at Week 0 (Day 1) are taking MMF doses >2 gm/day will have their dose reduced to 2 gm/day by Week 8 unless they meet criteria for suboptimal response (see below for suboptimal response)

MMF dose between Week 8 and 24

The dose of MMF will be kept stable from Week 8 through Week 24 unless dose escalation to a maximum of 3 gm/day is necessary for suboptimal response (defined below) or a dose reduction is necessary to manage toxicity or intolerability.

Criteria for suboptimal response:

A suboptimal response is defined by UPCR values shown below at two independent measurements taken at least 2 weeks apart:

- Spot UPCR >3 mg/mg and
- Spot UPCR <15% decrease compared to baseline spot UPCR

If a subject meets the criteria at or after Week 8, the dose may be escalated or kept above 2 gm/day. After initial confirmation of suboptimal response, MMF can be increased up to 3 gm/day until Week 16 without re-testing for the suboptimal response criteria. The dose of MMF must be kept stable from Week 16 unless suboptimal response criteria are met or dose reduction is necessary for intolerability or MMF-related AEs. A temporary decrease below the minimum dose, or withholding MMF for 14 days or less, for MMF-related side effects, such as gastrointestinal side effects, for cytopenias or infection is acceptable.

Mycophenolate mofetil dose between Week 24 and Week 52:

For subjects who are taking >2 gm/day of MMF at Week 24, the dose of MMF must be decreased to a maximum dose of 2 gm/day by Week 32. The dose can be decreased below 2 gm/day after Week 24 until Week 40 at the discretion of the investigator. **The dose of MMF must be stable from Week 40 through Week 52 (unless a dose reduction is necessary to manage toxicity or intolerability).**

MMF dose from Week 52 to Week 104:

For subjects who continue in the second year extension the target dose of MMF will be ≤2 gm/day or ≤Week 52 dose, whichever is lower. If the MMF dose is >2 gm/day at Week 52,

it must be tapered to ≤2 gm/day by Week 60. Failure to achieve MMF dose ≤2 gm/day by Week 60 will lead to discontinuation from IP. A decrease in MMF dose or discontinuation of MMF is allowed at the investigator's discretion between Week 52 to Week 92. If the MMF dose is decreased during the extension period, return to an MMF dose of ≤2 gm/day but not exceeding the Week 52 dose is allowed.

MMF dose must not be changed from Week 92 to Week 104.

7.7.3.2 Corticosteroids

Initial corticosteroid treatment to control LN and SLE:

Subjects may enter the study taking daily OCS at a maximum dose of 0.5 mg/kg/day of prednisone-equivalent not to exceed 40 mg/day. In addition, subjects will receive IV (or oral, if applicable) methylprednisolone pulse 500 mg on the day of randomisation, prior to receiving the IP, unless they received a methylprednisolone pulse of ≥500 mg within 10 days prior to randomisation. Subjects may also receive one additional (optional) dose of IV (or oral, if applicable) methylprednisolone pulse (≤500 mg) for renal or extra-renal disease activity after the Week 0 (Day 1) visit up to and including the Week 8 visit. Methylprednisolone pulse can be divided and administered on two consecutive days but the cumulative dose must not exceed 500 mg.

Steroid tapering during the 52 week double-blind treatment period:

Oral corticosteroid dose tapering is required during the study with the goal of tapering OCS to prednisone-equivalent of ≤10 mg/day by Week 12 and prednisone-equivalent of ≤7.5 mg/day by Week 24. The rate of tapering is at the discretion of the Investigator; a recommended tapering schedule is provided in Appendix O. If subjects experience an increase in SLE disease activity upon tapering of OCS their dose may be returned to a dose equal or less as the dose prior to the taper. The return to the pre-taper dose will not be considered an OCS "burst and taper". The pre-taper dose for various periods is defined as follows:

- Week 0 to Week 12: dose at randomisation
- After Week 12 to Week 24: the Week 12 dose
- After Week 24 to Week 40: the Week 24 dose

Subjects unable to taper OCS to ≤15 mg/day at Week 12 or <15 mg/day at Week 24 will be discontinued from IP treatment. However, subjects who exceed the maximum daily OCS dose at the Week 12 or Week 24 visits may continue to receive IP if the current dose is part of a protocol-allowed temporary OCS dose (eg, burst and taper) increase. Subjects who cannot be returned to their pre-increase dose within 14 days from the start of burst will have their IP discontinued at the next visit.

The subjects discontinued from IP treatment will be followed until Week 52 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 52).

Investigators will not be required, but may continue, to taper OCS dose beyond the target of 7.5 mg/day up to Week 40. Steroid tapering will not be permitted from Week 40 to Week 52.

Steroid "burst and taper"

A steroid burst is defined as one of the following:

Oral corticosteroid increase up to a maximum daily dose of 0.5 mg/kg/day (maximum 40 mg/day) prednisone-equivalent dose for up to a total of 14 days and that must be fully administered and tapered to less than or equal to the pre-burst starting dose by the end of the 14th day. Any course of OCS burst must not extend beyond Week 40 during the first year (starting after Week 0) and Week 92 during the second year extension period (starting after Week 52), regardless of when the course was started.

OR

A maximum of 1 instance of intra-articular, tendon sheath or bursal injections (for a total methylprednisolone ≤80 mg or equivalent) can be given. Subjects who receive any intra-articular/tendon sheath/bursal injections should not receive OCS burst (and vice versa).

Steroid burst is allowed as follows:

- **From randomisation to Week 40**: One burst and taper of corticosteroids for increased SLE disease activity or for non-SLE activity is allowed.

  Subjects who receive more than one steroid "burst and taper" or who violate the above criterion may continue to receive IP after approval by Sponsor/Designee Medical Monitor, but will be considered non-responders for subsequent responder analyses (such as CRR), regardless of whether the OCS "burst" was administered for increased SLE activity or non-SLE causes.

- **Increase in corticosteroids from Week 40 to Week 52**: No increase in OCS, or the use of IV or intra-articular, tendon sheath or bursal injections is allowed from Week 40 until Week 52 assessment.

Corticosteroid dose from Week 52 to Week 100

- If the OCS dose is >7.5 mg/day at Week 52, tapering to ≤7.5 mg/day is required by Week 60. Failure to achieve ≤7.5 mg/day by Week 60 will lead to discontinuation from IP.
- OCS dose must be tapered to ≤5 mg/day at Week 80. OCS tapering below 5 mg/day is allowed at any time until Week 92.
- No change in OCS dose will be allowed from Week 92 to Week 104.
- One burst and taper will be allowed between Week 52 and Week 92.

Increase in corticosteroids for the prevention of adrenal insufficiency

For a severe illness, surgery, or symptoms of adrenal insufficiency, if clinically warranted, the following can be used, in addition to the "burst and taper" described above:

- Oral or IV hydrocortisone up to 100 mg every 8 hours on the first day followed by half that dose for 2 days before returning to their usual dose or
- Subjects who are taking ≤7.5 mg/day prednisone or equivalent will be allowed to receive up to an additional 7.5 mg/day to a total of 15 mg/day oral prednisone or equivalent for a total of up to 14 days.

Subjects who receive either of these corticosteroid regimens for the prevention of adrenal insufficiency between Week 40 and Week 52 will be considered as a non-responder for the Week 52 analyses.

7.7.4 Other concomitant medications

Medications other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the electronic Case Record Form (eCRF). Subjects should not start naturopathic, herbal, ayurvedic remedies, nutritional/dietary supplements, vitamins, and/or minerals without discussing with the Investigator.

7.7.4.1 Topical therapy

Concurrent use of topical therapy for cutaneous lupus erythematosus (eg, topical corticosteroids, topical immunosuppressants) is permitted. During the study, topical therapy may be reduced or discontinued based on clinical manifestations and Investigator discretion. Should cutaneous skin manifestations reoccur, the same topical therapy may be resumed at same dose as was being used at the time of randomisation.

It is encouraged that no new dermatologic preparations be initiated for the duration of the study. Subjects should use sunscreen (list as concomitant medication for SLE) and avoid sun exposure for the duration of the study.

7.7.4.2 Anti-proteinuric agents (ACEI or ARB)

Use of these are allowed during the study if they had been started at least 10 days prior to the assessment of the second screening 24-hour UPCR sample (the first sample for 24-hour UPCR is collected at the start of the screening process and the second sample is collected within 14 days prior to the expected date of randomisation). The dose may be adjusted to optimise anti-hypertensive effects or to reduce ACEI/ARB-related side effects up to Week 4. The dose must be kept stable from Week 4 through Week 104 (unless discontinued IP). Decreases in the dose are allowed only to reduce ACEI/ARB-related side effects such as hypotension, increase in creatinine, or cough. If cough develops, ACEI can be changed to ARB.

7.7.4.3 Anti-malarials

The dose of anti-malarials will remain stable throughout the study except where a reduction of dose is necessary to manage anti-malarial related AEs. Any anti-malarial related abnormality should be managed according to local standards. Discontinuation of anti-malarials is allowed, if necessary, to manage anti-malarial related AEs. The subject can remain in the study even if anti-malarials are stopped.

Randomised subjects who receive anti-malarial therapy within 12 months prior to signing the ICF must have an eye exam by a qualified professional either within 12 months prior to signing the ICF or subjects who start on anti-malarial therapy during the Screening Period within 12 weeks after signing the ICF. Anti-malaria-related abnormalities should be managed according to local standards. Anti-malarial-related abnormalities do not exclude subjects if they meet all other eligibility criteria. If eye exam is not performed within the protocol-specified timeframe, it will be considered to be a protocol deviation.

7.7.4.4 Non-steroidal anti-inflammatory drugs

No increase in the dose of or initiation of a new prescription non-steroidal anti-inflammatory drug (NSAID) should be made between signing the ICF and randomisation. For subjects receiving NSAIDs, concomitant proton pump inhibitors should be considered according to local practice and in concordance with considerations in the mycophenolate label.

- The dose of prescription NSAIDs must remain stable from randomisation through Week 104 (unless discontinued IP) but can be reduced for reasons of toxicity but not for efficacy. Prescription NSAIDs should not be administered with other NSAIDs (including over-the-counter NSAIDs) except for low-dose aspirin (≤325 mg/day).

- Non-prescription NSAIDs

- NSAIDs for analgesic purposes that never exceed label-approved doses of NSAIDs may be used for pain as required, based on Investigator judgement for up to 1 week at a time

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

7.7.4.5 Acetaminophen (Paracetamol):

- Normal release (not extended release) acetaminophen/paracetamol may be used for pain as required

- For a subject with a previous infusion-related reaction, acetaminophen or equivalent can be given after all visit assessments have been completed and prior to starting the infusion

7.7.4.6 Narcotic analgesics

These can be used during the study as clinically indicated.

7.8 Post Study Access to Study Treatment

After Week 52, eligible participants will continue treatment for another 12 months in the second year extension period.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved in the conduct of the study will remain blinded until the database soft lock and identification of protocol violations for the primary analysis at Week 52. Analyses will be performed by AstraZeneca or its delegates.

The database will be soft-locked and the primary analysis will be performed once all subjects complete Week 52 or discontinue the study prior to Week 52. The Sponsor and Sponsor‘s delegates who are not directly involved in the management of sites will be unblinded to treatment assignments at the time of the primary analysis.

Investigators and subjects who continue in the second year extension phase will continue to be blinded to their treatment. The database will be locked for the final analysis of the second year extension period once the last subject in the second year extension period completes Week 112, or discontinues the second year extension period prior to Week 112.

One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit. CCI [redacted]

[redacted] Further details of the interim analysis will be specified in the interim analysis and communication plans prior to unblinding.

A comprehensive SAP v1.0 was completed prior to first subject in to the study. Any subsequent amendments to the SAP will be documented, with final amendments completed prior to unblinding of the data. Details of all analyses, including sensitivity analyses are presented in the SAP.

8.2 Sample size estimate

A total of 150 subjects will be randomised 1:1:1 to receive one of the two IV anifrolumab dosing regimens (Basic Regimen or Intensified Regimen) or placebo.

The sample size is based on the following assumptions:

- Reductions from baseline to Week 52 in 24-hour UPCR of 65% and 46% for the anifrolumab and placebo arms, respectively (ie, ratios of 24-hours UPCR from Week 52 to baseline of 0.35 and 0.54, respectively), based on data presented in Furie et al, 2014.
- The log-transformed 24-hour UPCR values follow a normal distribution with a standard deviation (SD) of 0.8, based on data from the anifrolumab Phase 2b study (CD1013)

Based on these assumptions, a sample size of 50 subjects per arm would result in an observed relative difference in the change from baseline to Week 52 in 24-hour UPCR of 0.65 (here expressed as the ratio, comparing anifrolumab to placebo), and a corresponding 95% confidence interval (CI) of (0.50, 0.85) comparing the pooled anifrolumab group (Basic and Intensified) with the placebo group. If the interim analysis is performed, a 0.001 two-sided alpha will be spent, and the final analysis will be based on 2-sided alpha of 0.049 (East Version 6.4). This sample size provides approximately 86% power with a 2-sided alpha of 0.049 to reject the hypothesis of no effect (relative difference =1) for comparing the pooled anifrolumab treatment group with placebo. The minimal detectable relative difference in the change from baseline to Week 52 in 24-hour UPCR between the pooled anifrolumab treatment group versus placebo is approximately 0.76, corresponding to a reduction from baseline to Week 52 in 24-hour UPCR of 59% in the pooled anifrolumab group (ratio of 24-hour UPCR from Week 52 to baseline of 0.41).

8.3 Definitions of analysis sets

8.3.1 All subjects analysis set

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

8.3.2 Full analysis set

The full analysis set will be used as the primary population for reporting efficacy and safety data. This comprises all subjects randomised into the study who receive at least 1 dose of IP and will be analysed according to randomised treatment (mITT principle). Any major deviations from randomised treatment will be listed and considered when interpreting the safety data.

8.3.3 Pharmacokinetic analysis set

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

8.4 Outcome measures for analyses

The baseline is defined as the last measurement prior to Day 1 dose administration. If the Day 1 value is missing or is invalid, the latest assessment prior to dose administration on Day 1 will serve as baseline.

8.4.1 Primary outcome variable

The primary endpoint used to evaluate the effect of anifrolumab compared with placebo on LN disease activity is the relative difference in change from baseline to Week 52 in the 24-hour UPCR.

8.4.2 Secondary outcome variables

8.4.2.1 Complete renal response

To evaluate the effect of anifrolumab compared with placebo on renal response in LN subjects, the proportion of subjects achieving CRR at Week 52 will be used. A subject achieves CRR if **all** of the following criteria are met:

- Estimated glomerular filtration rate (eGFR):

  ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20%

- 24-hour UPCR ≤0.7 mg/mg

No discontinuation of IP or use of restricted medication beyond the protocol-allowed threshold before assessment. Allowed restricted medication is defined in Section 7.7

8.4.3 Exploratory outcome variables

8.4.3.1 CCI

[redacted]

8.4.3.2 CCI

[redacted]

8.4.3.3 CCI

[redacted]

8.4.3.4 CCI

[redacted]

[redacted]

8.4.3.5 Alternative Complete renal response

To evaluate the effect of anifrolumab compared with placebo on renal response in LN subjects when urine sediment is considered in the definition, the proportion of subjects achieving aCRR at Week 52 and Week 104 will be used. A subject achieves aCRR if all of the following criteria are met:

- eGFR:

  ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20%

- 24-hour UPCR ≤0.7 mg/mg
- Inactive urine sediment (defined as <10 RBC/hpf)
- No discontinuation of IP or use of restricted medication beyond the protocol-allowed threshold before assessment. Allowed restricted medication is defined in Section 7.7

Please see Section 8.4.2.1 for definition of CRR.

8.4.3.6 Graded alternative complete renal response

The effect of anifrolumab compared with placebo on renal response in LN subjects is further assessed using the difference in proportions of subjects achieving graded aCRR at Week 52 and of subjects achieving aCRR at Week 104. A subject achieves graded aCRR if all following criteria are met:

- A decrease in 24-hour UPCR:
  - For subjects with baseline UPCR >3 mg/mg: UPCR ≤1 mg/mg
  - For subjects with baseline UPCR ≤3 mg/mg: UPCR ≤0.7 mg/mg

- eGFR:

  ≥60 mL/min/1.73 m^2 or no confirmed decrease of eGFR from baseline of ≥20%

- Inactive urine sediment (defined as <10 RBC/hpf)

- No discontinuation of IP or use of restricted medication beyond the protocol-allowed threshold before assessment. Allowed restricted medication is defined in Section 7.7

8.4.3.7 Sustained reduction of oral corticosteroid dose

The effect of anifrolumab compared with placebo on the ability to reduce the OCS dose will be assessed in subjects with baseline OCS ≥10 mg/day prednisone-equivalent. Sustained reduction on OCS dose is assessed using the difference in proportions of subjects meeting all the following criteria:

- Achieve an OCS dose of ≤7.5 mg/day prednisone-equivalent by Week 24
- Maintain an OCS dose ≤7.5 mg/day prednisone-equivalent from Week 24 to Week 52
- No discontinuation of IP or use of restricted medication beyond the protocol-allowed threshold before assessment (see Section 7.7)

The proportion of subjects achieving OCS tapering requirement will also be assessed at Week 104:

- Achieve an OCS dose of ≤5.0 mg/day prednisone-equivalent by Week 80
- Maintain an OCS dose ≤5.0 mg/day prednisone-equivalent from Week 80 to Week 104
- No discontinuation of IP or use of restricted medication beyond the protocol-allowed threshold before assessment (see Section 7.7)

8.4.3.8 CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.4.3.9 CCI [redacted]

[redacted]

8.4.3.10 CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.4.3.11 CCI

[redacted]

8.4.3.12 CCI

[redacted]

8.4.3.13 Other exploratory endpoints

CCI [redacted]

[redacted]

SLEDAI-2K

The effect of anifrolumab compared with placebo on SLEDAI-2K score will be evaluated using the difference in mean change from baseline to Week 52 and to Week 104.

Non-renal SLEDAI-2K

Extra-renal disease activity will be assessed by using the SLEDAI-2K score without the renal components ("non-renal SLEDAI-2K"). The effect of anifrolumab compared with placebo on non-renal SLEDAI-2K will be evaluated using the difference in mean change from baseline to Week 52 and to Week 104.

Physician's Global Assessment

The effect of anifrolumab compared with placebo on PGA will be evaluated using the difference in mean change in PGA from baseline to Week 52 and to Week 104.

SLICC/ACR Damage Index

The endpoint used to evaluate the effect of anifrolumab compared with placebo on irreversible damage in SLE subjects is the mean change in SDI global score from baseline to Week 52 and to Week 104.

8.4.4 Patient-reported outcome variables

Patient Global Assessment

The difference between anifrolumab and placebo in the mean change from baseline in PtGA (measured on a VAS ranging from 0 to 100 mm) to Week 52 and to Week 104 will be assessed.

8.4.5 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, haematology, clinical chemistry, urinalysis, reported AEs (including AESIs, see Section 6.4), PHQ-8 (up to Week 52), C-SSRS (up to Week 52), tuberculosis questionnaire, assessment of Cushingoid features, assessment of cardiovascular risk (fast lipid profile), and extra-renal flares using SLEDAI-2K based Flare Assessment Instrument. Marked abnormal ECG values or changes from baseline will be identified based on pre-determined criteria. Occurrence of

suicidal behaviour and ideation, based on the C-SSRS, from baseline up to Week 52 will be explored.

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

8.4.5.1 Other significant adverse events

During the evaluation of the AE data, a medically qualified expert from Sponsor/Sponsor's delegate team will review:

- AESI: AESI are listed in Section 6.4. These will be reported in the CSR.
- A list of AEs that were not reported as SAEs, or AEs leading to discontinuations: Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Astra Zeneca Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

8.4.6 Immunogenicity variables

ADA assessments will be conducted utilising a tiered approach (screen, confirm, titre). The presence of nAb will be tested only in samples that were previously found to contain ADA, using a ligand binding assay.

Immunogenicity variables will also be assessed for the second year extension period.

8.4.7 Pharmacokinetic variables

Due to the limited sampling schedule, the PK assessments for both anifrolumab and mycophenolic acid will be primarily based on the observed steady-state serum trough (pre-dose) concentrations, Ctrough. For anifrolumab, maximum concentrations after the first and last dose will also be evaluated.

Only C_{trough} will be assessed for the second year extension period.

8.4.8 Lupus serology variables

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

Lupus serology variables will also be assessed for the second year extension period.

8.4.9 Pharmacodynamic outcome variables

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

IFN-21 gene PD signature will also be assessed for the second year extension period.

8.5 Methods for statistical analyses

Missing data

The study was designed to reduce the risk for missing data as much as possible through the following measures (see Section 7.7.3 for details):

- From randomisation to Week 40, the study design allows for one burst and taper of corticosteroid for increased SLE disease activity or non-SLE causes.
- The dose of MMF may be increased up to 3 gm/day in case of suboptimal response.
- Subjects will receive IV methylprednisolone 500 mg on Week 0 (Day 1), prior to receiving the IP.
- Subjects may also receive up to one additional (optional) dose of IV methylprednisolone (≤500 mg) for renal or extra-renal disease activity between Week 0 (Day 1) visit and Week 8 visit.
- Subjects who require additional bursts of OCS will still be allowed to remain in the study, but will be considered non-responders for subsequent responder analyses (such as CRR).

Subjects who discontinue IP will be followed up to come to each visit for the scheduled assessments through the Week 52 visit (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 52).

The following measures will be applied to the second year extension period to also reduce the risk for missing data:

- From Week 52 to Week 92, the study design allows for one burst and taper of corticosteroid.
- Subjects who require additional bursts of OCS during the second year extension period will still be allowed to remain in the study, but will be

considered non-responders for subsequent responder analyses (such as CRR at Week 104).

Subjects who discontinue IP in the second year extension period will continue to be followed until Week 104 (or for a minimum of 12 weeks after last dose of IP for subjects for whom IP was discontinued within 12 weeks prior to Week 104).

Sensitivity analyses where missing data is handled in different ways will be carried out. Details will be pre-specified in the SAP.

Presentation of results

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

Summary tables will be presented by treatment group including a pooled group comprising of both anifrolumab regimens. Details are presented in the SAP.

95% CIs will be presented for estimated differences between treatments. If a model is used to estimate the treatment difference, the corresponding 95% CI according to the model will be presented. Otherwise, the unadjusted 95% CI will be used. Nominal p-values may be presented for endpoints not included in the strategy for preserving the type 1 error rate, but these cannot be interpreted in terms of statistical significance.

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

8.5.1 Analysis of the primary variable

The primary estimand is evaluating the efficacy on disease activity of the pooled anifrolumab groups relative to placebo in subjects with active proliferative LN. This is measured by the relative difference in change from baseline to Week 52 in the 24-hour UPCR. The full analysis set, defined as subjects who are randomised and received at least 1 dose of IP (modified Intention-To-Treat), will be used, in order to reflect the effect of the initially assigned and dosed IP. Further details regarding multiplicity adjustments can be found in Section 8.6.

The analysis will be performed using a mixed model repeated measures (MMRM) fitted to log-transformed data comparing the pooled anifrolumab group with the placebo group, with fixed effects for treatment group, visit, stratification factors and log-transformed 24 hour UPCR at baseline. An interaction term for visit and treatment will also be included in the model to allow the relationship to differ across treatment groups. Note that visit will be fitted as a repeated variable in the model. Model assumptions will be checked and, if not met,

appropriate data transformations may be applied or non-parametric approaches will be considered. Details will be presented in the SAP.

The estimated treatment effect, corresponding 95% CI, and 2-sided p-value for the difference at Week 52 will be presented. The individual anifrolumab regimens will also be assessed using the same methodology. 24-hour UPCR will also be assessed at Week 104 and presented similary with nominal 2-sided p-values.

Further, longitudinal presentations of results over time based on the same analysis, with the corresponding 95% CI, will be created.

8.5.2 Analysis of the secondary variable

In addition to the 24-hour UPCR, a composite endpoint will be used to further evaluate the effect of anifrolumab on renal response using the composite endpoint defined in Section 8.4.2, combining response to treatment and lack of restricted therapy. For this analysis, the estimand of interest is the difference in change from baseline in renal response between anifrolumab and placebo, to reflect the effect of the initially assigned and dosed IP (full analysis set). Non-responder imputation is used, ie, subjects treated with restricted treatments beyond protocol-allowed threshold, and those discontinued for other reasons, will be regarded as non-responders. This estimand answers a clinically relevant question comparing the number of subjects able to both tolerate therapy sufficiently to remain on treatment to a given point in time and to achieve adequate response without further medication being required.

The proportion of subjects achieving CRR in the anifrolumab pooled group will be compared to that in the placebo group using a Cochran-Mantel-Haenszel approach (Cochran, 1954) stratified by:

- Results of IFN test at screening using a 4-gene type I IFN diagnostic test (IFN test-high versus. IFN test-low)
- 24-hour UPCR ≤3.0 mg/mg versus >3.0 mg/mg (within 14 days prior to the expected date of randomisation). Without the results of the second (stratification) sample, subjects cannot be randomised. Turn-around time for results from central laboratory is up to 7 days. On rare occasion an extension of 30-day screening window may be allowed if re-collection of the 24-hour UPCR or other required samples is necessary or if the results needed for randomisation are delayed.

Strata with low counts will be collapsed prior to the analysis. Details for collapsing of strata will be pre-specified in the SAP. Further details regarding multiplicity adjustments can be found in Section 8.6.

The estimated treatment effect (ie, the difference in response rate for the pooled anifrolumab group versus the placebo group) and corresponding 95% CI for the difference at Week 52 and

Week 104 will be presented. In addition, the response rate and the corresponding 95% CI within each pooled and treatment group will be presented. The treatment effect at other time points may also be evaluated in a similar way. The individual anifrolumab regimens will also be assessed and presented similarly.

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

CRR will also be assessed at Week 104 using the same methodology. Please see Section 8.4.2 for more details.

8.5.3 Analysis of exploratory variables

All exploratory analyses will be performed using the pooled and individual anifrolumab groups, as well as placebo. No formal statistical hypotheses will be tested, but nominal p-values may be presented.

Exploratory binary responder endpoints (at least PRR, aCRR, graded CRR, graded aCRR, sustained reduction of OCS, modified CRR and modified PRR) will be assessed similarly to CRR endpoint as described in Section 8.4.2.1. Response rate and the corresponding 95% CI comparing each anifrolumab group (including pooled anifrolumab group) with the placebo group will be presented. The treatment effects at Week 52 and Week 104 will be evaluated. Analyses of ordinal outcomes (such as CRR, PRR, no response) will also be performed. Further details are presented in the SAP.

The time to achieve renal response and time to first renal flare will be reported descriptively. The number of renal flares and the flare rates will also be summarised. Details are presented in the SAP.

Continuous endpoints (including eGFR, spot UPCR, SLEDAI-2K, PGA, SDI, and PtGA) will be analysed using MMRMs with fixed effects for the appropriate baseline value, treatment group, visit, stratification factors and visit-by-treatment interaction term. Results will be presented in terms of the adjusted means for each treatment group, estimates of treatment differences, and associated CIs. Model assumptions will be checked and, if not met, appropriate data transformations may be applied or non-parametric approaches will be considered. Details are presented in the SAP.

Exploratory renal variables which are assessed at Week 52 will also be assessed at Week 104 using the same methodology. 24-hour UPCR will also be assessed at Week 104 as an exploratory variable. Please see Section 8.4.3 for more details.

8.5.4 Analysis of safety variables

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

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

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

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

SLEDAI-2K based Flare Assessment Instrument to capture extra-renal flares: The SLEDAI 2K based Flare Assessment Instrument has 2 sets of definitions: one for severe and one for mild/moderate flares. For the purpose of assessing extra-renal flares the renal components will not be considered for the SLEDAI 2K score. SLEDAI-2K based Flare will be summarised as appropriate.

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

8.5.5 Renal biopsy: ISN/RPS classification, NIH activity and chronicity indices

ISN/RPS classification, NIH activity and chronicity indices will be summarised as appropriate. For second biopsies, change from baseline in ISN/RPS classification and NIH activity and chronicity indices will also be summarised in a similar way. Details are presented in the SAP.

8.5.6 Analysis of immunogenicity variables

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

All immunogenicity variables will also be assessed as described for the second year extension period.

8.5.7 Analysis of pharmacokinetic variables

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

Mycophenolic acid serum concentrations will be summarised using descriptive statistics at each visit by treatment group. Serum concentration-time profiles of MPA by treatment group will be generated. If applicable, additional PK parameters will be explored.

All PK variables will also be assessed as described for the second year extension period.

8.5.8 Analysis of pharmacodynamic variables

Pharmacodynamic variables will be summarised as appropriate. Further details are provided in the SAP.

8.5.9 Analysis of lupus serology variables

Lupus serology variables will be reported as appropriate. Further details are provided in the SAP.

8.5.10 Subgroup analysis

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

- IFN test (IFN test-high versus IFN test-low)
- 24-hour UPCR ≤3 mg/mg versus >3 mg/mg
- Age (≥18 to 64 and ≥65 years)
- Placebo response region (low placebo response rate versus high placebo response rate)

Countries with low placebo response rate versus high placebo response rate are defined as:

  - Low: Australia, Belgium, France, Germany, Italy, South Africa, Spain, United Kingdom, United States

  - High: Argentina, Hungary, Republic of Korea, Mexico, Peru, Poland, Russian Federation, Serbia, Taiwan

- Race (white; black or African American; Asian, native Hawaiian or other Pacific Islander; American Indian or Alaska native; other)
- Screening biopsy classification (Class III, Class IV)
- Number of methylprednisolone pulses (1, >1)
- ADA result (positive at any time, negative)
- OCS at baseline (≤20 mg/day, >20 mg/day)
- eGFR at baseline (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2)

Full details of the subgroup analyses for both the first year period and the second year extension period will be pre-specified in the SAP.

8.5.11 Interim analysis

Primary efficacy and safety analyses will be performed once all data from the main study (up to and including Week 52) is available, cleaned and frozen. The study will also be unblinded at this stage for the team performing the analysis.

One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit. CCI [redacted] Even though there is no provision to stop the study early due to an efficacy claim, if the interim analysis is performed, a portion of the 2-sided alpha will be spent. A Peto-Haybittle spending function would therefore be used with a fixed 2-sided p-value threshold of 0.1% at the interim. The p-value threshold at the final analysis will be adjusted to account for the interim analysis, based on the actual observed information fraction for the primary endpoint. If as planned there are 75 patients included at the interim and 150 patients at the final analysis, the critical threshold at the final analysis will be 4.9% (East Version 6.4).

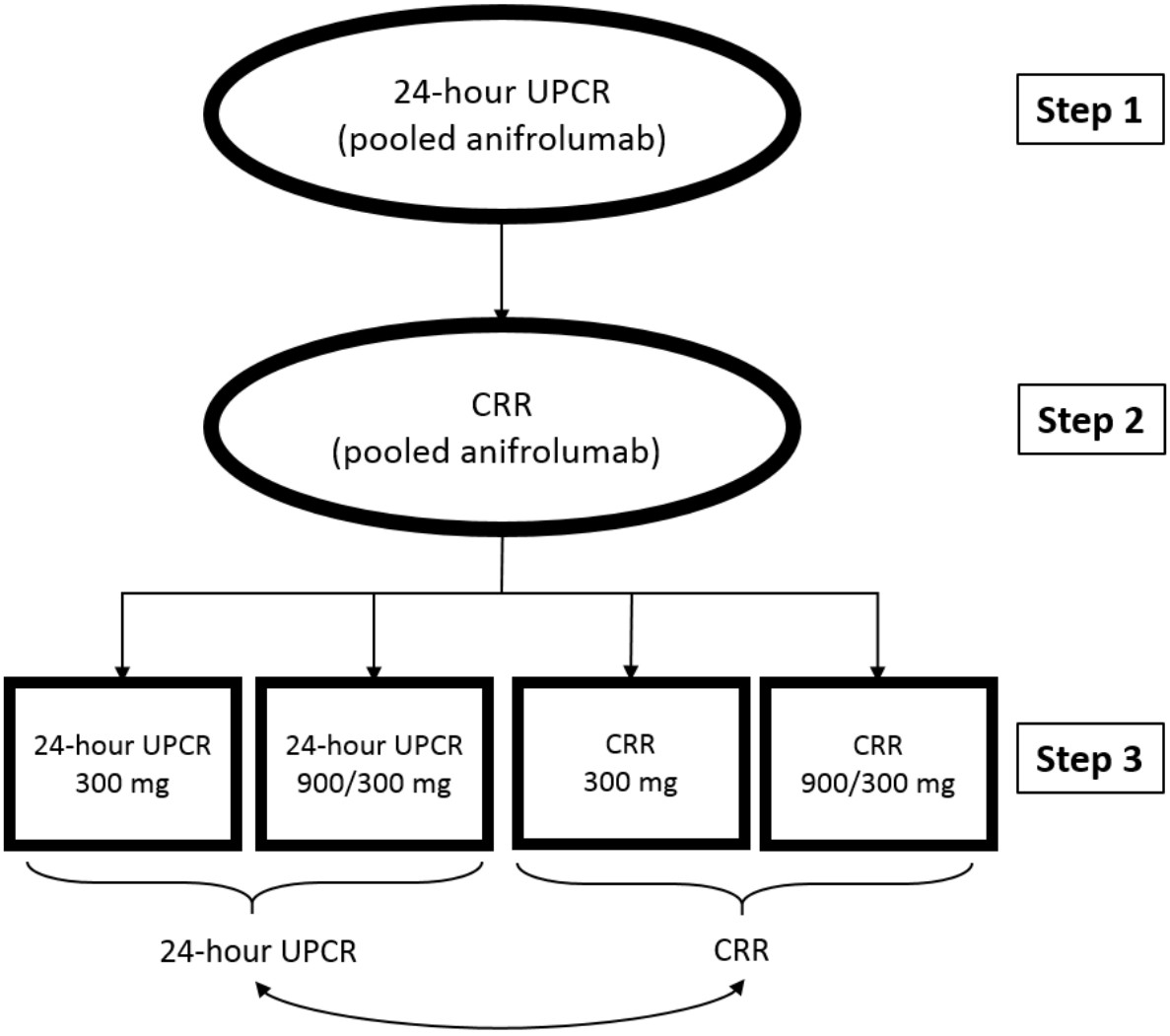
Additional and repeat analyses as previously defined will be performed at the end of the second year extension period. Additional details are provided in the SAP.

8.6 Testing strategy to account for multiplicity considerations

While the primary and secondary objectives are defined based on the comparison between the pooled anifrolumab and placebo groups, the respective endpoints will also be tested for the individual anifrolumab regimens. The following hierarchical testing strategy (presented in Figure 3) will be used to provide strong control of the familywise error rate (FWER). As

described in Section 8.5.11, if the interim analysis is performed, some alpha will be spent, and the alpha at final analysis will be calculated based on a Peto-Haybittle spending function and the number of subjects at each analysis. The description below assumes that a 2-sided alpha of 0.049 is being used at the final analysis.

Figure 3 Multiplicity correction at final analysis



- Step 1: The pooled anifrolumab regimens will be tested versus placebo at a 2-sided 4.9% significance level with regards to 24-hour UPCR (primary endpoint).
- Step 2: If the null hypothesis is rejected at Step 1, then the pooled anifrolumab regimens will be tested versus placebo at a 2-sided 4.9% significance level with regards to CRR (secondary endpoint).

- Step 3: If the null hypothesis is rejected at Step 2, then both anifrolumab regimens are individually tested against placebo, each at 2.45% significance level, for both endpoints (24-hour UPCR and CRR). If both regimens can be rejected for either endpoint, then alpha can be recycled and both regimens can be tested at 4.9% significance level for the remaining endpoint.

At Steps 1 and 2, strong control is due to the sequence testing. At Step 3, alpha is controlled given that the pooled hypothesis is tested first and if false, the two hypotheses corresponding to the two regimens for that endpoint cannot both be true.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first subject is entered into the study, an AstraZeneca Designee 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 systems utilised.

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

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

9.1.1 Training and certification for systemic lupus erythematosus assessments

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

- SLEDAI-2K
- PGA
- SLEDAI-2K based Flare Assessment Instrument
- SDI

These evaluations must be performed by the Investigator or another qualified physician, unless prior Sponsor approval has been obtained for any other clinically trained site personnel with documentation of adequate assessment experience.

After attending study presentations (ie, Investigator Meeting) or after completion of training modules, all Investigators and designated site physicians must pass an examination in order to obtain certification for all disease evaluation assessments. Investigators and designated site personnel must be trained and certified prior to subjects entering screening at their respective sites. All assessments and certifications must be renewed via the study online training website prior to expiration and must remain current (not expire) throughout the course of the study. If there is a change in site personnel over the course of the study, new Investigators or physicians must be certified prior to performing the SLE assessments.

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

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

9.2 Monitoring of the study

During the study, an AstraZeneca Designee 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 Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

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).

9.2.1 Source data

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

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol (CSP) and the CSA, the terms of CSP 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 AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.2.4 SLE Data Medical Review Team

Data for SLE disease activity and damage indices (SLEDAI-2K, PGA, and SDI) as well as SLEDAI-2K based Flare Assessment Instrument will be reviewed by an independent Sponsor's delegate Medical Team. The SLE Data Medical Review Team (MR team) members are medically qualified individuals. The MR team will review all LN and SLE data in conjunction with any other relevant data (including medical history, AE, laboratory data, and concomitant medications as appropriate) that is necessary to characterise the subject's SLE. The MR team members will have access to an internal expert on SLE disease activity and damage indices for unanticipated issues with regard to interpretation of these indices.

A separate procedure will outline the review and escalation details. The MR Team will be utilised throughout the study to confirm SLEDAI-2K, PGA, SLEDAI-2K based Flare Assessment Instrument, and SDI scoring. The purpose of the independent review is to ensure medical plausibility, coherence, consistency, and clarity of data. The MR team will query any inconsistent scoring and follow for resolution of any discrepancy. The MR team will monitor trends in issues encountered during their review and liaise with the study team for additional training to be provided for the site staff or study monitoring team as appropriate. The MR team will remain blinded for the duration of the study. The MR team is separate from the Medical Monitoring team and works closely with the Medical Monitoring team.

9.3 Study timetable and end of study

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

The study is expected to start in Quarter 3, 2015 and to end by Quarter 3, 2020.

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

9.4 Data management

Data management will be performed by Sponsor Designee, according to the Global Data Operations Plan.

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

The Principal Investigator ensures the accuracy, completeness, and timeliness of the data recorded and the provision of answers to data queries according to the CSA. The Principal Investigator will sign the completed CRFs. After the study is completed, CRFs are archived on a CD and sent to each site.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Sponsor/Designee 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 per Sponsor/Sponsor's delegate's processes.

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 patient safety database and/or the investigational site. SAE reconciliation between safety data and clinical data will be performed by the Sponsor/Sponsor's delegate. The frequency depends on the expected volume of SAE reports and will be defined in the SAE Reconciliation Plan.

Management of external data

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

Steering committee

The primary objective of the Lupus Nephritis Steering Committee is to ensure the validity and integrity of all of the data (efficacy and safety) as well as the conduct of the trial according to GCP guidelines and to provide guidance for program progression. The safety of this trial will be reviewed by a distinct, separate committee known as the Data Safety Monitoring Board (DSMB) for whom a charter clearly documents their independent safety monitoring responsibilities.

Interim analysis

One interim analysis may be conducted after approximately 50% of subjects have completed the Week 52 visit.

Primary analysis

Primary efficacy and safety analyses will be performed once all data from the main study (up to and including Week 52) is available, cleaned and soft-locked. The study will also be unblinded at this stage for the team performing the analysis.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

10.3 Ethics and regulatory review

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

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

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

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

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

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

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

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

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

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

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

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

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

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

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

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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