CLINICAL STUDY PROTOCOL

ALX0061-C204

A Phase II Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-range Finding Study to Evaluate the Safety and Efficacy of ALX-0061 Administered Subcutaneously in Subjects with Moderate to Severe Active Systemic Lupus Erythematosus

Short Title:	A Phase II Study to Evaluate Safety and Efficacy of ALX-0061 in Subjects with Systemic Lupus Erythematosus
Study Drug:	ALX-0061
EudraCT n°:	2015-000372-95
IND:	123233
Sponsor Protocol Code:	ALX0061-C204
Sponsor:	Ablynx NV Technologiepark 21 9052 Zwijnaarde, Belgium
Phase of Development:	Phase II
Indication:	Systemic Lupus Erythematosus (SLE)
Protocol Date:	May 3, 2016
Protocol Version:	V3.0
Protocol Status:	Final

This study will be performed in compliance with the Clinical Study Protocol, the principles of Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

CONFIDENTIALITY STATEMENT

The information contained in this document, especially unpublished data, is the property of Ablynx NV (or under its control), and therefore provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your study staff, and applicable Independent Ethics Committee (IEC) /Institutional Review Board (IRB), and Competent Authorities (CA). It is understood that this information will not be disclosed to others without written authorization from Ablynx NV, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.

APPROVAL OF CLINICAL STUDY PROTOCOL

The Sponsor and the Investigator(s) agree to conduct the study as outlined in this Clinical Study Protocol. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator(s), and must be documented in writing.

Sponsor:

Name: [redacted]
Function: Medical Director, Ablynx NV

Signature – Date: *See signature page at the end of the document*

Investigator:

I have read Clinical Study Protocol ALX0061-C204 and agree to personally conduct or supervise the clinical study in accordance with the Clinical Study Protocol.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

I confirm that the study team and I will not implement any deviations from the Clinical Study Protocol without agreement of Ablynx NV, except where necessary to eliminate an immediate hazard to the patients.

I confirm that I am thoroughly familiar with the appropriate use of the study drug, as described in the Clinical Study Protocol and any other information provided by Ablynx NV.

I confirm that I am aware of and will comply with ICH-GCP.

Hence, I agree to supply Ablynx NV with any necessary information regarding the ownership interest and financial ties, to promptly update this information if any relevant changes occur during the course of the study, and that Ablynx NV may disclose any available information about such ownership interest and financial ties to regulatory authorities.

Signature – Date:

Principal Investigator Name:

Degree/Function:

Site details/Address:

CONTACT INFORMATION

Serious adverse event (SAE) reporting contact information and other contact details of the Sponsor and third parties are available in the "Investigator Site File".

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
aCL	Anti-cardiolipin
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
Anti-dsDNA	Anti double-stranded DNA
AST	Aspartate aminotransferase
β2 GPI	β2-glycoprotein I
BICLA	BILAG-based composite lupus assessment
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator
C3	Complement component 3
C4	Complement component 4
CA	Competent Authority
CDAI	Clinical Disease Activity Index
CH50	Hemolytic complement component 50
CHF	Congestive heart failure
CL	Total body clearance
CLASI	Cutaneous lupus erythematosus disease area and severity index
CMV	Cytomegalovirus
CNS	Central nervous system
CPK	Creatine phosphokinase
CRO	Contract research organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Clinical Trial Directive
CYP450	Cytochrome P450
DAS28	Disease activity score using 28 joint counts
dsDNA	Double-stranded deoxyribonucleic acid
DSMB	Data safety monitoring board
EBV	Epstein-Barr Virus
ECG	Electrocardiogram

(e)CRF	(Electronic) Case report form
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HSA	Human serum albumin
i.a.	Intra articular
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGRA	Interferon-gamma release assay
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
i.m.	Intramuscular(ly)
INR	International normalized ratio
IRB	Institutional review board
i.v.	Intravenous(ly)
IWRS	Interactive web response system
JAK	Janus kinase
LA	Lupus anti-coagulant
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MAD	Multiple ascending dose
mADA	Modified anti-drug antibodies
mBICLA	Modified BILAG-based composite lupus assessment
MCP	Metacarpophalangeal
MDRD	Modification of diet in renal disease

mIL-6R	Membrane-bound interleukin-6 receptor
mITT	Modified intent-to-treat
mSLEDAI	Modified systemic lupus erythematosus disease activity index
mSRI	Modified systemic lupus erythematosus responder index
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PBO	Placebo
PD	Pharmacodynamic
PGA	Physician global assessment
PIP	Proximal interphalangeal
PK	Pharmacokinetic
PP	Per-protocol
q2w	Every 2 weeks
q4w	Every 4 weeks
RA	Rheumatoid arthritis
SAA	Serum amyloid A
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous(ly)
SF-36	Short Form (36) Health Survey
SFI	SLEDAI flare index
sIL-6R	Soluble interleukin-6 receptor
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic lupus erythematosus disease activity index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SRI	Systemic lupus erythematosus responder index
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TGFβ	Transforming growth factor-β
Th17	T helper 17 cell
TK	Toxicokinetics
Treg	Regulatory T cell
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
uMCP-1	urinary monocyte chemoattractant protein-1

VAS	Visual analogue scale
VH	Heavy chain variable region
WHO	World Health Organization

CHANGES COMPARED TO PREVIOUS VERSION(S)

Version 2.0 (dated May 7, 2015) compared to Version 1.0 (dated March 25, 2015)	
Version n° and date were adapted throughout the document (incl. headers and footers). Section "Changes compared to previous version(s)" was completed.	
Original section/page	Change/Rationale
P 1 Title page, P 13 (protocol synopsis)	For consistency, the IND n° was added in addition to the EudraCT n°.
P 1 (Title page)	Contact information with regard to the CRO was deleted as multiple CROs are involved in this study.
P 14-15 (protocol synopsis) P 48 (Section 3.2.1.)	Inclusion criterion 1 was updated to take into account that the definition of adult age can differ between countries and regions. In addition, inclusion criterion 7 was reworded for clarification purposes.
P 16-17 (protocol synopsis) P 50-51 (Section 3.2.2.)	Exclusion criterion 1 was updated to clarify which assessment result (screening) is to be considered for eligibility. In addition, a typo has been corrected in exclusion criterion 6 and a clarification was added in exclusion criterion 20.
P 19-21 (protocol synopsis) P 52 (Section 3.2.3.2.) P 57-59 (Section 3.3.6.)	Wording with regard to the terms background and rescue medication was changed to clarify that this concerns the standard of care medication as per local practice or a change of this medication.
P 21 (protocol synopsis) P 52 (Section 3.2.3.2.)	A discontinuation criterion was updated to clarify that discontinuation of study drug administration will be considered in case subjects experience a renal or CNS flare.
P 26-27 (Schedule of Assessments)	The schedule of assessments was updated to clarify that CLASI and exploratory biomarkers will also be assessed at the time of early termination.
P 27 (Schedule of Assessments) P 78 (Section 3.4.10.)	An incorrect abbreviation was corrected.
P 28 (Schedule of Assessments) P 46 (Section 3.1.2.) P 75-76 (Section 3.4.8.2.) P 77-78 (Section 3.4.9.)	The assessment of ESR was removed from the protocol for following reasons: - This is not an essential parameter needed for the planned analysis. - Other parameters (CRP, fibrinogen) that reflect the inflammation status of the subject are measured. - Avoid unblinding of the treatment when ESR is locally assessed and reported by study staff.
P 31 (Section 1.1.2.)	A sentence with missing verb was completed.
P 75 (Section 3.4.8.2.)	For pregnancy testing, it was clarified that in case local regulations require more frequent pregnancy testing, this will apply.
P 76 (Section 3.4.8.2.)	The wording on laboratory re-tests was updated to differentiate between re-test at screening and re-tests during the study.
P 83 (Section 3.5.3.)	A statement was deleted as it only applies in European countries and this study will be conducted in non-EU countries as well.
P 84 (Section 3.5.5.)	The text in the section with regard to follow-up of AEs was updated to clarify that all AEs will be followed until satisfactory outcome.
P 106 (Appendix 9.1.)	Appendix 9.1. was updated to correct a typo error.

Version 3.0 (dated May 3, 2016) compared to Version 2.0 (dated May 7, 2015)	
Version n° and date were adapted throughout the document (incl. headers and footers). Table of Contents and List of Abbreviations was updated and the Section "Changes Compared to Previous Version(s)" was completed.	
Section	Change/Rationale
Synopsis and Section 3.2.1.	Clarification of inclusion criterion 2 to reflect that the diagnosis of SLE should have occurred for at least 6 months prior to screening and that at screening the ACR and/or SLICC criteria need to be fulfilled.
Synopsis and Sections 3.2.1. and 3.4.5.2.	Wording has been updated to delete the incorrect reference range of the assay to measure anti-dsDNA (inclusion criterion 5) and clarify that the Farr assay is used at the central lab.
Synopsis, Sections 3.2.1., 3.2.2., and 3.3.6.1.	The dose of the allowed medication mycophenolate mofetil has been updated from max 1.5 g/day to max 2.0 g/day to allow inclusion of patients receiving the usual dose in SLE patients (inclusion and exclusion criteria 6). In addition, the units of methotrexate and cyclosporine dosing regimens have been corrected/further specified (typographical errors).
Synopsis and Section 3.2.2.	Wording has been updated to specify that exclusion criterion 1, i.e., having an A score on the revised BILAG-2004, not only applies to the screening assessment but also at baseline for the organ systems that can be clinically assessed at that timepoint. Exclusion criterion 3 (on concurrent infections) has been updated to clarify that subjects with clinically non-significant infections (e.g., mild localized herpes simplex infections or tinea pedis) can be enrolled in the study and exclusion criterion 7 (on central neurological problems) has been updated for clarification purposes.
Synopsis, Sections 3.2.3.2. and 3.3.6.2.	Wording has been updated to clarify that "until Week 4" means the Week 4 visit (including the per-protocol allowed time window of 5 days).
Synopsis and Section 3.6.5.1.	Wording has been added in the description of the analysis of the primary efficacy endpoint to specify that only subjects discontinuing before Week 24 will be treated as non-responders for this endpoint at this timepoint.
Schedule of Assessments	For clarity, the local laboratory assessment has been emphasized by moving this to a separate line in the Schedule of Assessments.
Sections 3.1.1. and 3.6.8.	A typographical error has been corrected.
Section 3.1.2.	The volume of syringe A with placebo was corrected from 0.5 mL to 1 mL (typographical error) in the description of blinding for dosing Group 3.
Section 3.3.6.1.	A clarification with regard to prior therapies has been added.
Sections 3.3.6.1. and 3.3.6.2.	Wording has been added to clarify that after Week 24, the dose of NSAIDs may be adjusted based on the Investigator's discretion.
Section 3.3.6.3.	Wording has been added to clarify that an intrauterine device or diaphragm with condom by partner is also acceptable in case the Investigator judges that hormonal contraception is not appropriate.
Section 3.4.1.1.	Wording has been added to clarify that if the screening period has to be exceeded due to exceptional logistical issues, the Medical Monitor is to be contacted as soon as possible for further instructions.
Sections 3.4.3.8. and 3.6.2.	Wording has been added to specify that the SFI will be calculated as detailed in the statistical analysis plan (SAP).

Sections 3.4.5.1., 3.4.7.1., 3.4.8., and 3.4.9.	The blood volumes needed for some assessments have been corrected (e.g, due to use of other tubes than originally planned).
Section 3.4.8.1.	Wording has been added to clarify that the Investigator may exceptionally decide to interrupt study drug treatment for one dose according to his/her medical judgment in case of an AE.
Section 3.4.8.2.	The laboratory parameter creatine phosphokinase (CPK) has been added to the list of biochemistry parameters to be analyzed, as is creatinine to the list of urinalysis parameters. Wording has been added to more accurately reflect what will be tested to screen for hepatitis and to clarify that additional pregnancy testing can be done in case local medical practice requires this. In addition, clarifications have been added to the statements with regard to follow up of unexplained or unexpected clinical laboratory tests.
Section 3.5.1.1.	To avoid confusion, the statement on assessment of severity of AEs related to laboratory abnormalities has been deleted.
Appendix 9.6.	Appendix 9.6 of the protocol, which included the initial version of the BILAG-2004, was updated to include the current version of BILAG-2004 (dated 2009) as this version will be used during the course of this study (as this is the latest validated version).

PROTOCOL SYNOPSIS

Protocol Title:

A Phase II Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-range Finding Study to Evaluate the Safety and Efficacy of ALX-0061 Administered Subcutaneously in Subjects with Moderate to Severe Active Systemic Lupus Erythematosus

Protocol Short Title:

A Phase II Study to evaluate safety and efficacy of ALX-0061 in subjects with systemic lupus erythematosus

Study Drug:

ALX-0061, a Nanobody directed towards the interleukin-6 receptor (IL-6R)

EudraCT n°:	**IND n°:**
2015-000372-95	123233

Sponsor Protocol Code:

ALX0061-C204

Sponsor:

Ablynx NV
Technologiepark 21
9052 Zwijnaarde, Belgium

Phase of Development:

Phase II

Indication:

Systemic Lupus Erythematosus (SLE)

Study centers:

Multicenter, multinational study

Objectives:

Primary objective:

- To assess the efficacy and safety of different dose regimens of ALX-0061 administered subcutaneously (s.c.) to subjects with moderate to severe active, seropositive SLE compared to placebo.

Secondary objectives:

- To assess the pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, flare rate, steroid reduction and health-related quality of life, with different dose regimens of ALX-0061.

Study Type and Treatments Administered:

This is a multicenter, randomized, double-blind, placebo-controlled, dose-range finding Phase II study of ALX-0061 administered s.c. on top of standard of care, in subjects with moderate to severe active, seropositive SLE.

Subjects will be randomly assigned in a 1:1:1:1:1 ratio to receive either 75 mg ALX-0061 every 4 weeks (q4w), 150 mg ALX-0061 q4w, 150 mg ALX-0061 every 2 weeks (q2w), 225 mg ALX-0061 q2w or placebo, up to and including Week 46. To maintain the blind, all randomized subjects will receive study drug as 2 s.c. injections every 2 weeks, as described further below.

Subjects will be followed for efficacy through Week 48, and for safety through Week 58.

Study Population:

Subjects with moderate to severe active, seropositive SLE

Number of Subjects:

Approximately 300 subjects in 5 treatment arms randomized in a 1:1:1:1:1 ratio, stratified by geographic region.

Inclusion Criteria:

Each subject must satisfy the following criteria at screening and baseline to be enrolled in the study:

1. Male or female adults ≥ 18 years and < 65 years of age at the time of signing the informed consent form (ICF). The minimum age for adults will depend on local regulations.

2. Have a diagnosis of SLE for at least 6 months prior to screening and fulfill the 1997 American College of Rheumatology (ACR) or 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria.
3. Have moderate to severe active SLE, for the purpose of this study defined by a 2000 SLE disease activity index (SLEDAI-2K) score ≥ 6 at screening.
4. Have at least one A or one B score on the revised 2004 British Isles Lupus Assessment Group (BILAG-2004) criteria for the mucocutaneous and/or musculoskeletal system.
5. Have seropositive disease at screening for antinuclear antibodies (ANA ≥ 1:80) and/or anti-dsDNA (value above upper limit of laboratory normal range as measured by Farr assay) measured at the central laboratory.
6. Subject at least must be on one or more of the following treatments for SLE:
   a. If subject is on oral corticosteroids, the dose should be equivalent to a maximum dose of 25 mg of prednisone/day and stable for at least 4 weeks prior to baseline.
   b. If subject is on antimalarials, he or she must have received antimalarials for at least 12 weeks with a stable dose of max. 400 mg/day for at least 4 weeks prior to baseline.
   c. If subject is on immunosuppressants: azathioprine (max. 150 mg/day), mycophenolate mofetil (max. 2.0 g/day), methotrexate (max. 25 mg/week), cyclosporine (max. 200 mg/day), leflunomide (max. 20 mg/day), treatment duration must be at least 12 weeks with a stable dose for at least 4 weeks prior to baseline; either alone or in combination with corticosteroids and/or hydroxychloroquine.
7. If immunosuppressants were previously given but have been stopped, the last dose should have been received more than 4 weeks prior to baseline; for leflunomide and hydroxychloroquine, a leflunomide or hydroxychloroquine treatment-free period of at least 12 weeks should be respected (unless an adequate cholestyramine wash-out was done for leflunomide).
8. If subject is on angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker, the dose should have been stable for 4 weeks prior to baseline.
9. Chest radiograph performed within 12 weeks prior to the screening visit (or performed during the screening period) documenting no evidence of malignancy, infection, or abnormalities suggestive of tuberculosis (TB; report must be obtained and available in the subject's study file prior to baseline).
10. Are considered eligible according to the following TB screening criteria:
    a. Have no history of latent or active TB prior to screening. An exception is made for subjects with a history of latent TB and documentation of having completed appropriate treatment for latent TB prior to screening. It is the responsibility of the Investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination during screening.
    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specialized in TB to undergo additional evaluation and, if warranted, receive appropriate treatment.

d. Have a negative interferon gamma release assay (IGRA) screening test result. A subject whose initial IGRA test result is indeterminate should have the test repeated while still fulfilling the other TB criteria for inclusion. The test should not be repeated in case other risk factors for TB are present. In case the test is again indeterminate, the subject will be excluded. In case of a positive IGRA test result due to previous latent TB, the subject is eligible if adequate documentation of completed anti-TB treatment prior to screening is available.
e. Have a chest radiograph, read by a qualified radiologist, whose diagnostic assessment is consistent with no evidence of current active TB or old inactive TB, and taken within 12 weeks prior to screening as part of standard of care or during the screening period. In case local regulations do not allow radiographs during the study, a radiograph as part of standard of care should be available prior to screening.

11. Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized and hysterectomized women) must have a negative pregnancy test and must agree to use two generally accepted adequate contraceptive methods (1 highly effective and 1 barrier method e.g., hormonal contraception in combination with condom by partner) from screening until at least 3 months after last dosing.
    Male subjects must use condoms for the duration of the study and for at least 3 months after last dosing.
12. Capability to comprehend and willingness to sign an ICF, which must be obtained prior to any study-related procedures (vulnerable subjects will be excluded, except subjects from ethnic minority groups who may participate).
13. An understanding, ability and willingness to adhere to the study visit schedule and other protocol requirements.

Exclusion Criteria:

Subject meeting the following criteria at screening and baseline will not be enrolled in the study:

1. Have an A score on the revised BILAG-2004 other than in the mucocutaneous and/or musculoskeletal system at screening and at baseline for the organ systems that can be clinically assessed.
2. Have a systemic inflammatory disease other than SLE, including but not limited to psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis or Lyme disease.
3. Clinically significant infection treated or needing treatment with intravenous (i.v.) antibiotics, i.v. antivirals, or i.v. antifungals within 4 weeks prior to baseline or oral antibiotics, oral antivirals, or oral antifungals within 2 weeks prior to baseline. Patients with clinically non-significant infections, e.g., mild cases of localized herpes simplex infections or tinea pedis can be enrolled.
4. Any active or recurrent viral infection that based on the Investigator´s clinical assessment makes the subject unsuitable for the study, such as current

Cytomegalovirus (CMV) or Epstein-Barr Virus (EBV) infection or recurrent / disseminated herpes zoster.

5. Have a history of, or current, class III or IV congestive heart failure (CHF), as defined by the New-York Heart Association; history of unstable angina pectoris, myocardial infarction, cerebrovascular accident, thromboembolic event within 12 months before screening.
6. Have active lupus nephritis requiring cyclophosphamide or mycophenolate mofetil more than 2.0 g/day or other therapy not permitted by the protocol.
7. Have active or recent (within 6 months) lupus-related central neurological problems (including lupus headache) or severe central nervous system (CNS) disease.
8. Have drug-induced lupus.
9. Have a history of demyelinating diseases such as multiple sclerosis.
10. History of diverticulitis or symptoms of acute diverticulitis with confirmatory imaging (i.e., CT scan).
11. Any history of malignancy or lymphoproliferative disease, except for successfully-treated non-melanoma skin cancer or resected cervical carcinoma *in situ.*
12. Have a transplanted organ or received stem cell transplantation.
13. Major surgery (including joint surgery) within 8 weeks prior to screening or hospitalization for a clinically relevant event within the 4 weeks prior to screening or planned major surgery during study or within 3 months after study end.
14. Have been treated with i.v. immunoglobulins, cyclophosphamide or tacrolimus within 12 months prior to baseline.
15. Have received i.v., intra-articular (i.a.), intramuscular (i.m.) or high dose (> 25 mg/day) oral corticosteroids during the 4 weeks prior to baseline.
16. Have a known hypersensitivity to the active product or any excipient of the study drug.
17. Have received approved or investigational biological therapies within 6 months or 5 half-lives of the concerned therapy (whichever is longer) prior to baseline.
18. Have received non-biological investigational therapies within 4 weeks or 5 half-lives of the concerned therapy (whichever is longer) prior to baseline.
19. Have received prior therapy blocking the IL-6 pathway, such as but not limited to ALX-0061, sirukumab, tocilizumab, sarilumab, clazakizumab, olokizumab, or Janus kinase (JAK) inhibitors at any time.
20. Abnormality in screening laboratory test results:
    a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 1.5 times the upper limit of normal (ULN).
    b. Hemoglobin ≤ 85 g/L (8.5 g/dL).
    c. Platelet count ≤ 75 x 10^9/L (75,000 cells/mm³).
    d. White blood cell count ≤ 2.2 x 10^9/L (2,200 cells/mm³).
    e. Neutrophils: ≤ 1.5 X 10^9/L.
    f. Estimated proteinuria > 1 g/day measured by spot urine protein to creatinine ratio of 1.
    g. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m² (based on the 'modification of diet in renal disease' [MDRD] formula).

h. Any other clinically significant abnormal screening laboratory results as evaluated by the Investigator.

21. Positive screening for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
22. Known history or presence of alcohol or drug abuse.
23. Blood donation (> 500 mL) or a comparable blood loss within 3 months prior to baseline.
24. Planned donation of germ cells, blood, organs, bone marrow during the course of the study or within 6 months thereafter.
25. Female subjects who are planning to become pregnant during the study or within 3 months after last dosing or male subjects who are considering fathering a child during the study and within 3 months after last dosing.
26. Pregnant woman or female subjects who are breastfeeding.
27. History of anaphylactic reactions.
28. Administration of a live, attenuated vaccine within 3 months before dosing with ALX-0061, or anticipation that such a live attenuated vaccine will be required during the study or within 6 months after last dosing.
29. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Study medication and treatments administered:

- ALX-0061 Drug Product:
  - Active substance: ALX-0061 Nanobody
  - Activity: ALX-0061 Nanobody binds to the Interleukin-6 receptor (IL-6R) and inhibits the interaction between the IL-6 ligand and the receptor subunit, thereby preventing receptor signaling.
  - Pharmaceutical formulation: ALX-0061 Drug Product is a clear, yellow to brown-yellow solution in an aqueous medium with a nominal concentration of 150 mg/mL of ALX-0061 and containing the following excipients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 (Tween 80), sucrose, and water for injection. ALX-0061 will be supplied as a sterile liquid for s.c. injection at a volume of 0.5 mL or 1.0 mL in pre-filled single-use syringes. No preservatives are present.
  - Route and volume of administration: s.c. injections at a volume of 0.5 mL or 1 mL.

- Placebo:
  - Substance: placebo
  - Activity: none
  - Pharmaceutical formulation: the composition of placebo is identical to that of ALX-0061 Drug Product, except for the active substance. Placebo will be supplied as a sterile liquid for s.c. injection at a volume of 0.5 mL or 1.0 mL in pre-filled single-use syringes. No preservatives are present.
  - Route and volume of administration: s.c. injections at a volume of 0.5 mL or 1 mL.

To maintain the blind, all randomized subjects will receive study medication as 2 s.c. injections (one of 0.5 mL and one of 1.0 mL) every 2 weeks as described in detail in section "Treatment Blinding".

Group 1 (N=60) Placebo
Placebo s.c. injections at Week 0 (Day 1) and q2w thereafter, up to and including Week 46.

Group 2 (N=60) 75 mg q4w
ALX-0061 75 mg s.c. injections at Week 0 and q4w thereafter, up to and including Week 44. To maintain the blind, subjects in this group will also receive placebo s.c. q2w up to and including Week 46.

Group 3 (N=60) 150 mg q4w
ALX-0061 150 mg s.c. injections at Week 0 and q4w thereafter, up to and including Week 44. To maintain the blind, subjects in this group will also receive placebo s.c. q2w, up to and including Week 46.

Group 4 (N=60) 150 mg q2w
ALX-0061 150 mg s.c. injections at Week 0 and q2w thereafter, up to and including Week 46. To maintain the blind, subjects in this group will also receive placebo s.c. q2w, up to and including Week 46.

Group 5 (N=60) 225 mg q2w
ALX-0061 225 mg s.c. injections at Week 0 and q2w thereafter, up to and including Week 46. These subjects will not receive placebo injections.

Standard of care medication for SLE:

- The dose of oral corticosteroids (equivalent to ≤ 25 mg of prednisone/day) should have been stable for at least 4 weeks prior to baseline, and the corticosteroid dose needs to be kept stable as much as possible through Week 24.
- As an exception, the protocol allows for both dose decrease (tapering) and dose increase with the following limits:
  a) If necessary based on the Investigator's clinical judgment, initiation of a short period (maximum 1 week) increase of prednisone (up to a maximum dose of 15/20/25/30 mg/day depending on the baseline dose; see table below) is allowed until the Week 4 visit (i.e., Week 4 ± 5 days) with a return to the baseline value by Week 12. This increase is not allowed if the disease activity improves.
  b) In case lowering of the dose of prednisone is desired before the primary endpoint, tapering can be allowed up to Week 12 according to the specifications below:

	Baseline dose	Increase for max. 1 week during first 4 weeks	Tapering allowed between Baseline and Week 12
1	16 to 25 mg/day	Increase to a maximum of 30 mg/day	No dose decrease below 50% of baseline dose
2	11 to <16 mg/day	Increase to a maximum of 25 mg/day	No dose decrease below 75% of baseline dose
3	7.5 to <11 mg/day	Increase to a maximum of 20 mg/day	No dose decrease < 7.5 mg/day
4	<7.5 mg/day	Increase to a maximum of 15 mg/day	No tapering will be allowed

c) Between Week 12 and Week 24, no increase nor decrease of the dose in prednisone is allowed.

d) After Week 24, tapering of the dose of oral corticosteroids to a target of ≤ 7.5 mg/day by Week 40 is recommended, at a rate that can be decided by the Investigator as clinically indicated. While tapering the dose between Weeks 24 and 40, an increase to the dose preceding the last taper step will be allowed.

e) Doses for concomitant antimalarials and/or immunosuppressants must be stable for the duration of the entire study. The dose may be reduced or the medication temporarily discontinued for abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the dose change and reason should be clearly documented.

f) In case of worsening of disease or a flare, the Investigator will decide on the need for increase of dose of oral corticosteroids, use of i.v. or i.m. corticosteroids, start or increase of the dose of anti-malarial or immunosuppressant, according to his/her local clinical practice. The Investigator can also decide on whether study drug can be continued or not. Subjects needing such change to standard of care therapy for SLE will be considered as treatment failures and imputed as non-responders in the analysis of the primary endpoint. This does not apply to the transient increase in oral corticosteroid dose that is allowed within the protocol until the Week 4 visit (Week 4 ± 5 days; see above).

Study Duration:

The anticipated maximum study duration per subject is 58 weeks after randomization; subjects will be followed for efficacy through Week 48 and for safety through Week 58.

The end of study is defined as the time of the last visit of the last subject participating in the study.

- Screening Period:
  Subjects will be screened to confirm their eligibility for participation in this study within 4 weeks prior to baseline.

- Treatment and Assessment Period:
  Eligible subjects will receive treatment at Week 0/Day 1 and up to and including Week 46. Subjects will return for ambulatory visits every 2 weeks.
  All post-baseline visits may occur at the indicated week ± 5 days throughout the study.

- Final Visit/ Early Termination Visit:
  - Subjects should return for the assessment visit at Week 48, and for the Follow-Up Visit at Week 58 (12 weeks after the last study drug administration at Week 46).
  - Subjects who discontinue study drug but are not withdrawing consent for post-treatment follow-up, should return for an early termination visit within 3 weeks after the last study drug administration. Subjects should also return for a Follow-up Visit 12 weeks after last study drug administration.

For details on visit assessments, see the Schedule of Assessments.

Discontinuation criteria:

Study drug administration must be discontinued in case of:

- Withdrawal of consent.
- Serious hypersensitivity reaction.
- Abnormalities in laboratory test results:
  - ALT and/or AST elevations:
    - > 3 - ≤5 x ULN, confirmed by repeat testing on 2 consecutive visits
    - > 5 x ULN (CTCAE ≥ grade 3)
  - absolute neutrophil count < 1 x 10^9/L (CTCAE ≥ grade 3)
  - platelet count < 50 x 10^3/µL (CTCAE ≥ grade 3)
- Diagnosis or suspicion of a serious infection (requiring parenteral antibiotics and/or hospitalization) if interruption of study drug is needed for more than one dose or if deemed necessary by the Investigator.
- Diagnosis of TB.
- Malignancy.
- Pregnancy or pregnancy planned within study period.
- Initiation of prohibited medication, as discussed with Sponsor/Medical monitor.
- In case of interruption of study drug administration for 2 consecutive doses.
- The randomization code is broken prematurely by the Investigator or his/her staff.
- Demyelinating disease.
- CHF class III or IV as defined by the New York Heart Association, unstable angina pectoris, myocardial infarction, cerebrovascular accident, thromboembolic event.
- If the Investigator or the Sponsor's Medical Monitor deems it is in the subject's best interest, e.g., in case of renal or CNS flare.

Discontinuation of study drug must be considered for subjects who develop a severe study drug injection-site reaction or a severe hypersensitivity reaction.
The Investigator will assess if study drug administration can be continued or not in case of change to standard of care therapy for SLE (except for forbidden treatment e.g.,

cyclophosphamide or another biologic, when study drug administration will be discontinued).

Assessments:

The following assessments are performed at the time points defined in the Schedule of Assessments:

Efficacy evaluation

Primary endpoint: The primary endpoint is the percentage of subjects who achieved a response at Week 24 according to the composite mBICLA (BILAG-based Combined Lupus Assessment) score. mBICLA responders are defined as subjects who meet all of the following criteria:

(1) BILAG-2004 improvement: all A scores at baseline improved to B/C/D, and all B scores improved to C or D.
(2) no worsening in disease activity: no new BILAG-2004 A scores and ≤1 new B score.
(3) no worsening of total mSLEDAI-2K score from baseline.
(4) no significant deterioration (< 10% worsening) in Physician global assessment (PGA).
(5) no treatment failure (i.e., new or increased immunosuppressives or anti-malarials; or non-protocol allowed increased oral or parenteral corticosteroids; or premature discontinuation from study treatment).

A modified SLEDAI-2K index (mSLEDAI-2K) will be derived from the standard index by omitting 1 of the standard items (low complement).

Secondary endpoints will include:
- Composite endpoint (m)BICLA over time.
- Composite endpoint mSRI as well as standard SRI over time.
- (m)SRI with more stringent (m)SLEDAI-cut-offs: SRI-5, SRI-6, SRI-7, SRI-8 over time.
- Change from baseline in mSLEDAI-2K total score as well as standard SLEDAI-2K measured over time.
- Number and percent of subjects with BILAG-2004 improvement.
- BILAG-2004 (total score) over time.
- Improvement in individual organ systems of the BILAG-2004 over time.
- Number of BILAG-2004 systems in which activity increased, decreased or remained the same compared to previous visit (BILAG-2004 systems tally) over time.
- Change from baseline in PGA over time.
- Change from baseline in patient's global assessment over time.
- Change from baseline in proteinuria/urine sediment/serum creatinine/eGFR over time.
- Proportion of treatment failures (defined as non-protocol allowed increase in steroid dose, start i.v. or i.m. steroids, start or increase of immunosuppressant) at Week 24 and at Week 48.

- Reduction in flare rate at Week 24 and at Week 48.
  - Severe flare defined as a new A score in any system of the BILAG-2004 index; moderate flare defined as a new B score following a C, D or E score.
  - SLEDAI flare index (SFI).
- Percent change from baseline in daily dose of steroids at Week 24 and 48.
- Percent subjects whose prednisone equivalent dose was >7.5 mg/day at baseline and reduced to ≤7.5 mg/day during Weeks 40–48 without experiencing a flare.
- Percent subjects who are able to discontinue prednisone by Week 48 without experiencing a flare.
- Changes from baseline in the physical and mental component scores of SF-36 at Week 24 and at Week 48.
- 28 Joints count over time and change from baseline in 28 joint count over time.
- Cutaneous lupus erythematosus disease area and severity index (CLASI) over time and change from baseline evaluation at Week 12, 24 and Week 48.
- PK parameters.
- PD markers, including total sIL-6R, CRP, fibrinogen, anti-dsDNA, C3, C4, CH50.

Pharmacokinetics

Samples for determination of ALX-0061 serum levels.

Pharmacodynamics

Samples for determination of biomarker levels, including but not limited to total sIL-6R, CRP, fibrinogen, anti-dsDNA, C3, C4, CH50.

Samples for determination of additional biomarker levels (exploratory), including but not limited to uMCP-1, plasma cells, T helper 17 (Th17) and regulatory T (Treg) cells.

Immunogenicity

Samples for determination of anti-ALX-0061 antibodies.

Safety

Safety assessments will include:
- Physical examination.
- Vital signs measurement.
- Electrocardiogram (ECG).
- Blood chemistry (including liver enzymes and lipids), hematology (including neutrophils and platelets) and coagulation parameters. Lupus anti-coagulant (LA), anti-cardiolipin (aCL) and anti-β_2-glycoprotein I (β_2-GPI) antibodies will be evaluated at screening and Week 24.

- Adverse events (AEs) (including local tolerability and hypersensitivity reactions) and serious AEs.

Statistical Methods:

Sample size and Power
Up to approximately 300 subjects will be randomized over 5 treatment arms in a 1:1:1:1:1 ratio. Randomization will be stratified by geographic region.

Simulations were performed to evaluate the power of detecting a significant dose-response relationship, i.e., whether changes in ALX-0061 dose regimen lead to significant changes in mBICLA response rate at Week 24 by using the MCP-Mod methodology [1]. A set of 5 plausible candidate models containing both monotonous and non-monotonous exposure-response shapes was defined. For these models an estimated placebo response rate of 25%, and a difference in response rate between the ALX-0061 dose regimen with the largest response rate and placebo of 25% was assumed, taking into account a discontinuation rate of 15% (homogeneous over treatment arms). With this methodology a sample size of 60 subjects per arm will provide at least 85% power at a family-wise 5% significance level.

Primary efficacy endpoint evaluation:
mBICLA response rates at Week 24 will be analyzed using the MCP-Mod methodology. The analysis will be performed using the modified intent-to-treat (mITT) population of all subjects who have received at least 1 administration of study drug and according to the treatment for which they were assigned.

Subjects with missing mBICLA response data at Week 24, including those who have discontinued study drug before Week 24, as well as subjects with treatment failure, will be treated as non-responders (non-response imputation approach). Treatment failure is defined as non-protocol allowed increase in steroid dose, start i.v. or i.m. steroids, start or increase of immunosuppressant.

Primary efficacy endpoint evaluation will also be performed using the per-protocol (PP) population.

Summary statistics (frequencies, proportions) for mBICLA response rate at Week 24 and Week 48 will be provided by treatment group.

All other evaluations:
All secondary efficacy endpoints will be summarized by treatment group, using the observed data in the mITT population. For continuous secondary efficacy endpoints, summary statistics include mean, standard deviation, median, minimum and maximum, while for categorical secondary efficacy endpoints frequencies and proportions are provided.

All safety, PD and ADA analyses will be performed using the safety population of all subjects who received at least 1 dose of study drug. Analyses will be performed using the treatment that the subject actually received.

Pharmacokinetic analysis will be performed on the PK population.

PK/PD modeling will be performed to characterize the change of efficacy endpoints versus ALX-0061 exposure. The results of this exploratory analysis will be presented in a separate report.

All other data will be summarized using descriptive statistics as appropriate.

SCHEDULE OF ASSESSMENTS[A]

Study Period	Screening	Base-line (Day)	Treatment and Assessment Period (Week ± 5 days)																							Early Termination Visit	Follow-up (± 2 weeks)
Study Visit	**Within 28 days prior to baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**Within 3 weeks after last dosing**	**12 weeks after last dosing**
Written informed consent	x																										
Demographics, medical history	x																										
Physical examination	x	x						x						x						x						x	x	x
Vital signs [b]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x	x	x
12-lead ECG [c]	x																									x	x	
Screening Hep B, Hep C, HIV [d]	x																											
IGRA test	x																											
Chest radiograph [e]	x																											
TB evaluation [f]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Review of entry criteria	x	x																										
Prior medication	x																											
Concomitant medication		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Randomization		x																										
ANA, LA, aCL, β_2-GPI [g]	x													x														
Study drug allocation and administration		x	x	x	x	x	x	x	x	x	x	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	x	
BILAG-2004	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
Physician's Global Assessment		x		x		x		x		x		x		x		x		x		x		x		x		x	x	
Patient's Global Assessment		x												x												x	x	
SF-36		x												x												x	x	
28 joint count	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
CLASI [h]		x						x						x												x	x	

Study Period	Screening	Base-line (Day)	Treatment and Assessment Period (Week ± 5 days)																							Early Termination Visit	Follow-up (± 2 weeks)
Study Visit	**Within 28 days prior to baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**Within 3 weeks after last dosing**	**12 weeks after last dosing**
SLICC/ ACR damage score		x																										
Adverse events[i]	→																									→	→
Clinical laboratory analyses[j]	x	x	x	x		x		x		x		x		x		x		x		x		x		x		x	x	x
Urinalysis	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	
Pregnancy test (serum at screening/urine at other visits)	x	x						x						x												x	x	x
PK [k]		x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x	x	
PD biomarker (sIL-6R) [k,]		x		x		x		x		x				x				x				x				x	x	x
PD biomarker (others) [k,l]	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	x
Exploratory biomarkers[m]		x				x								x												x	x	
Immunogenicity [k,i]	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	x
Local lab analyses (Direct Coombs) [n]	x	x		x		x		x		x		x		x		x		x		x		x		x		x	x	

[a] If assessments are planned at the same time, following guidance should be followed: 1) ECG and vital signs should be assessed prior to blood sampling, 2) Patient assessments (patient's global assessment and SF-36) should occur prior to physician's assessments, 3) Study drug should be dosed after all other assessments have been performed.

[b] Vital signs (assessment after 5 min in supine position): including height, weight, blood pressure, pulse and temperature. Height measurement is only required at the screening visit.

[c] To be performed after 5 min in supine position.

[d] Lab tests for hepatitis B will be done according to the guidelines [2].

[e] If a chest radiograph has not been performed within 12 weeks prior to screening as part of standard of care, a chest radiograph must be performed during the screening period. In case local regulations do not allow radiographs during the study, a radiograph as part of standard of care should be available prior to screening.

[f] If TB is suspected at any time during the study, chest radiography and IGRA or a comparable local practice test should be performed.

[g] Lupus anti-coagulant (LA), anticardiolipin (aCL) and anti-β_2-glycoprotein I (β_2-GPI) antibodies will be evaluated at screening and Week 24. Anti-nuclear antibodies (ANA) will be evaluated at screening only.

[h] The CLASI will be performed in interested sites having experience in this assessment.

[i] In case of acute or delayed severe/serious hypersensitivity reactions, an additional blood sample should be collected as soon as possible after the start of the event.

[j] On dosing days, blood sampling will be performed pre-dose. Subjects will be fasted for at least 10h at baseline and Weeks 4, 8, 12, 24, 36 and 48 and/or the Early Termination Visit for assessment of fasting serum lipids. Samples will be assessed by a central laboratory.

[k] On dosing days, PK, PD biomarker and immunogenicity samples will be taken predose.

[l] CRP, fibrinogen, anti-dsDNA, C3, C4, CH50.

[m] Urine samples for uMCP-1 will be collected in all subjects. Blood samples for immunophenotyping will be collected in a subset of subjects (at selected sites based on qualification).

[n] Parameters to be assessed by the local laboratory include Direct Coombs and INR (INR for subjects on vitamin K antagonist only). INR will be performed at Weeks 0, 2, 4, 8, and 12, and every 4 weeks (or more frequent if considered necessary by Investigator) thereafter up to Week 48 (or Early Termination Visit), and Follow-Up Visit.

1. INTRODUCTION

ALX-0061 has been developed by the Sponsor as a new compound neutralizing pro-inflammatory activity in the Interleukin-6 (IL-6) pathway. Based on its mode of action, ALX-0061 is currently in development for the treatment of autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

The currently proposed clinical study is intended to evaluate the efficacy and safety of different dose regimens of ALX-0061 administered subcutaneously (s.c.) on top of standard of care to subjects with moderate to severe active, seropositive SLE.

1.1. SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a complex autoimmune disorder, characterized by the presence of pathogenic autoantibodies directed against nuclear components, such as anti-nuclear antibodies [ANA] and anti-double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies. More than 90% of patients with SLE have ANA, which are sensitive but not specific for SLE. Anti-dsDNA are more specific and fluctuate with disease activity [3].

The prevalence of SLE is estimated to be approximately 1 per 1000, but varies with ethnicity (higher in African-Americans and Hispanics compared to Caucasians). The disease is approximately 10-times more prevalent in women compared to men [3].

SLE is a clinically heterogeneous disease that affects multiple organs, with the most common manifestations ranging from rash, fatigue and mucocutaneous and musculoskeletal conditions, to more severe renal and neurological manifestations. SLE is characterized by periods of active disease, alternated with temporary remission and relapses.

1.1.1. TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Treatment aims to manage and control symptoms during the acute periods of active disease, and to minimize the risk of flares during periods of remission. In mild, non-organ threatening disease, antimalarials, low-dose steroids, and transient use of non-steroidal anti-inflammatory drug (NSAIDs) can be recommended [4]. In case of worsening of disease, hydroxychloroquine is usually maintained along with additional therapy, and the steroid doses are usually increased [3].

For patients with more severe disease, or when steroid dose cannot be reduced to acceptable levels, immunosuppressive agents such as azathioprine, mycophenolate mofetil,

and methotrexate (MTX) are usually recommended. For renal disease, cyclophosphamide and mycophenolate mofetil in combination with steroid treatment is often evaluated.

In addition to these more conventional therapies, biological agents which target specific cells or molecules within the abnormally functioning immune system are being developed. Belimumab, a B-lymphocyte stimulator (BLyS)-specific inhibitor, has been approved among others by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in addition to standard therapy to treat adults with active, autoantibody-positive SLE with a high degree of disease activity. In addition, rituximab, an anti-CD20 monoclonal antibody that induces B-cell depletion, is used in patients with severe disease not responding to conventional treatments, albeit off-label [5].

The drugs currently used to treat SLE can be associated with additional risks and complications. The chronic use of steroids for instance can lead to Cushingoid syndrome, increased risk of opportunistic infections, and the development of osteoporosis. Not surprisingly, ability to limit tapering chronic use of corticosteroids is generally considered of great clinical value in SLE management. Overall, there is substantial unmet medical need for newer, more effective and better-tolerated therapies for the treatment of SLE [6].

1.1.2. ROLE OF IL-6(R) IN PATHOPHYSIOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS

Several lines of evidence indicate that overexpression of IL-6 and IL-6R, as well as extended activation of the IL-6 pathway, are important factors in chronic auto-immune, inflammatory and proliferative diseases, B cell malignancy, Castleman's disease and various cancers [7, 8]. Based on its mode of action, ALX-0061 is currently under development for the treatment of autoimmune diseases such as SLE and RA. The IL-6 pathway is considered to be an important factor in SLE:

- An association between IL-6 and progression of lupus has been published for several murine models of SLE [9]. Therapeutic inhibition or knockout of IL-6(R) in several mouse models abrogated the SLE phenotype, while exogenous IL-6 increased SLE manifestations [10-16].
- In SLE patients, IL-6 levels are elevated in serum, urine, skin and cerebrospinal fluid (CSF), and are closely linked with specific disease manifestations, such as anti-dsDNA antibodies [10, 11, 14, 17, 18]. IL-6 levels are also increased in urine and in glomerular and tubular tissue of lupus nephritis patients [19-21].
- In addition, IL-6 plays a role in the B-cell hyperactivity and immune pathology of human SLE, and may have a direct role in mediating tissue damage (Figure 1) [10-12]. The dominant role of IL-6 in SLE pathogenesis is to accelerate autoantibody production by promoting the proliferation of autoreactive B cells. SLE autoreactive B cells constitutively express IL-6R and produce high levels of IL-6. Local production of IL-6 also contributes

to tissue damage via induction of chemokines and cell-adhesion molecules, leading to recruitment and infiltration of inflammatory cells. Furthermore, in SLE, an imbalance has been described between T-helper 17 (Th17) cells, a subset of inflammatory T cells that drives autoimmunity, and regulatory T (Treg) cells, which are important for the maintenance of immune tolerance [22, 23]. IL-6 is a crucial factor in the Th17/Treg cell balance, as it promotes the generation of Th17 cells and inhibits Treg cell development.

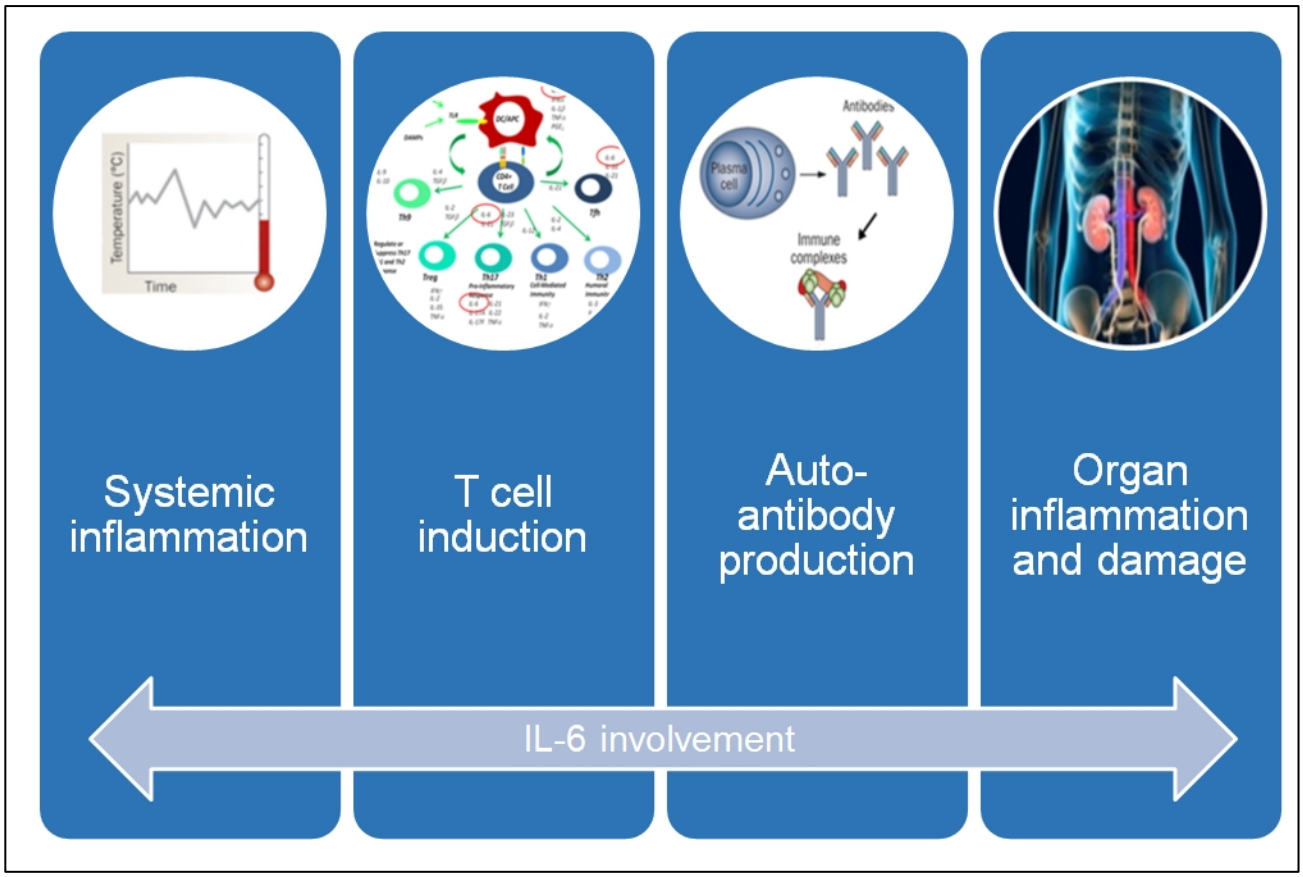


Figure 1: Involvement of IL-6(R) in the pathophysiology of SLE.

Several IL-6(R) targeting drugs, either receptor blockers or cytokine inhibitors, have been evaluated in early phase clinical studies in SLE, and preliminary safety and efficacy data have been obtained with e.g., the anti-IL-6R monoclonal antibody (mAb) tocilizumab, the anti-IL-6 (ligand) mAb sirukumab and a human anti-IL-6 (ligand) mAb (PF-04236921).
A small open-label study with tocilizumab (an anti-IL-6R monoclonal antibody [mAb]) in 16 patients with SLE showed encouraging results, with improvements in inflammatory and serologic markers, as well as clinical manifestations of lupus (including efficacy on joints and skin) [24]. Sirukumab was well tolerated in a Phase I study in patients with mild, stable, active cutaneous lupus erythematosus and SLE [25]. In a phase II study a notable reduction in proteinuria was observed in approximately 15-20% of treated immunosuppressed patients with refractory lupus nephritis (but no median improvement in proteinuria) and a

high frequency of serious adverse events (SAEs) [26]. A Phase II clinical trial with PF-04236921 in patients with active generalized SLE showed an efficacy signal, i.e., an improvement in composite endpoints of disease activity and a reduction of the risk for severe flares [27].

1.2. ALX-0061

The following paragraphs provide summary information on ALX-0061; for more detailed background information, please refer to the Investigator's Brochure.

1.2.1. GENERAL PROPERTIES

The active component in ALX-0061 solution for injection is a therapeutic protein, designated "ALX-0061 Nanobody". Nanobodies are a novel class of therapeutic proteins, and are based on the smallest functional fragments of single-chain antibodies that occur naturally in the *Camelidae* family. They have a high degree of homology (in terms of sequence and structure) to human immunoglobulin heavy chain variable region (V_H) domains, and can be further engineered and expressed by a variety of expression systems such as *Pichia pastoris*.

ALX-0061 Nanobody consists of 2 humanized and sequence-optimized variable domains derived from heavy chain-only llama:

- One domain (designated 20A11) binds to human IL-6 receptor (IL-6R).
- The second domain (designated ALB11) binds to human serum albumin (HSA), as a means to improve the pharmacokinetic (PK) properties of the Nanobody (half-life extension).

ALX-0061 Nanobody inhibits the interaction between the IL-6 ligand and receptor subunit, thereby preventing receptor signaling.

- IL-6 is a pleiotropic cytokine with a wide range of biological activities in the immune, hematopoietic, hepatic and neural system. IL-6 exerts its effect through binding to a non-signaling IL-6R subunit. This complex further interacts with two glycoprotein 130 (gp130) subunits, enabling signal transduction and subsequent biological effects.
- IL-6R is present in both a membrane-bound and a soluble form (mIL-6R and sIL-6R respectively). In its soluble form, IL-6R can activate gp130-positive cells that do not express mIL-6R on their surface (such as endothelial cells and synoviocytes), through a process called trans-signaling. Cells expressing the membrane-bound form of IL-6R (such as hepatocytes and selected white blood cell populations) can directly engage IL-6 in a process called classical signaling.

- ALX-0061 is a highly specific biological drug that targets and neutralizes both forms of IL-6R, with higher affinity for sIL-6R than mIL-6R.

The second domain of ALX-0061 was designed to improve the PK properties of the Nanobody by binding to HSA. Albumin is the most abundant protein in plasma and has a half-life of approximately 19 days in humans [28]. Binding to albumin (as a carrier) has been shown to lead to retention of the bound protein in circulation, with a resident time approaching that of the carrier molecule [28]. The domain directed against HSA (designated ALB11) extends the half-life of ALX-0061 by (i) minimizing Nanobody excretion via renal filtration through the formation of a Nanobody-albumin complex, and (ii) exploiting the long inherent half-life of albumin due to the neonatal Fc receptor mediated pathway, similar as for monoclonal antibodies via their Fc domain, but avoiding the effector functions of the latter.

1.2.2. MANUFACTURE

The manufacture of ALX-0061 Nanobody consists of an upstream process (i.e., fermentation of a *Pichia pastoris* strain that expresses the ALX-0061 Nanobody and secretes the product into the medium), and a downstream process (essentially harvest, capture, intermediate purification, polish, and formulation of the Nanobody). Additional information on the manufacture and pharmaceutical properties of ALX-0061 is included in the Investigator's Brochure.

1.2.3. NONCLINICAL STUDIES

Pharmacology
ALX-0061 was extensively characterized *in vitro*. The *in vivo* efficacy and the PK/pharmacodynamic (PD) properties of ALX-0061 were examined in naive cynomolgus monkeys, in an acute cynomolgus monkey model of IL-6-induced inflammation, and in a collagen-induced arthritis model in rhesus monkeys. PK was assessed during the toxicology studies in cynomolgus monkeys (toxicokinetics [TK]). Additionally, the impact of anti-drug antibodies (ADA) on the PK and PD of ALX-0061 was evaluated.

Toxicology
The toxicology program was carried out in cynomolgus monkeys, and consists of a single-dose intravenous (i.v.) dose-range finding toxicity study, Good Laboratory Practice (GLP)-compliant 13-week and 26-week repeated-dose i.v. toxicity studies, and a GLP-compliant 4-week repeated dose i.v./s.c. toxicity study.

All relevant nonclinical studies conducted with ALX-0061 are described in the Investigator's Brochure. The nonclinical data revealed no specific safety risks, based on the available safety pharmacology data, and local and systemic tolerability assessment.

1.2.4. EFFECTS IN HUMANS

A combined Phase I/II study in subjects with moderately to severely active RA, on a stable background of MTX, has been completed (Study ALX-0061-1.1/10). This placebo-controlled study included 28 subjects in an initial single ascending dose (SAD) part where single i.v. doses of 0.3, 1, 3, or 6 mg/kg were administered. In a subsequent multiple ascending dose (MAD) part, 37 subjects received multiple i.v. doses of 1 or 3 mg/kg every 4 weeks (q4w), or 6 mg/kg every 8 weeks, for 24 weeks in total.

A Phase I study (Study ALX0061-C102) assessing the bioavailability of single doses of ALX-0061, administered s.c. at 3 dose levels, using 2 corresponding single i.v. dose levels as reference, in healthy adult subjects, has been completed. This study included 70 subjects and studied doses of 50, 150, and 300 mg. The PK and PD results were used to bridge from i.v. to s.c. administration, and to determine the appropriate doses for the current Phase II study.

In addition, 2 Phase II studies in RA are ongoing:

- Study ALX0061-C201 is a multicenter, randomized, double-blind, placebo-controlled dose range finding Phase IIb study, conducted to evaluate the efficacy and safety of ALX-0061 administered s.c. in combination with MTX, in subjects with active RA despite MTX therapy.
- Study ALX0061-C202 is a multicenter, randomized, double-blind Phase IIb study conducted to evaluate efficacy and safety of dose regimens of ALX-0061 administered s.c. as monotherapy in subjects with active RA who are intolerant to MTX or for whom continued MTX treatment is inappropriate.

1.2.4.1. STUDY ALX-0061-1.1/10 IN SUBJECTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS

The results of the SAD and MAD parts of this study are discussed in detail in the Investigator's Brochure, and are briefly summarized below.

Efficacy
In the MAD part of the study, all ALX-0061 treatment combinations showed rapid and long-lasting improvements in disease activity (as measured by American College of Rheumatology [ACR], European League Against Rheumatism [EULAR], Disease Activity Score using 28 joint counts [DAS28], C-reactive protein [CRP], Clinical Disease Activity

Index [CDAI], and Boolean remission responses). There were high numbers of responders in all ALX-0061 treatment groups, with DAS28 remission or low disease activity observed in 54% of ALX-0061-treated subjects at Week 12. Overall, the efficacy profile obtained at Week 12 continued to improve during the subsequent 12 weeks of ALX-0061 treatment.

Pharmacokinetics
The PK of ALX-0061 appears dose-dependent, suggesting target-mediated disposition of the drug. A 2-compartment disposition model with parallel first-order (linear total body clearance [CL]) and Michaelis-Menten elimination (nonlinear or concentration-dependent CL) describes well the PK behavior of the drug, and is consistent with the more than proportional increase of exposure and half-life of drug with the increase of dose. Similar to monoclonal antibodies, the nanobody has a limited volume of distribution, corresponding to the plasma volume.

Pharmacodynamics
- All ALX-0061 groups received biologically effective doses: rapid and long-lasting increases in IL-6 and sIL-6R concentrations were observed across all ALX-0061 dose groups. The PD results confirmed that sIL-6R (and IL-6) concentrations can be used as a biomarker for target engagement by ALX-0061.
- Dosing q4w at 3 mg/kg yielded the highest exposure, as indicated by the observed average trough levels (~ 10 µg/mL), strongest biomarker response (based on sIL-6R profile), and the highest clinical remission rates.

Safety
- Single and repeated administration of ALX-0061 was well tolerated in all treatment groups, with a manageable and consistent safety profile for all ALX-0061 dose combinations.
- In the MAD part, the most commonly reported adverse events (AEs) observed after intake of ALX-0061 included headache, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), arthralgia, back pain, and joint swelling. Most of the events were mild or moderate and resolved during the treatment period.
- There were no clear trends in the occurrence or type of treatment-related AEs when comparing the individual ALX-0061 treatment groups, and there was no evidence to suggest that an maximum tolerated dose was reached.
- 3 subjects reported SAEs.
  In the SAD part, 1 subject (3 mg/kg ALX-0061) experienced an acute hypersensitivity during the first infusion of ALX-0061, which was stopped immediately. The subject was successfully treated in the hospital with anti-histaminic drugs, prednisone, and salbutamol.
  In the MAD part of the study, 1 subject (3 mg/kg q4w ALX-0061) experienced an SAE of cerebrovascular accident after having received 2 infusions of ALX-0061 in total. Although the subject recovered from the initial event, a second, more severe SAE of

cerebrovascular accident occurred several days later and the subject died. Both events were considered remotely related to study treatment by the Investigator.
One other subject with a confirmed Helicobacter pylori gastritis and history of short NSAID intake experienced an SAE of hemorrhagic gastritis (not related) and a linked SAE of upper gastrointestinal hemorrhage (remotely related). Both SAEs resolved before the end of the study.

- Four subjects reported AEs leading to withdrawal of study drug in the MAD part of the study: 1 subject with the SAE cerebrovascular accident (described above), 1 subject with rash and non-immunoglobulin (Ig) E mediated hypersensitivity reaction (probably related to the study drug), 1 subject with uncontrolled hypertension (remotely related to the study drug), and 1 subject with infected dermal cyst (remotely related to the study drug).
- Regarding laboratory abnormalities, a rapid and reversible decrease in neutrophils and platelets was seen in the majority of subjects after administration of ALX-0061. These decreases in neutrophil and platelet count seemed to be dose-related but did not reach clinically relevant levels. No AEs related to the decreases in neutrophil and platelet count (or other hematology parameters) were reported, except for 1 subject with mild leukopenia (without neutropenia).
- With the exception of individual subjects showing increases in liver parameters (mainly AST and/or ALT) beyond the normal range, there were no clinically relevant trends in mean liver or other safety-related biochemistry parameters (including lipids) across dose levels.

1.2.4.2. STUDY ALX-0061-C102 IN HEALTHY VOLUNTEERS

Overall, a single s.c. dose of ALX-0061 in the dose range of 50 to 300 mg was well-tolerated in a group of healthy male and female subjects. There were no severe AEs, deaths, other SAEs or AEs that resulted in study drug discontinuation.

In the s.c. treatment groups, the majority of possibly-related AEs were injection site reactions (mainly pain and/or erythema), which appeared to be dose-dependent across the dose range tested (50 mg to 300 mg). All injection site reactions were transient and of mild intensity and apart from these reactions, no specific AEs were reported very frequently or showed a dose relationship. Apart from these injection site reactions, no differences were observed compared to the i.v. administration groups.

As expected from the mechanism of action, a mild transient decrease in fibrinogen, neutrophils and high sensitivity (hs) CRP levels was observed following administration of ALX-0061. One subject in the 300 mg i.v. group showed an increase in ALT up to a maximum of 150 U/L, accompanied by a mild rise in AST and no rise in bilirubin. The ALT level had returned to baseline at follow-up.

The PK and PD results were used to determine the appropriate doses for the current Phase II study and are summarized in the Investigator's Brochure, and section 3.1.1.

1.2.5. BENEFITS AND RISK ASSESSMENT

IL-6 is a pleiotropic cytokine with an important role in a broad spectrum of biological events, therefore, potential risks related to inhibition of the IL-6 pathway, as well as potential risks inherent to the administration of therapeutic proteins, are considered.

- Inhibition of the IL-6 pathway has immunomodulatory effects, and has been reported to increase the risk for infection [29, 30]. So far, serious infections have not been reported for ALX-0061.

- Suppression of IL-6 activity is known to reduce the levels of acute phase proteins such as CRP, serum amyloid A (SAA), and fibrinogen [31, 32].
  - Rapid and long-lasting decreases in CRP, erythrocyte sedimentation rate (ESR), fibrinogen and SAA were observed across all ALX-0061 dose groups in study ALX-0061-1.1/10. In general, these pharmacological effects were reversible and associated with clinical response in signs and symptoms of RA.
  - In Study ALX0061-C102, results indicate a trend towards a minor decrease in fibrinogen and high sensitive (hs)CRP levels following administration of ALX-0061 in most subjects.

- Suppression of IL-6 signaling has been shown to lead to decreases in neutrophil and platelet counts [33].
  - In Study ALX-0061-1.1/10, a rapid and reversible decrease in neutrophils and platelets was seen in the majority of subjects after administration of ALX-0061 in the MAD part of the study. No AEs related to the decreases in neutrophil and platelet count (or other hematology parameters) were reported, except for 1 subject with mild leukopenia (without neutropenia; MAD part of the study).
  - In Study ALX0061-C102, the results show a tendency towards a mild and transient decrease neutrophil count.

- Increased transaminase levels (AST/ALT) in serum and increased cholesterol (high density lipoproteins [HDL], low density lipoproteins [LDL], and triglycerides) levels have been reported following pharmacological inhibition of the IL-6 pathway [34]. With the exception of individual subjects showing increases beyond the normal range, there were no clinically relevant trends in mean liver (ALT/AST/gamma glutamyltransferase [GGT]/lactate dehydrogenase [LDH]/bilirubin) parameters, mean lipid concentrations, or other safety-related biochemistry parameters across dose levels in Study ALX-0061-1.1/10 or ALX0061-C102.

- Recent data indicate that RA subjects have a generally increased rate of gastrointestinal perforation [35]. At this time, it is not clear whether IL-6 inhibitors further increase the risk of this complication beyond that observed in the general RA population. To date, no cases of gastrointestinal perforation have been observed following ALX-0061 administration.

- As with all therapeutic proteins used in humans, infusion reactions (e.g., either anaphylactic or anaphylactoid) cannot be excluded.
  - In Study ALX-0061-1.1/10, two hypersensitivity reactions were reported (one serious and one moderate). For additional details, please refer to the Investigator's Brochure (also see section 1.2.4.1).
  - In Study ALX0061-C102, no hypersensitivity reactions were reported.

- Administration of any protein therapeutic can lead to the development of ADA [36]. The currently available immunogenicity (ADA) results after i.v. and s.c. administration of ALX-0061 do not indicate risks related to pre-existing or treatment-emergent antibodies to ALX-0061.

In view of the early stage of development, it is not established whether the above-mentioned risks are clinically relevant for administration of ALX-0061. Potential benefit of ALX-0061 has been observed in Study ALX-0061-1.1/10, where RA patients had clinical response in signs and symptoms of their disease activity. Given the preclinical rationale, and the preliminary clinical data showing that IL-6 could be a relevant target in SLE patients, the currently proposed study will allow further assessment of the potential benefits as well as the risks in this patient population with an important unmet medical need.

2. OBJECTIVES

Primary objective:

- To assess the efficacy and safety of different dose regimens of ALX-0061 administered s.c. to subjects with moderate to severe active, seropositive SLE compared to placebo.

Secondary objectives:

- To assess the PK, PD, immunogenicity, flare rate, steroid reduction and health-related quality of life, with different dose regimens of ALX-0061.

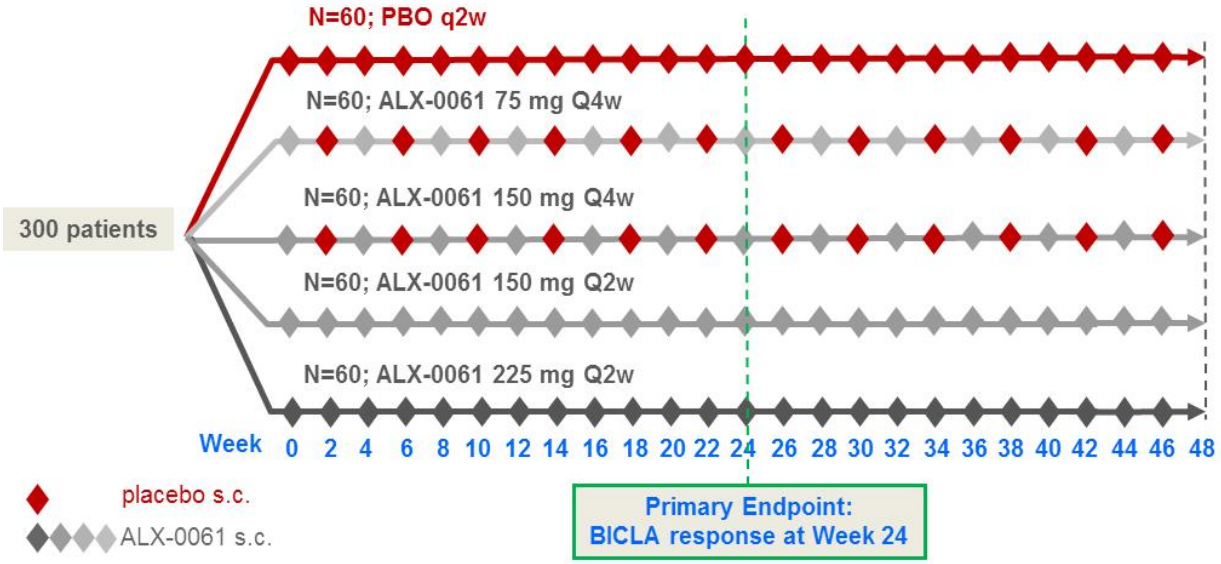
3. STUDY DESIGN

3.1. OVERALL STUDY DESIGN

3.1.1. STUDY OVERVIEW

This is a multicenter, randomized, double-blind, placebo-controlled, dose-range finding Phase II study of ALX-0061 administered s.c. on top of standard of care, in subjects with moderate to severe active, seropositive SLE. Approximately 300 subjects will be enrolled. An overview of the study design is included in Figure 2.

Figure 2: Overview of the design of Study ALX0061-C204



This study is expected to allow dose-range-finding of s.c. ALX-0061 in subjects with moderate to severe SLE. The selection of the doses to be used in this study was based on the results of study ALX0061-C102 in healthy volunteers (for PK, safety and tolerability), study ALX-0061-1.1/10 in RA patients (for efficacy or pharmacological activity), and the exposure levels measured in preclinical toxicology studies (for safety margin calculation).

A PK/PD model, developed based on data pooled from studies ALX-0061-1.1/10 and ALX0061-C102, was used to predict pharmacological activity or efficacy (using the available DAS28 response in RA patients) at different dose levels/regimens.

- Simulations of the PK assumed a mean body weight of 78 kg, with a standard deviation of 19 kg and a minimum and maximum body weight of 40 kg and 150 kg, respectively.
- The exposure-response provided an estimate of the EC_{50} (1.46 µg/mL) based on DAS28 as an indicator of pharmacological activity. To assess ALX-0061 exposure at doses

relevant for future Phase II studies, C_{trough} levels for different s.c. dosing regimens were simulated by the PK model, based on a typical individual with 78 kg body weight. These data suggest that trough serum levels after 75 mg q4w and 150 mg q4w dosing regimens would be below the estimated EC_{50} for pharmacological activity (DAS28).

Under the assumption that ALX-0061 activity is mainly driven by trough concentrations, and based on these simulations, the following dosing regimens were proposed for this study:

- 75 mg q4w
- 150 mg q4w
- 150 mg every 2 weeks (q2w)
- 225 mg q2w

The highest dose of 225 mg s.c. q2w is expected to be safe and well tolerated, based on the observations that doses of 3 mg/kg i.v. q4w, 6 mg/kg i.v. q8w and 6 mg/kg i.v. q4w (last dose evaluated in few non-responders) were well tolerated and had an acceptable safety profile in study ALX-0061-1.1/10.

The median model-predicted exposure at steady state for the highest dose group (225 mg s.c. q2w) was estimated at 595 day*µg/mL. This estimated exposure in human ($AUC_{ss,Tau}$) was compared with the observed exposure at steady state ($AUC_{ss,Tau}$) in the repeated dose toxicity studies in cynomolgus monkeys:

- In the 26-week repeated dose toxicity study, a median exposure at steady state of 17867 day*µg/mL was reported for the 100 mg/kg weekly i.v. dose, leading to an estimated safety margin of 60.
- In the 4-week repeated dose toxicity study, a median exposure at steady state of 10381 day*µg/mL was reported for the 100 mg/kg weekly s.c. dose, leading to an estimated safety margin of 35.

Based on these calculations, the doses selected to assess the exposure-response relationship of ALX-0061 in this study are covered by appropriate exposure margins.

As this is an add-on therapy study, all subjects (including subjects in the placebo group) will receive standard of care treatment for SLE in line with their severity of disease and according the Investigator's clinical practice. Having this placebo group will be of great value in the assessment of whether or not any abnormalities observed were due to ALX-0061 or to study procedures, and to allow statistical comparison of efficacy between ALX-0061 and placebo.

Subjects will have visits q2w up to Week 48. A Follow-up Visit is planned 12 weeks after the last dosing.

The composite British Isles Lupus Assessment Group (BILAG)-based composite lupus assessment (BICLA) response was chosen as primary endpoint to evaluate reduction in

disease activity in this diverse and heterogeneous disease since this composite endpoint allows an assessment of improvement in the involved organ system(s) without a concurrent worsening of the general condition or worsening in other organ systems. For details on primary statistical analysis in this study, please refer to section 3.6.5.1.

An adjudication process of the BILAG-2004 and Systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) assessments will be performed at Baseline, Week 24, and Week 48 (also see section 3.4.1.1).

Secondary endpoints will include the composite systemic lupus erythematosus responder index (SRI), the individual components (SLEDAI-2K, BILAG-2004 [normal improvement, enhanced improvement, and individual item improvement], and physician's global assessment [PGA]), patient's global assessment, 28 joint count, cutaneous lupus erythematosus disease area and severity index (CLASI), incidence of flare rate and potential for steroid reduction. Health-related quality of life (SF-36) will be used as supportive evidence of efficacy. In addition, endpoints, including BICLA responses, SRI responses and SLEDAI-2K, and BILAG-2004, will be documented over time, including earlier time points allowing assessment of time of onset of the effect.

Safety and tolerability assessments will include evaluation of (serious) AEs (including injection site and hypersensitivity reactions), laboratory assessment (including but not limited to acute phase proteins, neutrophils, platelets, liver enzymes and lipids), urinalysis, vital signs, electrocardiogram (ECG), and physical examination.

Additional planned assessments include the determination of ALX-0061 levels in serum and PD biomarkers (including sIL-6R) in blood. To assess immunogenicity, the presence of ADA will be measured in serum using a conventional ADA assay, with potentially further characterization by modified ADA (mADA) and neutralizing antibody (nAb) assay.

Study Treatment Allocation and Eligibility Process
At the Screening Visit, informed consent will be obtained from all subjects who are deemed potentially eligible for the study, according to the protocol-specified inclusion and exclusion criteria, for enrollment in the study. All data obtained at screening will also be centrally assessed in an eligibility evaluation, the sites will be informed whether a subject can be randomized.

At randomization, subjects will be randomized to receive either ALX-0061 or placebo, as described below (also see section 3.4.1.2 for additional information on randomization).

Eligible subjects will be randomized to 1 of 5 treatment groups in a 1:1:1:1:1 ratio. Subjects and investigational staff will be blinded for treatment and dose. Subjects will be followed for efficacy through Week 48, and for safety through Week 58.

Treatment Arms
Subjects assigned to one of the 4 ALX-0061 treatment groups will receive blinded treatment with ALX-0061 at a dose of 75 mg q4w, 150 mg q4w, 150 mg q2w, or 225 mg q2w. As the highest dose of ALX-0061 will be administered via 2 injections q2w, subjects in Groups 1-4 will also be administered 2 injections q2w with 1 or both syringes containing placebo, depending on the assigned treatment group, to maintain the blind. Blinding will be maintained until the last subject enrolled completes the final evaluations and the database is locked.

Group 1 (N=60) Placebo
Placebo s.c. injections at Week 0 (Day 1) and q2w thereafter, up to and including Week 46.

Group 2 (N=60) 75 mg q4w
ALX-0061 75 mg s.c. injections at Week 0 and q4w thereafter, up to and including Week 44. To maintain the blind, subjects in this group will also receive placebo s.c. q2w up to and including Week 46.

Group 3 (N=60) 150 mg q4w
ALX-0061 150 mg s.c. injections at Week 0 and q4w thereafter, up to and including Week 44. To maintain the blind, subjects in this group will also receive placebo s.c. q2w, up to and including Week 46.

Group 4 (N=60) 150 mg q2w
ALX-0061 150 mg s.c. injections at Week 0 and q2w thereafter, up to and including Week 46. To maintain the blind, subjects in this group will also receive placebo s.c. q2w, up to and including Week 46.

Group 5 (N=60) 225 mg q2w
ALX-0061 225 mg s.c. injections at Week 0 and q2w thereafter, up to and including Week 46. These subjects will not receive placebo injections.

Subjects will come to the site every 2 weeks for study drug administration, up to and including Week 46.

ALX-0061 will be supplied as a sterile liquid for s.c. injection at a volume of 1.0 mL or 0.5 mL in prefilled single-use syringes. More details (including information on drug accountability) are provided in section 3.3.

Each subject will stay in the study for approximately 62 weeks (up to 4 weeks of screening and 58 ± 2 weeks after randomization). The end of the study is defined as the last visit of the last subject participating in the study.

3.1.2. BLINDING

Since the 225 mg dose of ALX-0061 exceeds the volume that can be administered in a single injection, the placebo and ALX-0061 groups will have 2 different combinations of dosing to ensure the double-blinded design. All subjects are to receive 2 injections in succession (syringe A containing 1 mL and syringe B containing 0.5 mL) at each dosing day, every two weeks. Syringes containing ALX-0061 or placebo are a visual match.

Therefore, there will be a total of 5 dosing combinations in the study, with 4 possible active dose regimens. These dosing combinations are shown below:

When containing the active product, syringes A and B contain 150 mg and 75 mg of ALX-0061, respectively.

Placebo (Group 1)

Syringe A with placebo (1 mL) q2w starting at Week 0 (Day 1), up to and including Week 46.
Syringe B with placebo (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 1: Dosing schedule for Group 1

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Placebo 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 1 mL																								
ALX 0.5 mL																								

75 mg q4w (Group 2)

Syringe A with placebo (1 mL) q2w starting at Week 0, up to and including Week 46.
Syringe B with ALX-0061 (0.5 mL) q4w at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44, and *syringe B with placebo (0.5 mL)* q4w at Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42 and 46.

Table 2: Dosing schedule for Group 2

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Placebo 0.5 mL		X		X		X		X		X		X		X		X		X		X		X		X
ALX 1 mL																								
ALX 0.5 mL	X		X		X		X		X		X		X		X		X		X		X		X	

150 mg q4w (Group 3)

Syringe A with ALX-0061 (1 mL) q4w at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44, and *syringe A with placebo (1 mL)* q4w at Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42 and 46.
Syringe B with placebo (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 3: Dosing schedule for Group 3

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL		X		X		X		X		X		X		X		X		X		X		X		X
Placebo 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 1 mL	X		X		X		X		X		X		X		X		X		X		X		X	
ALX 0.5 mL																								

150 mg q2w (Group 4)

Syringe A with ALX-0061 (1 mL) q2w starting at Week 0, up to and including Week 46.
Syringe B with placebo (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 4: Dosing schedule for Group 4

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL																								
Placebo 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 0.5 mL																								

225 mg q2w (Group 5)

Syringe A with ALX-0061 (1 mL) q2w starting, at Week 0, up to and including Week 46.
Syringe B with ALX-0061 (0.5 mL) q2w starting at Week 0, up to and including Week 46.

Table 5: Dosing schedule for Group 5

	Visit (Weeks)																							
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Placebo 1 mL																								
Placebo 0.5 mL																								
ALX 1 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALX 0.5 mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

In order to protect the integrity of the data, ALX-0061 treatment assignment will be kept blinded for investigative sites, site monitors, subjects, vendors and Sponsor until the final database lock (including the Follow-up Visit 12 weeks after the last dosing).

Identification of Sponsor and vendor personnel who will have access to the unblinded data before final database lock, will be documented prior to their unblinding. The number of Sponsor personnel having access to the unblinded data will be limited.

Given the pronounced effect of an anti-IL-6 compound on the acute phase reactants, the results of CRP and fibrinogen tests performed by the central laboratory will not be communicated to the investigational sites and Contract research organization (CRO)/Sponsor (unless in case of an alert). If an investigational site requests these data, it will be provided after the end of the study.

Except for CRP and fibrinogen, laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator.
If the clinical condition of the subject warrants knowledge of the values of CRP or fibrinogen in order to provide appropriate medical care, the Investigator can request these assessments to be performed locally.

Emergency unblinding procedure
Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via the Interactive web response system (IWRS), which will be accessible 24 hours per day/7 days per week.

Unblinding by the Investigator should occur only in the event of AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject.

If the Investigator must identify the treatment assignment of an individual subject, the Investigator or qualified designee is to call the IWRS. Unblinding performed by the IWRS at the request of the Investigator is to be reported to the Sponsor. When possible the Investigator must first discuss options with the Medical Monitor.

Subjects for whom the code has been broken by the Investigator will have to discontinue treatment and all efforts must be made to conduct the Early Termination Visit and Follow-up Visit.

3.2. SELECTION OF STUDY POPULATION

It is estimated that 300 subjects will be enrolled in the study at approximately 100 sites globally.

3.2.1. INCLUSION CRITERIA

Each subject must satisfy the following criteria at screening and baseline to be enrolled in the study:

1. Male or female adults ≥ 18 years and < 65 years of age at the time of signing the informed consent form (ICF). The minimum age for adults will depend on local regulations.
2. Have a diagnosis of SLE for at least 6 months prior to screening and fulfill the 1997 ACR (see Appendix 9.1) or 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (see Appendix 9.2).
3. Have moderate to severe active SLE, for the purpose of this study defined by a SLEDAI-2K score ≥ 6 at screening.
4. Have at least one A or one B score on the revised BILAG-2004 criteria for the mucocutaneous and/or musculoskeletal system.
5. Have seropositive disease at screening for ANA (≥ 1:80) and/or anti-dsDNA (value above upper limit of laboratory normal range as measured by Farr assay) measured at the central laboratory.
6. Subject at least must be on one or more of the following treatments for SLE:
   a. If subject is on oral corticosteroids, the dose should be equivalent to a maximum dose of 25 mg of prednisone/day and stable for at least 4 weeks prior to baseline.
   b. If subject is on antimalarials, he or she must have received antimalarials for at least 12 weeks with a stable dose of max. 400 mg/day for at least 4 weeks prior to baseline.
   c. If subject is on immunosuppressants: azathioprine (max. 150 mg/day), mycophenolate mofetil (max. 2.0 g/day), methotrexate (max. 25 mg/week), cyclosporine (max. 200 mg/day), leflunomide (max. 20 mg/day), treatment duration must be at least 12 weeks with a stable dose for at least 4 weeks prior to baseline; either alone or in combination with corticosteroids and/or hydroxychloroquine.
7. If immunosuppressants were previously given but have been stopped, the last dose should have been received more than 4 weeks prior to baseline; for leflunomide and hydroxychloroquine, a leflunomide or hydroxychloroquine treatment-free period of at least 12 weeks should be respected (unless an adequate cholestyramine wash-out was done for leflunomide).
8. If subject is on angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker, the dose should have been stable for 4 weeks prior to baseline.

9. Chest radiograph performed within 12 weeks prior to the screening visit (or performed during the screening period) documenting no evidence of malignancy, infection, or abnormalities suggestive of tuberculosis (TB; report must be obtained and available in the subject's study file prior to baseline).
10. Are considered eligible according to the following TB screening criteria:
    a. Have no history of latent or active TB prior to screening. An exception is made for subjects with a history of latent TB and documentation of having completed appropriate treatment for latent TB prior to screening. It is the responsibility of the Investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination during screening.
    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specialized in TB to undergo additional evaluation and, if warranted, receive appropriate treatment.
    d. Have a negative interferon gamma release assay (IGRA) screening test result. A subject whose initial IGRA test result is indeterminate should have the test repeated while still fulfilling the other TB criteria for inclusion. The test should not be repeated in case other risk factors for TB are present. In case the test is again indeterminate, the subject will be excluded. In case of a positive IGRA test result due to previous latent TB, the subject is eligible if adequate documentation of completed anti-TB treatment prior to screening is available.
    e. Have a chest radiograph, read by a qualified radiologist, whose diagnostic assessment is consistent with no evidence of current active TB or old inactive TB, and taken within 12 weeks prior to screening as part of standard of care or during the screening period. In case local regulations do not allow radiographs during the study, a radiograph as part of standard of care should be available prior to screening.
11. Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized and hysterectomized women) must have a negative pregnancy test and must agree to use two generally accepted adequate contraceptive methods (1 highly effective and 1 barrier method e.g., hormonal contraception in combination with condom by partner) from screening until at least 3 months after last dosing.
    Male subjects must use condoms for the duration of the study and for at least 3 months after last dosing.
12. Capability to comprehend and willingness to sign an ICF, which must be obtained prior to any study-related procedures (vulnerable subjects will be excluded, except subjects from ethnic minority groups who may participate).
13. An understanding, ability and willingness to adhere to the study visit schedule and other protocol requirements.

3.2.2. EXCLUSION CRITERIA

Subject meeting the following criteria at screening and baseline will not be enrolled in the study:

1. Have an A score on the revised BILAG-2004 other than in the mucocutaneous and/or musculoskeletal system at screening and at baseline for the organ systems that can be clinically assessed.
2. Have a systemic inflammatory disease other than SLE, including but not limited to psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis or Lyme disease.
3. Clinically significant infection treated or needing treatment with i.v. antibiotics, i.v. antivirals, or i.v. antifungals within 4 weeks prior to baseline or oral antibiotics, oral antivirals, or oral antifungals within 2 weeks prior to baseline. Patients with clinically non-significant infections, e.g., mild cases of localized herpes simplex infections or tinea pedis can be enrolled.
4. Any active or recurrent viral infection that based on the Investigator´s clinical assessment makes the subject unsuitable for the study, such as current Cytomegalovirus (CMV) or Epstein-Barr Virus (EBV) infection or recurrent / disseminated herpes zoster.
5. Have a history of, or current, class III or IV congestive heart failure (CHF), as defined by the New-York Heart Association (Appendix 9.3); history of unstable angina pectoris, myocardial infarction, cerebrovascular accident, thromboembolic event within 12 months before screening.
6. Have active lupus nephritis requiring cyclophosphamide or mycophenolate mofetil more than 2.0 g/day or other therapy not permitted by the protocol.
7. Have active or recent (within 6 months) lupus-related central neurological problems (including lupus headache) or severe central nervous system (CNS) disease.
8. Have drug-induced lupus.
9. Have a history of demyelinating diseases such as multiple sclerosis.
10. History of diverticulitis or symptoms of acute diverticulitis with confirmatory imaging (i.e., CT scan).
11. Any history of malignancy or lymphoproliferative disease, except for successfully-treated non-melanoma skin cancer or resected cervical carcinoma in situ.
12. Have a transplanted organ or received stem cell transplantation.
13. Major surgery (including joint surgery) within 8 weeks prior to screening or hospitalization for a clinically relevant event within the 4 weeks prior to screening or planned major surgery during study or within 3 months after study end.
14. Have been treated with i.v. immunoglobulins, cyclophosphamide or tacrolimus within 12 months prior to baseline.
15. Have received i.v., intra-articular (i.a.), intramuscular (i.m.) or high dose (> 25 mg/day) oral corticosteroids during the 4 weeks prior to baseline.
16. Have a known hypersensitivity to the active product or any excipient of the study drug.

17. Have received approved or investigational biological therapies within 6 months or 5 half-lives of the concerned therapy (whichever is longer) prior to baseline.
18. Have received non-biological investigational therapies within 4 weeks or 5 half-lives of the concerned therapy (whichever is longer) prior to baseline.
19. Have received prior therapy blocking the IL-6 pathway, such as but not limited to ALX-0061, sirukumab, tocilizumab, sarilumab, clazakizumab, olokizumab, or JAK inhibitors at any time.
20. Abnormality in screening laboratory test results:
    a. ALT and/or AST ≥ 1.5 times the upper limit of normal (ULN).
    b. Hemoglobin ≤ 85 g/L (8.5 g/dL).
    c. Platelet count ≤ 75 x 10^9/L (75,000 cells/mm³).
    d. White blood cell count ≤ 2.2 x 10^9/L (2,200 cells/mm³).
    e. Neutrophils: ≤ 1.5 X 10^9/L.
    f. Estimated proteinuria > 1 g/day measured by spot urine protein to creatinine ratio of 1.
    g. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m² (based on the 'modification of diet in renal disease' [MDRD] formula [Appendix 9.4]).
    h. Any other clinically significant abnormal screening laboratory results as evaluated by the Investigator.
21. Positive screening for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
22. Known history or presence of alcohol or drug abuse.
23. Blood donation (> 500 mL) or a comparable blood loss within 3 months prior to baseline.
24. Planned donation of germ cells, blood, organs, bone marrow during the course of the study or within 6 months thereafter.
25. Female subjects who are planning to become pregnant during the study or within 3 months after last dosing or male subjects who are considering fathering a child during the study and within 3 months after last dosing.
26. Pregnant woman or female subjects who are breastfeeding.
27. History of anaphylactic reactions.
28. Administration of a live, attenuated vaccine within 3 months before dosing with ALX-0061, or anticipation that such a live attenuated vaccine will be required during the study or within 6 months after last dosing.
29. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

3.2.3. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

3.2.3.1. CRITERIA FOR WITHDRAWAL OF SUBJECTS FROM STUDY

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time, for any reason.

Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death will not have any follow-up assessments.

In the event a subject is discontinued from the study, the study monitor and the Sponsor will be informed immediately.

3.2.3.2. DISCONTINUATION OF STUDY DRUG

Subjects who have to discontinue study drug but are not withdrawing consent for post-treatment follow-up should return for the Early Termination Visit, planned within 3 weeks after the last study drug administration, as well as for the Follow-up Visit planned 12 weeks after the last study drug administration, according to section 3.4.1.3.

Study drug administration must be discontinued in case of:

- Withdrawal of consent.
- Serious hypersensitivity reaction.
- Abnormalities in laboratory test results:
  - ALT and/or AST elevations:
    - > 3 - ≤5 x ULN, confirmed by repeat testing on 2 consecutive visits
    - > 5 x ULN (CTCAE ≥ grade 3)
  - absolute neutrophil count < 1 x 10^9/L (CTCAE ≥ grade 3)
  - platelet count < 50 x 10^3/µL (CTCAE ≥ grade 3)
- Diagnosis or suspicion of a serious infection (requiring parenteral antibiotics and/or hospitalization) if interruption of study drug is needed for more than one dose or if deemed necessary by the Investigator.
- Diagnosis of TB.
- Malignancy.
- Pregnancy or pregnancy planned within study period.
- Initiation of prohibited medication, as discussed with Sponsor/Medical Monitor.
- In case of interruption of study drug administration for 2 consecutive doses.
- The randomization code is broken prematurely by the Investigator or his/her staff.

- Demyelinating disease.
- CHF class III or IV as defined by the New York Heart Association, unstable angina pectoris, myocardial infarction, cerebrovascular accident, thromboembolic event.
- If the Investigator or the Sponsor's Medical Monitor deems it is in the subject's best interest, e.g., in case of renal or CNS flare.

Discontinuation of study drug must be considered for subjects who develop a severe study drug injection-site reaction or a severe hypersensitivity reaction.

In case of worsening of disease or a flare, the Investigator will decide on the need for increase of dose of oral corticosteroids, use of i.v. or i.m. corticosteroids, start or increase of the dose of anti-malarial or immunosuppressant, according to his/her local clinical practice. The Investigator will also assess if study drug administration can be continued or not, except in case of initiation of forbidden treatment e.g., cyclophosphamide or another biologic, when study drug administration will be discontinued. Subjects needing such change to standard of care therapy for SLE will be considered as treatment failures and imputed as non-responders in the analysis of the primary endpoint. This does not apply to the transient increase in oral corticosteroid dose that is allowed within the protocol until the Week 4 visit (i.e., Week 4 ± 5 days).

A description of assessments to be performed for subjects who discontinue from the study or study drug is provided in section 3.4.1.3 (also see Early Termination Visit in the Schedule of Assessments).

For all subjects, every effort should be made to contact the Medical Monitor prior to discontinuing study drug administration, where medically feasible. If there is a medical reason for discontinuation, the subject will remain under the supervision of the Investigator until satisfactory health has returned unless the subject withdraws his/her consent and is no longer willing to come to the visits. Subjects who discontinue will not be replaced.

3.2.3.3. STUDY TERMINATION

If the Sponsor abandons the study prior to commencement of any protocol activities, and/or after IEC/IRB and Competent Authority (CA) approvals have been received, the Investigator or Sponsor must notify the IEC/IRB and CA by letter outlining the reasons for abandonment of the study, as required per national regulations.

At any time during the study, the Sponsor may suspend or terminate the study or part of the study for any reason. If the Investigator plans to suspend or terminate participation in the study, the Investigator will promptly inform the Sponsor and the IEC/IRB and provide them with a detailed written explanation.

Upon study completion, the Sponsor will provide the Investigator, IEC/IRB, and CA with final reports and summaries as required by regulations.

In case of suspension or halt due to safety reasons, the CA and IEC/IRB will be notified immediately and at the latest within the number of days as specified by local regulations after the study is halted, clearly explaining the reasons, and describe follow-up measures, if any, taken for safety reasons.

3.3. TREATMENT OF SUBJECTS

For an overview of the treatments to be administered, please refer to section 3.1.

3.3.1. RANDOMIZATION

After obtaining oral and written informed consent, subjects will be screened according to the inclusion and exclusion criteria and will receive a unique subject identification (ID) number, assigned by IWRS.

After approval by the eligibility review committee (also see section 3.4.1.1), subjects can be randomized.

At randomization, subjects will be reassessed and, if they meet the specified entry criteria, subjects will be allocated in a randomization to 1 of 5 treatment groups in a 1:1:1:1:1 ratio, and will receive a randomization number just prior to dosing according to the randomization scheme. Randomization will be stratified by geographic region.

3.3.2. IDENTITY OF STUDY DRUG

- ALX-0061 Drug Product:
  - Active substance: ALX-0061 Nanobody.
  - Activity: ALX-0061 Nanobody binds to the IL-6R and inhibits the interaction between the IL-6 ligand and the receptor subunit, thereby preventing receptor signaling.
  - Pharmaceutical formulation: ALX-0061 Drug Product is a clear, yellow to brown-yellow solution in an aqueous medium with a nominal concentration of 150 mg/mL of ALX-0061 and containing the following excipients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 (Tween 80), sucrose, and water for injection. ALX-0061 will be supplied as a sterile liquid for s.c. injection at a volume of 0.5 mL or 1.0 mL in pre-filled single-use syringes. No preservatives are present.
  - Route and volume of administration: s.c. injections at a volume of 0.5 mL and/or 1.0 mL.

- Placebo:
  - Substance: placebo.
  - Activity: none.
  - Pharmaceutical formulation: the composition of placebo is identical to that of ALX-0061 Drug Product, except for the active substance, and consists of excipients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 (Tween 80), sucrose, and water for injection. Placebo will be supplied as a sterile liquid for s.c.

injection at a volume of 0.5 mL or 1.0 mL in pre-filled single-use syringes. No preservatives are present.
- Route and volume of administration: s.c. injections at a volume of 0.5 mL and/or 1.0 mL.

The Sponsor will be providing adequate supplies of ALX-0061 and placebo for this study.

Details on study drug allocation and dosing are provided in section 3.1.1.

3.3.3. DRUG ACCOUNTABILITY

The Pharmacist or his/her designee is responsible for acknowledge receipt of each shipment of study drug and will verify the condition and quantity of the study drug.

The study drug will be kept in a locked and secured storage facility accessible only to those authorized by the Investigator to dispense the study drug.

The responsible person will keep an inventory. This will include the quantity of study drug received for the study and a record of the materials that are dispensed, to whom (subject number) and when.

The pharmacist, the Investigator and/or designated personnel will conduct a final inventory of the study drug supply and will record the results of this inventory in the Drug Accountability Form. Upon Sponsor approval, all study drug supplies will be returned to the depot, and/or will be locally destroyed according to local regulations and site procedures.

Instructions for drug accountability are available in the manuals concerning study drug and IWRS.

3.3.4. STUDY DRUG HANDLING

Instructions for study drug receipt, handling, storage and administration are available in the manuals concerning study drug and IWRS.

Packaging and Labeling
The study drug will be labeled in accordance with Annex 13 of EudraLex Volume 4 requirements and local regulations. Each label will contain but will not be limited to, study number, storage conditions, dosing instructions, Sponsor's name, address and telephone number.

One kit consists of a box containing 2 syringes. A randomization system will assign each of the treatment kits to a subject. The content of each treatment kit will be determined according to the randomization schedule.

Storage
Study drug will be provided under refrigerated conditions and must be stored in a secure, limited-access location under the storage conditions specified by the Sponsor.

ALX-0061 and placebo must be refrigerated at 2°C to 8°C (35.6 °F to 46.4 °F) and should be stored in the secondary packaging (sealed box) until administration. It should not be frozen or shaken.

Site storage conditions should be monitored by the site personnel and reviewed by the monitor during site visits. Deviations from the storage requirements must be documented and reported to the Sponsor, according to the instructions provided in the manual concerning study drug.

Dispensing
The Investigator or qualified designee(s) will dispense study drug to subjects who have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

Product Quality Complaint
Any malfunctioning pre-filled syringe has to be communicated (written or electronically) and returned to the Sponsor or its designee upon Sponsor's request.

3.3.5. STUDY DRUG INJECTIONS

ALX-0061 s.c. or placebo s.c. injections, as applicable, will be administered using the single-use pre-filled syringe by an appropriate licensed and authorized health professional.

At each administration, the subject will receive two s.c. injections in succession at a different quadrant in the abdominal region. As injections are to be performed q2w, the injections can be performed in an abdominal quadrant of choice. However, note that the area of administration needs to be evaluable for local skin reaction (normal skin without skin burns, scars or large tattoos in the area of administration). The abdominal quadrants used for the administrations will be recorded in the (electronic) Case Report Forms ([e]CRFs). At least until Week 12, subjects will remain at the site for 60 minutes after the injection in order to assess adverse reactions.
In case of an injection site reaction, it has to be followed-up and documented in which exact quadrant the skin reaction appears.

Detailed instructions for study drug administration are available in the manual concerning study drug.

3.3.6. MEDICATIONS OTHER THAN STUDY DRUG

Previous and concomitant medication will be recorded in the Patient's Medical File and in the (e)CRF up to the Follow-up Visit.

An overview of corticosteroid handling throughout the study can be found in Appendix 9.5.

3.3.6.1. MEDICATIONS STARTED PRIOR TO FIRST DOSING

Standard of care therapy for SLE:

The dose of oral corticosteroids (equivalent to ≤ 25 mg of prednisone/day) should have been stable for at least 4 weeks prior to baseline.

If subject is on antimalarials, he or she must have received antimalarials for at least 12 weeks with a stable dose of max. 400 mg/day for at least 4 weeks prior to baseline.

If subject started immunosuppressants prior to first dosing and is still taking this medication at baseline: azathioprine (max. 150 mg/day), mycophenolate mofetil (max. 2.0 g/day), methotrexate (max. 25 mg/week), cyclosporine (max. 200 mg/day), leflunomide (max. 20 mg/day), treatment duration must be at least 12 weeks with a stable dose for at least 4 weeks prior to baseline; either alone or in combination with corticosteroids and/or hydroxychloroquine.

If subject is on ACE inhibitor or angiotensin receptor blocker, the dose should have been stable for 4 weeks prior to baseline.

If subject is on NSAIDs, including aspirin and selective cyclooxygenase 2 inhibitors and other analgesics for SLE-related symptoms, the subject should receive stable doses of the usual marketed doses approved in the country in which the study is being conducted. After Week 24, the dose may be adjusted based on Investigator's discretion.

Prior use of any of the following medications is prohibited:

- If prior medications include immunosuppressants (i.e., if immunosuppressants were taken prior to first dosing but were stopped prior to the baseline visit), the last dose should have been received more than 4 weeks prior to baseline; for leflunomide and

hydroxychloroquine, a leflunomide or hydroxychloroquine treatment-free period of at least 12 weeks should be respected (unless an adequate cholestyramine wash-out was done for leflunomide).
- Use of any investigational or biological drug starting 6 months or 5 half-lives (whichever is longer) prior to baseline.
- Use of non-biological investigational therapies starting 4 weeks or 5 half-lives of the concerned therapy (whichever is longer) prior to baseline.
- Use of i.v. immunoglobulins, cyclophosphamide or tacrolimus within 12 months prior to baseline.
- Use of i.v., i.a., i.m. or high dose (> 25 mg/day) oral corticosteroids during the 4 weeks prior to baseline.
- Use of prior therapy blocking the IL-6 pathway, such as but not limited to ALX-0061, sirukumab, tocilizumab, sarilumab, clazakizumab, olokizumab, or JAK inhibitors at any time.
- Any live, attenuated vaccine within 3 months before dosing with ALX-0061, during the study or within 6 months after dosing.

3.3.6.2. THERAPY STARTED AFTER FIRST DOSING

Standard of care therapy for SLE:

- The dose of oral corticosteroids (equivalent to ≤ 25 mg of prednisone/day) should be kept stable as much as possible through Week 24.
- As an exception, the protocol allows for both dose decrease (tapering) and dose increase with the following limits:
  - If necessary based on the Investigator's clinical judgment, initiation of a short period (maximum 1 week) increase of prednisone (up to a maximum dose of 15/20/25/30 mg/day depending on the baseline dose; see table below) is allowed until the Week 4 visit (i.e., Week 4 ± 5 days) with a return to the baseline value by Week 12. This increase is not allowed if the disease activity improves.
  - In case lowering of the dose of prednisone is desired before the primary endpoint, tapering can be allowed up to Week 12 according to the specifications below:

	Baseline dose	Increase for max. 1 week during first 4 weeks	Tapering allowed between Baseline and Week 12
1	16 to 25 mg/day	Increase to a maximum of 30 mg/day	No dose decrease below 50% of baseline dose
2	11 to <16 mg/day	Increase to a maximum of 25 mg/day	No dose decrease below 75% of baseline dose
3	7.5 to <11 mg/day	Increase to a maximum of 20 mg/day	No dose decrease < 7.5 mg/day
4	<7.5 mg/day	Increase to a maximum of 15 mg/day	No tapering will be allowed

  - Between Week 12 and Week 24, no increase nor decrease of the dose in prednisone is allowed.

- After Week 24, tapering of the dose of oral corticosteroids to a target of ≤ 7.5 mg/day by Week 40 is recommended, at a rate that can be decided by the Investigator as clinically indicated. While tapering the dose between Weeks 24 and 40, an increase to the dose preceding the last taper step will be allowed.

- Doses for concomitant antimalarials and/or immunosuppressants must be stable for the duration of the entire study. The dose may be reduced or the medication temporarily discontinued for abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the dose change and reason should be clearly documented.

- NSAIDs, including aspirin and selective cyclooxygenase 2 inhibitors and other analgesics for SLE-related symptoms during the study should receive the usual marketed doses approved in the country in which the study is being conducted. Doses must remain stable but may be changed at the discretion of the Investigator after Week 24 or if the subject develops unacceptable side effects.

Change to Standard of care therapy for SLE

In case of worsening of disease or a flare, the Investigator will decide on the need for increase of dose of oral corticosteroids, use of i.v. or i.m. corticosteroids, start or increase of the dose of anti-malarial or immunosuppressant. Subjects needing such change to standard of care therapy for SLE will be considered as treatment failures and imputed as non-responders in the analysis of the primary endpoint. This does not apply to the transient increase in oral corticosteroid (prednisone) dose that is allowed within the protocol until the Week 4 visit (i.e., Week 4 ± 5 days) of the study (see above).

Prohibited Medication

Concomitant use of any of the following medications is prohibited while the subject is receiving the study drug and will prompt discontinuation of study drug:

- any investigational or biological drug.
- any live, attenuated vaccine within 3 months before dosing with ALX-0061, during the study or within 6 months after dosing.
- i.v. immunoglobulins, cyclophosphamide or tacrolimus.
- therapy blocking the IL-6 pathway, such as but not limited to ALX-0061, sirukumab, tocilizumab, sarilumab, clazakizumab, olokizumab, or JAK inhibitors.

Medicinal products which are metabolized via CYP450 3A4

Since IL-6 blocking might influence cytochrome P450 (CYP450) expression, subjects taking medicinal products which are metabolized via CYP450 3A4 (please refer to Flockhart, 2007

and Endres et al., 2006) will be closely monitored and their treatment will be adapted if necessary. For example, subjects on vitamin K antagonists will be monitored by assessment of international normalized ratio (INR) (see Schedule of Assessments), for subjects on statins, the lipid levels will be evaluated (see Schedule of Assessments), for subjects on cyclosporine, drug monitoring according to site routine practice should be performed.

3.3.6.3. CONTRACEPTIVES

Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized, and hysterectomized women) must agree to use 2 generally accepted adequate contraceptive methods of which 1 is a barrier method and 1 is a highly effective method (e.g., hormonal contraception stabilized for at least 1 month [oral, patch, depot, injectable, vaginal ring] in combination with condom by partner or should agree upon continuous abstinence from heterosexual contact from screening until at least 3 months after last dosing. If hormonal contraception is not appropriate according to the Investigator's judgment, an intrauterine device or diaphragm with condom by partner may also be acceptable.

No additional contraceptive method is needed in case of surgical sterilization (at least 3 months prior to screening), hysterectomy, or a partner who has been vasectomized (at least 3 months prior to screening).

Male subjects should use condoms for the duration of the study and for at least 3 months after last administration of study drug.

If additional local regulations apply, contraceptives should be used consistent with these.

3.3.7. TREATMENT COMPLIANCE

To ensure treatment compliance, study drug dosing will be administered by the Investigator or his/her designee at all visits.

The exact times of medication dosing at the clinical site will be recorded in the (e)CRF. Compliance will be further confirmed by bioanalytical assessment of ALX-0061 in serum samples. Treatments that are administered outside of the scheduled windows, as well as missed visits, will be recorded on the (e)CRF.

All subject's (e)CRFs will be monitored by a site monitor (also see section 5.2.4).

3.4. ASSESSMENTS

3.4.1. TIMING OF ASSESSMENTS

Written informed consent will be obtained before the first study-related procedure.

After informed consent has been obtained, each subject will be assigned a unique subject ID number.

AEs and prior/concomitant medications will be recorded from the time a signed and dated ICF is obtained until completion of the subject's last visit.

3.4.1.1. ELIGIBILITY PROCEDURES

At screening, which will take place within 28 days prior to baseline, subjects will be asked to attend the clinical site to be screened according to the inclusion and exclusion criteria (section 3.2) and to have other assessments performed as specified in the Schedule of Assessments. If the baseline visit cannot be performed within the 28-day screening period due to exceptional logistical issues, the Medical Monitor is to be contacted as soon as possible for further instructions.

Subjects discontinuing, for any reason, without completing all screening evaluations successfully and all subjects completing all screening evaluations successfully but who discontinue prior to randomization, will be considered "screen failures".

The results from the screening procedures needed to evaluate eligibility must be available prior to randomization. Assessment of eligibility of subjects will also be performed centrally and the sites will be informed if a subject can be randomized.

Week 0/Day 1 (Baseline)
For details with regard to randomization, please refer to section 3.3.1.

On Week 0/Day 1, assessments and procedures should be performed as outlined in the Schedule of Assessments.

3.4.1.2. TREATMENT AND ASSESSMENT PERIOD

Post-randomization Assessments
Eligible subjects will receive treatment at Week 0/Day 1 and q2w up to and including Week 46. Subjects will return for 24 ambulatory visits planned at Weeks 2, 4, 6, 8, 10, 12,

14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, and 48. All visits during the treatment and assessment period may occur at the indicated week ± 5 days throughout the study versus the date of the Baseline Visit.

Subjects prematurely discontinuing the study will return for an Early Termination Visit within 3 weeks after the last administration of study drug and a Follow-up Visit 12 weeks after the last administration of study drug. Note that for subjects who withdraw for reasons of lost to follow-up, informed consent withdrawal, or death, will not have any follow-up assessments.

The End of Treatment Visit will take place at Week 48 and a Follow-up Visit will be performed 12 weeks after the last administration of study drug.

All assessments will be performed as specified in the Schedule of Assessments.

Adjudication of BILAG and SLEDAI scores of baseline, Week 24, and Week 48 visits will be done centrally upon receipt of results.

Unscheduled visits may be planned to assess, confirm, and follow up on clinically relevant AEs or laboratory abnormalities. Findings made during these unscheduled visits should be reported in the designated sections of the (e)CRF.

Missed Visits:

- If a subject misses a visit/dose but a new visit can be performed within 1 week of the originally planned missed visit (i.e., within 3 weeks of the previous visit), then all assessments per missed visit should be performed at this new visit and the study staff should administer the study drug to the subject and maintain the subject's original injection schedule. In case of rescheduling of missed visits, total duration of the assessment period should remain 48 weeks.
  - For example, if a subject receives the first dose of study drug on January 1st, that is considered "Day 1 (Week 0) of the study"; the next target day of administration will be January 15th.
  - If the subject misses this second visit and comes in on January 19th (i.e., within 3 weeks of the previous visit), then the study staff should administer the study drug on that day. The next visit should be scheduled for January 29th (i.e., 4 weeks after January 1st).
- If a subject misses a visit and the visit cannot be performed within 3 weeks of the previous visit, the site should contact the monitor.

For all subjects, injections should not occur less than 1 week apart. The monitor/Sponsor should be contacted if this cannot be respected.

In case of interruption of 2 consecutive drug administrations, the subject should discontinue from the study.

3.4.1.3. END OF TREATMENT VISIT AND FOLLOW-UP

Subjects who have received all study medication through Week 46 should return for the assessment visit at Week 48, and for the Follow-Up Visit at Week 58 (12 weeks after the last study drug administration at Week 46).

Discontinuation of Study Drug Administration
Subjects who have to discontinue study drug but are not withdrawing consent for post-treatment follow-up, should return for an early termination visit within 3 weeks after the last study drug administration. Subjects should also return for a Follow-up Visit 12 weeks after last study drug administration to undergo the assessments as specified in the Schedule of Assessments.

Termination of Study Participation
Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death should not return for the Early Termination Visit or for the Follow-up Visit.

3.4.2. DEMOGRAPHICS AND MEDICAL HISTORY

Demographic and medical history data will be collected at visits as indicated in the Schedule of Assessments.

Demographic data will include (but are not limited to): age, date of ICF signed, gender, race (if allowed), ethnicity (if allowed), and smoking history/smoking status.

Both general and SLE-specific medical history will be collected.

3.4.3. ASSESSMENTS OF EFFICACY

3.4.3.1. BRITISH ISLES LUPUS ASSESSMENT GROUP INDEX

The clinical BILAG-2004 assessments will be performed by the Investigator and the laboratory assessments will be performed by local and central laboratory at visits as indicated in the Schedule of Assessments.

The same trained and qualified physician should preferably be performing the assessment at each visit for each subject.

A process to check eligibility will also be installed centrally as well as central adjudication of BILAG-2004 at baseline, Week 24 and Week 48.

The BILAG-2004 is a comprehensive composite clinical index that has been developed based on the principle of a physician's intention to treat using a nominal consensus approach. In the index, the nine systems (not organs) considered are: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, renal, ophthalmic and hematology. Disease activity in each of the nine systems is categorized into five levels (Grades A-E) [37-39].

- Grade A, is defined as the individual clinical features, or combinations of features, which the group believes would lead to the prescriptions of medium/large doses of corticosteroids (> 20 mg prednisolone or equivalent) and/or starting or increasing immunosuppressive drugs or high-dose anticoagulation (INR > 3).
- Grade B is given to those subjects with known disease activity requiring somewhat lower doses of immunosuppressives (e.g., < 20 mg prednisolone) and/or specific drugs, such as antimalarial, anti-epileptic, antidepressant and NSAIDs or topical steroids.
- Grade C in each system defines subjects with mild persistent activity only requiring symptomatic therapy (e.g., analgesics or NSAIDs).
- Grade D implies the organ or system was once active but is no longer so.
- Grade E indicates that the organ or system has never been active.

The BILAG-2004 score will be evaluated as an individual item (normal and enhanced improvement and individual organ system score) as well as a component of the composite BICLA and SRI score.

The BILAG-2004 scoring table is provided in Appendix 9.6.

3.4.3.2. SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000

The clinical SLEDAI-2K [40] assessments will be performed by the Investigator and the laboratory assessments will be performed by the central laboratory at visits as indicated in the Schedule of Assessments.

The same trained and qualified physician should preferably be performing the assessment at each visit for each subject.

A process to check eligibility will also be installed centrally as well as central adjudication of SLEDAI-2K at baseline, Week 24 and Week 48.

The SLEDAI-2K is a one-page weighted scale for 24 items (seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, leukopenia). The manifestations felt to be most commonly contributing to disease activity are included and scored based on the presence or absence within 30 days prior to the evaluation. The total score can range from 0-105 and reflects all aspects of disease activity.

A modified SLEDAI-2K index (mSLEDAI-2K) will be derived from the standard index by omitting 1 of the standard items (low complement). An anti-IL-6R compound strongly decreases production of acute phase reactants, including complement [24, 25]. Therefore, the complement (C3/C4) values (parameters of the low complement item in the SLEDAI-2K index) may be decreased due to decreased production while effect on complement consumption (relevant for disease activity evaluation) cannot be assessed.

The SLEDAI-2K (both the standard and modified [excluding the low component item] version) score will be evaluated as an individual item as well as a component of the composite mBICLA score, composite mSRI index and SLEDAI flare index (SFI) index. Note that the mBICLA score and mSRI index uses the mSLEDAI-2K score only.

The SLEDAI-2K scoring table is provided in Appendix 9.7.

3.4.3.3. PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (VAS)

The PGA of disease activity will be measured at visits as indicated in the Schedule of Assessments.

The physician must complete the physician's global assessment independently of the subject when completing the patient's global assessment (see section 3.4.3.4).

The same physician should preferably be performing the assessment at each visit for each subject.

The physician will make a mark between 0 ("very good") and 100 mm ("very bad") on the visual analogue scale (VAS) scale to indicate disease activity (independent of the subject's self-assessment).

The PGA will be evaluated as an individual item as well as a component of the composite (m)BICLA and SRI score, and SFI index.

3.4.3.4. PATIENT'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (VAS)

The patient's global assessment of disease activity will be measured at visits as indicated in the Schedule of Assessments.

The subject must complete the patient's global assessment independently of the physician when completing the physician global assessment (see section 3.4.3.3).

The subject will make a mark between 0 ("very good") and 100 mm ("very bad") on the visual analogue scale (VAS) scale to indicate disease activity.

3.4.3.5. MEDICAL OUTCOME SURVEY SHORT FORM 36 (SF-36)

The SF-36 will be completed by the subject at visits as indicated in the Schedule of Assessments.

The SF-36 consists of 36 items that can be summarized into 8 domains: physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. Two summary measures, the physical component summary and the mental component summary, can be derived based on these domain scores.

The concepts measured by the SF-36 are not specific to any disease, allowing comparison of relative burden of different diseases, in addition to the relative benefit of different treatments.

3.4.3.6. BILAG-BASED COMPOSITE LUPUS ASSESSMENT (BICLA)

The composite BICLA response comprises criteria of 3 different validated indices (SLEDAI, BILAG, and PGA) and is defined as follows:

- BILAG-2004 improvement: all A scores at baseline improved to B/C/D, and all B scores improved to C or D.
- no worsening in disease activity: no new BILAG-2004 A scores and ≤1 new B score.
- no worsening of total (m)SLEDAI-2K score from baseline.

- no significant deterioration (< 10% worsening) in PGA.
- no treatment failure (i.e., new or increased immunosuppressives or anti-malarials; or non-protocol allowed increased oral or parenteral corticosteroids; or premature discontinuation from study treatment).

3.4.3.7. SYSTEMIC LUPUS ERYTHEMATOSUS RESPONDER INDEX (SRI)

The composite index SRI enables quantification of decrease and increase in disease activity in a broad spectrum of manifestations thereby offering a comprehensive assessment of SLE disease status [41].
SRI combines advantages from three validated measurement tools:

- SLEDAI covers global disease improvement,
- BILAG covers organ specific disease worsening or improvement and
- PGA is used as a validity and safety net for items that were not addressed by the other two indices.

The composite SRI criteria for response are:

- SLEDAI-2K: ≥ 4 point reduction.
- BILAG: no new A domain score and no more than 1 new B domain score.
- PGA: no worsening (<10% increase).

When all three criteria are met, the subject is a responder according to the SRI at that time point, i.e., a clinically meaningful improvement of disease is detected.

In addition the modified SRI (mSRI) will be assessed, i.e., using the modified (excluding the low component item) version of the SLEDAI-2K as a criterion.

3.4.3.8. SLEDAI FLARE INDEX (SFI)

Because of the relapsing remitting pattern of SLE, lupus 'flare' is an important outcome variable in clinical studies in subjects with SLE [42].
The SFI provides definitions of mild/moderate flare and severe flare that can be used in a clinical trial setting and encompasses (1) SLEDAI disease activity index scores, (2) disease activity scenarios that might be missed by the indices, (3) treatment changes, and (4) PGA.

In this study, the number of flares will be assessed as determined by the SFI (which will be calculated as detailed in the Statistical Analysis Plan [SAP]).

3.4.3.9. CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX

The CLASI will be performed in interested sites having experience in this assessment at visits as indicated in the Schedule of Assessments.

The CLASI is a measurement instrument for SLE developed by Dermato-Rheumatologists and validated by the "American College of Rheumatology Response Criteria Committee on SLE [43].

The CLASI consists of two scores, i.e., one for damage and one for activity:
- Activity is scored based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and nonscarring alopecia.
- Damage is scored based on dyspigmentation and scarring, including scarring alopecia.

Subjects are asked whether dyspigmentation due to SLE lesions usually remains visible for more than 12 months, which is considered to be permanent and resulting in doubling of the dyspigmentation score. The scores are calculated by addition of the different subscores for clinical symptoms.
The CLASI is designed as a table where the rows represent anatomical areas and the columns represent major clinical symptoms. The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas taking into account the worst affected lesion within that area for each symptom.

A sample of the CLASI is provided in Appendix 9.8.

3.4.3.10. 28-JOINT ASSESSMENT

To be performed by qualified study staff at visits as indicated in the Schedule of Assessments.

An overview of the joints to be assessed is provided in Table 6.

Table 6: Tender and swollen joint count

	Joint	Patient Right		Patient Left	
		Tender	**Swollen**	**Tender**	**Swollen**
1	Shoulder				
2	Elbow				
3	Wrist				
4	MCP I				
5	MCP II				
6	MCP III				
7	MCP IV				
8	MCP V				
9	Thumb Interphalangeal				
10	PIP II				
11	PIP III				
12	PIP IV				
13	PIP V				
14	Knee				
	TOTAL				
	TOTAL Tender Joint Count:				
	TOTAL Swollen Joint Count:				

MCP=metacarpophalangeal; PIP=proximal interphalangeal

If tenderness or swelling is noted, enter a ”1” for that joint in the appropriate field. If tenderness or swelling is absent, enter a “0” for that joint in the appropriate field.

Joints that undergo intra-articular corticosteroid injection will be considered as swollen and tender for 28 days/4 weeks in the data analyses from the date of the procedure onward.

3.4.3.11. SLICC/DAMAGE SCORE

The SLICC/damage score assessment is to be performed by the Investigator at the baseline visit as indicated in the Schedule of Assessments.

The SLICC/damage index is developed as an instrument to allow evaluation of accumulated damage over time and identifies changes in damage seen in subjects with active and inactive disease [44].

The SLICC/damage index consists of 12 different organ systems, i.e., ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, premature gonadal failure, diabetes, and malignancy and it records damage regardless of its cause (e.g., previous disease activity, medications). An item has to be present for at least 6 months to be included in the damage index to differentiate between active inflammation and damage.

A sample of the SLICC/damage score is provided in Appendix 9.9.

3.4.4. PHARMACOKINETIC ASSESSMENTS

3.4.4.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, blood samples of approximately 3.5 mL will be taken for analysis of ALX-0061 in serum, according to the time points defined in the Schedule of Assessments.

The times of blood sampling will be recorded. Of note, the day and approximate time of administration of the last dose will be available in the (e)CRF.

The blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to the Lab Manual.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry (only in case allowed per local regulations). No human DNA or RNA analysis will be performed.

3.4.4.2. BIOANALYSIS

Concentrations of ALX-0061 in serum will be determined by a validated ligand-binding assay method according to the bioanalytical methodology and procedures described in a dedicated Bioanalytical Analysis Plan. Results will be presented in a Bioanalytical Analysis Report.

3.4.5. PHARMACODYNAMIC ASSESSMENTS

3.4.5.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, blood samples will be taken for analysis of the biomarkers sIL-6R, anti-dsDNA, C3, C4, and CH50 according to the time points defined in the Schedule of Assessments.

- For determination of plasma sIL-6R, blood samples of approximately 2.7 mL will be collected and aliquoted.
- For determination of serum anti-dsDNA, C3, C4, and CH50 blood samples of approximately 6 mL will be collected and aliquoted.

For more details on the acute phase response parameters CRP and fibrinogen, please refer to section 3.4.8.2.

All PD blood samples will be taken via an indwelling i.v. catheter or by direct venipuncture. The times of blood sampling will be recorded. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry (only in case allowed per local regulations). No human DNA or RNA analysis will be performed.

3.4.5.2. BIOANALYSIS

Concentrations of sIL-6R in plasma will be determined by a validated enzyme-linked immunosorbent assay (ELISA) method according to the bioanalytical methodology and procedures described in a dedicated Bioanalytical Analysis Plan. Results will be presented in a Bioanalytical Analysis Report.
Concentrations of C3, C4, and CH50 in serum will be determined by qualified ELISA methods and anti-dsDNA will be determined by the Farr-assay.

Information on CRP and fibrinogen is specified in section 3.4.8.2.

3.4.6. ADDITIONAL PHARMACODYNAMIC ASSESSMENTS (EXPLORATORY)

Additional (exploratory) biomarkers that will be analyzed are the frequency of specific cell types (plasma cells, Th17 and Treg cells) by chipcytometry and the concentration of Monocyte Chemotactic Protein-1 in urine (uMCP-1).

In SLE patients, plasma cells are responsible for the production of (pathogenic) autoantibodies and the frequency of these cells in peripheral blood correlates with SLE disease activity [45]. IL-6 induces the differentiation of activated B cells into plasma cells [46] and a phase I study with tocilizumab showed a reduction in circulating plasma cells upon treatment [24, 47].
The imbalance between Th17 cells, which are potent inflammatory cells, and Treg cells, which are crucial for maintenance of peripheral tolerance, contributes to the pathogenesis of SLE [48, 49]. These cell types are of particular interest because of their correlation with SLE disease activity and the crucial role of IL-6 in their differentiation [45]. In the presence of IL-6 and Transforming Growth Factor-β (TGFβ), naïve T cells differentiate into Th17 cells, while in the absence of IL-6, Treg cells are induced. This mode of action is also reflected in

the observation that tocilizumab treatment corrected the Th17/Treg balance in RA patients [50, 51].
Currently, no validated biomarkers are available to detect early kidney disease in SLE. MCP-1 has been proposed as a potential biomarker for renal involvement in SLE, as MCP-1 levels are increased in urine of SLE patients and in particular those with kidney involvement [52, 53]. Furthermore, IL-6 is implicated in the (local) production of MCP-1.

3.4.6.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, urine samples of at least 1.0 mL will be taken for determination of the exploratory urine biomarker uMCP-1 according to the time points defined in the Schedule of Assessments.

In a subset of subjects (at selected sites based on qualification), additional blood samples of approximately 4.0 mL will be collected at the same time points for immune cell phenotyping including, but not limited to, plasma cells, Th17 and Treg cells.

All blood samples for these exploratory assessments will be taken via an indwelling i.v. catheter or by direct venipuncture. The times of blood sampling will be recorded. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry (only in case allowed per local regulations). No human DNA or RNA analysis will be performed.

3.4.6.2. BIOANALYSIS

Concentrations of uMCP-1 in urine will be determined by a qualified ELISA method and immune cell phenotyping will be performed using the chipcytometry method. Both exploratory analyses will be performed according to the bioanalytical methodology and procedures described in dedicated Bioanalytical Analysis Plans. Results will be presented in dedicated Bioanalytical Analysis Reports.

3.4.7. IMMUNOGENICITY ASSESSMENTS

3.4.7.1. SAMPLE COLLECTION AND HANDLING

To assess systemic immunogenicity of ALX-0061, blood samples of approximately 8.5 mL will be collected at the time points defined in the Schedule of Assessments for the determination of anti-ALX-0061 antibodies (ADA).

Blood samples will be taken via an indwelling i.v. catheter or by direct venipuncture. The times of blood sampling will be recorded. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

As described previously (see section 3.4.6), in case of acute or delayed severe/serious hypersensitivity reactions, an additional blood sample should be collected as soon as possible after the start of the event (blood volume: 8.5 mL) to characterize the cause of hypersensitivity by immunogenicity testing and/or protein analysis. No human DNA or RNA analysis will be performed.

Samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work on PK, PD, immunogenicity, metabolites, plasma protein binding, protein analysis, potency, and biochemistry (only in case allowed per local regulations). No human DNA or RNA analysis will be performed.

3.4.7.2. BIOANALYSIS

ADA will be determined using a validated screening and confirmation ADA bridging assay, potentially with further characterization by mADA assay and nAb assay. The immunogenicity data will be processed according to a dedicated Bioanalytical Analysis plan. Results will be presented in a Bioanalytical Analysis Report.

3.4.8. ASSESSMENTS OF SAFETY

Safety and tolerability assessments consist of AEs (including local tolerability and injection reactions), as well as laboratory assessments, urinalysis, vital signs, 12-lead ECG, and physical examinations. The time points are defined in the Schedule of Assessments.

In case of acute or delayed severe/serious hypersensitivity reactions, an additional blood sample should be collected as soon as possible after the start of the event (blood volume: 8.5 mL) to characterize the cause of hypersensitivity by immunogenicity testing and/or protein analysis. No human DNA or RNA analysis will be performed.

Independent Data and Safety Monitoring Board (DSMB)
The DSMB will be an independent committee. None of the members will be participating in the study. The major function of this committee will be to monitor the safety of the subjects participating in the ALX-0061 clinical program by periodically reviewing unblinded safety data. They will advise concerning continuation, modification or termination of study.

Prior to any DSMB review, the DSMB charter will define and document the content of the safety summaries, the DSMB's role and responsibilities, and the general procedures (including communications).

3.4.8.1. ADVERSE EVENTS

General information on definition, evaluation and reporting of AEs is provided in section 3.5.

All AEs occurring during the clinical investigation must be documented in the source documents and the (e)CRF.

Criteria for determining whether an abnormal objective test finding (e.g., laboratory, vital signs), a complication of a protocol mandated procedure (e.g., blood draw, injection of study drug) or a change in physical examination findings should be reported as an AE are as follows, but not limited to:

1. Result/finding is associated with accompanying clinical signs and symptoms (new onset or aggravated in severity of frequency from baseline condition), and/or
2. Result/finding requires extra diagnostic testing (other than diagnostic exclusion tests) or medical/surgical intervention, and/or
3. Result/finding would require a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Result/finding leads to any of the outcomes included in the definition of an SAE, and/or
5. Result/finding is considered to be an AE by the Investigator.

Any abnormal test result that is determined to be an error and merely repeating an abnormal test does not require reporting as an AE.

A "serious infection" is any infection that fulfills seriousness criteria and/or requires intravenous antibiotics.

The Investigator may exceptionally decide to interrupt study drug treatment for one dose according to his/her medical judgment in case of an AE.

3.4.8.2. LABORATORY ASSESSMENTS

Blood samples for clinical laboratory analysis will be collected predose at the time points indicated in the Schedule of Assessments.

In general, blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. Detailed laboratory instructions on sample handle and processing will be provided.

All samples will be assessed by a central laboratory, except for samples for Direct Coombs and INR (for subjects on vitamin K antagonist) that will be assessed by a local laboratory.

The following tests will be included in the clinical laboratory analysis:

- Biochemistry: total bilirubin, alkaline phosphatase, GGT, AST, ALT, lactate dehydrogenase, creatinine, creatine phosphokinase (CPK), urea, total protein, albumin, glucose, inorganic phosphate, sodium, potassium, calcium, and chloride.
- Hematology: leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, partial automated differentiation (lymphocytes, monocytes, eosinophils, basophils, neutrophils), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration.
- Acute phase proteins: fibrinogen, and CRP.
- Urinalysis: erythrocytes/blood, albumin, creatinine, urobilinogen, ketones, glucose, protein, pH, leukocytes, and urine sediment.
- Coagulation: activated partial prothrombin time, prothrombin time, INR (the latter for subjects on vitamin K antagonists only).

Fasting samples (i.e., samples taken after the subject has been fasting for at least 10 h) will be collected at baseline and Weeks 4, 8, 12, 24, 36 and 48 (or the Early Termination Visit) for assessment of total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides (i.e., fasting serum lipids).

Lupus anti-coagulant (LA), anti-cardiolipin (aCL) and anti-β2-glycoprotein I (β2 GPI) antibodies will be evaluated at screening and at Week 24. ANA will be evaluated at screening only.

For subjects on vitamin K antagonists, INR will be performed at Weeks 0, 2, 4, 8 and 12, and every 4 weeks (or more frequent if considered necessary by Investigator) thereafter up to Week 48 (or Early Termination) visit, and Follow-Up Visit.

In females of childbearing potential, a blood pregnancy test will be performed at screening by the central laboratory and urine pregnancy screening locally at timepoints as indicated in the Schedule of Assessments. If local regulations or local medical practice require more frequent pregnancy testing, this will apply.

At screening, seropositivity for hepatitis B, hepatitis C, anti-HIV1 and anti-HIV2 will be tested. Lab tests for hepatitis B will be done according to the guidelines and will include Hepatitis B core antibody (HBcAb), Hepatitis B surface antibody (HBsAb) and Hepatitis B surface antigen (HBsAg)[2]. HBsAg positivity and/or HBcAb positivity will be considered as positive screening for hepatitis B. Anti-HCV antibody positivity will be considered as positive screening for hepatitis C. In case anti-HCV is indeterminate HCV-RNA viral load test will be done by central lab to confirm subject's eligibility.

In addition, an IGRA test to detect active TB and a chest radiograph (performed within 12 weeks prior to the screening visit as part of standard of care or performed during the screening period) to detect evidence of malignancy, infection, or abnormalities suggestive of TB will be performed at screening and at any time during the study if TB is suspected.

Except for CRP and fibrinogen, laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator. If clinical signs and symptoms are present for which the Investigator needs to know values of CRP or fibrinogen for medical care, he/she can request this to be assessed locally.

All clinically significant abnormal laboratory findings will be recorded as AEs in the (e)CRF (also see section 3.4.8.1) and lab results will be repeated and followed up until the results have returned to within the normal range and/or an adequate explanation for the abnormality is found.

In the event of unexplained or unexpected clinical laboratory test values during the study, the test(s) will be redone and the retest value can be considered for further assessment and management of the subject in the study.

Unexplained or unexpected clinical laboratory screening values, can be retested once within the screening period.

3.4.8.3. VITAL SIGNS

Vital signs parameters (assessed after 5 min in supine position) will be measured at the time points indicated in the Schedule of Assessments. All parameters will be recorded in the (e)CRF.

The following vital signs parameters will be assessed: height, weight, blood pressure, pulse, and temperature.

To obtain the actual body weight, subjects must be weighed lightly clothed. The height should be measured barefoot at the Screening Visit.

Clinically relevant abnormalities occurring during the study should be recorded as AE in the (e)CRF.

3.4.8.4. ELECTROCARDIOGRAM

12-lead ECG assessed after 5 min in supine position will be recorded at the time points indicated in the Schedule of Assessments.

ECG assessment will include the Investigator's conclusion on the ECG profile (as "normal", "abnormal, not clinically significant", or "abnormal, clinically significant").

3.4.8.5. PHYSICAL EXAMINATION

A complete physical examination will be performed at the time points indicated in the Schedule of Assessments. Of note, additional physical examinations may be performed upon the discretion of the Investigator (e.g., in case of AEs).

Physical examination will be recorded as "normal", "abnormal, not clinically significant", or "abnormal, clinically significant" at every assessment. A new finding or a change of a finding that is judged as an undesirable medical event (including all findings recorded as "abnormal, clinically significant") shall be reported as an AE.

The physical examination will include at least: head, eyes, ears, nose, throat; respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems; central and peripheral nervous system; skin; lymph node palpation; urogenital system (kidneys); and general appearance.

Any clinically relevant changes occurring during the study must be recorded in the (e)CRF and any clinically significant abnormalities persisting at the end of the study will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

3.4.9. TOTAL BLOOD VOLUME

The estimated number and volume of blood samples and the total volume of blood that will be collected per subject throughout the study are provided in Table 7.

If necessary, in order to obtain additional information to ensure safety to the subject, additional blood (and urine) samples may be taken at the discretion of the Investigator. Due to this possibility, the blood volumes presented in the following tables are provided as best estimations.
The total volume of blood taken during the study (over the one-year study duration) will be approximately 600 mL.

Table 7: Estimated number and volume of blood samples to be obtained during the study

Assessments	# samples	Volume (mL) /Sample	Volume (mL)
Pharmacokinetics	16	3.5	56
Pharmacodynamics: sIL-6R	10	2.7	27
Pharmacodynamics: anti-dsDNA, C3, C4, CH50	15	6	90
Exploratory biomarkers [a]	4	4	16
Laboratory analysis (central lab, including serum pregnancy test at screening)	16	10.7	171.2
Laboratory analysis (local lab)	16	4.7	75.2
Serology (at screening only)	1	6	6
IGRA test	1	3	3
Antinuclear antibodies	1	2	2
LA, aCL, β_2-GPI	2	12.7	25.4
Immunogenicity	15	8.5	127.5
Total			**599.3** [b]

[a] To be taken in a subset of subjects (at selected sites based on qualification)
[b] In case of acute or delayed severe/serious hypersensitivity reactions, an additional blood sample should be collected as soon as after the start of the event (blood volume: 8.5 mL)

3.4.10. APPROPRIATENESS AND TIMING OF MEASUREMENTS

The assessments which will be made in this study are standard, and generally recognized as reliable, accurate and relevant.

The timing of all assessments is detailed in the Schedule of Assessments.

All visits should occur in the specified week (± allowed time window) without further specification of the timing (visit may be planned at the time most appropriate for the subject). At baseline and at Weeks 4, 8, 12, 24, 36, 48 (or the Early Termination Visit), blood samples should be taken after at least 10 hours of fasting.
For PK, PD, immunogenicity and safety, predose samples will be obtained between arriving at site and dosing.

If assessments are planned at the same time, following guidance should be followed:
- ECG and vital signs should be assessed prior to blood sampling.
- Patient assessments (patient's global assessment and SF-36) should occur prior to physician's assessments.
- Study drug should be dosed after all other assessments have been performed.

3.5. ADVERSE EVENT EVALUATION AND REPORTING

3.5.1. ADVERSE EVENTS

AE definitions will be followed as stated in the "Note for Guidance on clinical safety data management: definitions and standards for expedited reporting" (International Conference on Harmonization [ICH] topic E2A).

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not considered related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

In differentiating between medical history and AEs, the following points will be considered:

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present up to the timing of signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, but with unchanged severity, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started before signing of informed consent but deteriorated after signing of informed consent will be documented as AEs.

All AEs will be reported from the time a signed and dated ICF is obtained until completion of the subject's last visit.

A treatment-emergent AE (TEAE) is any AE temporally associated with the use of study drug, whether considered related to the study drug or not. TEAEs are recorded from the start of study drug administration, until completion of the subject's last visit.

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation, and by routine

open questioning (e.g., "How have you felt since I saw you last?"; "Is there anything new that you wish to discuss?").

All AEs will be assessed by the Investigator and documented in both source documents and the AE CRF page. AE entry should indicate time of onset and end time and rating of the seriousness (see section 3.5.2), severity (see section 3.5.1.1), and outcome (see section 3.5.1.2) of the AEs, and relationship to study drug and study procedures (see section 3.5.1.3), action taken regarding study drug (see section 3.5.1.4), and concomitant therapy taken for the AE.

The Investigator will judge upon the severity of the AEs and relation to study drug and study procedures.

3.5.1.1. AE SEVERITY

The severity of AEs will be rated on a 3-point scale:

- Mild: discomfort noticed but no disruption of normal daily activity.
- Moderate: discomfort sufficient to reduce or affect normal daily activity.
- Severe: incapacitating with inability to work or perform normal daily activity.

It is emphasized that the term severe is a measure of intensity: a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

3.5.1.2. OUTCOME

The outcome of the AE is to be documented as follows:

- Recovered / resolved.
- Recovering / resolving.
- Recovered / resolved with sequelae.
- Not recovered / not resolved.
- Fatal.
- Unknown.

3.5.1.3. RELATION TO STUDY DRUG OR STUDY PROCEDURES

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the (e)CRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are:

- Unlikely/Not related.
- Possibly related.
- Related.
- Not applicable.

If the causal relationship to the study drug is unknown, the answer is defined as "related". If an Investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the Investigator for the SAE.

Note that only AEs starting after administration of study drug can be assigned a causal relationship between the AE and study drug administration. For AEs starting prior to study drug administration, causal relationship between the AE and study drug should be not applicable.

Assessment of causal relationship of any AE to protocol-required procedures can be completed with:

- Yes (specify).
- No.

3.5.1.4. ACTION TAKEN REGARDING STUDY DRUG

Any action taken regarding study drug due to an AE is to be documented using following categories:

- Dose not changed.
- Drug interrupted.
- Drug withdrawn.
- Not applicable.
- Unknown.

3.5.2. SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death.
- Is life-threatening: the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.

- Requires in-subject hospitalization or prolongation of existing hospitalization; an AE associated with a hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
  - The admission results in a hospital stay of less than 12 hours.
  - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study).
  - The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

  However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of "medically important" and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
- Results in persistent or significant disability/incapacity. Disability means a substantial disruption of a person's ability to conduct normal life's functions.
- Results in a congenital anomaly/birth defect.
- Is another medically important serious event as judged by the Investigator, or is defined as requiring intervention to prevent one of the outcomes listed in the definition above (including suspected transmission of an infectious agent by a medicinal product should be reported as an SAE). Other examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Any AE is considered an SAE if it is associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

Infections that meet the above SAE criteria or require intravenous antibiotics should be reported as SAE.

The Investigator or clinical site personnel should notify the CRO of all SAEs, regardless of relationship to the study drug, within 24 hours of clinical site personnel becoming aware of the event (see Investigator Site File).
The Investigator will provide the initial notification a completed "SAE Notification Form", which must include the Investigator's assessment of the relationship of the event to study drug, and must be signed by the Investigator.

The first report of an SAE may also be made by telephone. The Reporter must provide the minimal information: i.e., reporter identification, study number, age, medication code number, period of intake, nature of the AE, and relation to study drug.

This report of an SAE by telephone must always be confirmed by a written, more detailed report (the SAE Form) to be completed and signed by the Investigator.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the contacts provided in the Investigator Site File.

The SAE should also be recorded in the (e)CRF. Any medications necessary for the treatment of the SAE must be recorded on the concomitant medication section of the (e)CRF.

SAEs that begin after the subject's participation in the study is complete, but that the Investigator considers to be related to study drug, should be reported to the CRO/Sponsor at any time.

3.5.3. SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (as described in the Reference Safety Information, provided in the Investigator's Brochure).

The following SUSARs will be reported expedited to the IEC/IRB:

- SUSARs that have arisen in the current clinical study that was assessed by the IEC/IRB.
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same study drug and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the IEC/IRB.

The CRO will report expedited all SUSARs to the relevant CA on behalf of the Sponsor.

The Sponsor (or the CRO on behalf of the Sponsor) will also report to all concerned Investigators all SAEs that are unlisted (unexpected) and associated with the use of the drug.

The expedited reporting will occur no later than 15 calendar days after the Sponsor (or the CRO on behalf of the Sponsor) has first knowledge of the adverse reactions.

For fatal or life-threatening cases the term will be maximal 7 calendar days for a preliminary report with another 8 days for completion of the report.

3.5.4. REPORTING OF ADVERSE EVENTS

AEs reporting, including SUSARs, will be carried out in accordance with applicable local regulations. For reported deaths, the Investigator should supply the Sponsor and the

IEC/IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

After termination of the clinical study (last subject last visit in the study), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority(ies) concerned together with proposed actions.

3.5.5. FOLLOW-UP OF ADVERSE EVENTS

AEs will be handled according to common clinical practice. If necessary, in order to obtain additional information to ensure safety to the subject, additional blood and urine samples may be taken at the discretion of the Investigator. Information relative to other means of investigational diagnostics used in relation to the AE will also be communicated.

AEs are recorded from signing the ICF until completion of the subject's last visit.

All AEs occurring at any time during the study (including the follow-up period) will be followed until satisfactory outcome.

3.5.6. OTHER REPORTABLE INFORMATION

3.5.6.1. PREGNANCY

The Investigator must report to the Sponsor any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study and until 3 months after last study drug dose. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child (e.g., stillbirth, spontaneous abortion or elective abortion) should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome.

All pregnancies including study subjects and female partners should be reported using the pregnancy form.

Note that as indicated in section 3.2.3.2, subjects who get pregnant during the study should be withdrawn from the study.

3.5.6.2. MEDICATION ERROR

Medication errors include, but are not limited to, the following:

- Administration of the wrong dosage (including overdose) to the subject.
- Administration of the study drug that has not been assigned to the subject.
- Administration of expired study drug.
- Administration by a route (e.g., i.m.) other than s.c.
- Deviations to the study drug storage conditions only when administered to the subject.

Medications errors with signs and symptoms need to be reported as an AE/SAE.

Medication errors that occur during the study should be documented and reported to the Sponsor or designee whether or not it results in an AE/SAE.

3.6. STATISTICS

3.6.1. STUDY POPULATIONS

The following populations will be considered for analysis:

- **Modified Intent-to-treat (mITT) Population**: All randomized subjects who received at least 1 administration of study drug, as randomized.
- **Safety Population**: All subjects who received at least 1 administration of study drug, as treated.
- **PK Population**: Consists of a subset of the safety population, for whom the primary PK data are considered to be sufficient and interpretable.
- **Per Protocol (PP) Population**: Consists of a subset of the mITT population, and excludes those subjects who have had a major protocol violation or deviation. All violations and deviations will be reviewed prior to database lock and classified as major or minor.

Unless otherwise specified, the mITT Population will be used for the analysis of efficacy, the safety population for analysis of safety, PD, and immunogenicity data, while the PK population will be used for analysis of the PK variables.

3.6.2. STATISTICAL AND ANALYTICAL PLAN

The SAP, will be generated under responsibility of the Sponsor. The SAP will be finalized prior to database lock. Any deviation from the reporting and analysis plan will be reported in the section "Changes in the planned analysis" in the Clinical Study Report.

Details of the data analyses will be specified in the SAP.

3.6.3. DETERMINATION OF SAMPLE SIZE

Up to approximately 300 subjects will be randomized over 5 treatment arms in a 1:1:1:1:1 ratio. Randomization will be stratified by geographic region.

Simulations were performed to evaluate the power of detecting a significant dose-response relationship, i.e., whether changes in ALX-0061 dose regimen lead to significant changes in mBICLA response rate at Week 24 by using the MCP-Mod methodology [1]. A set of 5 plausible candidate models containing both monotonous and non-monotonous exposure-response shapes was defined. For these models an estimated placebo response rate of 25%, and a difference in response rate between the ALX-0061 dose regimen with the largest response rate and placebo of 25% was assumed, taking into account a discontinuation rate of 15% (homogeneous over treatment arms). With this methodology a

sample size of 60 subjects per arm will provide at least 85% power at a family-wise 5% significance level.

3.6.4. INITIAL CHARACTERISTICS OF SUBJECT SAMPLE

The statistical evaluation will be descriptive and by treatment (including mean, standard deviation, median, maximum, and minimum) for continuous variables and counts and percentages for categorical variables.

3.6.5. EVALUATION OF EFFICACY PARAMETERS

The adjudication committee will also evaluate appropriateness of data for evaluating the primary endpoint.

The primary endpoint is the percentage of subjects who achieved a response at Week 24 according to the composite mBICLA (BILAG-based Combined Lupus Assessment) score. BICLA responders are defined as subjects who meet all of the following criteria:

(1) BILAG-2004 improvement: all A scores at baseline improved to B/C/D, and all B scores improved to C or D.
(2) no worsening in disease activity: no new BILAG-2004 A scores and ≤1 new B score.
(3) no worsening of total mSLEDAI-2K score from baseline.
(4) no significant deterioration (< 10% worsening) in PGA.
(5) no treatment failure (i.e., new or increased immunosuppressives or anti-malarials; or non-protocol allowed increased oral or parenteral corticosteroids; or premature discontinuation from study treatment).

The following efficacy analyses will be performed in addition to the primary analysis:

- Composite endpoint (m)BICLA over time (through Week 48) will be summarized by treatment group.
- Composite endpoint mSRI as well as standard SRI over time (through Week 48) will be summarized by treatment group.
- (m)SRI with more stringent (m)SLEDAI-cut-offs: SRI-5, SRI-6, SRI-7, SRI-8 over time (through Week 48) will be summarized by treatment group.
- Change from baseline in mSLEDAI-2K total score as well as standard SLEDAI-2K measured over time (through Week 48) will be summarized by treatment group.
- Number and percent of subjects with BILAG-2004 improvement.
- BILAG-2004 (total score) over time (through Week 48) will be summarized by treatment group.
- Improvement in individual organ systems of the BILAG-2004 over time (through Week 48) will be summarized by treatment group.

- Number of BILAG-2004 systems in which activity increased, decreased or remained the same compared to previous visit (BILAG-2004 systems tally) over time (through Week 48) will be summarized by treatment group.
- Change from baseline in PGA over time (through Week 48) will be summarized by treatment group.
- Change from baseline in patient's global assessment over time (through Week 48) will be summarized by treatment group.
- Change from baseline in proteinuria/urine sediment/serum creatinine/eGFR over time (through Week 48) will be summarized by treatment group.
- Proportion of treatment failures (defined as non-protocol allowed increase in steroid dose, start i.v. or i.m. steroids, start or increase of immunosuppressant) at Week 24 and at Week 48 will be summarized by treatment group.
- Reduction in flare rate at Week 24 and at Week 48.
  - Severe flare defined as a new A score in any system of the BILAG-2004 index; moderate flare defined as a new B score following a C, D or E score.
  - SFI.
- Percent change from baseline in daily dose of steroids at Week 24 and 48 will be summarized by treatment group.
- Percent subjects whose prednisone equivalent dose was >7.5 mg/day at baseline and reduced to ≤7.5 mg/day during Weeks 40–48 without experiencing a flare will be summarized by treatment group.
- Percent subjects who are able to discontinue prednisone by Week 48 without experiencing a flare will be summarized by treatment group.
- Changes from baseline in the physical and mental component scores of SF-36 at Week 24 and at Week 48 will be summarized by treatment group.
- 28 Joints count over time and change from baseline in 28 joint count over time will be summarized by treatment group.
- CLASI over time and change from baseline evaluation at Week 12, 24 and Week 48 will be summarized by treatment group.
- PK parameters.
- PD markers, including total sIL-6R, CRP, fibrinogen, anti-dsDNA, C3, C4, CH50.

Descriptive subgroup analyses may be performed to evaluate consistency of the primary endpoint over covariates including demographics (including weight and region), baseline disease, and prior and concomitant medications. Details will be provided in the SAP.

3.6.5.1. PRIMARY EFFICACY ENDPOINT

mBICLA response rates at Week 24 will be analyzed using the MCP-Mod methodology [1]. The method entails a unified strategy to the analysis of data from dose-response studies which combines multiple comparison and modeling techniques. In general, the existence of several candidate parametric models is assumed and multiple comparison techniques are used to choose the model most likely to represent the true underlying dose-response curve,

while preserving the family-wise error rate. The selected model may further be used to guide the choice of adequate doses.

The analysis will be performed using the mITT population of all subjects who have received at least 1 administration of study drug and according to the treatment for which they were assigned.

Subjects with missing mBICLA response at Week 24, including those who have discontinued study drug before Week 24, as well as subjects with treatment failure, will be treated as non-responders (non-response imputation approach). Treatment failure is defined as non-protocol allowed increase in steroid dose, start i.v. or i.m. steroids, start or increase of immunosuppressant. Details on how missing mBICLA response is defined and handled will be provided in the SAP.

Primary efficacy endpoint evaluation will also be performed using the PP population.

Summary statistics (frequencies, proportions) for mBICLA response rate at Week 24 will be provided by treatment group.

3.6.5.2. SECONDARY EFFICACY ENDPOINTS

All secondary efficacy endpoints will be summarized by treatment group, using the observed data in the mITT population. For continuous secondary efficacy endpoints, summary statistics include mean, standard deviation, median, minimum and maximum, while for categorical secondary efficacy endpoints frequencies and proportions are provided.

3.6.6. EVALUATION OF PHARMACOKINETIC PARAMETERS

The procedures for obtaining ALX-0061 serum concentrations are found in section 3.4.4.

Evaluation of Pharmacokinetics
PK analysis will be performed on the PK population.

Individual study drug concentrations will be listed. In addition a listing of the actual sampling times relative to the study drug administration times will be presented.

Drug concentrations will be summarized by treatment group and scheduled sampling time.

The descriptive statistics on study drug concentrations will be performed under the responsibility of Ablynx NV.

Pharmacokinetic Model
ALX-0061 serum concentrations obtained from all subjects in the study will be pooled together with available data collected so far in previous studies. A population PK analysis will be conducted to describe the population mean and variability of ALX-0061 exposure in the study population based on pharmaco-statistical nonlinear mixed effect models.

PK Modeling will be performed under the responsibility of Ablynx NV. Results will be provided in a separate Modeling and Simulation report.

3.6.7. EVALUATION OF PHARMACODYNAMIC PARAMETERS

All PD data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. Additional exploratory modeling (e.g., predictive analysis of specific biomarkers) may be performed.

Exposure-response Model(s)
An Exposure-Response analysis will be performed to determine the relationship between ALX-0061 serum exposure and PD and efficacy endpoints, e.g., BICLA, mSRI, SLEDAI-2K, and BILAG-2004 using nonlinear mixed effects modeling.

Details on the exposure-response modeling will be included in a separate Data Analysis Plan, and will be performed under the responsibility of Ablynx NV. Results of this analysis will be provided in a separate Modeling and Simulation report.

3.6.8. EVALUATION OF SAFETY PARAMETERS

The following analyses will be used to assess the safety of subjects in this study.
- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of related AEs (including study drug injection-site reactions and hypersensitivity reactions).
- The laboratory parameters and change from baseline in these laboratory parameters.
- The incidence of antibodies to ALX-0061.

All summaries will display, by treatment group, the overall frequency of subjects with events, the frequency of subjects with events within each primary system organ class and by preferred term. For each preferred term and each system organ class a subject will be counted only once. For summaries of severe or drug-related AEs, for a given subject, the highest severity or relationship for a specific preferred term will be considered.

All safety, PD and immunogenicity analyses will be performed using the Safety Population of all subjects who received at least 1 dose of study drug. Analyses will be performed using the treatment that the subject actually received. In addition, subgroup analyses will be performed to evaluate consistency of safety over covariates including demographics (including weight), and concomitant medication (including immunosuppressants and corticosteroids).

AEs will be fully described and coded according to the Medical Dictionary for regulatory Activities. A treatment-emergent analysis of AEs will be done. Frequency of subjects presenting AEs, AEs leading to withdrawal, AEs considered to be related to the study drug, and SAEs will be tabulated for each treatment group by system organ class and preferred term.

For laboratory parameters, descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be computed on the actual values and the change from baseline (absolute) for each parameter. All laboratory values will be categorized according to their normal ranges as below, within or above normal. A shift table versus baseline (including final value versus baseline and worst value versus baseline) will be created.

Vital signs variables will be fully depicted using descriptive statistics (for actual values and changes from baseline) and shift tables according to their normal ranges. ECG values will be assessed through listing of individual results by subject and summary tables.

Abnormal findings in physical examinations will be listed.

Immunogenicity will be assessed through listing of individual results by subject and summary tables.

The DSMB will periodically evaluate the safety data (see section 3.4.8).

3.7. DATA QUALITY ASSURANCE AND DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

An audit could be conducted to evaluate systems, processes, and expertise for the subcontracted activities and to assess compliance with the contractual agreements, the protocol, applicable Standard Operating Procedures, and regulatory requirements. During or after the conduct of the study, process-related audits may be performed as well. When performed, an audit certificate will be provided in appendix of the final study report.

The clinical research facility will be monitored by the study monitor, to ensure correct performance of the study procedures and to assure that the study is conducted according to the relevant regulatory requirements.

Regulatory authorities, the IEC/IRB, and/or the Sponsor representative may request access to all source documents, (e)CRFs and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study.

3.8. DATA PROTECTION

During this clinical study, all clinical data will be identified only through an ID number in order to protect the rights of the subjects to privacy and to the protection of their personal data in accordance with the European Data Protection Directive 95/46/EC. Global principles and standards for Processing Personal Data and for meeting Data Transfer Obligations will be applied. If local requirements are more specific or expansive, Ablynx NV and subcontractors will abide to the strongest requirements.

4. ETHICS

4.1. ETHICS COMMITTEES AND COMPETENT AUTHORITIES

The Clinical Study Protocol(s) and the ICF(s) will be submitted for review and approval by the IEC/IRB prior to the eligibility screening/baseline. The composition of the IEC/IRB is in accordance with the recommendations of the World Health Organization, the ICH E6 Guideline for GCP, and the European Union Clinical Trial Directive (CTD) (Directive 2001/20/EC).

The Investigator/Sponsor (or CRO on behalf of the sponsor) will keep the IEC/IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the responsible persons. The study may be suspended pending further review by the IEC/IRB, unless suspension would jeopardize the subject's health. The Investigator will take care that all subjects are kept informed.

No substantial amendments will be made to the study without prior IEC/IRB approval and CA approval (if applicable according to local regulations), except when required to eliminate apparent immediate hazards to human subjects.

Notification of the end of the study will be sent to the CA and to the IEC/IRB, within the number of days as specified by local regulations after completion of follow-up for the last subject. In case the study is ended prematurely, the IEC/IRB and the CA will be notified within the number of days as specified by local regulations, including the reasons for the premature termination. A summary of the results of the study will be sent to the CA and the IEC/IRB within 1 year after the end of the study.

4.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with the ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

ICH-adopted guidelines and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate Local laws.

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

4.3. SUBJECT INFORMATION AND CONSENT

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor or designee and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before undertaking any study-related procedure in the study, the Investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, objectives, no intended clinical benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled and that all data collected up to the point of withdrawal will be used and reported in an anonymized way. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities, authorized Sponsor staff, and Sponsor representative without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his/her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The language used in the oral and written information about the study, including the ICF, should be as nontechnical as practical and should be understandable to the subject. The subject will be given sufficient time to read the ICF and given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature and by the Investigator or an authorized member of the investigational staff who conducted the ICF discussion. After having obtained the consent, a copy of the ICF must be given to the subject. The other original of the ICF will be retained by the Investigator in the "Investigator Site File".

In addition, insurance coverage provided during the study is explained.

4.4. PRIVACY

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. Subjects will be identified by his/her assigned unique subject number or subjects ID number and his/her age. Personal data will only be collected and processed using these unique identification items.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his/her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

5. DATA HANDLING AND RECORD KEEPING

5.1. DISTRIBUTION OF ACTIVITIES

Contact details of the Sponsor and third parties are available in the "Investigator Site File".

5.2. DOCUMENTATION

Study documentation required for study start (as specified in the ICH E6 Guideline for GCP (CPMP/ICH/135/95) shall be exchanged between Ablynx NV and the CRO prior to the administration of study drug.

5.2.1. CASE REPORT FORM COMPLETION

Case report forms are provided for each subject (incl. screen failures).

The Investigator will ensure that data are recorded on the (e)CRF as specified in the Clinical Study Protocol and in accordance with the instructions in the (e)CRF. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the (e)CRF, and of the provision of answers to data queries according to the Clinical Study Agreement. All (e)CRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel. The Investigator will sign the completed (e)CRF. A copy of the completed (e)CRF will be archived at the study site.

5.2.2. SOURCE DOCUMENTATION

At a minimum, source documentation must be available for the following: informed consent process, medical history, subject identification, eligibility, and study identification; date of informed consent; dates of visits; results of all efficacy evaluations; results of safety parameters as required by the protocol; record of all AEs; and follow-up of AEs; prior and concomitant medication; study drug receipt records; study drug administration information; any medical notes (original documents, data and records, e.g., laboratory data); date of study completion, and reason for early discontinuation of study procedures or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care (Patient's Medical File).

Following the ICH-GCP guidelines, direct access to source documentation (medical records) must be allowed.

5.2.3. RECORD RETENTION

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all (e)CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP section 8, Essential Documents for the Conduct of a Clinical Study, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/ Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 15 years after completion of the study, at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. The Sponsor will receive the original (e)CRFs and study-related documents.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

The Investigator should take measures to prevent accidental or premature destruction of the study documents.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

The vendor is responsible for organizing and maintaining a clear documentation of the course of the study.

The Trial Master File maintained during the study by the responsible persons will be sent back to the Sponsor upon Sponsor approval.

Patients medical files, consent forms, and identification codes if relevant, will be kept by the Investigator in his/her personal files during the timeframe specified in local regulations or until the Sponsor decides that these documents no longer need to be retained (CPMP/ICH/135/95 § 4.95).

5.2.4. MONITORING

The monitor will perform on-site monitoring visits as specified in a monitoring plan to ensure that all aspects of the protocol, contractual agreements and regulatory requirements are followed and that subjects' human rights, safety, and well-being are protected. The monitor will record dates of monitoring in a study center visit log that will be kept at the site. At these visits, the monitor will perform source data verification and check the data entered into the (e)CRF for completeness and accuracy. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the (e)CRF are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation ([electronic] medical records) must be allowed at any time. Findings from this review of captured data will be discussed with the investigational staff. The Sponsor expects that, during on-site monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits will be resolved.

6. FINANCING AND INSURANCE

Insurance

Ablynx NV holds and will maintain an adequate insurance policy covering damages arising from Ablynx-sponsored clinical research studies.

Ablynx NV will indemnify the Investigator in accordance with the provisions as set in an a separate written agreement between Ablynx and the relevant Investigator/clinical site.

Financing

The financial aspects of the study will be documented in an agreement between the Sponsor and the Investigator/Institution.

The subjects will be compensated for reasonable expenses made related to the study such as travel costs to visit the study center for assessments related to the study.

Financial Disclosure

Any identified Investigator or subinvestigator directly involved in the treatment or evaluation of research subjects will disclose for the time period during which the Investigator is participating in the study and for 1 year following completion of the study that he/she entered a financial arrangement between the Sponsor and the Investigator/Institution. The Investigator should promptly update this information if any relevant changes occur during this period.

7. USE OF INFORMATION AND PUBLICATION

By signing this protocol, the Investigator reaffirms to the Sponsor that he or she will maintain in confidence all information furnished to him, or resulting from this study. He or she will only divulge such information as may be necessary to the IEC/IRB and the members of the staff and the subjects who are involved in this study.

All data and records provided by the Sponsor or generated during the study (other than subject's medical records) and all data and inventions covered in the course of conducting the study, whether patentable or not, are the sole and exclusive property of the Sponsor.

The Investigator and all other study team members at any service provider involved will keep strictly confidential all information provided by the Sponsor related to this study and all data and records generated in the course of the study. They will not use the information, data, or records for any other purpose than conducting the study without prior written approval of the Sponsor.

Publication of any results from this study will be according to the principles of the Declaration of Helsinki, in particular point 30, and will require prior review and written agreement of the Sponsor.

8. REFERENCES

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9. APPENDICES

9.1. 1997 AMERICAN ACR CLASSIFICATION CRITERIA

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

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *1. OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis *1. OR* 2. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions *1. OR* 3. Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions *1. OR*

	4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer *1. OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen *1. OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

9.2. 2012 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) CLASSIFICATION CRITERIA

Clinical and Immunologic Criteria Used in the SLICC Classification Criteria [54]

Clinical Criteria

1. Acute cutaneous lupus

Including: lupus malar rash (do not count if malar discoid)

bullous lupus

toxic epidermal necrolysis variant of SLE

maculopapular lupus rash

photosensitive lupus rash

in the absence of dermatomyositis

or subacute cutaneous lupus

(nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

2. Chronic cutaneous lupus

Including: classical discoid rash

localized (above the neck)

generalized (above and below the neck)

hypertrophic (verrucous) lupus

lupus panniculitis (profundus)

mucosal lupus

lupus erythematosus tumidus

chillblains lupus

discoid lupus/lichen planus overlap

3. Oral ulcers: palate

buccal

tongue

or nasal ulcers

in the absence of other causes, such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods

Clinical Criteria

4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)

in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia

5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.

6. Serositis

typical pleurisy for more than 1 day

or pleural effusions

or pleural rub

typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day

or pericardial effusion

or pericardial rub

or pericarditis by EKG

in the absence of other causes, such as infection, uremia, and Dressler's pericarditis

7. Renal

Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr

or

Red blood cell casts

8. Neurologic

Seizures

psychosis

mononeuritis multiplex

in the absence of other known causes such as primary vasculitis

myelitis

peripheral or cranial neuropathy

in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus

acute confusional state

in the absence of other causes, including toxic-metabolic, uremia, drugs

9. Hemolytic anemia

Clinical Criteria

10. Leukopenia (< 4000/mm^3 at least once)

in the absence of other known causes such as Felty's, drugs, and portal hypertension

OR

Lymphopenia (< 1000/mm^3 at least once)

in the absence of other known causes such as corticosteroids, drugs and infection

11. Thrombocytopenia (<100,000/mm^3) at least once

in the absence of other known causes such as drugs, portal hypertension, and TTP

Immunological Criteria

1. ANA above laboratory reference range

2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range

3. Anti-Sm

4. Antiphospholipid antibody: any of the following:

lupus anticoagulant

false-positive RPR

medium or high titer anticardiolipin (IgA, IgG or IgM)

anti-β2 glycoprotein I (IgA, IgG or IgM)

5. Low complement

low C3

low C4

low CH50

6. Direct Coombs test in the absence of hemolytic anemia

Criteria are cumulative and need not be present concurrently.

9.3. THE NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

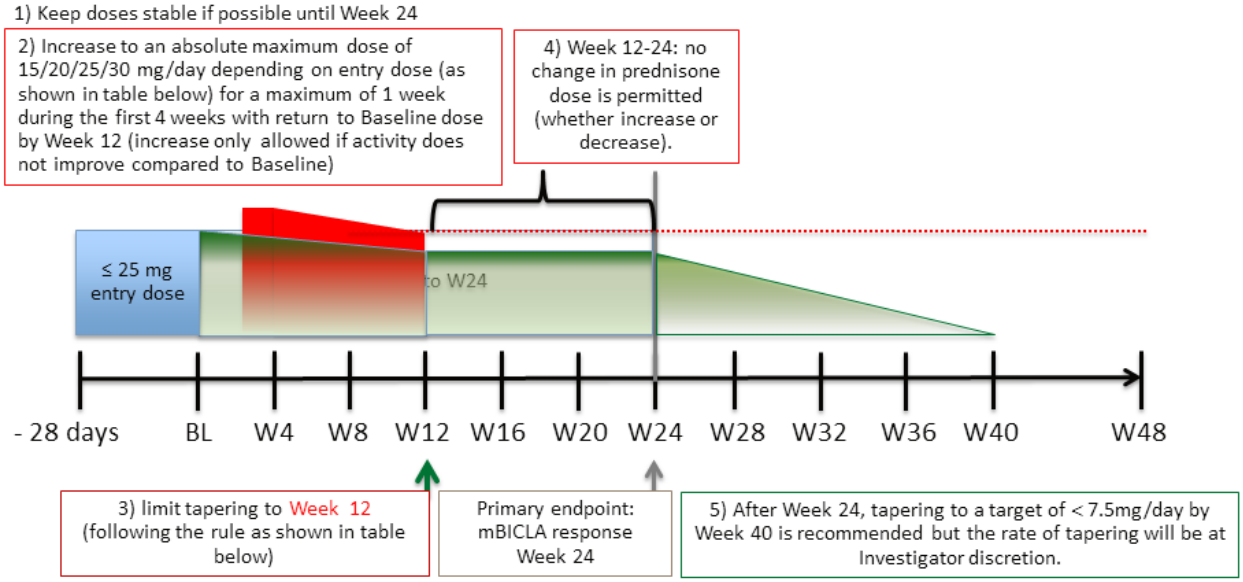
Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

9.4. MODIFICATION OF DIET IN RENAL DISEASE' (MDRD) FORMULA

Estimated GFR (ml/min/1.73m^2) = 186 x (Creat* / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black)

* Serum creatinine level in µmol/L

9.5. OVERVIEW OF CORTICOSTEROID HANDLING THROUGHOUT THE STUDY



	Baseline dose	If necessary, increase allowed for 1 week during first 4 weeks	If desired, tapering allowed between baseline and Week 12
1	16 to 25 mg/day	Increase to a maximum of 30 mg/day	No dose decrease below 50% of baseline dose
2	11 to < 16 mg/day	Increase to a maximum of 25 mg/day	No dose decrease below 75% of baseline dose
3	7.5 to < 11 mg/day	Increase to a maximum of 20 mg/day	No dose decrease < 7.5 mg/day
4	< 7.5 mg/day	Increase to a maximum of 15 mg/day	No tapering will be allowed

9.6. BILAG-2004

The BILAG-2004 [37-39] scoring system is based on the physician's intention to treat.

Grade	Definition
A	Severe disease activity requiring any of the following treatment: 1.Systemic high dose oral corticosteroids (equivalent to Prednisolone > 20 mg/day) 2.Intravenous pulse corticosteroids (equivalent to pulse methylprednisolone ≥ 500 mg) 3.Systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis) 4.Therapeutic high dose anticoagulation in the presence of high dose corticosteroids or immunomodulators eg: warfarin with target INR 3 - 4
B	Moderate disease activity requiring any of the following treatment: 1.Systemic low dose oral corticosteroids (equivalent to prednisolone ≤ 20 mg/day) 2.Intramuscular or intra-articular or soft tissue corticosteroids injection (equivalent to methylprednisolone < 500 mg) 3.Topical corticosteroids 4.Topical immunomodulators 5.Antimalarials or thalidomide or prasterone or acitretin 6.Symptomatic therapy eg: NSAIDs for inflammatory arthritis
C	Mild disease
D	Inactive disease but previously affected
E	System never involved

The following 9 systems are evaluated: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, renal, ophthalmic and hematology.

BILAG-2004 INDEX

Centre: **Date:** **Initials/Hosp No:**

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

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

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

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

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

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

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

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

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

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

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

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

Revision: 1/Sep/2009

For information on the BILAG2004 Index Glossary, please refer to [37].

9.7. SLEDAI-2K

Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the **preceding 30 days.**

SLEDAI 2K		Descriptor	Definition
Weight	**SCORE**		
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	$\geq$ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).

SLEDAI 2K Weight	SCORE		Descriptor	Definition
4	_____		Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____		Urinary casts	Heme-granular or red blood cell casts.
4	_____		Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____		Proteinuria	>0.5 gram/24 hours
4	_____		Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____		Rash	Inflammatory type rash.
2	_____		Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____		Mucosal ulcers	Oral or nasal ulcerations.
2	_____		Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	P	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____		Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____		Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____		Fever	>38° C. Exclude infectious cause.
1	_____		Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____		Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.

TOTAL SCORE: _____

9.8. CLASI

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

activity **damage**

Extent

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

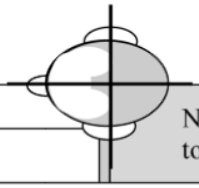
Mucous membrane

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

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient)	
0- dyspigmentation usually lasts less than 12 months 1- dyspigmentation usually lasts at least 12 months	

Alopecia



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

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

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

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

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy,		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation,	

9.9. SLICC/DAMAGE SCORE

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus* [44]

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change *or* optic atrophy	1
Neuropsychiatric	
Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) *or* major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 if > 1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria ≥3.5 gm/24 hours	1
or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if > 1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur > 3/6)	1
Pericarditis for 6 months, *or* pericardiectomy	1

Item	Score
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if > 1 site)	1 (2)
Venous thrombosis with swelling, ulceration, *or* venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, *or* gall bladder ever, for cause any (score 2 if >1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if> 1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1 (2)

* Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

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Title: SENIOR MEDICAL DIRECTOR
Date: Tuesday, 03 May 2016, 13:19 Romance Daylight Time
Meaning: Approved
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