Cover page

Official Title:

A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe systemic lupus erythematosus (SLE)

ClinicalTrials.gov identifier:

NCT03742037

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4 February 2022

Cenerimod / ACT-334441

Systemic lupus erythematosus

Protocol ID-064A202

CARE: Cenerimod **A**ssessing $S1P_1$ **R**eceptor modulation in Systemic Lupus **E**rythematosus

A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe systemic lupus erythematosus (SLE)

Study Phase:	2b
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SPONSOR CONTACT DETAILS

Sponsor	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 CH-4123 Allschwil Switzerland ☎ +41 58 844 00 00
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File.
Medical Emergency Hotline Toll phone number:	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File.

CONTRACT RESEARCH ORGANIZATIONS' INFORMATION

Some study activities will be delegated to Contract Research Organizations (CROs). A list of site-specific contact details can be found in the Investigator Site File.

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia or sponsor

Treatment name / number

Cenerimod / ACT-334441

Indication

Systemic lupus erythematosus

Protocol number, study acronym, study title

ID-064A202, CARE

A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe systemic lupus erythematosus (SLE).

I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of cenerimod, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Title	Name	Date	Signature
Clinical Trial Physician	[redacted]	[redacted]	[redacted]

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Cenerimod / ACT-334441

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A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe systemic lupus erythematosus (SLE).

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws.

Principal Investigator	Country	Site number	Town	Date	Signature

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LIST OF ABBREVIATIONS AND ACRONYMS

ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
anti-Sm	Anti-Smith
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from 0 to 24 hours
AV	Atrioventricular
BILAG-2004	British Isles Lupus Assessment Group-2004
BP	Blood pressure
bpm	Beats per minute
CFR	Code of Federal Regulations (US)
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Copy reference
CRA	Clinical Research Associate
CRO	Contract Research Organization
cSFI	Classic Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI flare index
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration

CTT	Clinical Trial Team
CVA	Cerebrovascular accident
CXCL10	C-X-C motif chemokine 10
CYP	Cytochrome protein
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECS	Echocardiography set
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FEV1	Forced expiratory volume in 1 second
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HIV	Human immunodeficiency virus
HR	Heart rate
i.v.	Intravenous(ly)
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISAC	Independent Statistical Analysis Center
ISF	Investigator Site File
J2R	Jump to Reference
LSM	Least Squares Mean
LT	Liver test
MAD	Multiple-ascending dose
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
MoA	Mode of action
mSLEDAI-2K	Modified Systemic Lupus Erythematosus Disease Activity Index-2000
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
o.d.	Once daily
OCS	Oral corticosteroids
OCT	Optical coherence tomography
PD	Pharmacodynamic(s)
pEOT	Premature discontinuation of study treatment or premature End-of-Treatment
PFT	Pulmonary function test

PGA	Physician's Global Assessment
PGIC-F	Patient Global Impression of Change – Fatigue
PGIS-F	Patient Global Impression of Severity – Fatigue
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PPS	Per-protocol set
PRO	Patient Reported Outcome
QoL	Quality of Life
QS	Quality System
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	Red blood cells
RSI	Reference Safety Information
s.c.	Subcutaneous(ly)
S1P	Sphingosine-1-phosphate
$S1P_1$	Sphingosine-1-phosphate receptor 1
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCR	Screened analysis set
SF-36v2™	36-Item Short Form Health Survey version 2
SFI	SLE Flare Index
SIV	Site initiation visit
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
SOC	System Organ Class
SOP	Standard Operating Procedure

SRBC	Sheep red blood cell
SRI	Systemic Lupus Erythematosus Responder Index
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent terminal elimination half-life
TB	Tuberculosis
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TP1	Treatment Period 1
TP2	Treatment Period 2
ULN	Upper limit of normal
USPI	United States Prescribing Information
WBC	White blood cell
WOCBP	Women of childbearing potential

NON-SUBSTANTIAL GLOBAL AMENDMENT 4

Amendment rationale

The rationale of this amendment applies to the global protocol ID-064A202 Version 4 dated 2 December 2020. The resulting amended global protocol is Version 5 dated 4 February 2022.

The main reasons for this amendment consist of the following:

A) Month-12 analysis:

The cut-off for the protocol planned 'Month-12 analysis' has been updated to allow an early readout of the efficacy and safety data. The Month-12 analysis readout will supplement the 6-month primary analysis to support the start of the upcoming Phase 3. The analysis will be performed when all randomized subjects have completed Treatment Period 2 (TP2) or discontinued the study. The Month-12 analysis will take place before the completion of the safety follow-up period by all subjects and final End-of-Study (EOS) analysis.

After the Month-6 and the Month-12 analyses, the study will remain double-blinded. Investigators, site staff, subjects, and the sponsor staff responsible for the study conduct (with appropriate firewalls) will remain blinded to study treatment allocation until study closure.

The final EOS analysis will be performed as initially planned, when all randomized subjects have completed the posttreatment follow-up period or discontinued the study.

B) Extension of the follow-up period and the period that the use of highly effective contraception in women of childbearing potential (WOCBP) is required:

The follow-up period during which the use of highly effective contraception in WOCBP is required has been extended from 4 to 6 months after EOS treatment (End-of-Treatment [EOT]) or after permanent study treatment discontinuation based on data from the Phase 1 study ID-064-105.

Recently available pharmacokinetic (PK) data from the clinically completed Phase 1 study ID-064-105 has shown that the geometric mean apparent terminal elimination half-life ($t_{½}$) of cenerimod was approximately 33 days as compared to 22 days prior observed in the multiple-ascending-dose (MAD) study. This may be related to the longer sampling period for PK assessment after stopping treatment with cenerimod in study ID-064-105 (120 days) compared to the MAD study (60 days).

A period of 5 half-lives after EOT or after permanent study treatment discontinuation is considered adequate to monitor adverse events (AEs), serious AEs (SAEs) as well as to define the period where the use of highly effective contraception in WOCBP is required.

This measure is in line with the recommendations of the Clinical Trial Facilitation Group to use highly effective methods of contraception until the end of relevant systemic exposure for teratogenic compounds.

Thus, the follow-up period in the CARE study is extended by 2 months with 2 follow-up (FU) phone call visits (FU3a and FU3b) to be performed 4 and 5 months after EOT. The EOS visit should occur 6 months after the EOT or permanent treatment discontinuation.

Furthermore, a summary of the PK results of the recently clinically completed ID-064-105 has been added to the background information.

In addition to this protocol and its amendments, a separate addendum to the protocol is in place to cover exceptional measures to ensure subject safety in the context of the coronavirus disease 2019 (COVID-19) pandemic and counteract any trial conduct disruption that may occur. The addendum (Version 2 dated from 27 May 2020) applies to those sites affected by the COVID-19 outbreak and is limited to the time during which such sites are affected.

Amendment protocol sections

2 versions of the amended protocol will be prepared: 1) a clean version, and 2) a comparison document showing deletions and insertions in comparison to the previous protocol version.

The main sections of the protocol affected by this global amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

Sections	Change
1.4.2	Updates of $t_{½}$.
3.1	Description of Month-12 analysis and final EOS analysis. Extension of the follow-up period to 6 months.
3.1, 5.1.3.1	Blinding management after the Month-12 analysis was added.
4	Extension of the contraception post study drug discontinuation from 4 months to 6 months

7	Update of the follow-up period to 6 months: • Addition of 2 FU visits (phone calls) at 4 months and 5 months after EOT. • EOS visit performed 6 months after last study treatment intake.
5.1, 6.3, 8.1, 8.4, 9	Update of study completion according to the extension of the follow-up period to 6 months.
10.4	Details on Month-12 and final EOS analyses added.

Furthermore, minor editorial changes have been made to improve clarity, and typographical errors have been corrected in other sections of the protocol.

Summary of previous amendments

Amendments	Date	Change/Rationale (covered in this amendment)
3	2 December 2020	Substantial global amendment: • Due to the slower than anticipated enrollment and the unpredictable future impact of the COVID-19 pandemic, the sponsor has decided to reduce the sample size of the study from 500 to approximately 325 randomized subjects. With this sample size of approximately 65 subjects per treatment group (instead of the initially planned 100 subjects per group), the study will retain adequate power for the analysis of the primary endpoint and will provide evidence of efficacy and safety to design the Phase 3 program. • Study treatment will be extended to 12 months for all randomized subjects in order to generate additional safety and efficacy data over time. Therefore, all subjects who complete Treatment Period 1 (TP1) will enter and complete TP2 for an additional 6 months. The study will end when all subjects have completed TP2 and the posttreatment follow-up period. The study objectives remained unchanged. The primary analysis is the Month-6 analysis; it will

Amendments	Date	Change/Rationale (covered in this amendment)
		be performed when all randomized subjects have completed TP1 or discontinued the study.
2	3 March 2020	Substantial global amendment: • Revision of the specific stopping criteria and discharge criteria on Day 1 / re-initiation for systolic blood pressure to account for eligible subjects with historical and baseline pre-dose systolic blood pressure values < 90 mmHg. • Introduction of the re-screening procedure for subjects who failed screening due to a transient non-eligibility reason, to mitigate the screening failure rate. • Other modifications were made to improve consistency and accuracy of the protocol.
1	31 July 2019	Substantial global amendment: • Addition of Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire at Month 3 to allow for an earlier assessment of fatigue. • Inclusion of anchor patient global assessment questions for FACIT-Fatigue (Patient Global Impression of Severity – Fatigue [PGIS-F] and Patient Global Impression of Change – Fatigue [PGIC-F]), to inform definition of responders and clinical meaningfulness of difference between groups. • Other modifications were made to improve consistency, accuracy, clarity and readability of the protocol, including the changes covered by the non-substantial local amendment below.

Amendments	Date	Change/Rationale (covered in this amendment)
1.USA.A	3 April 2019	Non-substantial local amendment: • Belimumab information on the s.c. dosage was missing. Clarification was provided to account for the intravenous and s.c. dosage. • Additional information on allowed concomitant therapy was provided regarding the use of topical ocular treatment administration during the course of the study. • Clarification on premature discontinuation: footnote 14 of Table 4 was modified to ensure full alignment with the protocol text.

PROTOCOL SYNOPSIS ID-064A202

TITLE	A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe systemic lupus erythematosus (SLE).
ACRONYM	**CARE**: **C**enerimod **A**ssessing S1P1 **R**eceptor modulation in Systemic Lupus **E**rythematosus
OBJECTIVES	The primary objective is to assess the efficacy of 6 months' cenerimod treatment given at 4 different dose levels (0.5, 1, 2, and 4 mg once daily [o.d.]) on disease activity in adult subjects with moderate to severe SLE concurrently receiving background therapy. The secondary objectives of the study are to evaluate the following over 6 months in adult subjects with moderate to severe SLE concurrently receiving background therapy: • The safety and tolerability of cenerimod treatment. • The effect of cenerimod treatment on quality of life and fatigue using relevant Patient Reported Outcome (PRO) instruments. • The effect of cenerimod treatment on SLE biomarkers.
DESIGN	This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult subjects with moderate to severe SLE. Approximately 325 adult subjects with SLE will be randomized in a 1:1:1:1:1 ratio to placebo, 0.5, 1, 2, or 4 mg o.d. of cenerimod, in addition to background SLE therapy. Once randomized, all subjects will enter a 6-month double-blind study treatment period called Treatment Period 1 (TP1). Subjects randomized to, and still receiving placebo, 0.5, 1, or 2 mg at Month 6 will be assigned to the same treatment arm for an additional 6 months in Treatment Period 2 (TP2), i.e., for a total maximum of 12 months.

	Subjects randomized to the 4 mg arm will receive study treatment at this dose for a maximum of 6 months in TP1. Afterwards, subjects in this group still receiving this dose at Month 6 will be re-randomized in a 1:1 ratio to placebo or cenerimod 2 mg to enter TP2 and will continue for a total maximum of 12 months. Treatment allocation is stratified by dose of oral corticosteroids (OCS) at Randomization (OCS with two strata: < 7.5 mg/day or ≥ 7.5 mg/day prednisone or equivalent), and by disease activity at Screening (with two strata: modified Systemic Lupus Erythematosus Disease Activity Index-2000 [mSLEDAI-2K] < 10 or ≥ 10). There will be three study analyses: the Month-6 analysis, the Month-12 analysis, and the final EOS (End-of-Study) analysis [see Section 10.4]. Month-6 analysis will be performed when all randomized subjects have completed TP1 or discontinued the study. Month-12 analysis will be performed when all randomized subjects have completed TP2 or discontinued the study. Final EOS analysis will be performed when all randomized subjects have completed the posttreatment follow-up or discontinued the study. After Month-6 and Month-12 analyses, ongoing subjects will continue to be treated and followed up in a double-blinded manner up to their EOS visit. Investigators, site staff, subjects, and the sponsor staff responsible for the study conduct (with appropriate firewalls) will remain blinded to study treatment allocation until study closure. To maintain the blinding of the study up to final EOS analysis, appropriate measures will be put in place to ensure the good conduct of this process.

	Study periods The study comprises the following periods: **Screening period and OCS optimization period for subjects receiving OCS** The screening period starts with the signing of the informed consent form (ICF) and ends on the day of Randomization, before the first study drug intake. This period can last up to 60 days. During this period, the subject's SLE background medication should be maintained stable except for OCS which should be tapered to the minimum required dose and maintained stable for at least 15 days prior to Randomization [see Section 5.2.2.1]. **Treatment period** This period comprises 2 periods – TP1 and TP2. TP1 lasts 6 months. It starts with the administration of the first dose of study treatment, after subject randomization, and ends at the Month 6 visit. Starting at the Month 6 visit, TP2 lasts 6 months and ends at the Month 12 visit. All randomized subjects in the study will have to complete TP1 before continuing in TP2. **Follow-up period** This period starts after the End-of-Treatment (EOT) and lasts 6 months until the EOS. For the first 5 months after the EOT visit, subjects will have to conduct monthly follow-up (FU) visits, FU1, FU2, FU3, FU3a, and FU3b to collect information on adverse events (AEs) and serious AEs (SAEs) and/or pregnancy as well as efficacy data. The EOS visit should occur 6 months after the EOT.
NUMBER OF SUBJECTS	Approximately 325 subjects diagnosed with SLE will be randomized.
PLANNED DURATION	Approximately 44 months from First Patient First Visit to Last Patient Last Visit.

SITES / COUNTRIES	Approximately 180 sites from 21 countries notably from the regions of Asia Pacific, Eastern Europe, Latin America, North America, and Western Europe.
INCLUSION CRITERIA	**Screening criteria:** 1. Signed ICF prior to any study-mandated procedure. 2. Diagnosis of SLE made at least 6 months prior to Screening, by fulfilling at least 4 of the 11 criteria for SLE as defined by the American College of Rheumatology (ACR) criteria [Appendix 2]. 3. Male and female subjects, age 18 to 75 years old (both inclusive). 4. A mSLEDAI-2K score ≥ 6 of at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers). Note: The mSLEDAI-2K score does not take into account "leukopenia". 5. History or presence of positive anti-nuclear antibodies (ANA) or anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies. 6. Currently treated with stable doses of one or more of the following background medications: • Non-steroidal anti-inflammatory drugs (NSAIDs), • Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine), • Mycophenolate mofetil (≤ 2 g/day), • Mycophenolic acid (≤ 1440 mg/day), • Azathioprine (≤ 2 mg/kg/day), • Methotrexate (≤ 20 mg/week), • Corticosteroids (≤ 40 mg/day prednisone or equivalent), • Belimumab (≤ 10 mg/kg every 4 weeks intravenously [i.v.], or 200 mg/week subcutaneously [s.c.]). 7. Women of childbearing potential (WOCBP):

	• Must have a negative serum pregnancy test at Screening. • Must agree to undertake monthly urine pregnancy tests during the study. • Must use highly effective methods of contraception from the Screening visit until 6 months after taking the last dose of study treatment as described in Section 4.4.2. **Randomization criteria:** 8. A clinical mSLEDAI-2K score ≥ 4. Note: The clinical mSLEDAI-2K is the mSLEDAI-2K assessment score without the inclusion of points attributable to hematuria, proteinuria, pyuria, low complement, increased DNA binding and thrombocytopenia. 9. Presence of at least one of the following autoantibodies measured by central laboratory defined as follows (based on the screening sample): (a) positive ANA test measured by immunofluorescence assay with titer ≥ 1:80; or (b) positive anti-dsDNA antibodies with titer ≥ 30 IU/mL. 10. On a stable dose of background SLE medication consisting of any of the following medications (alone or in combination) for a period of at least 30 days (15 days for corticosteroids) prior to Randomization: • NSAIDs, • Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine), • Mycophenolate mofetil (≤ 2 g/day), • Mycophenolic acid (≤ 1440 mg/day), • Azathioprine (≤ 2 mg/kg/day), • Methotrexate (≤ 20 mg/week), • Corticosteroids (≤ 40 mg/day prednisone or equivalent) [see Section 5.2.2.1],

	• Belimumab (≤ 10 mg/kg every 4 weeks i.v., or 200 mg/week s.c.). 11. WOCBP: • Must have a negative urine pregnancy test at Randomization visit.
EXCLUSION CRITERIA	**Screening criteria** **Disease/condition** 1. Female subjects who are breastfeeding or planning to become pregnant during the study. 2. Active lupus nephritis (defined by proteinuria > 1.5 g/24 h, or equivalent using spot urine protein-to-creatinine ratio: > 150 mg/mmol) or a renal biopsy demonstrating immune complex-mediated glomerulonephritis compatible with lupus nephritis within 90 days prior to Screening. 3. Severe active central nervous system (CNS) lupus requiring therapeutic intervention (including aseptic meningitis, seizures, psychosis, cerebritis, cerebrovascular accident [CVA], organic brain syndrome, CNS vasculitis) and severe forms of vasculitis requiring systemic immunosuppressive treatment (including retinal vasculitis, coronary vasculitis, pulmonary vasculitis, mesenteric vasculitis) within 90 days prior to Screening. 4. A diagnosis of mixed connective tissue disease or any history of overlap syndromes of SLE with rheumatoid arthritis, erosive arthritis, scleroderma or autoimmune hepatitis. 5. History or presence of Mobitz type II or third-degree atrioventricular block, sick sinus syndrome, symptomatic bradycardia or syncope associated with cardiac disorders. 6. Subjects who experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, vascular thrombosis, decompensated heart failure requiring hospitalization, or heart failure defined by the New York

	Heart Association (NYHA) Class III/IV within 6 months prior to Screening. 7. An elevated QT corrected for heart rate (HR) using Fridericia's formula (QTcF) interval of > 470 ms (females) / > 450 ms (males). 8. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function and chest X-ray performed at Screening or within 6 months prior to Screening or medically significant abnormal pulmonary function test: forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted normal value or FEV_1/FVC ratio < 0.7. 9. History of clinically relevant bronchial asthma or chronic obstructive pulmonary disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 6 months prior to Screening. 10. Active or latent tuberculosis (TB), as assessed by chest X-ray performed at Screening or within 6 months prior to Screening, and interferon (IFN) gamma release assay (QuantiFERON-TB-Gold Plus®), except if there is documentation that the subject has completed adequate and successful treatment for TB previously. 11. Ongoing bacterial, viral or fungal infection that is of clinical concern in the judgment of the investigator or history of any serious infection, defined as life-threatening or requiring i.v. antibiotics or hospitalization. 12. Positive results for serological markers for hepatitis A, B, C and E indicating acute or chronic infection: – Anti-HAV IgM – HBsAg – Anti-HCV IgG or IgM – Anti-HEV IgG or IgM (if positive IgM and/or IgG, perform HEV-RNA PCR and if negative patient can be randomized).

	13. Subjects who have congenital or acquired severe immunodeficiency or known HIV infection or positive HIV testing. 14. Negative antibody test for varicella-zoster virus. Vaccination of antibody-negative subjects may be considered, which must occur at least 30 days prior to re-test and Randomization. 15. History or presence of malignancy (except for surgically excised basal or squamous cell skin or mucosal lesions, including dysplasia and carcinoma in situ), lymphoproliferative disease, or history of total lymphoid irradiation. 16. History or presence of bone marrow or solid organ transplantation. 17. Presence of macular edema or active uveitis. 18. Type 1 or 2 diabetes that is poorly controlled according to investigator judgment, or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy. 19. History of chronic liver or biliary disease (other than Gilbert's Syndrome) or subjects with alanine aminotransferase or aspartate aminotransferase $> 2 \times$ upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ ULN (unless in the context of known Gilbert's Syndrome). 20. Significant hematology abnormality: lymphocyte count < 800 /µL (0.8×10^9/L); hemoglobin < 9 g/dL; white blood cell count < 2500/µL (2.5×10^9/L) or platelets $< 75{,}000$/µL (75×10^9/L). 21. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2. 22. History of clinically significant drug or alcohol abuse. 23. Known allergy to sphingosine-1-phosphate (S1P) receptor modulators or any of the cenerimod formulation excipients.

	24. Any other clinically relevant medical condition that would put the subject at risk if participating in the study, or any other diseases that may confound the disease activity assessments. **Medications** 25. Treatment with the following medications within 15 days or 5 half-lives of the medication (whichever is longer) prior to Randomization: a. β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering systemic therapy [list of drugs provided in Appendix 3]. b. QT-prolonging drugs with known risk of torsade de pointes irrespective of indication [list of drugs provided in Appendix 4]. 26. Treatment with the following medications within 30 days or 5 half-lives of the medication (whichever is longer) prior to Randomization: a. Cyclophosphamide, ciclosporine, tacrolimus, sirolimus. b. Pulse methylprednisone. c. Vaccination with live vaccines. 27. Intra-articular, intramuscular or i.v. glucocorticosteroids within 6 weeks prior to Randomization. 28. Treatment with the following medications within 90 days or 5 half-lives of the medication (whichever is longer) prior to Randomization: a. Leflunomide. b. i.v. immunoglobulins. 29. Treatment with any investigational agent within 90 days or 5 half-lives of the drug (whichever is longer) prior to Randomization. 30. Treatment with B cell-depleting biological agents such as rituximab or ocrelizumab within 12 months prior to Randomization.

	31. Treatment with any of the following medications any time prior to Screening: a. Alemtuzumab, b. S1P receptor modulators (e.g., fingolimod). **Randomization exclusion criteria** 32. Resting HR < 50 bpm as measured by the pre-dose 12-lead ECG. 33. An elevated QTcF interval of > 470 ms (females) / > 450 ms (males) as measured by the pre-dose 12-lead ECG on Day 1. 34. Severe active CNS lupus requiring therapeutic intervention (including aseptic meningitis, psychosis, seizures, cerebritis, CVA, organic brain syndrome, CNS vasculitis) and severe forms of vasculitis requiring systemic immunosuppressive treatment (including retinal vasculitis, coronary vasculitis, pulmonary vasculitis, mesenteric vasculitis). 35. Clinically relevant bronchial asthma or chronic obstructive pulmonary disease.
STUDY TREATMENTS	**Investigational treatment** Cenerimod is supplied as film-coated tablets at the doses of 0.5, 1, 2, and 4 mg to be administered orally o.d. **Placebo** Placebo matching cenerimod film-coated tablets administered orally o.d. in the morning.
CONCOMITANT THERAPY	**Background SLE therapy** To be eligible for the study, subjects must currently receive at least one of the below SLE background medication: • NSAIDs – Aspirin (acetylsalicylic acid), – Ibuprofen, – Naproxen, – Celecoxib, – Others.

	• Corticosteroids (≤ 40 mg/day prednisone or equivalent [see Appendix 1]) – Prednisolone, – Prednisone, – Methylprednisolone, – Dexamethasone, – Betamethasone, – Hydrocortisone, – Triamcinolone, – Cortisone. • Anti-malarials – Hydroxychloroquine (≤ 400 mg/day), – Chloroquine (≤ 500 mg/day), – Quinacrine (≤ 100 mg/day). • Mycophenolate mofetil (≤ 2 g/day) • Mycophenolic acid (≤ 1440 mg/day) • Azathioprine (≤ 2 mg/kg/day) • Methotrexate (≤ 20 mg/week) • Belimumab (≤ 10 mg/kg every 4 weeks i.v., or 200 mg/week s.c.) Treatment with anti-malarials, mycophenolate mofetil, mycophenolic acid, azathioprine, methotrexate or belimumab must have been started at least 90 days prior to Screening. All other background SLE therapies must have been started at least 30 days prior to Screening. Background SLE therapy doses must be stable for at least 30 days prior to Randomization. For corticosteroids, doses must be stable for at least 15 days prior to Randomization. **Oral corticosteroids** **Screening period / oral corticosteroid optimization period for subjects receiving OCS** For subjects who are being treated with corticosteroids prior to enrollment in this study, an optimization period aiming to reduce the doses of OCS to (or as close as possible to) the

	minimum effective dose should be considered during the screening period. This will allow minimization of OCS changes during the treatment period, which is the preferred approach. Dose reductions are at the investigator's discretion and can be done up to 15 days prior to Randomization when the OCS dose must be stable for eligibility criteria. **Treatment Period 1 (from Randomization to Month 6)** For subjects who are being treated with corticosteroids, it is preferable that doses are maintained stable until the end of Month 6 of the study to avoid introducing confounding factors for the interpretation of the primary objective. The dose adjustment recommended during Screening aims to minimize the change in OCS dose during the treatment period. For subjects showing improving SLE disease activity for at least 8 weeks, OCS dose reduction may be considered at the investigator's discretion during the first 3 months of TP1 [see suggested guidance in Table 3]. No steroid sparing is allowed between Month 3 and Month 6 (i.e., between Visit 5 and 8). Rationale for dose change and details of the change should be documented in the electronic Case Report Form (eCRF). Subjects with increased SLE disease activity may receive one OCS burst during the first 3 months of TP1, which should be tapered to the Randomization dosage within 2 weeks of the start of the upgrade/initiation of the OCS. Alternatively, a single intramuscular or i.v. dose of methylprednisone (80 to 160 mg or equivalent) is permitted instead of OCS burst. Rationale for dose change and details of the change should be documented in the eCRF. **Treatment Period 2 (after Month 6 of treatment)** After the first 6 months of study, OCS dose reduction may be considered for subjects showing improving SLE disease activity for at least 8 weeks. Investigators should consider the guidance provided in Table 3. This table reflects the ACR draft guidance regarding steroid reduction during periods of stable SLE disease [see Section 5.2.2.1].

	Subjects with increased SLE disease activity may receive an OCS burst after Month 6, which should be tapered to Randomization dosage within 2 weeks of the start of the upgrade/initiation of the OCS. Alternatively, a single intramuscular or i.v. dose of methylprednisone (80 to 160 mg or equivalent) is permitted instead of OCS burst. **Allowed concomitant therapy** After Randomization, background medications should be kept stable throughout the study. However, if clinically required, changes in certain medications as outlined below are allowed: • Stable chronic NSAID therapy: therapy is not to be started or stopped during the study. – Temporary use and/or dose change for treatment of non-SLE-related conditions (e.g., headache, menstrual cramps) is allowed. • Stable immunosuppressant therapy (i.e., methotrexate, azathioprine, or mycophenolate mofetil, mycophenolic acid as well as belimumab). Therapy is not to be started or stopped during the study, and the dose should be kept stable. • Atropine (i.v.) in the event of symptomatic bradycardia. • Topical ocular therapy (e.g., chronic treatment for glaucoma, ocular inflammation), including dilating eye drops, mydriatics, parasympathetic antagonists (e.g., tropicamide) or sympathetic agonists (e.g., phenylephrine). • Vaccination with non-live vaccines. • Topical treatment therapy including topical, inhaled, and nasal use of corticosteroid. • All other medications that are not forbidden. **Forbidden concomitant therapy** • Immunosuppressive agents not listed in allowed concomitant medication such as cyclophosphamide, ciclosporine, leflunomide, sirolimus, tacrolimus, etc.

	• Immunosuppressive or immunomodulatory biological agents (e.g., i.v. immunoglobulin, rituximab, S1P receptor modulators other than cenerimod). • β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering therapy. • QT-prolonging drugs with known risk of torsade de pointes. • Vaccination with live vaccines. • Inhibitors of the breast cancer resistance protein transporter: curcumin, ciclosporine, eltrombopag, elacridar, gefitinib, teriflunomide. For further details, see table of forbidden medications in Appendix 3 and Appendix 4.
ENDPOINTS	**Efficacy** **Primary endpoint** • Change from baseline to Month 6 in the mSLEDAI-2K score. This endpoint is based on the SLE Disease Activity Index-2000 (SLEDAI-2K) index, modified to exclude leukopenia. The SLEDAI-2K will be assessed by the investigator or delegate who will enter the relevant data into the SLEDAI-2K form of the eCRF. Further details are available in Section 7.2.6.1. Baseline is defined as the last available measurement before the start of randomized treatment. All values of mSLEDAI-2K from baseline through Month 6 visits will be accounted for in the assessment of this endpoint. **Secondary endpoints** • Response on SLE Responder Index (SRI)-4 at Month 6 as compared to baseline, defined as follows: – Reduction from baseline of at least 4 points in the mSLEDAI-2K.

	AND – No new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than one new BILAG B organ domain score compared with baseline. AND – No increase of more than 0.3 points on the Physician's Global Assessment (PGA) since baseline. • Response (no worsening) at Month 6 on BILAG-2004 disease activity index defined as no new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline. **Other efficacy endpoints** • Response at Month 6 based on improvement in the mSLEDAI-2K score defined as a reduction from baseline of at least 4 points. • Response (no worsening and improvement) at Month 6 on BILAG-2004 disease activity index defined as follows: – No new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline. AND – Any BILAG A organ domain score at study baseline improved to B/C/D or any BILAG B organ domain score at study baseline improved to C/D. • SRI-5, -6, -7, -8 responses at Month 6. • Occurrence of mild, moderate and severe flares for 6 months [see SLE Flare Index in Appendix 12]. • Time to first severe flare from baseline to Month 6 (severe flares defined as BILAG-2004 A organ domain score presence due to items that are new or worse). • Time to first flare from baseline to Month 6. • Change from baseline to Month 6 in PGA score.

	PRO / Quality of life endpoints • Change from baseline to each post-baseline assessment in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale score. • Change from baseline to each post-baseline assessment in Patient Global Impression of Severity – Fatigue (PGIS-F). • Patient Global Impression of Change – Fatigue (PGIC-F) score at each post-baseline assessment. • Change from baseline to each post-baseline assessment in 36-Item Short Form Health Survey version 2 (SF-36v2™). • Change from baseline to each post-baseline assessment in the Lupus Quality of Life questionnaire. **Exploratory endpoints** See Section 6.1.5. **Safety endpoints** • Occurrence of treatment-emergent AEs/SAEs, and AEs of special interest [see Appendix 5]. • Occurrence of AEs leading to premature discontinuation of study treatment. • Changes in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for heart rate using Bazett's formula [QTcB] and QTcF), from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 / Re-initiation and each post-dose analysis visit up to EOS) for each parameter. • Occurrence of treatment-emergent 12-lead ECG notable abnormalities (e.g., HR, PR, QTc) [see Appendix 7]. • Occurrence of treatment-emergent 12-lead ECG abnormal findings. • Change in supine systolic blood pressure and diastolic blood pressure from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 / Re-initiation and each post-dose analysis visit up to EOS).

	• Change in FEV_1 and FVC from baseline to each post-baseline assessment up to EOS. • Occurrence of treatment-emergent decrease of FEV_1 or FVC > 15% from baseline values at any post-baseline assessment. • Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline to each post-baseline assessment up to EOS. • Occurrence of treatment-emergent laboratory notable abnormalities [see Appendix 7]. • Change in body weight from baseline up to EOS. • Change in left ventricular ejection fraction as assessed by Standard 2D echocardiography from Screening to Month 6 in subjects randomized to ancillary echocardiography study. • Occurrence of clinically relevant abnormalities as assessed by Standard 2D/Doppler echocardiography from Screening to Month 6 in subjects randomized to ancillary echocardiography study. **Pharmacokinetic endpoints** • Cenerimod plasma concentrations post-dose on Day 1, 6 h after dosing. • C_{trough} cenerimod plasma concentrations prior to dosing at Months 1, 2, 3, and 6 or at EOT visit after premature study treatment discontinuation (if applicable). • Cenerimod plasma concentration at the EOS visit (i.e., 6 months after last dose of study treatment). **Biomarker endpoints** • Change from baseline to each post-baseline assessment up to EOS in total lymphocyte count. • Change from baseline to each post-baseline assessment in the following biomarkers: ANA, anti-dsDNA, anti-Smith, and C3, C4 complement.
ASSESSMENTS	Refer to the schedule of assessments in Table 4.

STATISTICAL METHODOLOGY	**Analysis sets** **Screened Analysis Set** The Screened analysis set (SCR) includes all subjects who entered Screening and have a subject identification number. **Full Analysis Set** The Full analysis set (FAS) includes all subjects who have been assigned (i.e., randomized) to double-blind study treatment at the start of TP1. Subjects will be analyzed based on their assigned study treatment. **Full Analysis Set – TP2** The Full analysis set TP2 (FAS-TP2) includes all subjects from the FAS who have been assigned (i.e., randomized) to double-blind study treatment at the start of TP2. Subjects will be analyzed based on their assigned study treatment. **Per-Protocol Analysis Set** The Per-protocol set (PPS) includes all subjects from the FAS without clinically important protocol deviations occurring during TP1 which could affect the analysis of the primary endpoint variable. The precise reasons for excluding subjects from the PPS will be fully defined and documented in the statistical analysis plan (SAP) before breaking the randomization blind. The PPS will only be defined for the period TP1. **Safety Analysis Set** The Safety analysis set (SAF) includes all subjects who received at least one dose of double-blind study treatment during TP1. Subjects will be analyzed based on the treatment received. **Safety Analysis set – TP2** The Safety analysis set TP2 (SAF-TP2) includes all subjects from the SAF who received at least one dose of double-blind study treatment during TP2. Subjects will be analyzed based on the treatment received.

	Echocardiography Set The Echocardiography set (ECS) includes subjects who were assigned to the Echocardiography sub-study by Interactive Response Technology (IRT) with at least one post-baseline echocardiography assessment. Subjects will be analyzed based on the treatment received. **Pharmacokinetic Analysis Set** The Pharmacokinetic (PK) analysis set (PKS) includes all randomized subjects who received at least one cenerimod dose, had at least one blood sample for PK evaluation collected after cenerimod initiation, had evaluable plasma concentrations, and did not deviate from the protocol in a way that might affect the evaluation of the PK endpoint. Subjects will be analyzed based on actual dose taken, not the randomized dose. **Usage of the analysis sets** The analyses of efficacy endpoints including baseline and disease characteristics from TP1 will be performed using the FAS and the PPS for sensitivity analyses. FAS-TP2 will be used for specific analyses only including TP2 data. The FAS will be used for analyses which combine TP1 and TP2 data. The Safety Set will be used for the analysis of safety endpoints (including study treatment exposure) from TP1. SAF-TP2 will be used for specific analyses only including TP2 data. The Safety Set will be used for analyses which combine TP1 and TP2 data. Subject data will be listed using the SCR, unless otherwise specified. **Description of statistical analyses** All available data for each subject will be used in all statistical analyses unless otherwise specified.

Overall testing strategy

The Type I error rate will be controlled for the testing of multiple null hypotheses associated with the primary and secondary endpoints and the four dose levels included in this study: 0.5, 1, 2, and 4 mg.

The four statistical null hypotheses associated with the primary efficacy endpoint are:

Change of mSLEDAI-2K from Baseline to Month 6:

$H1_{mSLEDAI\text{-}2K}$: $cenerimod_{0.5\ mg}$ – placebo = 0,

$H2_{mSLEDAI\text{-}2K}$: $cenerimod_{1.0\ mg}$ – placebo = 0,

$H3_{mSLEDAI\text{-}2K}$: $cenerimod_{2.0\ mg}$ – placebo = 0,

$H4_{mSLEDAI\text{-}2K}$: $cenerimod_{4.0\ mg}$ – placebo = 0.

These hypotheses represent the difference in mean change from baseline to Month 6 in mSLEDAI-2K between the four doses of cenerimod and placebo.

The eight statistical null hypotheses associated with the secondary efficacy endpoints are:

SRI-4

$H1_{SRI\text{-}4}$: $cenerimod_{0.5\ mg}$ / placebo = 1,

$H2_{SRI\text{-}4}$: $cenerimod_{1.0\ mg}$ / placebo = 1,

$H3_{SRI\text{-}4}$: $cenerimod_{2.0\ mg}$ / placebo = 1,

$H4_{SRI\text{-}4}$: $cenerimod_{4.0\ mg}$ / placebo = 1,

and BILAG

$H1_{BILAG}$: $cenerimod_{0.5\ mg}$ / placebo = 1,

$H2_{BILAG}$: $cenerimod_{1.0\ mg}$ / placebo = 1,

$H3_{BILAG}$: $cenerimod_{2.0\ mg}$ / placebo = 1,

$H4_{BILAG}$: $cenerimod_{4.0\ mg}$ / placebo = 1.

These eight hypotheses represent the odds ratios of the secondary endpoints SRI-4 and BILAG-2004 between the four doses of cenerimod and placebo.

Each null hypothesis will be tested against the alternative hypothesis that a difference exists between cenerimod and placebo, at a given dose, in mSLEDAI-2K, SRI-4, and BILAG-2004.

Within each primary and secondary endpoint analysis, the Hochberg procedure will be used to control the familywise error rate to ensure an overall two-sided Type I error rate of 5% for the four treatment group comparisons vs placebo. Further control of the study-wise error rate is conducted such that, for a given hypothesis to be rejected at a two-sided Type I error rate of 5% the same dose-level hypothesis must have also been rejected for the previous endpoint(s), considering the above ordering of the endpoint hypotheses [see Figure 4].

Analysis of the primary efficacy variable

The primary efficacy variable, based on the mSLEDAI-2K [Section 6.1.1], is continuous in definition such that higher scores indicate more severe SLE disease.

Primary statistical analysis

The primary statistical analysis will be performed on the FAS, according to the intent-to-treat approach.

The null hypotheses for the primary endpoint will be tested using a mixed model for repeated measures on all available changes from baseline in mSLEDAI-2K for post-baseline scores from Months 1 to 6.

The following terms will be included in the model: baseline mSLEDAI-2K score, treatment group, month, treatment group by month interaction, baseline mSLEDAI-2K score by month interaction, and the single stratification factor OCS (from IRT). The stratification factor mSLEDAI-2K (from IRT) will not be included in the model as the continuous baseline value is already included. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject.

The treatment effect for each cenerimod dose vs placebo will be estimated from the Least Squares Mean differences for

	each dose vs placebo at Month 6 and their corresponding 95% confidence intervals (CIs). The hypothesis tests will be based on the associated p-values at the two-sided significance level of alpha of 5%, controlling for multiplicity using the Hochberg procedure as mentioned above. **Analysis of the secondary efficacy variables** **Response at Month 6 based on SRI-4** A repeated measurement generalized linear model will be fitted with the secondary endpoint SRI-4 as response (from Month 1 to Month 6). The model will include the treatment group, month, the treatment group by month interaction, and will be stratified by the OCS and mSLEDAI-2K stratification variables (from IRT). The odds ratios and corresponding 95% CI for each treatment group comparison vs placebo will be provided along with the p-values from the Wald test. **Response at Month 6 based on BILAG-2004** The analysis will be performed based on the same repeated measurement model as described above. **Analysis of other efficacy variables** The analyses of all other efficacy variables will be described in detail in the SAP. Other efficacy endpoints will be analyzed at each relevant time point as specified in Section 6.1.3. **Analysis of the safety variables** The Safety Set will be used to perform all safety analyses. Safety analysis may be split by treatment period [Section 10.3.5]. This will be further detailed in the SAP. If not otherwise stated, only treatment-emergent safety data will be considered in tables and figures. All safety data will be included in outputs, with flags for safety data not considered to be treatment-emergent.

Study analyses

Three study analyses will be performed: the Month-6 analysis, the Month-12 analysis, and the final EOS analysis.

Month-6 analysis will be performed when all randomized subjects have completed TP1 or discontinued the study, using all data collected up to this time. Month-12 analysis will be performed when all randomized subjects have completed TP2 or discontinued the study, using all data collected up to this time. Final EOS analysis will be performed when all randomized subjects have completed the posttreatment follow-up period, or discontinued the study.

Sample size

Assumptions used to calculate power are provided in Table 6.

Assumptions for the expected mean difference and corresponding between-subject standard deviation for the mSLEDAI-2K primary endpoint are based on the recently completed 12-week Phase 2 study, AC-064A201 conducted in SLE subjects receiving 0.5, 1, 2, and 4 mg of cenerimod or placebo. [redacted] Such a difference is greater than that seen in other treatments approved for the treatment of SLE [GlaxoSmithKline 2018].

Based on the above effect size assumption for the continuous mSLEDAI-2K primary endpoint, 10,000 simulations using analysis of covariance to test four doses vs placebo indicate that 325 subjects (65 per group) will provide 89.6% power at a two-sided 5% level of significance to reject at least one of the four treatment hypotheses.

Under the same conditions, for the response based secondary endpoints, this sample size provides 71.4% power to reject at least one of the four treatment hypotheses.

All power calculations provided account for multiplicity of the four comparisons vs placebo, using the Hochberg procedure.

STUDY COMMITTEES	An Independent Data Monitoring Committee will be monitoring the benefit-risk ratio and making appropriate recommendations based on all the reported data and thus ensuring that the study is being conducted with the highest scientific and ethical standards.
ECHOCARDIOGRAPHY ASSESSMENTS/ ANCILLARY STUDY	Echocardiography assessments will be performed for all subjects within 30 days prior to Randomization. <u>Echocardiography ancillary study</u> An additional echocardiography assessment will be performed at Month 6 (or at premature EOT [pEOT] visit in the event of premature study treatment discontinuation during TP1) in approximately 175 subjects participating in the echocardiography sub-study. Standard 2D/Doppler echocardiography will assess cardiac morphology and function including regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction.

PROTOCOL

1 BACKGROUND INFORMATION

1.1 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex and heterogeneous autoimmune disease of unknown etiology, characterized by the production of pathogenic autoantibodies, tissue deposition of immune complexes, and tissue damage across multiple organ systems. The adaptive T and B cells and the innate immune system are considered to play a major pathophysiological role in this disease as demonstrated by increased levels of circulating plasmablasts, infiltration of autoreactive CD4 and CD8 T cells, B cells, and innate immune cells into tissues, formation of tertiary lymphoid structures, and increased resistance to apoptosis [Carroll 2004, Foster 2007, Shah 2010].

SLE occurs primarily in young women with a peak incidence during the reproductive age years [Borchers 2010, Pons-Estel 2010, Pons-Estel 2017] and an estimated female to male ratio of 7:1 to 10:1 [Govoni 2006]. The disease is more prevalent in African-Americans than Caucasians (as per the National Women's Information Center and the Department of Health and Human Services) and the estimated overall incidence rate for SLE varies from approximately 0.3–23.7 per 100,000 person-years whereas prevalence rates ranges from 6.5–178 per 100,000 [Pons-Estel 2017]. In the United States, the prevalence of SLE is higher among Asians, African-Americans, African-Caribbeans, and Hispanic Americans compared to Caucasians [Pons-Estel 2010, Danchenko 2006, Rus 2002, Petri 2002]. In European countries, the prevalence of SLE is also higher among people of Asian and African descent [Pons-Estel 2010].

With improved diagnosis and management, the life expectancy of SLE patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a 15-year survival rate of 80% [Abu-Shakra 1995, Mok 2011, Pons-Estel 2010].

Clinical manifestations of SLE include rash, arthritis, anemia, thrombocytopenia, serositis, nephritis, seizures, and psychosis among others [Rahman 2008].

The natural history of SLE is characterized by relapses or flares, alternated with periods of remission. It results in considerable morbidity due to flares of disease activity and accumulated organ damage, and an increased risk of premature death, mostly due to renal and cardiovascular disease, and infection [Pons-Estel 2010, Yurkovich 2014].

SLE patients' quality of life is directly influenced by the symptoms they experience. Between 80 and 90% of patients with lupus report fatigue to be the most debilitating symptom of their disease with wide ranging effects on quality of life [Bakshi 2017]. Studies have shown that the disease can affect emotions, social well-being, family, employment and leisure activities, cognition, appearance, and independence. SLE patients have

consistently reported lower scores on quality of life measures (36-Item Short Form Health Survey version 2 [SF-36v2™]) compared to the general population [Gallop 2012, Kiani 2013].

The current treatment of SLE comprises non-steroidal anti-inflammatory drugs (NSAIDs), anti-malarials, corticosteroids, and immunosuppressive drugs, often prescribed in that order as the disease progresses [Xiong 2014]. Acetylsalicylic acid, hydroxychloroquine, and belimumab are the only FDA-approved treatments for SLE, whereas rituximab (anti-CD20 monoclonal antibody) and other immunosuppressive therapies are commonly used off-label [Xiong 2014].

- NSAIDs and anti-malarials are often insufficient to control the disease, and the escalation to long-term corticosteroid use and to more and more potent immunosuppressants is the norm rather than the exception.
- Corticosteroids are commonly used in SLE and are a cornerstone of treatment, but have serious side effects associated with long-term use [Lateef 2012].
- Immunosuppressive drugs commonly used as SLE background therapy in the treatment of SLE include azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide. Potential risks of use of these drugs include bone marrow suppression and increased risk of infections.
- Belimumab, the most recently approved treatment for SLE, demonstrated treatment effect at 52 weeks but not at 76 weeks of treatment in its pivotal trials.

1.2 Unmet needs in SLE

Despite the significant improvements in diagnosing and managing the disease, treatment of SLE remains an area of significant unmet need. Except for belimumab, no new drug has received approval for treatment of SLE in the last 50 years. Therapies for SLE consist of relatively non-specific immunosuppressive and anti-inflammatory drugs of modest efficacy, and are associated with significant side effects.

Accelerated atherosclerosis and cardiovascular disease represent a significant burden for patients with SLE that may be exacerbated by chronic use of corticoids. Effective and safe steroid-sparing therapies that can help to reduce toxicity from long-term use of high-dose glucocorticoids remain an unmet medical need.

Fatigue is a very common symptom of SLE that negatively affects quality of life in the majority of SLE patients; none of the currently available treatments have shown significant effects on fatigue. Furthermore, the prevention of disease flares also represents a high medical need.

1.3 Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P) plays a central role in lymphocyte trafficking [Cyster 2005, Brinkmann 2007, Brinkmann 2010, Schwab 2007]. S1P is synthesized and secreted by many cell types, including platelets, erythrocytes, and mast cells and elicits a variety of physiological responses [Cyster 2005, Alvarez 2007]. Among other effects, lymphocyte egress from primary and secondary lymphoid organs is dependent on the S1P receptor. S1P receptor modulators block lymphocyte migration out of lymphoid tissue into the lymphatic and vascular circulation, thereby preventing lymphocyte recruitment to sites of inflammation. Following withdrawal of an S1P receptor modulator, the functional lymphocytes return to the circulation from their sites of sequestration. First-line immunological protection by granulocytes and monocytes, and antigen-dependent T-cell activation and expansion are not affected by this mechanism [Pinschewer 2011].

S1P itself induces pleiotropic effects, which are mediated by a family of five G protein-coupled receptors, $S1P_1$-$S1P_5$, located on endothelial cells, vascular and cardiac smooth muscle cells, and cardiac myocytes [Alvarez 2007, Brinkmann 2007, Brinkmann 2010]. The first S1P receptor modulator, fingolimod (FTY720, Gilenya®), which has been approved by the FDA [Gilenya® USPI] and the EMA [Gilenya® SmPC] for the treatment of multiple sclerosis, is a non-selective S1P receptor modulator with activity on $S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$ [Brinkmann 2007, Brinkmann 2010].

1.4 Cenerimod (ACT-334441)

Cenerimod is a potent, orally active, selective $S1P_1$ receptor modulator that blocks the egress of lymphocytes from lymphoid organs and thus reduces the tissue availability of circulating lymphocytes (T and B cells). This pharmacodynamic (PD) effect is sustained with continued daily oral dosing but is reversible upon drug discontinuation.

Cenerimod is being developed for the treatment of SLE. The compound was selected on the basis of its potential for once daily (o.d.) oral administration and its high selectivity for the $S1P_1$ receptor.

1.4.1 Nonclinical data

The main findings in the nonclinical studies conducted on cenerimod were:

- Cenerimod dose-dependently reduced lymphocyte counts in peripheral blood of rats and dogs after oral administration, reaching maximal effect at single doses $\geq$ 3 mg/kg in both species.
- Cenerimod had only a modest effect on antibody response to sheep red blood cell (SRBC) immunization in rats with a small effect on SRBC-specific IgM antibody production and no evident effect on IgG antibodies.

- Cenerimod is a lipophilic, highly plasma protein-bound compound and has a low clearance in rats and dogs.
- Bioavailability increased from 8 to 23% over a dose range of 0.1–40 mg/kg in the dog and from 9.7 to 23% at 0.3 and 3 mg/kg in the rat.
- Cenerimod is a moderate inhibitor of cytochrome protein (CYP)2C9 and CYP2C19, with inhibition constants of 18 µM and 15 µM, respectively. Cenerimod is neither an activator of human pregnane X receptor nor an inducer of CYP3A4 messenger ribonucleic acid or enzyme expression in human hepatocytes.
- Considering the low cenerimod doses and the high degree of binding to plasma proteins, it is expected that cenerimod has a limited potential for pharmacokinetic (PK) drug-drug interactions (DDIs) with concomitant medications whose PK are dependent on CYP clearance.
- Cenerimod induced lung findings in rats and dogs. The findings were related to $S1P_1$ modulators increasing pulmonary vascular permeability and consisted of increased lung weights, perivascular edema (both species, up to 4 weeks of treatment), and an increased incidence in alveolar histiocytosis (both species). In general, the findings appeared less pronounced after sub-chronic to chronic treatment and were not associated with clinical signs indicative of respiratory dysfunction.
- Coronary arterial lesions were observed in papillary muscles of the left ventricle in the dog after 4 weeks of treatment at 30 mg/kg/day and after 13 and 39 weeks at ≥ 10 mg/kg/day. The coronary arterial lesions were not observed in other species (rat) during nonclinical studies with cenerimod, and are considered to be an expression of dog-specific sensitivity to hemodynamic changes, with limited human relevance.
- Embryo-fetal toxicity studies in rats and rabbits showed that cenerimod is embryotoxic and teratogenic but not genotoxic nor mutagenic.
- Cenerimod did not affect fertility in rats.
- Safety margins were considered appropriate to support clinical trials up to 4 mg. For more details, see section 4.3.9 of the Investigator's Brochure (IB) [Cenerimod IB].

More detailed information on the data collected thus far on cenerimod can be found in the IB [Cenerimod IB]. The sponsor will notify the principal investigator of important nonclinical safety data that may become available during the study.

1.4.2 Clinical studies in humans

The human clinical experience with cenerimod includes four completed Phase 1 studies in healthy subjects (AC-064-101, AC-064-102, AC-064-103 and ID-064-104), one clinically completed Phase 1 study (ID-064-105) and one Phase 2 study in SLE subjects

(AC-064A201) [Hermann 2019]. The main findings of the studies are summarized below. More detailed information can be found in the IB [Cenerimod IB].

1.4.2.1 Phase 1 study in healthy subjects: results

Clinical pharmacokinetics

Following administration of single doses to male healthy subjects, the PK profile of cenerimod was characterized by low inter-subject variability (coefficient of variation < 30% for area under the plasma concentration-time curve [AUC], maximum observed plasma concentration [C_{max}], and apparent terminal elimination half-life [$t_{½}$]). C_{max} was achieved within 5–6 h after dosing and $t_{½}$ was between 170–199 h (~7–9 days).

Following administration of multiple o.d. doses, steady-state conditions were attained between 20–32 days of treatment. The $t_{½}$ after the last administration was between 12–22 days with 60 days sampling period for PK assessment after stopping treatment with cenerimod and approximately 33 days with 120 days sampling period for PK assessment after stopping treatment [see Cenerimod IB for further details]. Cenerimod accumulated in plasma, with 5- to 9-fold higher C_{max} and AUC from 0 to 24 hours (AUC_{0-24}) at steady state when compared to the first day of treatment. C_{max} and AUC_{0-24} were shown to be dose proportional across the 0.5–4 mg dose range.

The effect of food on the PK of a single 1 mg dose was investigated in study AC-064-101. No relevant effect of food on the PK parameters of cenerimod was observed.

Only limited clinical data is currently available regarding the metabolism of cenerimod. No information is available regarding the effects of disease (e.g., renal or hepatic impairment), age, or ethnicity on the PK of cenerimod. Only limited data is available on the effects of sex on the PK of cenerimod (examination of the data from the 2 female subjects who received cenerimod suggest that the PK profile is not influenced by sex).

Pharmacodynamics in humans

Oral administration of cenerimod at single doses ≥ 3 mg reduced lymphocyte count in humans. The extent of lymphocyte count reduction was dose-dependent. A reduction from baseline of approximately 76% was achieved after the highest single dose of 25 mg. The nadir in lymphocyte count was attained within 16 h following a given dose. After a single dose of cenerimod, the lymphocyte count generally returned to normal range within 6 days.

Repeated o.d. dosing of cenerimod (0.5, 1, 2, or 4 mg) for 35 days led to a gradual, dose-dependent reduction in absolute lymphocyte count. Compared to baseline, multiple doses of cenerimod induced a decrease ranging from 34 to 64% with doses from 0.5–4 mg. The time the mean lymphocyte counts returned to within normal range (i.e., $\geq 1 \times 10^9$ cells/L) dose-dependently increased and was 28 days for the 4 mg dose group.

No relevant differences in the effect on lymphocyte count reduction were seen after single-dose administration of 1 mg cenerimod in the fed and fasted states.

Safety and tolerability

Single doses of 1, 3, 10, and 25 mg were evaluated in healthy subjects. The 10 mg dose was identified as the maximal tolerated single dose of cenerimod. In the 25 mg group, a serious life-threatening event of hypotensive shock (preferred term: circulatory collapse) was reported. Per study stopping criteria, dose escalation was halted after the 25 mg dose group. One event of non-serious syncope of moderate intensity was also reported in the 10 mg treatment group.

Multiple doses of 0.5, 1, 2, and 4 mg cenerimod were administered o.d. for up to 35 days. All doses were found to be well tolerated, with no serious adverse events (SAEs) and no adverse events (AEs) leading to treatment discontinuation. The most frequently reported AEs in the active treatment groups were headache (37.5%), chest pain (all combined chest pain, chest discomfort, musculoskeletal chest pain, noncardiac chest pain; 33.3%), followed by nasopharyngitis (16.7%), and dizziness (16.7%).

Effect on heart rate

In the single-ascending dose part of the study, a transient decrease in heart rate (HR) was observed as the most frequent drug-related effect with cenerimod, with maximal reduction reached approximately 4 h post-dose and resolved within 12 h after dosing.

In the multiple-ascending dose (MAD) part of the study, a transient decrease in HR was observed on Day 1 following treatment with cenerimod in all dose groups, when compared to placebo. The HR changes from baseline were not clinically significant, did not increase with dose, and were followed by a return to baseline over time (between 7 and 14 days of treatment), with repeated administration of cenerimod.

In Part D of study AC-064-101, repeated administration of 2 mg cenerimod o.d. reduced the effect on HR of subsequent administration of 10 mg ponesimod, another $S1P_1$ receptor modulator with first-dose effect on HR. This shows that chronic o.d. administration of a 2 mg cenerimod dose can lead to desensitization of $S1P_1$ receptor.

Effect on blood pressure

Blood pressure (BP) reduction was observed following a single high-dose administration (10 and 25 mg), with a maximal reduction reached approximately 6–8 h post-dose. In the MAD study, no relevant changes in BP were observed in the 0.5–4 mg dose groups following multiple o.d. dosing of cenerimod.

Effect on liver enzyme elevations

A transient increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or gamma glutamyl transferase (GGT) was observed in 8 subjects on active treatment after multiple doses of cenerimod (Part B). These changes were transient and not accompanied by an increase in bilirubin. No relevant changes in other clinical chemistry variables were observed. None of the out-of-normal-range values in ALT, AST and/or GGT were considered as clinically significant, therefore none were reported as an AE.

Effect on pulmonary function test

No relevant effects on mean forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were observed.

Cardiodynamic effects

In the pilot phase of AC-064-102 single-dose administration of 2 mg cenerimod on top of steady-state atenolol led to a mean maximum decrease from baseline in HR of 30 bpm (mean decrease of 11 bpm following 5 days of atenolol 50 mg o.d. and a further mean maximum decrease of 19 bpm following concomitant administration of cenerimod). The study was prematurely terminated by the sponsor after completion of the pilot phase based on the observed cardiodynamic effect of single-dose administration of cenerimod on top of atenolol [see section 1.4.3.2 of the Cenerimod IB for further details].

1.4.2.2 Phase 2 study in SLE subjects: results

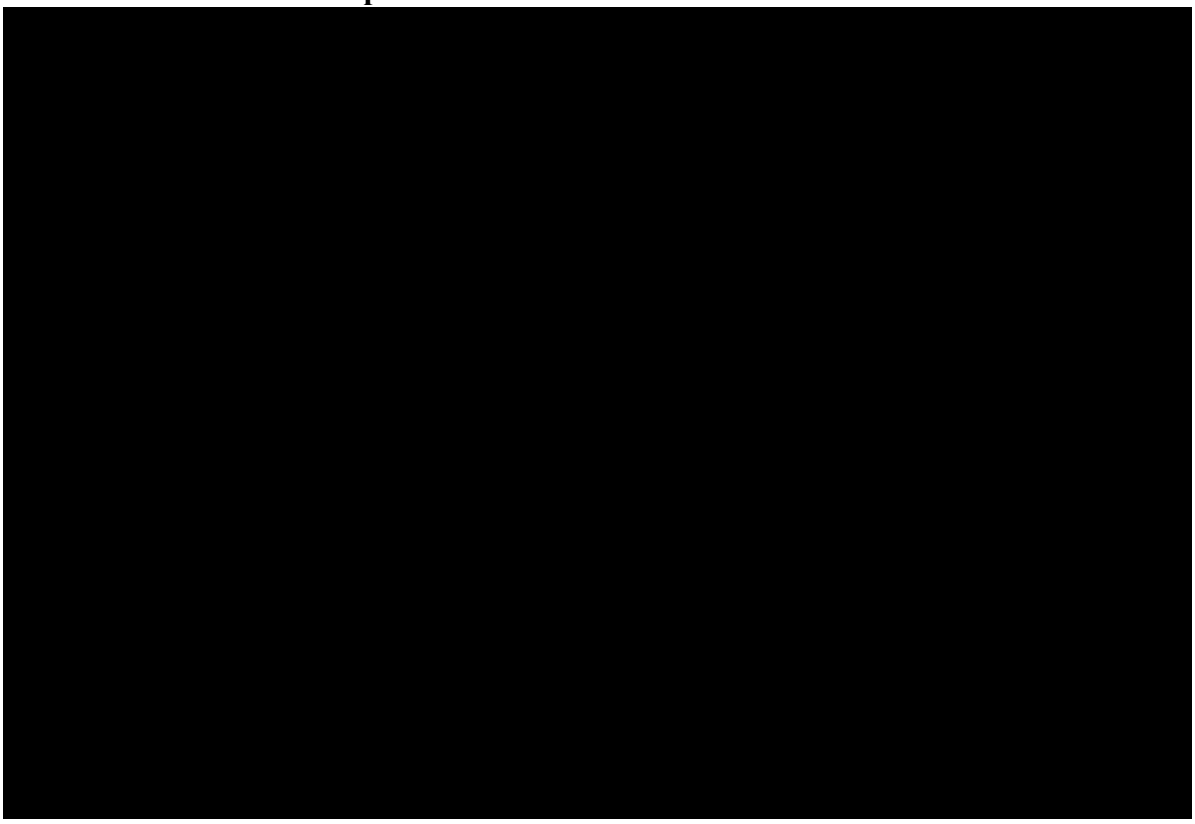
AC-064A201 was a prospective, multicenter, randomized, double-blind, placebo-controlled, dose-response Phase 2 study evaluating o.d. administration of cenerimod in SLE subjects. This study was conducted in two parts (Part A and Part B) with an interim safety review of Part A data prior to the start of Part B.

Sixty-seven subjects in total were randomized into the study, 49 in Part A and 18 in Part B. In Part A, 12, 12, and 13 subjects were randomized to 0.5, 1, and 2 mg of cenerimod, respectively, and 12 to placebo. In Part B, 13 subjects were randomized to cenerimod 4 mg and 5 to placebo. Subjects were treated for 12 weeks (End-of-Treatment [EOT]), with a follow-up period of 16 weeks. The follow-up period included an End-of-Study (EOS) visit, 6 weeks after the last dose of study drug intake (Week 18) and phone contacts at 11 and 16 weeks after EOT.

The study met its primary objective by establishing the dose-response relationship of cenerimod based on the reduction of lymphocyte count in peripheral blood. The AC-064A201 study demonstrated that cenerimod reduced lymphocyte counts in a dose-dependent manner ($p < 0.00001$) as expected from its primary mode of action (MoA). At doses of 1, 2, and 4 mg, reduction of circulating lymphocytes in the peripheral blood of SLE subjects was statistically significant in pairwise comparisons with placebo. Results

expressed as absolute change from baseline, unadjusted or adjusted on the baseline values, and associated p-values are presented in Table 1.

Table 1 AC-064A201: Lymphocyte count in peripheral blood (10^9/L) at baseline, EOT, and change from baseline to EOT (modified pharmacodynamic set), results from Part A, Part B and Part A and B combined placebo



BSL = baseline; CI = confidence interval; EOT = End-of-Treatment; SD = standard deviation; SE = standard error.
* Based on an analysis of covariance model including baseline as a covariate and with treatment group as factor.

The exploratory analysis of efficacy suggested clinical improvement, particularly with the higher cenerimod doses: a numerical reduction in the modified Systemic Lupus Erythematosus Disease Activity Index-2000 (mSLEDAI-2K) was observed for the 4 mg dose, and to a lesser extent the 2 mg dose, after 12 weeks of treatment, in addition to an improvement in the mucocutaneous SLEDAI-2K sub-score. The decrease in SLEDAI-2K score with the 4 mg dose was sustained 6 weeks after treatment cessation, in keeping with the long half-life of cenerimod. In addition, decrease in anti-double-stranded deoxyribonucleic acid (anti-dsDNA) was seen with the 2 mg than the 4 mg dose when compared to placebo, more pronounced with the latter than the former.

Cenerimod treatment was well tolerated in subjects with SLE at all doses tested. No death occurred in the trial.

Treatment-emergent AEs (TEAEs) occurred in 58.8, 41.7, 41.7, 46.2, and 38.5% of subjects on placebo and cenerimod 0.5, 1, 2, and 4 mg, respectively. Four treatment-emergent SAEs (cholecystitis chronic, pancreatitis chronic [twice], post-cholecystectomy syndrome) were reported during the study and occurred in a single subject on placebo (1/17 = 5.9%). These SAEs were severe and none were reported as a clinical manifestation of SLE flare or were judged by the investigator to be related to study treatment. In addition, one subject in the cenerimod 2 mg group had an SAE of SLE flare reported on Day 151 (66 days after the EOT visit). Three TEAEs (cholecystitis chronic, pancreatitis chronic, dyspepsia) led to discontinuation of study treatment in two subjects receiving placebo (2/17 = 11.8%). One subject in the cenerimod 1 mg group, with ongoing lymphadenitis at baseline, had an AE of severe autoimmune hepatitis that was diagnosed pre-dose on Day 1. The same subject had TEAE of severe pneumonitis (Day 4). Both events occurred in the context of an SLE flare. The non-TEAE of severe autoimmune hepatitis led to the discontinuation of study treatment on Day 9.

The analysis of safety areas of special interest (cardiovascular effects including HR on Day 1 and PR interval, systolic and diastolic BP [SDB/DBP], pulmonary function tests [PFTs; FEV_1 and FVC], immunomodulation including malignancies and infections, macular edema and liver enzyme elevations) revealed no clinically relevant safety concern.

Treatment-emergent AEs of special interest (AESIs) occurred in 2, 1, 1, and 1 subjects on cenerimod 0.5, 1, 2 and 4 mg, respectively, and in 1 subject on placebo, with all AESIs being liver or pulmonary events in both cenerimod and placebo groups. There was no evidence suggestive of a dose dependency of cenerimod on the occurrence of AESIs.

Clinically irrelevant dose-dependent decreases in HR from time-matched baseline values were observed with cenerimod compared to placebo during 24-hour Holter and 12-lead ECG on Day 1. No subject in any treatment group had a HR < 40 bpm on 12-lead ECG at any time during the 6 hours post cenerimod administration. None of the cenerimod-treated subjects had a PR interval > 200 milliseconds (ms) during the 6 hours post cenerimod (vs 1 subject in the placebo group). The incidences of ECG findings after Day 1 were generally similar among cenerimod- and placebo-treated subjects with no relationship to the administered cenerimod dose

Small decreases in mean/median pulmonary function variables were observed with cenerimod at EOT, but notable abnormalities in FEV_1 and FVC (i.e., a > 15% decrease in percentage change from baseline) occurred in few subjects. The few subjects who had a notable decrease in FEV_1 and/or FVC usually did so at a single visit, which was most often the EOT visit. One subject on placebo had such a decrease at 2 visits (Weeks 2 and 12).

Three subjects on cenerimod 0.5 mg had a notable decrease in both FEV_1 and FVC. No differences between cenerimod- and placebo-treated subjects or dose effect could be discerned. None of the cenerimod-treated subjects had notable decrease in FEV_1 and FVC at 2 measurement time points.

No pattern or dose response could be discerned in liver chemistry.

No macular edema or malignancy were observed during the study.

No SAEs and no AEs of severe intensity infections were reported during the study. No herpetic infections were observed during the study.

None of the 45 women of childbearing potential became pregnant during the study.

No subject in any treatment group met the protocol pre-defined safety stopping criteria.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to assess the efficacy of 6 months' cenerimod treatment given at 4 different dose levels (0.5, 1, 2, and 4 mg o.d.) on disease activity in adult subjects with moderate to severe SLE concurrently receiving background therapy.

2.2 Secondary objectives

The secondary objectives of the study are to evaluate the following over 6 months in adult subjects with moderate to severe SLE concurrently receiving background therapy:

- The safety and tolerability of cenerimod treatment.
- The effect of cenerimod treatment on quality of life and fatigue using relevant Patient Reported Outcome (PRO) instruments.
- The effect of cenerimod treatment on SLE biomarkers.

2.3 Exploratory objectives

Further objectives are assessed over a treatment period of up to 12 months:

- The effect of cenerimod 0.5, 1, 2 mg on disease activity, safety and tolerability, quality of life, fatigue and SLE biomarkers.
- Starting from Month 6, the effects of dose reduction and withdrawal in subjects randomized to 4 mg who are re-randomized to either 2 mg or placebo.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult subjects with moderate to severe SLE.

Approximately 325 adult subjects with SLE will be randomized in a 1:1:1:1:1 ratio to placebo, 0.5, 1, 2, or 4 mg o.d. of cenerimod, in addition to background SLE therapy.

Treatment allocation is stratified by dose of oral corticosteroids (OCS) at Randomization (OCS with two strata: < 7.5 mg/day or ≥ 7.5 mg/day prednisone or equivalent), and by disease activity at Screening (with two strata: mSLEDAI-2K < 10 or ≥ 10).

Following successful completion of Screening, randomized subjects will enter a 6-month double-blind study treatment period called Treatment Period 1 (TP1).

Subjects completing TP1 will continue treatment for an additional 6 months in TP2, i.e., for a total maximum of 12 months.

Treatment allocation in TP2 will depend on the treatment allocation in TP1 as follows, and does not require unblinding of TP1:

a) Subjects randomized in TP1 to placebo, 0.5, 1, or 2 mg arms will continue their study double-blind treatment unchanged during TP2.

b) Subjects randomized to the 4 mg arm in TP1 will be re-randomized in a double-blinded fashion in TP2 in a 1:1 ratio to placebo or cenerimod 2 mg.

The double-blinding of the entire study will be preserved by Interactive Response Technology (IRT) treatment allocation.

At the end of treatment, subjects will enter a 6-month follow-up period.

There will be three study analyses: the Month-6 analysis, the Month-12 analysis, and the final EOS analysis [see Section 10.4].

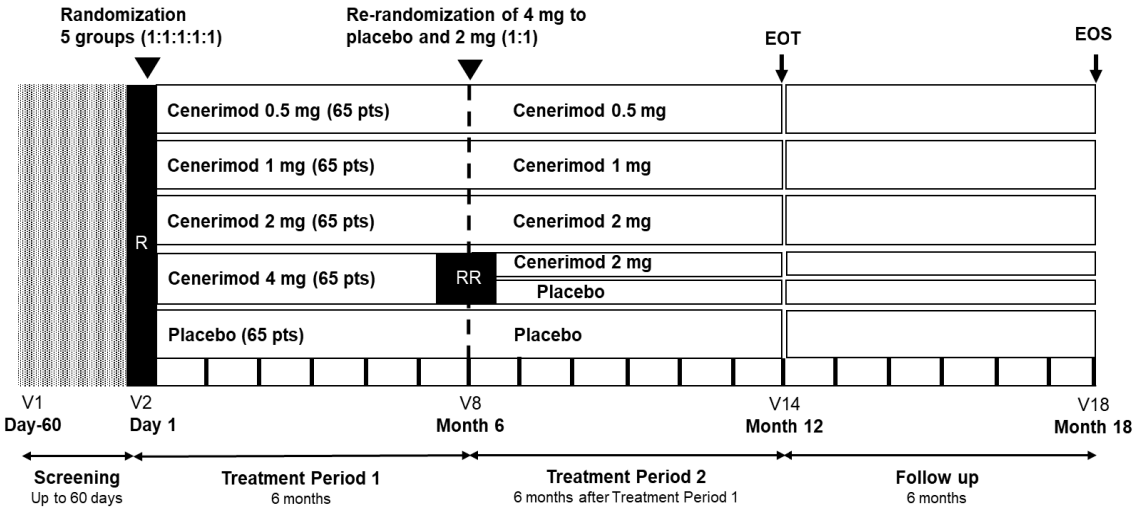
Month-6 analysis will be performed when all randomized subjects have completed TP1 or discontinued the study. Month-12 analysis will be performed when all randomized subjects have completed TP2 or discontinued the study. Final EOS analysis will be performed when all randomized subjects have completed the posttreatment follow-up period or discontinued the study.

After Month-6 and Month-12 analyses, ongoing subjects will continue to be treated and followed up in a double-blinded manner up to their EOS visit. Investigators, site staff, subjects, and the sponsor staff responsible for the study conduct (with appropriate

firewalls) will remain blinded to study treatment allocation until study closure. To maintain the blinding of the study up to final EOS analysis, two separate sponsor teams will be set up; Team 1 will be unblinded at the time of the Month-6 analysis while Team 2 will remain blinded until final EOS analysis in order to continue to review the data being collected up to EOS. The measures put in place to ensure the good conduct of this process will be described in a dedicated study document.

The study will be conducted at approximately 180 sites in approximately 21 countries.

Figure 1 Study design ID-064A202



EOS = End-of-Study; EOT = End-of-Treatment; R = Randomization; RR = re-randomization; pts = patients; V = visit.

3.1.1 Study periods

The study comprises the following periods:

3.1.1.1 Screening period (allowing OCS optimization period for subjects receiving OCS)

The screening period starts with the signing of the informed consent form (ICF) and ends on the day of Randomization, before the first study drug intake. This period can last up to 60 days.

During this period, the subject's SLE background medication should be maintained stable except for OCS which should be tapered to the minimum required dose and then maintained stable for at least 15 days prior to Randomization [see Section 5.2.2.1].

3.1.1.2 Treatment period

This period comprises 2 periods – TP1 and TP2.

TP1 lasts 6 months. It starts with the administration of the first dose of study treatment, after subject randomization, and ends at the Month 6 visit.

Starting from the Month 6 visit, TP2 lasts 6 months and ends at the Month 12 visit.

All randomized subjects in the study will have to complete TP1 before continuing in TP2.

Subjects randomized to placebo, 0.5, 1, or 2 mg arms who are still on treatment at Month 6 will continue their study treatment during another treatment period of 6 months duration called TP2, i.e., for a total maximum of 12 months.

Subjects randomized to the 4 mg arm who are still on treatment at Month 6 will be re-randomized in a 1:1 ratio to placebo or cenerimod 2 mg to enter TP2 and will continue study treatment for a total maximum of 12 months.

For details regarding premature discontinuation of study treatment, please refer to Section 5.1.7.

3.1.1.3 Follow-up period

This period starts after the EOT and lasts 6 months until the EOS. For the first 5 months after the EOT visit, subjects will have to conduct monthly follow-up (FU) visits, FU1, FU2, FU3, FU3a, and FU3b to collect information on AEs and SAEs and/or pregnancy as well as efficacy data.

The EOS visit should occur 6 months after the EOT.

3.1.2 Echocardiography ancillary study

At Randomization, approximately 175 subjects will be assigned to the echocardiography ancillary study through the IRT system. The echocardiography ancillary study will run concurrently with the main study. Subjects assigned to the echocardiography ancillary study will undergo an echocardiography assessment at Month 6 or at premature End-of-Treatment (pEOT) visit in the event of premature study treatment discontinuation during TP1, in addition to echocardiography assessments that will be performed for all subjects during the screening period.

Standard 2D/Doppler echocardiography will assess cardiac morphology and function including regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction.

See also echocardiography assessments in Section 7.2.3.6.

3.2 Study design rationale

3.2.1 General rationale

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult subjects with SLE with moderate to severe disease activity in addition to background therapy.

A randomized, double-blind design is used to control for bias in reporting safety, efficacy, and biological activity data.

Cenerimod therapy is intended as adjunctive treatment, hence all subjects in the study will receive cenerimod or placebo in addition to SLE background therapy. Given the early phase of cenerimod clinical development, the use of background therapy will ensure that all subjects, including subjects who are randomized to placebo, will have the benefit of being treated with available background therapy.

The use of placebo will allow discrimination of the efficacy and safety profile of cenerimod treatment in conjunction with SLE background therapy and compared to use of SLE background therapy.

Based on the available nonclinical and clinical data to date, there is no likely PK interaction between cenerimod and any of the co-administered background therapies allowed in this protocol [see Cenerimod IB]. A potential PD interaction between cenerimod and permitted immunosuppressive drugs cannot be excluded but will be monitored by white blood cell (WBC) and lymphocyte counts as well as AEs, particularly AEs denoting infections.

An important goal of the SLE therapy is to reduce the use of steroids, given their associated morbidity. However, reduction of steroid dose during the treatment period may confound interpretation of study results. Hence OCS dose reductions are highly encouraged prior to Randomization during the screening phase, up to 15 days only prior to Randomization. This will ensure a stable baseline assessment. After Randomization it is highly preferable that OCS doses remain stable to avoid confounding factors for data interpretation of primary and secondary endpoints at Month 6. However, to account for current management practice, some flexibility in the steroid management is allowed if absolutely necessary and well documented during the first 3 months of TP1 and during TP2 [see Section 5.2.2.1 for further details]. Consequently, during the entire study duration (a maximum of 20 months from beginning of Screening to end of FU), adjustment of OCS dose will be disallowed for 3 months only.

Given cenerimod's MoA and to limit the risk of introducing bias to the study due to unblinding, the study personnel and sponsor's team will not have access to results of total WBC (including differentials) and lymphocyte counts of subjects participating in the study. In the event of very low lymphocyte count (< 200 cells/µL) the central laboratory will send

an alert to the investigator to ensure proper follow-up of the subject [see Section 5.1.8.2 for details of management of low lymphocyte counts]. Based on data collected in the Phase 2a study, during which no cases of lymphocyte count < 200 cells/µL occurred, this is considered to be rare and not leading to significant unblinding of the trial.

Treatment allocation during both TP1 and TP2 will remain unknown to study sites, subjects, and sponsor's personnel until the end of the study. Treatment allocation will be stratified by dose of OCS, i.e., < 7.5 mg/day or ≥ 7.5 mg/day prednisone equivalent, and by disease activity, i.e., mSLEDAI-2K < 10 or ≥ 10, as both factors can influence SLE parameters that are used as study endpoints [van Vollenhoven 2012].

To protect the safety of the subject, strict subject-specific safety stopping rules are applied during the entire study as defined in the protocol for each safety area of interest.

As part of the risk mitigation plan, an echocardiography ancillary study will run concurrently with the main study. Approximately 175 subjects will be assigned to the ancillary study through the IRT system at Randomization to ensure balanced numbers of subjects across all treatment arms. Subjects participating in the ancillary study will undergo an echocardiography assessment at Month 6 or pEOT visit [see Section 3.1.2], in addition to an echocardiography assessment during the screening period that will be done for all subjects enrolled in the study.

3.2.2 Rationale for the four doses tested

The rationale for including 0.5, 1, 2, and 4 mg doses in this protocol is based primarily on results from study AC-064A201, a 12-week treatment study in SLE subjects [see Section 1.4.2.2 for further details]:

- No clinically relevant safety findings emerged in the completed Phase 1 and 2 studies in 97 healthy and 67 SLE subjects, respectively, at any of the doses proposed in this Phase 2 study.
- The study results indicated that the 4 mg dose of cenerimod was associated with clinically relevant improvement in the mSLEDAI-2K at EOT (12 weeks) which was sustained until the EOS, i.e., 6 weeks after EOT. The clinical results were further supported by the reduction in lymphocyte count, a decrease in disease-relevant T and B lymphocyte subsets, and a statistically significant reduction in anti-dsDNA autoantibodies. Based on these data, the 4 mg dose, which is expected to be associated with clinically meaningful efficacy without safety concern, warrants further investigation.
- Treatment with the intermediate doses of 1 and 2 mg resulted in approximately 50% reduction in lymphocyte count during the 12 weeks of treatment. For the 2 mg dose, a numerical clinical improvement (mSLEDAI-2K) and a reduction in anti-dsDNA

autoantibodies were also observed. Clinical efficacy may be anticipated with longer duration of treatment and justifies the further investigation of these doses.

- In the Phase 2 study, the 0.5 mg dose did not show clinical improvement and no reduction in lymphocyte count was observed compared to placebo. However, in the healthy subject Phase 1 AC-064-101 study the effect on lymphocyte counts was more pronounced. Given the totality of the data, it cannot be excluded that the 0.5 mg dose be the minimum effective dose. This justifies further investigation of this dose.

3.2.3 Rationale for the efficacy endpoints

The primary efficacy endpoint is the change from baseline to Month 6 in the mSLEDAI-2K score.

The SLEDAI-2K is a well-established and one of the Health Authority guideline-recommended clinical endpoints, allowing for rapid and standardized SLE disease activity assessment, and has been shown to be sensitive in clinical trials. It has an acceptable inter-observer variability and correlates well between individual subject scores [FDA 2009]. The SLEDAI-2K will be modified (m) to exclude leukopenia (reduction by 1 point out of 105 total points) since cenerimod induces reduction in lymphocyte count as part of its MoA. This approach is identical to the one which was used in the previous cenerimod AC-064A201 Phase 2 study. The minimal modification of the SLEDAI-2K is not considered to change the validity of the instrument. SLEDAI-2K will be also assessed.

Measurement of disease activity by a single index may be insufficient to fully describe the therapeutic effect of a product in SLE. Therefore, secondary efficacy endpoints at Month 6 include:

a) Responder on SLE Responder Index (SRI)-4, a Health Authority recommended composite endpoint, comprising:

(i) reduction from baseline of at least 4 points in the mSLEDAI-2K, and

(ii) no new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than one new BILAG B organ domain score compared with baseline, and

(iii) no increase of more than 0.3 points on the Physician's Global Assessment (PGA) since baseline.

SRI-4 allows tracking of concomitant improvement and worsening in different organs.

b) Response (no worsening) at Month 6 on BILAG-2004 disease activity index defined as no new BILAG A organ domain score and no more than one new BILAG B organ domain score as compared with baseline.

BILAG, also recommended by Health Authorities, is a comprehensive tool to assess disease activity and is sensitive to small changes over time.

3.2.4 Rationale for treatment duration

Based on the AC-064A201 data and the clinical experience with other S1P receptor modulators in autoimmune diseases [Vaclavkova 2014, Sandborn 2016], the full clinical effect of cenerimod is expected to occur at 6 months of treatment. Hence, it is anticipated that a 6-month treatment period study will provide substantial evidence of clinical efficacy of cenerimod supporting the timing of the primary efficacy endpoint of this study.

Without delaying the study results and identification of the dose(s) to be pursued, the study offers the possibility to perform the analysis of efficacy and safety at Month 6 after completion of TP1 while subjects continue to be treated in TP2 (i.e., 12 months in total). This will allow a faster decision on the conduct of the Phase 3 program, while also providing additional safety and efficacy data.

Although no clinically relevant safety finding emerged in all 67 subjects in study AC-064A201, safety data in the 4 mg dose remain limited, hence a staggered approach for testing the cenerimod 4 mg dose will be implemented in this development program, with the 4 mg dose being tested for 6 months only, a duration of exposure that may be extended in future studies depending on the results of this Phase 2b trial. Therefore, subjects who received 4 mg for 6 months will be re-randomized to receive either placebo or 2 mg. This switch to placebo will also allow the collection of information on the potential effects of treatment withdrawal and data from subjects switching to 2 mg will contribute to the decision of dose(s) selection for the future Phase 3 study.

3.3 Overall benefit-risk conclusion

The AC-064A201 study results demonstrated a dose-related reduction of circulating lymphocytes in peripheral blood in keeping with the expected MoA of cenerimod.

The exploratory analysis of efficacy of the AC-064A201 study suggested clinical improvement assessed by numerical reduction in the mSLEDAI-2K and improvement in the mucocutaneous SLEDAI-2K sub-score, particularly with the higher doses of cenerimod tested in study AC-064A201.

Cenerimod treatment was well tolerated at all doses tested in the Phase 2 study (0.5, 1, 2, and 4 mg), with no associated clinically relevant safety finding.

The totality of cenerimod data to date, i.e., nonclinical and clinical, justify further investigation of the clinical efficacy of cenerimod in the dose range proposed in the study: 0.5, 1, 2, and 4 mg.

Cenerimod has the potential of being a new, complementary therapeutic approach for SLE patients with acceptable efficacy and safety profiles. The foreseeable benefit-risk balance supports the inclusion of all cenerimod doses studied in this protocol (0.5, 1, 2 and 4 mg) and a comprehensive plan to mitigate potential risks is included in this protocol.

3.4 Study committee

3.4.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be monitoring the safety and efficacy data obtained in the study and making appropriate recommendations based on the reported (unblinded to the Committee as necessary) data.

The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC will be described in an IDMC charter.

4 SUBJECT POPULATION

4.1 Rationale for the selection of the study population

The target population of this study are subjects with generalized SLE who are receiving background therapy and with active, autoantibody positive disease, anti-nuclear antibodies (ANA) titer ≥ 1:80 and/or anti-dsDNA ≥ 30 IU/mL at Screening.

Subjects must have at least a 6-month history of SLE and meet the American College of Rheumatology (ACR) criteria for diagnosis [Hochberg 1997].

Subjects will be included in the study if they have a sufficient level of activity to justify therapeutic intervention and to provide measurable room for improvement. This is based on biomarker of activity and clinical symptomatology based on an mSLEDAI-2K score of at least 6 points and at least 2 points on the musculoskeletal or mucocutaneous sub-scores. The selection of this population is supported by the Phase 2 study results in which cenerimod improved the mSLEDAI-2K at 12 weeks and showed a trend for improvement in the musculoskeletal and mucocutaneous sub-scores.

However, in the context of a placebo-controlled study and the limited efficacy data available to date, it is premature to test cenerimod in the most severe spectrum of the disease. Subjects with active lupus nephritis and central nervous system (CNS) lupus are therefore excluded. It is possible that in the future, and assuming cenerimod provides benefit to SLE patients as defined in the present study, more studies will be done in more severe patients.

Given the heterogeneity in SLE disease manifestations, treatment is often not standardized. In order not to confound the results of the study, subjects should have initiated background treatment at least 3 months prior to Screening and need to have stable doses at least 30 days

prior to Randomization and throughout the study. For OCS, dose must be stable at least 15 days prior to Randomization [see Section 5.2.2.1 for details on OCS management in the study].

4.2 Inclusion criteria

For inclusion in the study, all the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject.

Screening criteria:

1. Signed ICF prior to any study-mandated procedure.
2. Diagnosis of SLE made at least 6 months prior to Screening, by fulfilling at least 4 of the 11 criteria for SLE as defined by the ACR criteria [Appendix 2].
3. Male and female subjects, age 18 to 75 years old (both inclusive).
4. A mSLEDAI-2K score ≥ 6 of at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers).
   Note: The mSLEDAI-2K score does not take into account "leukopenia".
5. History or presence of positive ANA or anti-dsDNA antibodies.
6. Currently treated with stable doses of one or more of the following background medications:
   - NSAIDs,
   - Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine),
   - Mycophenolate mofetil (≤ 2 g/day),
   - Mycophenolic acid (≤ 1440 mg/day),
   - Azathioprine (≤ 2 mg/kg/day),
   - Methotrexate (≤ 20 mg/week),
   - Corticosteroids (≤ 40 mg/day prednisone or equivalent),
   - Belimumab (≤ 10 mg/kg every 4 weeks intravenously [i.v.], or 200 mg/week subcutaneously [s.c.]).
7. Women of childbearing potential (WOCBP):
   - Must have a negative serum pregnancy test at Screening.
   - Must agree to undertake monthly urine pregnancy tests during the study.

- Must use highly effective methods of contraception from the Screening visit until 6 months after taking the last dose of study treatment as described in Section 4.4.2.

Randomization criteria:

8. A clinical mSLEDAI-2K score ≥ 4.
   Note: The clinical mSLEDAI-2K is the mSLEDAI-2K assessment score without the inclusion of points attributable to hematuria, proteinuria, pyuria, low complement, increased DNA binding and thrombocytopenia.

9. Presence of at least one of the following autoantibodies measured by central laboratory defined as follows (based on the screening sample): (a) positive ANA test measured by immunofluorescence assay with titer ≥ 1:80; or (b) positive anti-dsDNA antibodies with titer ≥ 30 IU/mL.

10. On a stable dose of background SLE medication consisting of any of the following medications (alone or in combination) for a period of at least 30 days (15 days for corticosteroids) prior to Randomization:
    - NSAIDs,
    - Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine),
    - Mycophenolate mofetil (≤ 2 g/day),
    - Mycophenolic acid (≤ 1440 mg/day),
    - Azathioprine (≤ 2 mg/kg/day),
    - Methotrexate (≤ 20 mg/week),
    - Corticosteroids (≤ 40 mg/day prednisone or equivalent) [see Section 5.2.2.1],
    - Belimumab (≤ 10 mg/kg every 4 weeks i.v., or 200 mg/week s.c.).

11. WOCBP:
    - Must have a negative urine pregnancy test at Randomization visit.

4.3 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject.

Screening criteria

Disease/condition

1. Female subjects who are breastfeeding or planning to become pregnant during the study.

2. Active lupus nephritis (defined by proteinuria > 1.5 g/24 h, or equivalent using spot urine protein-to-creatinine ratio: > 150 mg/mmol) or a renal biopsy demonstrating immune complex-mediated glomerulonephritis compatible with lupus nephritis within 90 days prior to Screening.

3. Severe active CNS lupus requiring therapeutic intervention (e.g., aseptic meningitis, seizures, psychosis, cerebritis, cerebrovascular accident [CVA], organic brain syndrome, CNS vasculitis) and severe forms of vasculitis requiring systemic immunosuppressive treatment (e.g., retinal vasculitis, coronary vasculitis, pulmonary vasculitis, mesenteric vasculitis) within 90 days prior to Screening.

4. A diagnosis of mixed connective tissue disease or any history of overlap syndromes of SLE with rheumatoid arthritis, erosive arthritis, scleroderma or autoimmune hepatitis.

5. History or presence of Mobitz type II or third-degree atrioventricular (AV) block, sick sinus syndrome, symptomatic bradycardia or syncope associated with cardiac disorders.

6. Subjects who experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, vascular thrombosis, decompensated heart failure requiring hospitalization, or heart failure defined by the New York Heart Association (NYHA) Class III/IV within six months prior to Screening.

7. An elevated QT corrected for HR using Fridericia's formula (QTcF) interval of > 470 ms (females) / > 450 ms (males).

8. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function and chest X-ray performed at Screening or within 6 months prior to Screening or medically significant abnormal PFTs: FEV_1 or FVC < 70% of predicted normal value or FEV_1/FVC ratio < 0.7.

9. History of clinically relevant bronchial asthma or chronic obstructive pulmonary disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 6 months prior to Screening.

10. Active or latent tuberculosis (TB), as assessed by chest X-ray performed at Screening or within 6 months prior to Screening, and interferon (IFN) gamma release assay (QuantiFERON-TB-Gold Plus®), except if there is documentation that the subject has completed adequate and successful treatment for TB previously.

11. Ongoing bacterial, viral or fungal infection that is of clinical concern in the judgment of the investigator or history of any serious infection, defined as life-threatening or requiring i.v. antibiotics or hospitalization.

12. Positive results for serological markers for hepatitis A, B, C and E indicating acute or chronic infection:
    - Anti-HAV IgM
    - HBsAg
    - Anti-HCV IgG or IgM
    - Anti-HEV IgG or IgM (if positive IgM and/or IgG, perform HEV-RNA PCR and if negative patient can be randomized).
13. Subjects who have congenital or acquired severe immunodeficiency or known HIV infection or positive HIV testing.
14. Negative antibody test for varicella-zoster virus. Vaccination of antibody-negative subjects may be considered, which must occur at least 30 days prior to re-test and Randomization.
15. History or presence of malignancy (except for surgically excised basal or squamous cell skin or mucosal lesions, including dysplasia and carcinoma in situ), lymphoproliferative disease, or history of total lymphoid irradiation.
16. History or presence of bone marrow or solid organ transplantation.
17. Presence of macular edema or active uveitis.
18. Type 1 or 2 diabetes that is poorly controlled according to investigator judgment, or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy.
19. History of chronic liver or biliary disease (other than Gilbert's Syndrome) or subjects with ALT or AST > 2 × upper limit of normal (ULN) or total bilirubin (TBIL) > 1.5 × ULN (unless in the context of known Gilbert's Syndrome).
20. Significant hematology abnormality: lymphocyte count < 800 /µL (0.8×10^9/L); hemoglobin < 9 g/dL; WBC count < 2500/µL (2.5×10^9/L) or platelets < 75,000/µL (75×10^9/L).
21. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2.
22. History of clinically significant drug or alcohol abuse.
23. Known allergy to S1P receptor modulators or any of the cenerimod formulation excipients.
24. Any other clinically relevant medical condition that would put the subject at risk if participating in the study, or any other diseases that may confound the disease activity assessments.

Medications

25. Treatment with the following medications within 15 days or 5 half-lives of the medication (whichever is longer) prior to Randomization:
    a. β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering systemic therapy [list of drugs provided in Appendix 3].
    b. QT-prolonging drugs with known risk of torsade de pointes irrespective of indication [list of drugs provided in Appendix 4].

26. Treatment with the following medications within 30 days or 5 half-lives of the medication (whichever is longer) prior to Randomization:
    a. Cyclophosphamide, ciclosporine, tacrolimus, sirolimus.
    b. Pulse methylprednisone.
    c. Vaccination with live vaccines.

27. Intra-articular, intramuscular or i.v. glucocorticosteroids within 6 weeks prior to Randomization.

28. Treatment with the following medications within 90 days or 5 half-lives of the medication (whichever is longer) prior to Randomization:
    a. Leflunomide.
    b. i.v. immunoglobulins.

29. Treatment with any investigational agent within 90 days or 5 half-lives of the drug (whichever is longer) prior to Randomization.

30. Treatment with B cell-depleting biological agents such as rituximab or ocrelizumab within 12 months prior to Randomization.

31. Treatment with any of the following medications any time prior to Screening:
    a. Alemtuzumab,
    b. S1P receptor modulators (e.g., fingolimod).

For further details, see table of forbidden medications in Appendix 3.

Randomization exclusion criteria

32. Resting HR < 50 bpm as measured by the pre-dose 12-lead ECG.

33. An elevated QTcF interval of > 470 ms (females) / > 450 ms (males) as measured by the pre-dose 12-lead ECG on Day 1.

34. Severe active CNS lupus requiring therapeutic intervention (e.g., aseptic meningitis, psychosis, seizures, cerebritis, CVA, organic brain syndrome, CNS vasculitis) and

severe forms of vasculitis requiring systemic immunosuppressive treatment (e.g., retinal vasculitis, coronary vasculitis, pulmonary vasculitis, mesenteric vasculitis).

35. Clinically relevant bronchial asthma or chronic obstructive pulmonary disease.

4.4 Contraception requirements for women of childbearing potential

4.4.1 Definition of childbearing potential

A woman is considered to be of childbearing potential (WOCBP), i.e., fertile, following menarches and until becoming post-menopausal unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Post-menopausal state is defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

The reason for not being of childbearing potential will be recorded in the electronic Case Report Form (eCRF).

4.4.2 Highly effective methods of contraception

WOCBP [see definition in Section 4.4.1] must follow a highly effective contraception scheme from Screening up to at least 6 months after taking the last dose of study treatment. In line with the Clinical Trials Facilitation Group recommendations, highly effective birth control methods are:

1. Hormonal contraceptives [1] : Combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation[2] using one of the following routes of administration: oral, intravaginal, transdermal, injectable, implantable[3].

   Hormonal contraception must be supplemented with a barrier method such as male condom (preferred method), female condom, cervical cap or diaphragm. Cervical cap and diaphragm must be used in combination with a spermicide. In countries where spermicides are not available/authorized, cervical cap and diaphragm must not be used.

[1] If a hormonal contraceptive is chosen from this group, it must be taken for at least 1 month prior to study treatment start day. If the subject switches to, or starts, a hormonal contraceptive method during the study treatment phase, caution must be taken to ensure a highly effective contraceptive method is used without discontinuation.

[2] Cenerimod has a limited potential for PK DDIs with concomitant medications whose PK are dependent on CYP clearance, hence no interaction with hormonal contraception is expected (*in vitro*). For further details see the IB [Cenerimod IB].

2. Intrauterine device[3].
3. Intrauterine hormone-releasing system[3].
4. Bilateral tubal occlusion/ligation[3].
5. Vasectomized partner[3,4].
6. Sexual abstinence[5].

The following contraception schemes **used alone** are NOT considered as highly effective methods of contraception:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

The following methods are NOT allowed as methods of contraception for this study:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Combination of female condom and male condom

The methods of birth control used (including non-pharmacological methods) of the WOCBP and/or partner (if applicable) must be recorded in the eCRF.

The investigator/delegate will record in the eCRF at monthly intervals the result of the pregnancy test, whether the method of contraception has changed, and will remind the subject to follow the protocol-mandated method of contraception up to at least 6 months after study treatment discontinuation.

[3] Contraception methods considered to have low user dependency.

[4] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[5] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject, and whether this is locally accepted as a highly effective method of contraception.

Note: the documentation of method of contraception can be based on the site personnel's review of the subject's medical records, medical examination or medical history interview of the subject.

If the investigator considers that the subject is not complying with the protocol methods of contraception instructions, study treatment **must** be permanently discontinued [see Section 5.1.8.4].

4.4.3 Male contraception

Based on nonclinical data and human distribution models, it is considered very unlikely that a relevant dose of cenerimod would be delivered to the female by seminal fluid transfer. Therefore, despite the teratogenic effect of cenerimod, the risk of harm to a human fetus by seminal transfer of cenerimod is considered to be very low. In addition, cenerimod is neither genotoxic nor mutagenic. Therefore, there is no specific recommendation for male contraception regarding cenerimod [see section 4.3.8.8 of the Cenerimod IB].

5 STUDY TREATMENT

5.1 Investigational treatment and matching placebo: description

Cenerimod is available for clinical study use in tablets. It will be supplied as identical film-coated tablets at the doses of 0.5, 1, 2, and 4 mg.

The inactive ingredients of the cenerimod film-coated tablet formulation are: hydroxypropyl methylcellulose, polyvinylpyrrolidone, mannitol, colloidal silicon dioxide, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, propylene glycol, titanium dioxide, iron oxide yellow, iron oxide red, and iron oxide black.

The matching placebo is supplied as identical film-coated tablets formulated with the same excipients but without the active ingredient, cenerimod.

5.1.1 Study treatment administration

One tablet of cenerimod or placebo will be taken orally irrespective of food intake. The tablet will be swallowed whole. It is preferable that the tablet is taken each day in the morning.

Subjects must be instructed not to take study treatment in the morning of study visit days. On the day of the study visits, study treatment must be administered only after the completion of the pre-dose assessments (i.e., SBP, DBP, ECGs, spirometry, laboratory tests, and PK sampling).

To ensure compliance, the study personnel must remind subjects at each visit of the study treatment intake requirements.

5.1.2 Treatment assignment

A total of approximately 325 subjects will be randomized in a 1:1:1:1:1 ratio to placebo, or to cenerimod 0.5, 1, 2, and 4 mg.

Once randomized, all subjects will enter a 6-month double-blind study treatment period TP1.

After the completion of the 6 months of study treatment, subjects randomized to placebo, 0.5, 1, or 2 mg arms will continue to receive double-blind study treatment for a maximum of 12 months in total.

Subjects randomized to the 4 mg arm will receive study treatment for a maximum of 6 months in TP1. After completion of the 6 months of study treatment, subjects in this group will be re-randomized in a 1:1 ratio to placebo or cenerimod 2 mg to enter TP2 and will continue to receive double-blind treatment for a maximum of 12 months in total.

For more details on premature discontinuation of study treatment, please refer to Section 5.1.7.

Treatment allocation via IRT will ensure maintenance of the double-blinding during the entire study.

Treatment allocation is stratified by:

- Dose of OCS at Randomization (OCS with two strata: < 7.5 mg/day or ≥ 7.5 mg/day of prednisone or equivalent),

  and

- Disease activity at Screening (with two strata: mSLEDAI-2K < 10 or ≥ 10).

Each of the clinical study sites will be assigned a unique site number. At Visit 1 (Screening), all screened subjects will be assigned a study-specific subject number by the IRT system, which identifies the subject throughout the study.

At the Randomization visit (Visit 2), and after having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT system to randomize the subject. The IRT system assigns a randomization number to the subject and assigns the bottle number that matches the treatment arm assigned by the randomization list to the randomization number.

The IRT system is handled by an external independent vendor which will generate the randomization list.

5.1.3 Blinding

5.1.3.1 Blinding of study drug material

This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the Clinical Research Associates (CRAs), all Clinical Trial Team (CTT) members from the sponsor and Contract Research Organizations (CROs) involved in the conduct of the study will remain blinded to the treatment allocation until study closure. The investigational treatment and its matching placebo are indistinguishable, and all bottles will be packaged in the same way.

To ensure adequate supply of study treatment, the IRT vendor personnel responsible for clinical study supply distribution need to be unblinded at site level. The sponsor individuals contributing to clinical supply distribution will be unblinded at depot level only (a depot may be used for the study treatment supply of several sites and countries). These persons will be clearly identified, their unblinding will be documented in the trial master file, and they will not take part in any CTT meetings after study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and is accessible only to the IRT vendor and limited sponsor authorized personnel (only from the bioanalytical laboratory group), who are not involved in any other aspects of the conduct of the study.

A sealed randomization code is kept by the sponsor's Global Quality Management department in a safe cabinet. A second set will be provided to the statistician of the Independent Statistical Analysis Center (ISAC) for the production of unblinded IDMC statistical outputs.

To prevent unblinding, the results of the biomarker and PK data will not be communicated to the investigator, study personnel, subjects, CRAs, any sponsor or vendor/CRO personnel involved in the conduct of the study. Results will be transferred by the central laboratory (for biomarkers) and the bioanalytical laboratory for PK measurement to the sponsor and CRO personnel involved in the conduct of the study only after database lock.

To maintain the blinding of the study up to final EOS analysis, two separate sponsor teams will be set up; Team 1 will be unblinded at the time of the Month-6 analysis while Team 2 will remain blinded until final EOS analysis in order to continue to review the data being collected up to EOS. The measures put in place to ensure the good conduct of this process will be described in a dedicated study document.

5.1.3.2 Functional blinding

Lymphocyte counts reduction has been identified as potentially unblinding information. Site's staff and sponsor's study team will not have access to this information until database lock.

The following measures will be taken to ensure that the main site staff and the sponsor study team will remain blinded to lymphocyte counts:

- After the first dose of study treatment until EOS, results of the total WBC (including differentials) and lymphocyte counts will not be communicated to the sites, sponsor, and CROs. Testing of total WBC (including differentials) and lymphocyte counts at a local laboratory should not be performed unless deemed absolutely necessary to ensure subject's safety.
- For safety reasons, if total lymphocyte count < 200 cells/µL at any study visit until EOT or < 800 cells/µL at EOS is recorded by the central laboratory, an alert will be sent to the principal investigator and to the sponsor including lymphocyte count. For further guidance, please refer to Section 5.1.8.2.

5.1.3.3 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database lock, in accordance with the sponsor's Quality System (QS) documents.

5.1.3.4 Unblinding for IDMC

An ISAC, not otherwise involved in the design, conduct, and analysis of the study, will have access to the randomization code to prepare unblinded periodic reports for review by the IDMC during the course of the trial. The randomization code will be made available to the ISAC in accordance with the sponsor's Standard Operating Procedures (SOPs).

5.1.3.5 Unblinding before final analyses

The randomization code will be made available to the bioanalytical laboratory for PK measurement in accordance with the sponsor's SOPs.

5.1.3.6 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) [see definition in Section 9.1.3] occurs in a subject participating in the study, the sponsor's Global Drug Safety department will request the unblinding of the treatment assignment to meet regulatory reporting requirements.

The treatment assignment will not be communicated to site personnel, subjects, sponsor CTT or any vendor/CRO personnel involved in the conduct of the study.

Unblinded SUSAR information will be reported to respective Health Authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs). SUSARs will be notified to investigators in a blinded fashion.

5.1.3.7 Emergency procedure for unblinding

The investigator, study personnel, subjects, CRAs, sponsor personnel, and any CRO personnel involved in the conduct of the study must remain blinded to the subject's treatment assignment.

The identity of the study treatment may be revealed only if the subject experiences an emergency medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the decision to unblind resides solely with the investigator and the investigator can receive the unblinded treatment assignment through the IRT system. Whenever possible and provided it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended unblinding with the sponsor personnel.

The occurrence of any emergency unblinding during the study must be clearly justified and explained by the investigator. In all cases, the sponsor personnel must be informed about the occurrence of an emergency unblinding as soon as possible before or after the unblinding. The sponsor personnel should not be informed about the unblinded treatment code.

The circumstances leading to unblinding must be documented in the hospital charts and in the Investigator Site File (ISF).

5.1.4 Study treatment supply

Manufacture, labeling, packaging, and supply of study treatments will be conducted according to Good Manufacturing Practice, GCP, and any local or national regulatory requirements.

All treatment supplies are to be used only in accordance with this protocol and not for any other purpose.

5.1.4.1 Study treatment packaging and labeling

5.1.4.1.1 Study treatment packaging

Study treatment (cenerimod or placebo) is provided as tablets and is supplied in childproof bottles.

5.1.4.1.2 Study treatment labeling

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

The batch number and the re-test date (or expiry date) will be indicated on the study treatment labels as required by local regulations.

5.1.4.2 Study treatment distribution and storage

Treatment supplies must be kept in an appropriate, restricted area and stored according to the conditions specified on the medication labels.

5.1.4.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used, and unused study treatment bottles at each visit. Should the treatment bottle dispensed at a scheduled visit be lost or damaged, a replacement bottle can be requested via the IRT system. The protocol-mandated study drug dispensing/return procedures may not be altered without prior written approval from the sponsor.

In exceptional circumstances (e.g., if the subject lost the study treatment between two visits, or if the subject is unable to return to the site due to a medical emergency / hospitalization at another hospital), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit. An accurate study treatment record of the date and amount of study treatment dispensed to each subject must be available at the site for inspection at any time.

5.1.4.4 Study treatment return and destruction

The protocol-mandated study treatment return procedures may not be altered without prior written approval from the sponsor. On an ongoing basis and/or upon termination of the study, the CRA will collect used and unused subject kits, which will be sent to the warehouse, where the sponsor or a representative will check treatment reconciliation.

In certain circumstances, used and unused treatment bottles may be destroyed at the site once treatment accountability is finalized and checked by the sponsor or a representative, and written permission for the destruction has been obtained from the sponsor.

5.1.5 Study treatment accountability and compliance with study treatment

5.1.5.1 Study treatment accountability

The inventory of study treatment dispensed and returned (i.e., study treatment accountability) must be performed by the study staff on the day of the subject visit and before providing further study treatment. It is recorded on the investigational medicinal product dispensing and accountability log and in the eCRF and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment bottle dispensed to the subject:

- Dispensed bottle number
- Date dispensed / number of tablets dispensed (pre-populated in eCRF)

- Date returned / number of tablets returned

All study treatment supplies, including partially used or empty bottles, must be retained at the site for review by the CRA.

If a subject omits to bring the remaining study treatment bottle to a study visit, he/she must be instructed to not take any tablets from the remaining study treatment bottle and to return it at one of the next visits.

5.1.5.2 Study treatment compliance

Treatment compliance will be assessed based on study treatment accountability:

***Accountability based compliance** = [(number of tablets dispensed at Visit n − number of tablets returned at Visit n+1) / number of tablets that should have been taken during the period*] × 100*

* The period is defined as the number of days elapsed between the respective visits.

During the study, study treatment compliance based on accountability is expected to be 80% or above. If below 80% without a medical justification (e.g., AE) this will be considered as a protocol deviation.

The investigator must check with the subject the reasons for this non-compliance and discuss actions to be taken to avoid re-occurrence at the next visit. If the subject forgets to bring the remaining study treatment to a study visit, he/she will be asked to bring it to the next visit.

5.1.6 Study treatment interruptions

Study treatment should not be interrupted. If study treatment intake is interrupted by the subject for a day or more for any reason, he/she must inform the principal investigator.

Study treatment may be temporarily interrupted in response to an AE, or other reasons (e.g., diagnostic or therapeutic procedure, study treatment forgotten). Interruptions of study treatment must be kept as short as possible. All study treatment interruptions must be recorded in the eCRF.

The following guidance is provided for re-initiation of study treatment after study treatment interruptions.

Note that under no circumstances should a subject take more than one tablet per day.

5.1.6.1 Study treatment interruption between Day 1 and Day 14

A re-initiating study visit is required after study drug interruption lasting more than 7 days between Day 1 and Day 14.

- During this period if the subject omits to take the dose for 7 or more consecutive days, the subject must inform the principal investigator and a re-initiation visit should take place no later than 7 days after the investigator is aware of the treatment interruption. Re-initiation of study treatment must be monitored on site following the cardiac assessment schedule and applying the discharge criteria as on Day 1.
- If, at any visit (scheduled or unscheduled), the subject reports to the investigator that he/she missed taking the dose for one or more days during the initial 2 weeks of treatment (Day 1 to Day 14) but then resumed study treatment without reporting the interruption promptly, information on any event potentially related to the interruption should be collected and the subject should be counseled on the risks of non-compliance. Information on the treatment interruption must be recorded in the eCRF. No re-initiation should be performed in such a case.

5.1.6.2 Study treatment interruption after Day 14

If the subject missed doses after Day 14 a re-initiation visit is not required. Information on any event potentially related to the interruption should be collected and the subject should be counseled on the risks of non-compliance. Information on the treatment interruption must be recorded in the eCRF. Subjects must be instructed to contact the investigator immediately if they experience any symptoms that may be related to bradycardia (e.g., dizziness, vertigo, syncope).

5.1.7 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Idorsia personnel. The main reason (e.g., AE, lack of efficacy) must be documented in the eCRF and in the subject's medical charts.

At the time of information to subject / informed consent process, the investigator should explain to the subject the importance of continuing treatment in compliance with the protocol once randomized for the scientific validity of the study. However, a subject has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study [see Section 8.2]). A subject who prematurely discontinues study treatment is not considered as withdrawn from the study provided that the subject's consent for participation in the study has not been withdrawn.

In the event of premature discontinuation of study treatment for any reason:

- Subjects should perform the pEOT visit, which must take place preferably no later than 7 days after the last dose of study treatment, and all assessments planned at the pEOT visit, must be performed.

- Subjects must be followed up as per the original planned scheduled visits up to 12 months after study treatment initiation. Subjects will have to perform all assessments of scheduled visits as planned and data should be collected.
- Subjects who are no longer on treatment at Month 6 will not require re-randomization through the IRT system and will continue to be followed up during TP2 as per protocol schedule.
- For subjects who were followed up for at least 6 months after last dose of study treatment, the EOS visit should be performed at Month 12.
- For subjects who perform the pEOT visit less than 6 months prior to the Month 12 visit, the 6-month posttreatment follow-up period must be completed in its entirety. For example, if a subject completes pEOT visit at Month 8, the visits originally scheduled for Month 9, Month 10, Month 11 and Month 12 are conducted as planned, in replacement of FU1, FU2, FU3 and FU3a visits, respectively. After the Month 12 visit, FU3b and EOS visits are conducted, which corresponds to 6 months of posttreatment follow-up. For further examples, please refer to Appendix 18.

It is also recommended that the investigator explains to the subject the importance of continuing in the study even if the subject wishes to be withdrawn from study treatment. This will reduce the amount of missing data. Measures in place to increase subject retention in the study are described in Section 5.1.9.

Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

The investigator should discontinue study treatment for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject. Study-specific criteria for discontinuation of study treatment are described in Section 5.1.8.

Premature discontinuation of study treatment may also result from a decision by the sponsor (e.g., in the event of premature termination or suspension of the study [see Section 8.3]).

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study are described in Sections 8.2 and 8.4, respectively.

5.1.8 Study-specific criteria for interruption / premature discontinuation of study treatment

5.1.8.1 Cardiovascular

All clinically relevant ECG or vital sign abnormalities as per investigator's judgment must be recorded as an AE in the eCRF as per protocol AE definitions [see Section 9.1.1].

5.1.8.1.1 Day 1 specific stopping criteria

Subjects must be permanently discontinued from study treatment if any of the following occurs on Day 1 of treatment or on days of re-initiation following study treatment interruptions [see Appendix 6]:

- HR < 40 bpm at two consecutive hourly 12-lead ECG post-dose assessments.
- SBP < 90 mmHg at two consecutive hourly BP measurements post-dose
  - For subjects with baseline pre-dose SBP < 90 mmHg: decrease in SBP of > 5 mmHg from pre-dose SBP value at two consecutive hourly BP measurements post-dose.
- The subject does not meet the criteria for discharge from the monitored setting at 12-hour post-dose.
- Continuous ECG monitoring is recommended for subjects who meet study treatment discontinuation criteria related to bradycardia, arrhythmia or low BP on Day 1. Subjects who are permanently discontinued should not be discharged from the monitored setting before vital signs return to near baseline values, there is no persisting ECG abnormality (e.g., AV block second degree or higher) and/or the ongoing AE requiring (continued) hospitalization is resolved [see Appendix 6].

5.1.8.1.2 Other cardiovascular stopping criteria

- If QTcF > 500 ms (females) or > 480 ms (males) is observed at any time throughout the study, as documented by 12-lead ECG (one immediate re-test is allowed). If at the re-test, QTcF is confirmed > 500 ms, (females) or > 480 ms (males), the subject must be permanently discontinued from study treatment. Subjects with QTcF prolongation should be monitored until the absence of the persisting ECG abnormality can be confirmed.
- Symptomatic bradycardia or hypotension (e.g., syncope) at any time.

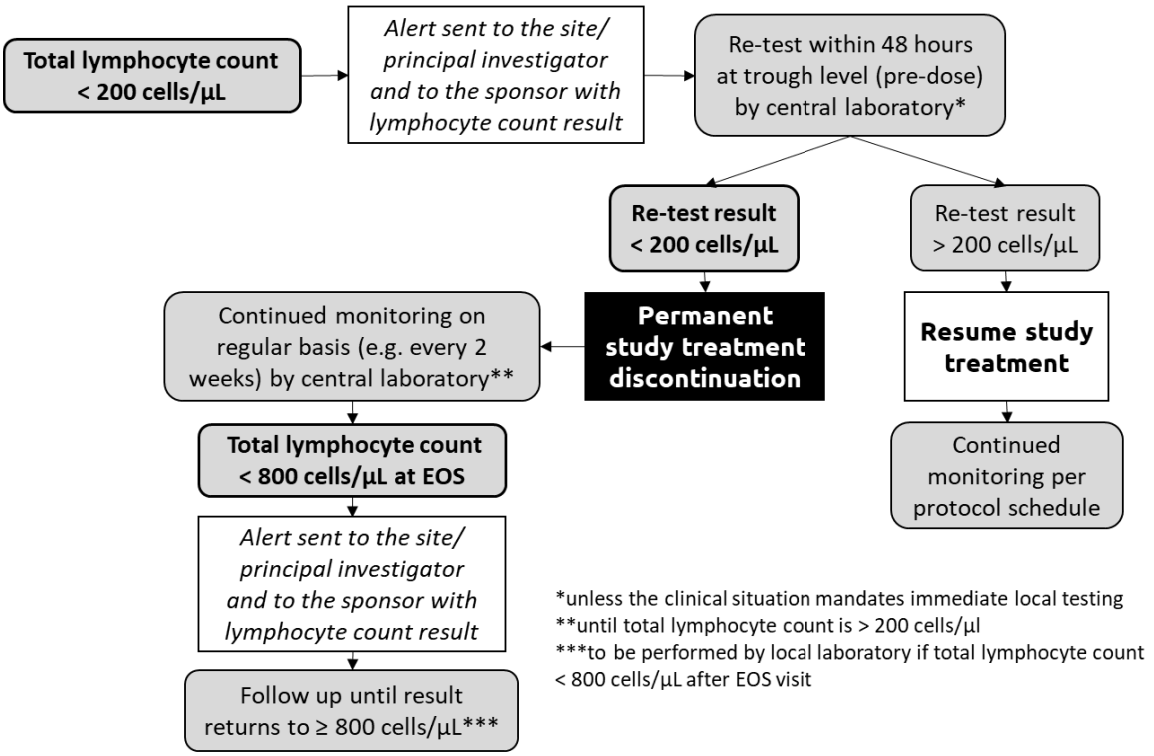
Follow-up monitoring will have to be provided until the AE resolves and the subject's condition is stable.

5.1.8.2 Immune system

Subjects must be permanently discontinued from study treatment at any time throughout the study in the event of confirmed total lymphocyte count < 200 cells/µL, according to the guidance provided below and in Figure 2.

Whenever a total lymphocyte count < 200 cells/µL is recorded by the central laboratory, an alert containing the lymphocyte count result will be sent to the site / principal investigator and the sponsor. The principal investigator will immediately contact the subject and ask him/her to return to the site within 48 hours at the latest to repeat the test at trough level (pre-dose) at the central laboratory (unless the clinical situation mandates immediate local testing). If the repeat test confirms a total lymphocyte count < 200 cells/µL, the study treatment must be permanently discontinued, and lymphocyte counts must be monitored on a regular basis (e.g., every 2 weeks). If the lymphocyte count is still < 800 cells/µL at the EOS visit, monitoring should be continued on a regular basis (e.g., every 2 weeks) by the local laboratory until the lymphocyte count has returned to ≥ 800 cells/µL.

Figure 2 Guidance for monitoring total lymphocyte count



5.1.8.3 Respiratory system

In the event of abnormal spirometry results the subject will be closely observed, spirometry assessments will be repeated, and study treatment must be permanently discontinued, according to the guidance provided in Table 2.

Table 2 Guidelines for FEV_1 decrease

Item	Parameter	Guideline
1	If FEV_1 > 15% decrease from Visit 1.	Repeat spirometry assessments preferably within 1 week. See item 1a, 1b.
1a	If at repeat spirometry assessment: FEV_1 > 15% decrease from Visit 1.	Permanently discontinue study treatment and perform FU spirometry assessments.
1b	If at repeat spirometry assessment: FEV_1 ≤ 15% decrease from Visit 1.	Resume regular spirometry assessment schedule.

FEV_1 = forced expiratory volume in 1 second; FU = follow-up.

Further diagnostic work-up and consultation with a pulmonologist or other specialist should be considered according to local practice.

In all cases of permanent study treatment discontinuation, follow-up monitoring must be provided until respiratory AEs are resolved and/or changes in pulmonary function are resolved, or steadily resolving.

5.1.8.4 Pregnancy / lack of compliance with protocol methods of contraception

If a subject becomes pregnant while on study treatment, study treatment **must** be permanently discontinued. The investigator/delegate must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

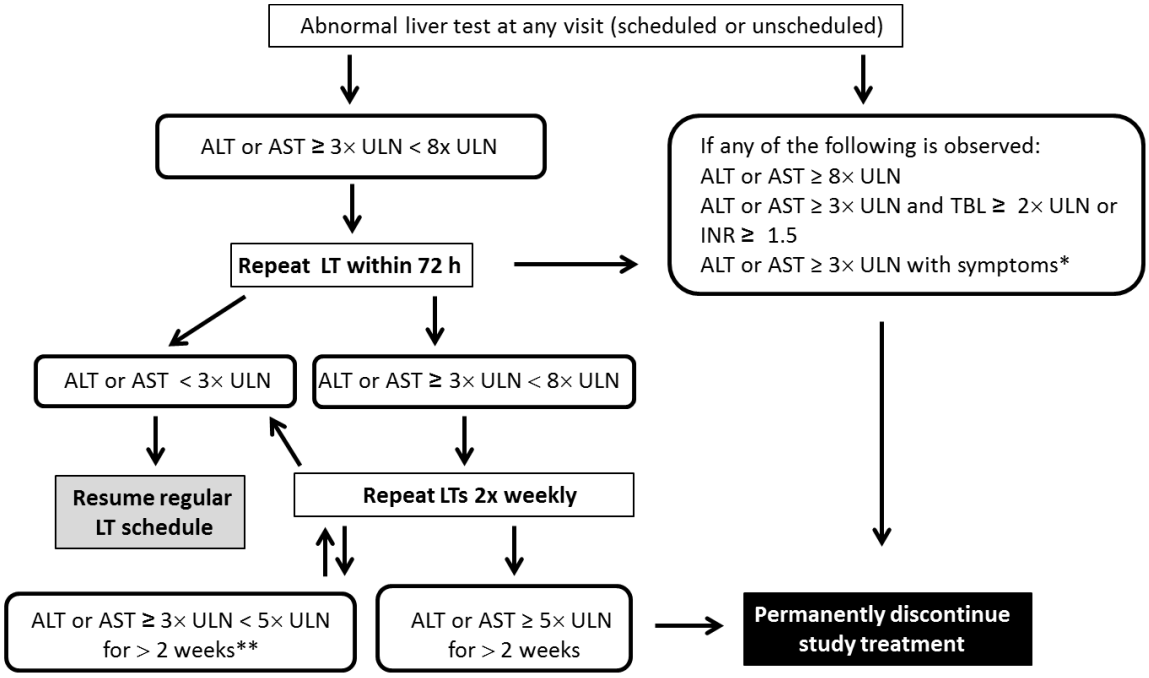
If a subject has a positive urine pregnancy test, study treatment must be interrupted immediately. A serum pregnancy test must be performed as soon as possible. If the pregnancy is confirmed, study treatment must be permanently discontinued (apart from study drug, also some co-medications may have to be considered for discontinuation). If the result of the serum pregnancy test is negative, study drug may be re-initiated as indicated in the study treatment interruptions section.

If the investigator considers that the subject is not complying with the protocol methods of contraception instructions, study treatment **must** be permanently discontinued.

5.1.8.5 Liver enzyme abnormalities

In the event of abnormal liver tests (LTs) or signs and symptoms suggestive of drug-induced liver injury, the subject will be closely observed, LTs will be repeated, and study treatment must be permanently discontinued, according to the guidance provided in Figure 3.

Figure 3 Guidance for monitoring liver test abnormalities



* Symptoms include unusual lethargy or fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, anorexia, dark urine, fever, rash, itching and/or eosinophilia (> 5%).
** Investigator may consider permanent discontinuation.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; LT = liver test; TBIL = total bilirubin; ULN = upper limit of normal.

When marked abnormalities for AST, ALT, TBIL, or international normalized ratio (INR) are reached as indicated in Figure 3, an alert will be sent by the central laboratory to the site / principal investigator and the sponsor. The sponsor will contact the site / principal investigator to ensure that he/she will immediately contact the subject to enquire about symptoms and ask him/her to return to the site within 72 hours at the latest to repeat the test at the central laboratory (unless the clinical situation mandates immediate local testing).

In the event of repeated abnormal LTs within 72 hours, the subject will be closely observed and liver enzyme and bilirubin tests will be repeated by the central laboratory or locally according to the scheme illustrated in Figure 3. Further diagnostic work-up and consultation with a hepatologist or other specialist should be considered according to local practice.

In all cases of permanent study treatment discontinuation, follow-up monitoring must be conducted until signs and symptoms have resolved and/or changes in liver function abnormalities have resolved or are steadily improving.

5.1.8.6 Ocular abnormalities

Subjects with suspected macular edema or retinal vasculitis:

- The diagnosis should be confirmed by diagnostic work-up as recommended by local guidelines (e.g., optical coherence tomography [OCT] or fluorescence angiography).
- The Ophthalmology Safety Board will receive all available, required information related to suspected cases of macular edema or any other relevant ophthalmologic cases and will perform a central, blinded review of OCT results and the subject's data.
- The study drug must be temporarily interrupted during the case assessment. In the event the Ophthalmology Safety Board assess the case as confirmed or suspicious macular edema, study treatment must be permanently discontinued. The subject must be followed up until resolution or condition is considered non-clinically significant by the investigator.

5.1.8.7 Infections

Subjects should be advised to be pro-active and alert in reporting any signs and symptoms indicative of systemic infections such as fever, malaise, and fatigue or any unusual neurological symptoms suggestive of brain infection.

In the event of a serious infection as per investigator judgment (e.g., opportunistic infection or serious infection requiring i.v. medication or hospitalization), the subject should be treated as clinically indicated and the investigator should consider permanent discontinuation of study treatment. Concomitant immunomodulatory medications may also be discontinued at the discretion of the investigator. The decision to permanently discontinue study treatment will be made after evaluation of all available information concerning all potential causes of infection and the clinical status of the subject. Further diagnostic work-up and consultation with an infectious disease specialist or other specialist should be considered according to local practice and the clinical situation.

In the event of permanent discontinuation from study treatment due to infection, adequate treatment needs to be provided, and the subject must be monitored until complete resolution of the infection. Furthermore, subjects should not receive any of the prohibited systemic immunosuppressive treatments during the follow-up period of 6 months after last study drug intake, unless clinically indicated and justifiable in the opinion of the investigator.

5.1.8.8 Other potential premature treatment discontinuation

In the event of incorrect study drug dispensing (incorrect kit dispensed) and incorrect study drug intake detected before assignment of a new kit, the subject must be permanently discontinued from study treatment.

Furthermore, in the event of permanent discontinuation from study treatment for any reason, subjects should not receive any of the prohibited systemic immunosuppressive treatments or other forbidden therapies during the follow-up period of 6 months after last study drug intake, unless clinically indicated and justifiable in the opinion of the investigator. Also, the allowed concomitant therapies should stay within the protocol-defined ranges during the follow-up period of 6 months after last study drug intake and may only be changed if clinically indicated and justifiable by the investigator.

5.1.9 Measures for subject retention

Subjects withdrawn from study treatment are encouraged to remain in the study until its completion.

In order to ensure compliance with the study procedures, subjects that are prematurely discontinued from study treatment should continue to be followed up as per the original planned visits [see Section 5.1.7].

The investigator is encouraged to explain to the subjects the importance of remaining in the study for data accuracy purposes and scientific relevance of the study results. The ICF will also highlight the scientific importance of the subject's data.

5.2 Previous and concomitant therapy

5.2.1 Definition of previous and concomitant therapy

A previous therapy is any treatment for which the end date is prior to start of study treatment. Relevant previous therapies (e.g., SLE treatment) for which the end date is less than 12 months prior to ICF signature will be recorded in the eCRF.

A study-concomitant therapy is any treatment (including methods of contraception and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) given for any reason including the background SLE therapy that is either ongoing at the start of study treatment or is initiated during the study treatment period, or during the follow-up period up to Visit 18 (EOS). All study-concomitant therapies administered will be reported in the eCRF.

The generic name, start/end dates of administration (as well as whether it started prior to first study treatment administration and/or was ongoing at EOS), route, dose, frequency, and indication for use will be recorded in the eCRF.

5.2.2 Background SLE therapy

To be eligible for the study, subjects must currently receive at least one of the below SLE background medications:

- NSAIDs
  - Aspirin (acetylsalicylic acid),
  - Ibuprofen,
  - Naproxen,
  - Celecoxib,
  - Others.
- Corticosteroids (≤ 40 mg/day prednisone or equivalent [see Appendix 1])
  - Prednisolone,
  - Prednisone,
  - Methylprednisolone,
  - Dexamethasone,
  - Betamethasone,
  - Hydrocortisone,
  - Triamcinolone,
  - Cortisone.
- Anti-malarials
  - Hydroxychloroquine (≤ 400 mg/day),
  - Chloroquine (≤ 500 mg/day),
  - Quinacrine (≤ 100 mg/day).
- Mycophenolate mofetil (≤ 2 g/day)
- Mycophenolic acid (≤ 1440 mg/day)
- Azathioprine (≤ 2 mg/kg/day)
- Methotrexate (≤ 20 mg/week)
- Belimumab (≤ 10 mg/kg every 4 weeks i.v., or 200 mg/week s.c.)

Treatment with anti-malarials, mycophenolate mofetil, mycophenolic acid, azathioprine, methotrexate or belimumab must have been started at least 90 days prior to Screening. All other background SLE therapies must have been started at least 30 days prior to Screening.

Background SLE therapy doses must be stable for at least 30 days prior to Randomization. For corticosteroids, doses must be stable for at least 15 days prior to Randomization [see Section 5.2.2.1].

Subjects must be reminded of the importance of the adherence to SLE background medication starting at the Screening visit and throughout the duration of the study. The non-adherence to SLE background therapy may confound interpretation of study results.

5.2.2.1 Oral corticosteroids

Eligibility criteria related to corticosteroids

For subjects who are being treated with corticosteroids prior to enrollment in this study, it is required for eligibility that corticosteroids:

- Were started for at least 30 days prior to Screening.
- Doses are stable for at least 15 days prior to Randomization.
- Doses are ≤ 40 mg/day prednisone or equivalent [see equivalence in Appendix 1].

Screening period / oral corticosteroid optimization period for subjects receiving OCS

For subjects who are being treated with corticosteroids prior to enrollment in this study, an optimization period aiming to reduce the doses of OCS to (or as close as possible to) the minimum effective dose should be considered during the screening period. This will allow the minimization of the OCS changes during the treatment period, which is the preferred approach.

Dose reductions are at the investigator's discretion and can be done up to 15 days prior to Randomization when the OCS dose must be stable as per eligibility criteria.

Investigators should consider the guidance provided in Table 3. This table reflects the ACR draft guidance regarding steroid reduction during periods of stable SLE disease.

Treatment Period 1 (from Randomization to Month 6)

For subjects who are being treated with corticosteroids, it is preferable that doses are maintained stable until the end of Month 6 of the study to avoid introducing confounding factors for the interpretation of the primary objective. The dose adjustment recommended during Screening aims to minimize the change in OCS dose during the treatment period.

For subjects showing improving SLE disease activity for at least 8 weeks, OCS dose reduction may be considered at the investigator's discretion during the first 3 months of TP1 [see suggested guidance in Table 3]. No steroid sparing is allowed between Month 3 and Month 6 (i.e., between Visit 5 and 8). Rationale for dose change and details of the change should be documented in the eCRF.

Subjects with increased SLE disease activity may receive one OCS burst during the first 3 months of TP1, which should be tapered to the Randomization dosage within 2 weeks of

initiation of the upgrade / initiation of the OCS. Alternatively, a single intramuscular or i.v. dose of methylprednisone (80 to 160 mg or equivalent) is permitted instead of OCS burst. Rationale for dose change and details of the change should be documented in the eCRF.

Treatment Period 2 (after Month 6 of treatment)

After the first 6 months of study, OCS dose reduction may be considered for subjects showing improving SLE disease activity for at least 8 weeks. Investigators should consider the guidance provided in Table 3. This table reflects the ACR draft guidance regarding steroid reduction during periods of stable SLE disease.

Subjects with increased SLE disease activity may receive one OCS burst after Month 6, which should be tapered to Randomization dosage within 2 weeks of initiation of the upgrade / initiation of the OCS. Alternatively, a single intramuscular or i.v. dose of methylprednisone (80 to 160 mg or equivalent) is permitted instead of OCS burst.

Table 3 Algorithm for reducing dose of prednisone

Daily dose (mg)	Dose reduction (mg)
Up to 7.5	1.0
> 7.5 to 15	2.5
> 15 to 30	5.0
> 30 to 40	10.0
> 40	Taper at the investigator's discretion using draft guidelines prepared for ACR

ACR = American College of Rheumatology.

5.2.3 Allowed concomitant therapy

After Randomization, background medications should be kept stable throughout the study. However, if clinically required, changes in certain medications as outlined below are allowed:

- Stable chronic NSAID therapy: therapy is not to be started or stopped during the study.
  - Temporary use and/or dose change for treatment of non-SLE-related conditions (e.g., headache, menstrual cramps) is allowed.
- Stable immunosuppressant therapy (i.e., methotrexate, azathioprine, or mycophenolate mofetil, mycophenolic acid as well as belimumab). Therapy is not to be started or stopped during the study, and the dose should be kept stable.

- Atropine (i.v.) in the event of symptomatic bradycardia.
- Topical ocular therapy (e.g., chronic treatment for glaucoma, ocular inflammation), including dilating eye drops, mydriatics, parasympathetic antagonists (e.g., tropicamide) or sympathetic agonists (e.g., phenylephrine).
- Vaccination with non-live vaccines.
- Topical treatment therapy including topical, inhaled, and nasal use of corticosteroid.
- All other medications that are not forbidden [see Section 5.2.4].

5.2.4 Forbidden concomitant therapy

- Immunosuppressive agents not listed in allowed concomitant medication such as cyclophosphamide, ciclosporine, leflunomide, sirolimus, tacrolimus, etc.
- Immunosuppressive or immunomodulatory biological agents (e.g., i.v. immunoglobulin, rituximab, S1P receptor modulators other than cenerimod).
- β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering therapy.
- QT-prolonging drugs with known risk of torsade de pointes.
- Vaccination with live vaccines.
- Inhibitors of the breast cancer resistance protein transporter: curcumin, ciclosporine, eltrombopag, elacridar, gefitinib, teriflunomide.

For further details, see table of forbidden medications in Appendix 3 and Appendix 4.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint

- Change from baseline to Month 6 in the mSLEDAI-2K score.

This endpoint is based on the SLEDAI-2K index, modified to exclude leukopenia.

The SLEDAI-2K will be assessed by the investigator or delegate who will enter the relevant data into the SLEDAI-2K form of the eCRF. Further details are available in Section 7.2.6.1.

Baseline is defined as the last available measurement before the start of randomized treatment. All values of mSLEDAI-2K from baseline through Month 6 visits will be accounted for in the assessment of this endpoint.

6.1.2 Secondary endpoints

- Response on SRI-4 at Month 6 as compared to baseline, defined as follows:
  - Reduction from baseline of at least 4 points in the mSLEDAI-2K.

    AND
  - No new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline.

    AND
  - No increase of more than 0.3 points on the PGA since baseline.
- Response (no worsening) at Month 6 on BILAG-2004 disease activity index defined as no new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline.

6.1.3 Other efficacy endpoints

- Response at Month 6 based on improvement in the mSLEDAI-2K score defined as a reduction from baseline of at least 4 points.
- Response (no worsening and improvement) at Month 6 on BILAG-2004 disease activity index defined as follows:
  - No new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline.

    AND
  - Any BILAG A organ domain score at study baseline improved to B/C/D or any BILAG B organ domain score at study baseline improved to C/D.
- SRI-5, -6, -7, -8 responses at Month 6.
- Occurrence of mild, moderate and severe flares for 6 months [see SLE Flare Index (SFI) in Appendix 12].
- Time to first severe flare from baseline to Month 6 (severe flares defined as BILAG-2004 A organ domain score presence due to items that are new or worse).
- Time to first flare from baseline to Month 6.
- Change from baseline to Month 6 in PGA score.

6.1.4 PRO / Quality of life endpoints

- Change from baseline to each post-baseline assessment in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale score.

- Change from baseline to each post-baseline assessment in Patient Global Impression of Severity – Fatigue (PGIS-F).
- Patient Global Impression of Change – Fatigue (PGIC-F) score at each post-baseline assessment.
- Change from baseline to each post-baseline assessment in SF-36v2™.
- Change from baseline to each post-baseline assessment in the Lupus Quality of Life (Lupus QoL) questionnaire.

6.1.5 Exploratory endpoints

Exploratory endpoints will be analyzed from baseline to Month 12 on all available assessments according to 2 groups:

- Group 1: All randomized subjects for whom baseline is defined as the last available measurement before the start of randomized treatment in TP1.
- Group 2: Subjects re-randomized at Month 6 for whom baseline is defined as the last available measurement before the start of re-randomized treatment in TP2.

Endpoints for Group 1:

- Sustained mSLEDAI-2K response defined as a reduction of at least [redacted]
- Change from baseline to each post-baseline assessment up to Month 12 in prednisone or equivalent dose.

Endpoints for Groups 1 and 2:

- Change from baseline to each post-baseline assessment up to Month 12 in mSLEDAI-2K score.
- Response at each post-baseline assessment on improvement in the mSLEDAI-2K score defined as a reduction from baseline of at least 4 points.
- Response (no worsening and improvement) at each post-baseline assessment on BILAG-2004 disease activity index defined as follows:
  - No new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline.

    AND
  - Any BILAG A organ domain score at study baseline improved to B/C/D or any BILAG B organ domain score at study baseline improved to C/D.
- SRI-4, -5, -6, -7, -8 responses at each post-baseline assessment.

- Change from baseline to each post-baseline assessment in PGA score.
- Occurrence of flares and severe flares at each post-baseline assessment (defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit).
- Time to first severe flare from baseline to Month 12 (severe flares defined as BILAG-2004 'A' score presence due to items that are new or worse).
- Time to first flare from baseline to Month 12.

6.2 Safety endpoints

- Occurrence of treatment-emergent AEs/SAEs, and AESIs [see Appendix 5].
- Occurrence of AEs leading to premature discontinuation of study treatment.
- Changes in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for heart rate using Bazett's formula [QTcB] and QTcF), from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 / Re-initiation and each post-dose analysis visit up to EOS) for each variable.
- Occurrence of treatment-emergent 12-lead ECG notable abnormalities (e.g., HR, PR, QTc) [see Appendix 7].
- Occurrence of treatment-emergent 12-lead ECG abnormal findings.
- Change in supine SBP and DBP from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 / Re-initiation and each post-dose analysis visit up to EOS).
- Change in FEV_1 and FVC from baseline to each post-baseline assessment up to EOS.
- Occurrence of treatment-emergent decrease of FEV_1 or FVC > 15% from baseline values at any post-baseline assessment.
- Change in laboratory variables (hematology, blood chemistry, and urinalysis) from baseline to each post-baseline assessment up to EOS.
- Occurrence of treatment-emergent laboratory notable abnormalities [see Appendix 7].
- Change in body weight from baseline up to EOS.
- Change in left ventricular ejection fraction as assessed by Standard 2D echocardiography from Screening to Month 6 in subjects randomized to ancillary echocardiography study.
- Occurrence of clinically relevant abnormalities as assessed by Standard 2D/Doppler echocardiography from Screening to Month 6 in subjects randomized to ancillary echocardiography study.

6.3 Pharmacokinetic endpoints

- Cenerimod plasma concentrations post-dose on Day 1, 6 h after dosing.
- C_{trough} cenerimod plasma concentrations prior to dosing at Months 1, 2, 3, and 6 or at EOT visit after premature study treatment discontinuation (if applicable).
- Cenerimod plasma concentration at the EOS visit (i.e., 6 months after last dose of study treatment).

6.4 Biomarker endpoints

- Change from baseline to each post-baseline assessment up to EOS in total lymphocyte count.
- Change from baseline to each post-baseline assessment in the following biomarkers: ANA, anti-dsDNA, anti-Smith (anti-Sm), and C3, C4 complement.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits and their respective assessments and time windows are listed in Table 4.

All efforts should be made to keep subjects on schedule, based on the date of their Day 1 (Visit 2), which is the day of Randomization.

To ensure compliance, at each visit the study personnel must remind WOCBP to use the methods of contraception defined for this study. When scheduling the different assessments for a subject visit, the following should be taken into account:

- The subject must come to the clinic in a fasted condition for all visits except for EOT, FU1, EOS and unscheduled visits. Subjects should be instructed not to take the study medication in the morning of the day of the visit.
- At Visit 2 (Randomization, Day 1) and at the Re-initiation visit (if applicable [see Section 7.1.2]), assessments during the visits will be divided into two parts: before (pre-dose) and after (post-dose) the administration of the study drug, which will be taken at the site [see Sections 7.1.2 and 7.1.5].
- At other visits, SBP/DBP, ECGs, spirometry, blood draws for hematology/biochemistry and PK, are to be performed pre-dose.
- Resting time:
  - When a subject has to go to another department within the hospital for a specific test, sufficient time should be allowed for the subject to rest prior to the examination.

- Sufficient time between blood drawing and cardiac assessments (i.e., ECGs and/or BP measurement) is to be allowed.

- All PK sampling should be done pre-dose except for Day 1.
- Safety follow-up information will be collected during the FU1 visit; FU2, FU3, FU3a, and FU3b visits (phone call visit), and at the EOS visit (6 months after last study drug intake). Efficacy data will be collected at FU1 and EOS visits.

7.1.1 Screening

The date of the Screening visit is the date when the ICF is signed [see Section 12.3 for the informed consent procedure].

The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

If the signing of the ICF and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed. If a study-specific procedure or assessment has been performed as part of routine assessments on the day of the Screening visit or before the Screening visit, and the results are available prior to the subject signing the ICF, such procedure or assessment may be used and does not have to be repeated (e.g., vital signs). In such cases, it must be clear from the source documents when and for which reason the assessment was done prior to the signing of the ICF.

For convenience reasons, study-specific procedures or assessments can take place on different days during the screening period.

Subjects who sign the ICF when the enrollment target has already been met may still be randomized.

Within the 60 days of the screening period, subjects may repeat abnormal laboratory tests and abnormal PFT (FEV_1 or FVC) required to meet eligibility criteria.

For subjects who are being treated with corticosteroids prior to enrollment in this study, an optimization period aiming to reduce the doses of OCS to (or as close as possible to) the minimum effective dose, should be considered during the screening period [see Section 5.2.2.1].

7.1.1.1 Re-screening

Subjects who did not meet the criteria for participation in the study (i.e., screen failure) may be re-screened once if the reason for non-eligibility was transient (e.g., laboratory test

result outside protocol limit, abnormal pulmonary function test, insufficient wash-out period of a forbidden medication, etc.).

Eligibility assessments must be repeated at the time of re-screening if more than 3 months have elapsed from the initial screening assessment.

Subjects who were not eligible due to a negative test for varicella-zoster antibodies may also be re-screened once after completing all required vaccination doses, which must occur at least 30 days prior to re-test and Randomization.

A new ICF must be signed prior to re-screening the subject if more than 3 months have elapsed since the first ICF signature. Re-screened subjects will be assigned the same subject number as for the initial screening.

7.1.2 Visit 2 – Day 1 – Randomization and pre- and post-dose assessment

After confirmation of eligibility (i.e., verification of all entry criteria before dosing) by the investigator, randomization should occur via IRT to obtain randomization and study treatment kit numbers. Study treatment should then be dispensed and the subject should take the first dose of study treatment at site after pre-dose assessments are completed.

Visit 2 pre-dose assessments include:

- Inclusion/exclusion criteria
- Physical examination
- Clinical mSLEDAI-2K, BILAG, PGA, and SFI
- PRO and quality of life (FACIT-Fatigue Scale, PGIS-F, SF-36v2™ and Lupus QoL)
- Hematology and blood chemistry
- SLE biomarkers serum sampling
- Urine pregnancy test
- Urinalysis
- Urine protein-to-creatinine ratio
- SBP/DBP assessment
- 12-lead ECG
- Start 24 hours ECG Holter
- Recording of AEs and SAEs
- Recording of changes in concomitant medications and background SLE therapies since previous visit.

Visit 2 post-dose assessments include:

- Hourly 12-lead ECG and SBP/DBP assessments for 6 hours or until the subject meets the discharge criteria [see Appendix 6].
- After 6 hours, subjects may be discharged from the monitored setting if they meet the discharge criteria, otherwise SBP/DBP assessments and 12-lead ECG will be performed hourly until discharge criteria are met. If discharge criteria are not met after 12 hours, the subject must be permanently discontinued from study treatment.
- PK sample 6 hours after dosing.
- Recording of AEs and SAEs.

The subject will be instructed to contact the site if he/she has any questions or problems. WOCBP will be reminded to use the methods of contraception defined for this study.

An appointment for the next visit will be scheduled and the subject will be instructed to:

- Bring back the remaining study medication for drug accountability,
- Come fasted to the site,
- Not take study treatment on the day of study visit prior to coming to the site,
- Contact the principal investigator immediately in the event of the appearance of any symptoms (e.g., suggestive of an SLE flare) or any AEs or SAEs or if a study treatment dose is missed.

7.1.3 Scheduled study visits

Study visit assessments from Visit 3 up to Visit 13 should be performed as described in Table 4.

- Study medication should be taken at the site.
- Whenever applicable, SBP/DBP, ECGs, spirometry, blood draws for hematology and biochemistry and PK, should be performed pre-dose.
- PK sampling at Visit 3, 4, 5 and 8 should be done pre-dose.
- All other scheduled assessments can be performed pre-dose or post-dose.

7.1.4 Follow-up visits and EOS visit

Five follow-up visits (FU1, FU2, FU3, FU3a, and FU3b) will be performed after the EOT visit and before the EOS visit.

FU1 visit will be performed at the site one month after EOT.

FU2, FU3, FU3a, and FU3b visits will be phone call visits and will be done 2 months, 3 months, 4 months and 5 months after EOT, respectively.

Assessments at FU visits will include:

- Recording of AEs and SAEs.
- Urine pregnancy test for WOCBP (performed at home prior to phone contacts with test kits dispensed at Visit 14/EOT).
- Recording of changes in concomitant medications and background SLE therapies since previous visit – FU1 and EOS only.
- Efficacy data: mSLEDAI-2K, BILAG, PGA, SFI (FU1 and EOS only) and FACIT-Fatigue, PGIS-F, PGIC-F, SF-36v2™, and Lupus QoL (EOS only).

EOS visit assessments will be performed 6 months after the last dose of study treatment as per schedule of assessment Table 4.

7.1.5 Unscheduled visits

Unscheduled visits (U1, U2, and others) may be performed at any time during the study based on medical needs. These visits include, but are not limited to, those performed due to safety (e.g., occurrence of an AE/SAE, laboratory abnormalities), and/or SLE disease exacerbations (e.g., flare).

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF.

During an unscheduled visit, the following assessments must be performed:

- Recording of changes in concomitant medications and background SLE therapies since last visit.
- Recording of AEs/SAEs.

Depending on the reason for the unscheduled visit (e.g., AE), additional assessments will be performed based on the judgment of the investigator, and the results will be recorded in the eCRF. Any clinically relevant abnormalities detected must be reported as an AE or SAE as appropriate in the corresponding Adverse Event form of the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

7.1.6 Additional visits for re-initiation of study treatment

Re-initiation visits should be conducted for study treatment interruption lasting more than 7 consecutive days between Day 1 and Day 14 [see Section 5.1.6].

Note that a subject can be re-initiated only once during the study duration.

The re-initiation post-dosing procedure must be followed:

- Hourly 12-lead ECG and SBP/DBP assessments for 6 hours or until the subject meets the discharge criteria. If discharge criteria are not met after 12 hours, the subject should be permanently discontinued.
- PK sample 6 hours after dosing.
- Recording of AEs and SAEs.
- Recording of changes in concomitant medications and background SLE therapies since previous visit.
- Study drug accountability for compliance review.

Table 4 Visit and assessment schedule

PERIODS	Name	SCREENING	TREATMENT PERIOD 1							
	Duration	Up to 60 days	From Day 1 to Month 6							
VISITS	Number	1	2	2a	3	4	5	6	7	8
	Name	Screening	Randomization [1]		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
	Time	Day –60 to Day –1	Day 1	Day 2	Day 30 (±2 days)	Day 60 (±7 days)	Day 90 (±7 days)	Day 120 (±7 days)	Day 150 (±7 days)	Day 180 (±7 days)
Informed consent		X								
Inclusion/exclusion criteria		X	X							
Demographics		X								
Smoking and alcohol consumption status		X								
Medical history and SLE history		X								
SLE and previous/concomitant therapies		X	X		X	X	X	X	X	X
Physical examination [2]		X	X		X	X	X	X	X	X
Body weight and height [3]		X								
mSLEDAI-2K, BILAG, PGA, SFI		X	X		X	X	X	X	X	X
FACIT-Fatigue, PGIS-F			X				X			X
PGIC-F							X			X
SF-36v2™ and Lupus QoL			X							X
Chest X-ray [5]		X								
Vital signs: SBP/DBP* [6] [7]		X	X		X	X	X	X	X	X
12-lead ECG* [7]		X	X				X			X
ECG Holter* [8]			X	X						
Echocardiography [4]		X								X
Spirometry*		X					X			X
Ophthalmological examinations		X					X			X
OCT		X					X			

PERIODS	**Name**	**SCREENING**	**TREATMENT PERIOD 1**							
	Duration	**Up to 60 days**	**From Day 1 to Month 6**							
VISITS	**Number**	**1**	**2**	**2a**	**3**	**4**	**5**	**6**	**7**	**8**
	Name	**Screening**	**Randomization [1]**		**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
	Time	**Day –60 to Day –1**	**Day 1**	**Day 2**	**Day 30 (±2 days)**	**Day 60 (±7 days)**	**Day 90 (±7 days)**	**Day 120 (±7 days)**	**Day 150 (±7 days)**	**Day 180 (±7 days)**
PK sampling* [9]			X		X	X	X			X
Hematology and blood chemistry* [10]		X	X		X	X	X	X	X	X
Pregnancy test [11]		X	X		X	X	X	X	X	X
Viral serology / TB test		X								
Additional sample for virology			X							
SLE biomarkers		X	X [13]		X	X	X [13]	X	X	X [13]
Urine protein-to-creatinine ratio		X	X		X	X	X	X	X	X
Urinalysis (dipstick)		X	X		X	X	X	X	X	X
Study treatment dispensing/return and accountability			X		X	X	X	X	X	X
AEs [12] / SAEs [12]		X	X		X	X	X	X	X	X

PERIODS	**Name**	**TREATMENT PERIOD 2**					
	Duration	**From Month 6 to Month 12**					
VISITS	**Number**	**9**	**10**	**11**	**12**	**13**	**14**
	Name	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12 / End-of-Treatment (EOT) / premature discontinuation of study treatment (pEOT) (14)**
	Time	**Day 210 (±7 days)**	**Day 240 (±7 days)**	**Day 270 (±7 days)**	**Day 300 (±7 days)**	**Day 330 (±7 days)**	
SLE and previous/concomitant therapies		X	X	X	X	X	X
Physical examination (2)		X	X	X	X	X	X
Body weight (3)							X
mSLEDAI-2K, BILAG, PGA, SFI		X	X	X	X	X	X
FACIT-Fatigue, PGIS-F, PGIC-F, SF-36v2™ and Lupus QoL				X			X
Echocardiography (4)							X
Vital signs: SBP/DBP* (6) (7)		X	X	X	X	X	X
12-lead ECG* (7)				X			X
Spirometry*				X			X
Ophthalmological examinations							X
OCT							X
Hematology and blood chemistry* (10)		X	X	X	X	X	X
Pregnancy test (11)		X	X	X	X	X	X
Urinalysis (dipstick)		X	X	X	X	X	X
SLE biomarkers		X	X	X	X	X	X (13)
Urine protein-to-creatinine ratio		X	X	X	X	X	X
PK sampling*							X (9)
Study treatment dispensing/return and accountability		X	X	X	X	X	X
AEs (12) / SAEs (12)		X	X	X	X	X	X

PERIODS	Name	FOLLOW-UP					
	Duration	6 months					
VISITS	Number	15	16	17	17a	17b	18
	Name	FU1	FU2 PHONE CALL	FU3 PHONE CALL	FU3a PHONE CALL	FU3b PHONE CALL	EOS
	Time	1 month after last dose [16] (±7 days)	2 months after last dose [16] (±7 days)	3 months after last dose [16] (±7 days)	4 months after last dose [16] (±7 days)	5 months after last dose [16] (±7 days)	6 months after last dose [16] (±7 days)
SLE and concomitant therapies		X					X
Physical examination [2]		X					X
Body weight [3]							X
mSLEDAI-2K, BILAG, PGA, SFI		X					X
FACIT-Fatigue, PGIS-F, PGIC-F, SF-36v2™, and Lupus QoL							X
Vital signs: SBP/DBP* [6] [7]		X					X
12-lead ECG* [7]							X
ECG Holter* [8]							
Echocardiography [4]							
Spirometry*							X
Ophthalmological examinations							X
OCT							
PK sampling* [9]							X

PERIODS	**Name**	**FOLLOW-UP**					
	Duration	**6 Months**					
VISITS	**Number**	**15**	**16**	**17**	**17a**	**17b**	**18**
	Name	**FU1**	**FU2 PHONE CALL**	**FU3 PHONE CALL**	**FU3a PHONE CALL**	**FU3b PHONE CALL**	**EOS**
	Time	**1 month after last dose [16] (±7 days)**	**2 months after last dose [16] (±7 days)**	**3 months after last dose [16] (±7 days)**	**4 months after last dose [16] (±7 days)**	**5 months after last dose [16] (±7 days)**	**6 months after last dose [16] (±7 days)**
Hematology and blood chemistry* [10]		X					X
Pregnancy test [11]		X	X	X	X	X	X
Viral serology / TB test							
Urinalysis (dipstick)		X					X
SLE biomarkers		X					X
Urine protein-to-creatinine ratio		X					X
Study treatment dispensing/return and accountability							
AEs [12]/ SAEs [12]		X	X	X	X	X	X

PERIODS	**Name**	**UNSCHEDULED**		
	Duration	**NA**		
VISITS	**Number**	**U1, U2, …**	**I1**	**I2**
	Name	**Unscheduled [15]**	**Re-initiation**	
	Time	**Any day between Day 1 and EOS (assessments to be performed as applicable)**	**Re-initiating study drug after interruption lasting more than 7 days between Day 1 and Day 14**	
SLE and concomitant therapies		X	X	
Physical examination [2]		X	X	
Body weight [3]		X		
mSLEDAI-2K, BILAG, PGA, SFI		X		
FACIT-Fatigue, PGIS-F, PGIC-F, SF-36v2™, and Lupus QoL		X		
Chest X-ray [5]		X		
Vital signs: SBP/DBP* [6] [7]		X	X	
12-lead ECG* [7]		X	X	
ECG Holter* [8]			X	X
Echocardiography [4]		X		
Spirometry*		X		
Ophthalmological examinations		X		
OCT		X		
PK sampling* [9]			X	

PERIODS	**Name**	**UNSCHEDULED**		
	Duration	**NA**		
VISITS	**Number**	**U1, U2, …**	**I1**	**I2**
	Name	**Unscheduled [15]**	**Re-initiation**	
	Time	**Any day between Day 1 and EOS (assessments to be performed as applicable)**	**Re-initiating study drug after interruption lasting more than 7 days between Day 1 and Day 14**	
Hematology and blood chemistry* [10]		X		
Pregnancy test [11]		X		
Viral serology / TB test		X		
Urinalysis (dipstick)		X		
SLE biomarkers		X		
Urine protein-to-creatinine ratio		X		
Study treatment dispensing/return and accountability			X	
AEs [12]/ SAEs [12]		X	X	

One month is considered to be 30 days.
Day 1 (date of Randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).
For WOCBP, the serum pregnancy test at Visit 1 must be performed at least 3 weeks before the urine pregnancy test performed at Visit 2 prior to Randomization.
* Study treatment should not be taken before the assessment (i.e., SBP/DBP, ECGs, spirometry, laboratory tests, and PK sampling).

(1) Prior to Randomization, the following central laboratory results must be available to confirm eligibility: ANA, anti-dsDNA, anti-HAV IgM, Hepatitis B surface antigen, Hepatitis C antibodies (anti-HCV IgG or IgM), anti-HEV IgM and/or IgG, HEV-RNA PCR (as needed), HIV1 and HIV2, varicella-zoster virus IgM antibody, urine protein-to-creatinine ratio, ALT/AST/TBIL and pregnancy test (if applicable).
(2) A complete physical examination (i.e., inspection, percussion, palpation, and auscultation) will only be performed at Visits 1, 2, 3, 5, 8, 11, 14, and 15. For all other visits, a symptom-driven abbreviated physical examination will be performed in order to capture assessments needed for the SLEDAI-2K, the PGA, the BILAG, and the SFI.
(3) Height only at Screening. Body weight should be measured as part of BILAG assessment at each applicable visit and recorded in the source documentation. If clinically relevant, body weight collected outside Screening, EOT and EOS visits may be reported as an Unscheduled assessment.
(4) Echocardiography will be performed at Visit 1 (Screening) preferably within 30 days prior to Randomization for all subjects and at Visit 8 (Month 6) in approximately 175 subjects, as part of the ancillary study. In the event of premature study treatment discontinuation during TP1 (i.e., before Visit 8), echocardiography will be performed at pEOT visit and will not be required at Visit 8.

(5) A chest X-ray that has been performed within 6 months prior to Screening can be used (in this case, there is no need to repeat the chest X-ray at Screening).
(6) At each pre-dose assessment, SBP/DBP measurements will be performed twice in the supine position.
(7) On Day 1 and at Re-initiation visit, SBP/DBP assessment and 12-lead ECG will be done pre-dose and hourly until 6 h post-dose; after 6 h, subjects may be discharged if they meet the discharge criteria, otherwise SBP/DBP assessments and 12-lead ECG will be performed hourly until discharge criteria are met. If discharge criteria are not met after 12 h, the subject must be permanently discontinued. At all other visits, only pre-dose SBP/DBP assessments and 12-lead ECG will be performed.
(8) On Day 1 and at Re-initiation visit, 24-hour ECG Holter should start before dosing. The subject must return to the site on Day 2 (Visit 2a) / Re-initiation (Visit I2) for removal of the device after 24-hour recording.
(9) On Day 1 and at Re-initiation visit, PK samples will be collected 6 hours after dosing. At Visits 3, 4, 5, and 8, PK samples will be collected pre-dose. At pEOT visit, in the event of premature treatment discontinuation during TP1 (i.e., before Visit 8) and at EOS visit, PK samples will be collected at any time during the visit and will not be required at Visit 8.
(10) Hematology assessments, including coagulation tests will be performed at each visit until EOS, except FU2, FU3, FU3a, and FU3b visits.
(11) Serum pregnancy tests will be performed at Screening and EOS. Urine pregnancy tests will be performed at all other visits. To ensure compliance, the study personnel must remind WOCBP at each visit to use the methods of contraception defined for this study from the Screening visit until 6 months after taking the last dose of study treatment.
(12) All AEs and SAEs occurring after signing the ICF and up to 6 months after study treatment discontinuation must be reported.
(13) Sample for SLE biomarkers analyses will include: SLE biomarkers serum sample, serum EDTA sample and PAXgene sample.
(14) If the subject discontinues study treatment prematurely, the pEOT visit should preferably take place no later than 7 days after last study drug intake. Subjects who prematurely discontinue treatment will remain in the study and continue to perform all assessments as per planned visit schedule. See Section 5.1.7 for additional details on premature discontinuation of study treatment.
(15) Unscheduled visits may be performed at any time during the course of the study. Recording the changes in concomitant medications and in background SLE therapies since the last visit needs to be performed at each unscheduled visit. Further assessment including body weight, chest X-ray, 12-lead ECG, SBP/DBP, echocardiography, SLEDAI-2K, PGA, BILAG, FACIT-Fatigue Scale, PGIS-F, PGIC-F, SF-36v2™, Lupus QoL, laboratory assessments and other disease activity assessments may be performed at the discretion of the investigator.
(16) Applicable for subjects having completed TP2 according to the protocol schedule up to Month 12 / EOT (Visit 14).

AE = adverse event; ALT = alanine aminotransferase; ANA = anti-nuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; anti-HAV = anti-hepatitis A virus; anti-HCV = anti-hepatitis C virus; anti-HEV = anti-hepatitis E virus; AST = aspartate aminotransferase; BILAG = British Isles Lupus Assessment Group; DBP = diastolic blood pressure; ECG = electrocardiogram; EDTA = ethylenediaminetetraacetic acid; EOS = End-of-Study; EOT = End-of-Treatment; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale score; FU = follow-up; HEV-RNA PCR = hepatitis E virus ribonucleic acid polymerase chain reaction; HIV = human immunodeficiency virus; I =re-initiation; ICF = informed consent form; Ig = immunoglobulin; mSLEDAI-2k = modified Systemic Lupus Erythematosus Disease Activity Index-2000; NA = not applicable; OCT = optical coherence tomography; pEOT = premature discontinuation of study treatment or premature End-of-Treatment; PFT = pulmonary function test; PGA= Physician's Global Assessment; PGIC-F = Patient Global Impression of Change – Fatigue; PGIS-F = Patient Global Impression of Severity – Fatigue; PK = pharmacokinetic(s); QoL = Quality of life; SAE = serious adverse event; SBP = systolic blood pressure; SF-36v2™ = 36-Item Short Form Health Survey version 2; SFI = SLE Flare Index; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; TB = tuberculosis; TBIL = total bilirubin; U = unscheduled; WOCBP = women of childbearing potential.

7.2 Study assessments

The study assessments are listed in Table 4.

All study assessments performed during study visits (scheduled or unscheduled) are done by the investigator/delegate and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

If the principal investigator delegates any study procedure/assessment for a subject (e.g., ECG, OCT, blood sampling, etc.) to an external facility, he/she should inform the sponsor to whom these tasks are delegated. The set-up and oversight will be agreed upon with the sponsor. The supervision of any external facilities remains under the responsibility of the principal investigator. At Visit 2 (Randomization / Day 1) and at study treatment re-initiation visits where post-dose monitoring is required, the pre- and post-dose 12-lead ECG assessments will be performed under the responsibility of the investigator who will interpret the results. The pre-dose 12-lead ECG interpretation (before Randomization) will support the subject's final eligibility decision made by the investigator according to the inclusion/exclusion criteria.

The post-dosing 12-lead ECGs will be performed together with BP assessments hourly until 6 hours post-dose. At this time, subjects may be discharged from the monitored setting if they meet the discharge criteria [see Appendix 6], otherwise 12-lead ECG and BP will be assessed hourly until discharge criteria are met. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be permanently discontinued from the study treatment and will be kept in the hospital for observation.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all subjects including screening failure subjects.

The below data are to be recorded in the eCRF:

- Baseline demographics and anthropometric variables (sex, age, race, and ethnicity [if allowed in the country]), body weight, and height.
- Relevant medical history / current medical conditions other than those related to SLE (e.g., chronic and ongoing acute conditions, serious past conditions) present before signing of the ICF. Where possible, main diagnoses and not symptoms will be recorded.

7.2.1.1 Medical history

7.2.1.1.1 General medical history

Relevant medical history, as defined below, must be recorded in the eCRF:

- Chronic medical conditions including pulmonary, CNS, liver function, renal function, eye disorder, and skin conditions at any time in the past. Cardiovascular medical conditions are to be recorded in a dedicated eCRF page [see Section 7.2.1.1.2].
- New acute medically relevant conditions including any serious infection, defined as life-threatening or requiring i.v. antibiotics or hospitalization in the past 6 months.
- Exposure to healthcare settings in the past 3 months (e.g., hospitalization, emergency care admissions, visit to emergency medical services facility).
- Pregnancy morbidity (e.g., fetus loss, spontaneous abortion, premature birth).
- Previous and concomitant therapy [see Section 5.2].
- History of chemotherapy, radiotherapy, operations, immunosuppression or any other relevant medical treatment.

7.2.1.1.2 Cardiovascular medical history

Relevant cardiovascular medical history, as defined below, must be recorded in the eCRF:

- Valvular heart disease, arrhythmias, tachycardia, bradycardia, atrial fibrillation, atrial flutter, PR interval shortened, QTc prolonged, left ventricular hypertrophy, right ventricular hypertrophy, angina pectoris, myocardial infarction, coronary artery disease, heart failure (current NYHA class should be provided), cardiomegaly, pericarditis, myocarditis, endocarditis, idiopathic cardiomyopathy, congenital heart disease, previous heart surgery, stroke, transient ischemic attack, peripheral vascular disease, deep vein thrombosis.
- Cardiovascular risk factors: hypertension, hypercholesterolemia, atherosclerosis, diabetes mellitus, sedentary lifestyle, overweight, obese, family history of heart disease.

7.2.1.1.3 SLE-relevant medical history

SLE disease characteristics as defined below, evidenced by documentation in the subject charts, will be recorded in the eCRF:

- Date of first SLE symptoms.
- Date of SLE diagnosis.
- SLE symptoms according to ACR criteria [ACR 1997, Appendix 2].

7.2.1.2 Data to be collected for screening failure subjects

A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects.

For subjects who failed Screening, the following data will be recorded in the eCRF:

- Age, sex, race, and ethnicity (if allowed in the country);
- Inclusion criteria not met and/or exclusion criteria met;
- SAEs.

7.2.2 Previous and concomitant therapies

All background/previous SLE therapies, as well as all study-concomitant therapies will be reported in the corresponding eCRF pages [see Section 5.2].

7.2.3 Safety assessments

The definitions, reporting, and follow-up of AEs and SAEs are described in Section 9.1.1.

7.2.3.1 Weight and height

Height will be measured at Visit 1 (Screening).

Body weight (in underwear) will be measured at Visit 1 (Screening), Visit 14 (EOT) and Visit 18 (EOS) and recorded in the eCRF. Body weight should be measured as part of BILAG assessment at each applicable visit [see Section 7.2.6.3] and recorded in the source documentation. If clinically relevant, body weight collected outside Visit 1 (Screening), Visit 14 (EOT) and Visit 18 (EOS) may be reported as an Unscheduled assessment in the eCRF.

7.2.3.2 Physical examination

Complete physical examination (i.e., inspection, percussion, palpation, and auscultation) will be performed at Visits 1, 2, 3, 5, 8, 11, 14 and 15. For all other visits, a symptom-driven abbreviated physical examination will be performed in order to capture assessments needed for the SLEDAI-2K, the PGA, the BILAG, and the SFI.

The observations should be reported in the eCRF as either normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page. All findings, including clinically not relevant findings that are present at study start (i.e., before signing the ICF), must be recorded on the Medical History or SLE-relevant disease history eCRF page. Physical examination findings made after study start that meet the definition of an AE/SAE [see Section 9.1] must be recorded by the principal investigator on an AE page of the eCRF and must be reported to the sponsor's Global Drug Safety department (SAEs only).

7.2.3.3 12-lead ECG

Digital 12-lead ECG devices will be provided to each site by the central ECG laboratory for the duration of the study.

Digital 12-lead ECG recordings will be performed at pre-dose for all subjects at Visits 1, 2, 5, 8, 11, 14/EOT and 18/EOS with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement. Pre-dose ECGs also need to be performed at unscheduled visits and re-initiation visits, if applicable. The data records will be sent to the evaluation center for central reading.

Details will be provided in the 12-lead ECG laboratory manual.

The following parameters will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QTc (ms) will be calculated according to Bazett's and Fridericia's formula ($QTcB = QT/(RR)^{0.5}$ and $QTcF = QT/(RR)^{0.33}$, respectively.

ECG printout tracings must be reviewed, signed, and dated by the investigator as soon as possible after the examinations; a copy of the tracing should be made and both original and copy will be kept in the subject file.

All ECG reports (received from central reader) must be signed and dated by the investigator and filed with the source documentation. The investigator must indicate on the ECG report whether abnormal values are considered clinically relevant or not. All ECG findings including clinically not relevant findings that are present at the time of signing the ICF must be recorded on the cardiovascular medical history page of the eCRF [see Section 7.2.1.1.2]. Any clinically relevant ECG abnormalities detected after signature of the ICF must be reported as an AE or SAE as appropriate [see Section 9.3]. The 12-lead ECGs will be performed under the responsibility of the investigator.

At Visit 2 (Randomization / Day 1) and at study treatment re-initiation visits where post-dose monitoring is required, the pre- and post-dose 12-lead ECG assessments will be also performed under the responsibility of the investigator who will interpret the results.

The pre-dose 12-lead ECG interpretation (before Randomization) will support the subject's final eligibility decision made by the investigator according to the inclusion/exclusion criteria.

The post-dosing 12-lead ECGs will be performed together with BP assessments hourly until 6 hours post-dose. At this time, subjects may be discharged from the monitored setting if they meet the discharge criteria [see Appendix 6], otherwise 12-lead ECG and BP will be assessed hourly until discharge criteria are met. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be permanently discontinued from the study treatment and will be kept in the monitored setting for observation.

7.2.3.4 ECG Holter

ECG Holter monitoring will be performed for 24 hours at Visit 2 (Randomization) and at Re-initiation visit.

Digital ECG Holter devices will be provided to the sites for the duration of the study. The data records will be sent to the ECG Holter core laboratory for central reading.

At Visit 2 (Randomization / Day 1) and Re-initiation visit, the 24-hour ECG Holter will be performed under the responsibility of the investigator. The recording must be initiated before first dosing. The subject will be allowed to leave the clinic with the Holter and to perform his/her usual daily activities. The recording will be stopped 24 hours post-dose. It is essential to have an uninterrupted recording during the 24 hours (including sleep hours).

The central reading results (including alert notifications in the event of specific findings) of the ECG Holter performed at Visit 2 (Randomization) and Re-initiation visit will be sent to the investigator.

The ECG Holter reports must be signed and dated by the investigator and filed with the source documentation. The investigator signing the ECG Holter report must indicate on the report whether abnormal values are considered clinically relevant or not. All Holter ECG findings including clinically not relevant findings that are present at the time of signature of the ICF must be recorded on the cardiovascular medical history page of the eCRF. Any clinically relevant Holter ECG abnormalities detected after signature of the ICF must be reported as an AE or SAE as appropriate [see Section 9.1.1] and must be followed until the event is resolved and/or the value returns to within the normal range or is steadily improving.

7.2.3.5 Blood pressure

BP measurements including SBP and DBP will be performed under the responsibility of the investigator and will be assessed at all scheduled visits except FU2 and FU3 visits.

BP assessment will be performed using the same type of device throughout the study on the same arm with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement. At each pre-dose assessment, SBP and DBP measurements will be performed twice. Each of the two obtained measurements (i.e., two SBP measurements and two DBP measurements) and the position and arm used are to be recorded in the eCRF. The means of the two obtained measurements will be calculated in the eCRF. Any clinically relevant BP abnormalities detected after informed consent signature must be reported as an AE or SAE as appropriate [see Section 9.1.1].

At Visit 2 (Randomization / Day 1), the pre- and post-dose SBP/DBP assessments will be performed in parallel to 12-lead ECGs until subject discharge. Pre-dose measurements

will be performed twice and recorded in the eCRF as described above for pre-dose assessments at all relevant scheduled visits.

The hourly post-dose assessments will only be measured once at each hourly time point. Single SBP measurements will be used for determining discharge criteria.

7.2.3.6 Echocardiography

An echocardiography assessment will be performed during the screening period for all subjects, preferably within 30 days prior to Randomization. Unscheduled echocardiography examinations may be conducted at any time during the study as judged by the investigator.

Standard 2D/Doppler echocardiography should assess cardiac morphology and function including regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction. The echocardiography equipment needs to be maintained with preventive maintenance service occurring at least yearly.

The physician conducting standard 2D/Doppler echocardiography must have a level of experience equivalent to at least Level 2 training, as defined in the American College of Cardiology Board / American Heart Association clinical competence statement on echocardiography. In case an expert sonographer is conducting the examination, the expert physician must review the echocardiography results.

An echocardiography monitoring plan was developed for the study to ensure standardized data collection and assessment. The evaluation of the echocardiography data will be done by a central imaging laboratory.

All echocardiography findings at Screening including clinically not relevant findings must be recorded on the cardiovascular medical history page of the eCRF. Any clinically relevant echocardiography abnormalities detected after Randomization must be reported as an AE or SAE as appropriate [see Section 9.1.1]

Detailed instructions on procedures, standardization, qualification, recording, and transfer of data will be provided in a separate manual.

For echocardiography ancillary study see Section 3.1.2.

7.2.3.7 Spirometry

Spirometry will be performed at Visit 1 (Screening), Visit 5 (Month 3), Visit 8 (Month 6), Visit 11 (Month 9), at EOT visit, at EOS visit and at unscheduled visits if required.

Spirometry assessments after the Randomization visit can be performed up to 7 days prior to or after the visit date. All spirometry assessments should preferably be performed in the

morning at approximately the same time to avoid diurnal variation, and prior to study drug intake. Spirometry testing will assess FVC and FEV_1.

A central reader will provide equipment and a PFT manual with detailed instructions for the procedures, calibration, and validation of spirometers. All recorded spirometry values will be transmitted to the centralized provider, and will be reviewed by independent central readers. Quality of the assessments will be evaluated for compliance with the American Thoracic Society / European Respiratory Society criteria and queries may be sent to the sites for clarification. If quality issues are identified, additional training will be provided. The selection of the highest (largest) FEV_1 and FVC values to be used for the endpoint derivations will be validated by the independent central readers prior to being electronically transferred to the sponsor. The date and time of the assessment will be reported in the eCRF. No other data will be reported in the eCRF.

PFT values that trigger study drug discontinuation will be flagged and sent to the sites and the sponsor. Any clinically relevant PFT abnormality detected after signature of the ICF must be reported as an AE or SAE as appropriate [see Section 9.1.1] and must be followed until the value returns to within the normal range or is steadily improving.

The predicted normal values for FEV_1 and FVC used to determine the exclusion criteria and the study treatment interruption/premature discontinuation criteria [see Section 4.3 and Section 5.1.8, respectively] will be those as defined by the European Community for Coal and Steel including ethnic group adjustments [Quanjer 1993].

7.2.3.8 Ophthalmological examination

An ophthalmological examination will be performed by an ophthalmologist at any time during the screening period but results must be available prior to the Randomization visit (Visit 2). Examinations after Screening will be performed at Visits 5, 8, 14/EOT, and Visit 18/EOS. The scheduled visits can be performed up to 7 days prior to or after the visit date [see Table 4].

The ophthalmological examination should include previous eye history and ophthalmic condition, any new or current ophthalmological symptoms, assessment of best corrected visual acuity per local standard practice, measurement of Goldmann applanation tonometry (recommended, if not available other applanation tonometer allowed), slit lamp examination of the anterior segment, and fundoscopy. While the visual acuity and measurement of applanation tonometry exams may be performed by a delegate (e.g., experienced technician, optometrist), the review and interpretation must be performed by the ophthalmologist. Conduct, review, and interpretation of all other ophthalmological exams must be performed by the ophthalmologist.

The purpose of the assessment prior to Randomization is to exclude subjects with macular edema or active uveitis from the study and to document a baseline assessment. Assessments at each visit will ensure that any new ophthalmological abnormality is detected and treated at an early stage.

In the eCRF, the date of the ophthalmological examination and the presence/absence of any abnormality (i.e., Yes/No) will be recorded. The results will be documented in the subject charts but will not be reported in the eCRF. Clinically relevant findings that are present at the time of signature of the ICF must be recorded on the medical history page of the eCRF. Any clinically relevant ophthalmological abnormalities (including OCT findings detected after signature of the ICF) must be reported as an AE or SAE as appropriate [see Section 9.1.1] and must be followed until the value returns to within the normal range or is steadily improving.

7.2.3.9 Optical coherence tomography

OCT will be performed at Visit 1 (Screening), Visit 5 (Month 3), and at EOT visit. Testing at Visit 1 can be performed at any time during the screening period. At Visit 5 and EOT visit, testing may be performed up to 7 days prior to the visit date but no later than 7 days after the visit. In addition, unscheduled OCT examination will have to be assessed in the event of visual symptoms or findings suggestive of macular edema according to the ophthalmologist's decision or if active uveitis is diagnosed during the study. While the OCT exam may be performed by a delegate (e.g., experienced technician, optometrist), the review and interpretation must be performed by the ophthalmologist.

The purpose of the assessment prior to Randomization is to exclude subjects with macular edema or active uveitis from the study, and to document a baseline assessment. The site will use the OCT device available locally and must ensure it is working properly. A copy of the calibration certificates done before the day of assessment must be stored as source documents at the site. To the extent that is logistically feasible, the same OCT machine is to be used for each individual subject throughout the study.

In the eCRF, the date of the OCT assessment and the presence/absence of any abnormality (i.e., Yes/No) will be recorded. The results will be documented in the subject charts but will not be reported in the eCRF. Any clinically relevant abnormalities detected after signature of the ICF must be reported as an AE or SAE as appropriate [see Section 9.1.1].

An Ophthalmology Safety Board will receive all information related to suspected cases of macular edema and will perform a central, blinded review of OCT images and subject's data of suspected cases of macular edema.

7.2.3.10 Chest X-ray

A chest X-ray will be performed at Visit 1 (Screening) and assessed by the local radiologist to exclude any subject with findings suggestive of active or latent TB and it is also part of the assessments of severe respiratory disease and pulmonary fibrosis. Any chest X-ray that had been performed within 6 months prior to Screening can be used; if available, there is no need to repeat the chest X-ray at Screening. The report of the chest X-ray must be recorded in the subject file.

7.2.3.11 Test for tuberculosis

An IFN gamma release assay (QuantiFERON-TB-Gold Plus®) will be performed at Visit 1 (Screening) to screen for active or latent TB. The test will be analyzed and interpreted at the central laboratory and transferred to the principal investigator.

Only subjects with a negative test at Screening and without chest X-ray findings [see Section 4.3] at Screening or within the previous 6 months suggestive of active or latent TB can be included in the study. If the test result is positive, subjects must not be included in the study, except if there is documentation that the subject has completed adequate and successful treatment for TB previously. If the test result is inconclusive (invalid, indeterminate, or borderline), the test may be repeated one time and a negative result must be obtained prior to Randomization to include the subject. If the result of the repeated test is inconclusive, subjects must not be included in the study.

Details on the performance of the test for TB will be provided in the specific central laboratory manual.

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

A central laboratory will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be transferred from the central laboratory database to the sponsor. See central laboratory manual for contact details.

In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency), local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated eCRF pages. Due to functional blinding [see Section 5.1.3.2], testing of total WBC (including differentials) and lymphocyte counts at a local laboratory should not be performed unless deemed absolutely necessary to ensure subject's safety. In this case, the local results of total WBC (including differentials) and lymphocyte counts collected until EOS visit will be recorded in the eCRF.

If a central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time window and these test results are available.

Central laboratory reports will be sent to the investigator. In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the sponsor and the concerned clinical site. Values that will trigger such alert notification are displayed in Appendix 7.

All laboratory reports must be signed and dated by the primary investigator or delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Laboratory findings that are present at the time of signature of the ICF must be recorded on the medical history page of the eCRF. Any clinically relevant laboratory abnormalities detected after signature of the ICF must be reported as an AE or SAE as appropriate [see Section 9.1.1] and must be followed until the value returns to within the normal range or is steadily improving. Further laboratory analyses should be performed as indicated and according to the judgment of the investigator.

Details about the collection, sampling, storage, shipment procedures, reporting of results, and abnormal findings can be found in the laboratory manual.

7.2.4.2 Laboratory tests

Blood samples will be drawn at all scheduled visits. At unscheduled visits, blood samples will be collected at the investigator's discretion. Sample collection dates will be recorded in the eCRF [for biomarkers see Section 7.2.8].

Hematology

- Hemoglobin
- Hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration
- Erythrocyte count (reticulocyte count)
- Leukocyte count with differential counts*
- Platelet count.

* For the purpose of functional blinding [see Section 5.1.3.2], total WBC (including differentials) and lymphocyte counts will not be available to sites and to the sponsor during the study. This data will be available only after database lock. For the management of lymphocyte count < 200 cells/µL, please refer to Section 5.1.8.2 for more details.

Clinical chemistry

- Aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Cholesterol, triglycerides
- Sodium, potassium, chloride, calcium
- Protein, albumin.

Test for tuberculosis

- An IFN gamma release assay will be performed at Visit 1 (Screening) to screen for active or latent TB [see Sections 4.3 and 7.2.3.11].

Coagulation tests

- Prothrombin time and INR.
- Activated partial thromboplastin time.

Pregnancy test

A serum pregnancy test for WOCBP will be performed at Visit 1 (Screening) and Visit 18 (EOS), and if pregnancy is suspected during the study. Urine pregnancy tests will be performed at all other visits.

WOCBP must have a confirmed negative serum pregnancy test at Visit 1 (Screening) and a second confirmed negative urine pregnancy test prior to Randomization (Visit 2). The two tests must be performed at least 3 weeks apart.

Serum pregnancy test results data will be automatically transferred from the central laboratory database to the sponsor. Urine pregnancy testing results will be recorded in the eCRF. In the event of pregnancy up to 6 months after the last dose of study medication, a Pregnancy form must be completed [see Section 9.4].

Virus serology

- Anti-HAV IgM, Hepatitis B surface antigen, Hepatitis C antibodies (anti-HCV IgG or IgM), anti-HEV IgG, anti-HEV IgM, HEV-RNA PCR (if positive anti-HEV IgM and/or IgG), HIV1 and HIV2 antibodies, varicella-zoster virus IgG antibodies will be assessed in serum at Visit 1 (Screening) (a confirmatory test might be required in the event of positive testing results [e.g., positive Hepatitis C antibodies]).

Additional analyses in the event of infections

- A serum sample will be taken at Visit 2 (Randomization) and stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections (e.g., suspected opportunistic infection) during the study.

Urinalysis

Including but not limited to:

- pH
- Glucose
- Proteins
- Blood
- Leukocytes

A midstream urine sample (approximately 30 mL) will be obtained, to avoid contamination with epithelial cells and sediments. Urine dipsticks provided by the central laboratory will be used to perform the urinalysis at all visits. The test will be performed and analyzed at the site, and the results will be recorded in the eCRF.

If the dipstick results are positive for protein, leukocytes, or blood, the urine sample will be subject to further analysis as clinically indicated (i.e., microscopic analysis of WBC, red blood cells [RBC], casts, and protein quantification). The results of any further analysis must be documented in the source documents / subject charts and can be used for assessment of the SLEDAI-2K score.

Urine protein-to-creatinine ratio is to be performed at all scheduled visits except FU2, FU3, FU3a, and FU3b visits. Urine samples will be collected and sent to the central laboratory for protein and creatinine measures, and determination of the protein-to-creatinine ratio. For the assessment of proteinuria, the protein-to-creatinine ratio in a single urine sample has been demonstrated as strongly correlated with the protein content of a 24-hour urine collection [Ginsberg 1983, Ruggenenti 1998, KDIGO 2012, Price 2005]. Due to this reason, the result from urine protein-to-creatinine ratio can be used in this study for assessment of both the SLEDAI-2K and BILAG scores. The relationship among these laboratory tests for proteinuria is provided below in Table 5 [KDIGO 2012].

Table 5 Relationship among laboratory tests for proteinuria

Measure	Unit	Conversion factor
24-hour urine protein excretion rate	g/24 hours	1
	mg/24 hours	1000
Urine protein-to-creatinine ratio	mg/g	1000
	mg/mmol	100*

* The conversion is rounded for pragmatic reasons. For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.

7.2.5 Pharmacodynamic and pharmacokinetic assessments

The PD marker is total lymphocyte counts, which will be measured as part of the hematology tests [see Section 7.2.4].

PK samples will be collected post-dose on Day 1 (Visit 2, Randomization) 6 hours after dosing.

PK samples will be collected pre-dose at Visit 3 (Month 1), Visit 4 (Month 2), Visit 5 (Month 3), and at Visit 8 (Month 6) or at EOT visit in the event of premature discontinuation of study treatment.

PK sample will also be collected at EOS visit (i.e., 6 months after last dose of study treatment).

The date and the time of blood sample collection will be entered in the eCRF.

Details about the collection, sampling, storage, and shipment procedures can be found in the laboratory manual. Sites will receive required material from the central laboratory before the start of the study (e.g., tubes, labels, shipment materials). The site personnel will take care of the shipment of the plasma samples to the central laboratory who will forward the PK samples to the Idorsia bioanalytical laboratory at a time interval agreed with the sponsor.

7.2.6 Disease activity assessments

7.2.6.1 Systemic Lupus Erythematosus Activity Index-2000

The SLEDAI-2K will be assessed by the principal investigator at all visits except Day 2, FU2, FU3, FU3a, and FU3b visits, and Re-initiation visit [see Appendix 9].

The principal investigator will perform physical examinations, question the subject on his/her current state and about any potential SLE symptoms and/or manifestation that may have occurred during the past 10 days, and collect all laboratory parameters relevant to the scoring (e.g., protein-to-creatinine ratio, anti-dsDNA titer, dipstick urinalysis). If the

dipstick results are positive, the urine sample will be further analyzed as clinically indicated (i.e., microscopic analysis of WBC, RBC, casts, and protein quantification).

All relevant data will be entered in the SLEDAI-2K form of the eCRF.

Notes:

- Reduction in total WBC count due to reduction of lymphocytes is the main PD effect of $S1P_1$ receptor modulators including cenerimod. Therefore, leukopenia is excluded from the SLEDAI-2K scoring to define the mSLEDAI-2K (i.e., mSLEDAI-2K score does not take into account "leukopenia".)
- The clinical mSLEDAI-2K is the mSLEDAI-2K assessment score without the inclusion of points attributable to hematuria, proteinuria, pyuria, low complement, increased DNA binding and thrombocytopenia.

7.2.6.2 Physician's Global Assessment of disease

The PGA will be assessed by the principal investigator at all visits except Day 2, FU2, FU3, FU3a, FU3b and Re-initiation visit.

[redacted]

7.2.6.3 British Isles Lupus Assessment Group

The scoring system for the BILAG index of disease activity is based upon the principle of the physician's intention to treat and the main feature of the BILAG index is that disease activity in different organs/systems is reported separately. The BILAG will be assessed by the principal investigator at all visits except Day 2, FU2, FU3, FU3a, FU3b and re-initiation visits. The investigator will record clinical features covered by the BILAG index of lupus disease activity and relevant data will be entered in the BILAG form of the eCRF. There are eight systems: general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematological. A score is calculated for each system depending on the clinical features present and whether they are new, worse, the same or improving in the last 4 weeks compared to previous assessment. Immunological data do not contribute to the BILAG scores, but basic hematology and assessment of renal function determine the scores of the relevant systems [see Appendix 11].

7.2.6.4 SLE Flare Index

The classic Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Flare Index (cSFI) was originally developed specifically for the SELENA study [Buyon 2005, Petri 2005] with the aim of sensitively capturing flares of all types as well as distinguishing severe flares. Mild and moderate flares are not discriminated in the cSFI.

The SFI is defined by an increase in the SLEDAI of 3 or more points (mild or moderate flare) or a 12 point increase (severe), a 0–3 visual analog scale with anchors for the physician global assessment (none, mild, moderate or severe flare) with an increase in 1 (for mild/moderate) or 2.5 (for severe) and adding NSAIDs or hydroxychloroquine (for mild) or steroids, but no more than 0.5 mg/kg/day and/or adding a new immunosuppressant (for severe) [Buyon 2005, Petri 2002].

The SFI will be assessed by the principal investigator at all visits except Day 2, FU2, FU3, FU3a, FU3b and re-initiation visits. The investigator will assess the SLE flare index [see Appendix 12] and relevant data will be entered in the SFI form of the eCRF.

7.2.7 Patient Reported Outcomes

All PRO questionnaires will be completed by the subject prior to any other protocol assessment and prior to any other discussion with the investigator or principal investigator.

7.2.7.1 36-Item Short Form Health Survey v2

The SF-36v2™ questionnaire [see Appendix 13] will be used to assess the subject's quality of life. The SF-36v2™ will be completed by the subject at Visit 2 (Randomization), at Visit 8 (Month 6), Visit 11 (Month 9), Visit 14 (Month 12/EOT; for subjects completing 12 months of treatment), Visit 18 (EOS) and unscheduled visit.

In the SF-36v2™ questionnaire, subjects are instructed to rate their health and capacity to perform daily living activities in eight domains including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health during the last 4 weeks. Raw domain scores are determined and transformed to a 0–100 scale as described in the SF-36v2™ manual, and individual domain scores are used to determine the physical and mental component summary scores as described in the SF-36v2™ manual [Maruish 2011].

The standard SF-36v2™ considering the previous 4-week period will be used. A sample of the SF-36v2™ (in English) is provided in Appendix 13. The subject will complete the questionnaire in the local language on a validated paper form that will be collected.

The sponsor has been granted a license agreement for the use of the SF-36v2™ questionnaire. The individual questionnaires will be completed only in countries for which validated translations are available.

7.2.7.2 Functional Assessment of Chronic Illness Therapy – Fatigue Scale

The FACIT-Fatigue Scale is an established instrument for measuring fatigue in a variety of healthy and ill patients and has been used and validated to varying degrees in numerous diseases, including those with an autoimmune basis (e.g., rheumatoid arthritis [Cella 2005]; inflammatory bowel diseases [Tinsley 2011]; psoriatic arthritis [Chandran 2007]), as well as in patients with SLE [Lai 2014, Strand 2014]. It is a short 13-item instrument [see sample on Appendix 14]. The words and phrases are geared to a 4th grade literacy level. FACIT-Fatigue Scale is simple to complete as there is only a single global instruction to circle or mark one choice for each item. Consultation with medical records is not required in order to complete the questionnaire.

The FACIT-Fatigue Scale will be completed by the subject at Visit 2 (Randomization) at Month 3, Month 6, Month 9, Month 12/EOT, EOS and unscheduled visits.

The sponsor has been granted a license agreement for the use of the FACIT-Fatigue Scale questionnaire. The individual questionnaires will be completed only in countries for which validated translations are available.

7.2.7.3 Patient Global Impression of Severity – Fatigue

The Patient Global Impression of Severity (PGIS) is a single-item, self-reported, generic scale to assess the subject's impression of disease severity. The PGIS-F was developed and validated to assess the severity of symptoms of fatigue in central nervous system populations [Targum 2012], including multiple sclerosis population [Targum 2013]. The PGIS has been adapted to the fatigue symptom in the SLE context (PGIS-F) and the subject will be asked to rate their impression of their fatigue severity during the last week [redacted]

The PGIS-F will be completed by the subject at Visit 2 (Randomization), at Month 3, Month 6, Month 9, Month 12/EOT, EOS and unscheduled visits.

7.2.7.4 Patient Global Impression of Change – Fatigue

The Patient Global Impression of Change (PGIC) is a single-item, self-reported, generic scale to assess the subject's impression of change in disease since the start of the study medication. [redacted]

[redacted]

The PGIC-F will be completed by the subject at Month 3, Month 6, Month 9, Month 12 / EOT, EOS and unscheduled visits.

7.2.7.5 Lupus Quality of Life

The Lupus QoL questionnaire is a disease-specific and validated instrument, developed in 2007 to measure health-related quality of life in adults with SLE [McElhone 2007].

The questionnaire contains eight domains assessed via 34 items [redacted] The recall period is the previous 4 weeks, time to complete is estimated at < 10 minutes, and time to score < 5 minutes [Yadzany 2011].

The Lupus QoL questionnaire will be completed by the subject at Visit 2 (Randomization) at Month 6, Month 9, Month 12/EOT, EOS and unscheduled visits.

The sponsor has been granted a license agreement for the use of the Lupus QoL questionnaire. The individual questionnaires will be completed only in countries for which validated translations are available. See sample of the Lupus QoL questionnaire in Appendix 15.

7.2.8 Biomarker assessments

Serum, EDTA plasma, and whole blood (PAXgene) samples will be drawn at the indicated visits. The sample collection date will be recorded in the eCRF.

Details of the collection, labeling, and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the sponsor or the central laboratory.

The following biomarkers will be measured in serum samples at central laboratory:

- ANA, anti-dsDNA, complement C3 and C4, anti-Sm (all visits except FU2, FU3, FU3a, and FU3b visits),
- Anti-cardiolipin (IgA, IgG, IgM) at the Randomization visit.

7.2.9 Emerging SLE biomarkers (tested by the sponsor)

SLE subject heterogeneity and the lack of disease activity biomarkers led to increasing efforts to identify biomarkers to characterize subjects and to investigate treatment response. CXCL10 and Type-I IFN, among others emerged as promising biomarkers. EDTA plasma samples will be collected at Randomization and at Visits 5, 8 and 14 (EOT). Samples will be frozen and stored by the sponsor for exploratory analysis of new emerging biomarkers. Samples will be kept for a maximum duration of 15 years and will be destroyed thereafter.

Whole blood (PAXgene) samples will be collected at Randomization and at Visits 5, 8 and 14 (EOT). Samples will be frozen and stored by the sponsor for exploratory analysis of biomarkers, e.g., Type-I IFN gene expression signature and antibody-secreting cells gene expression signature. Samples will be kept for a maximum duration of 15 years and will be destroyed thereafter.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion

For an individual subject, study completion is reached when EOT visit and EOS visit have been completed as per protocol.

The EOT visit of the last subject randomized in the study corresponds to Visit 14 and will occur at Month 12, or earlier if the study treatment is prematurely discontinued.

For the first 5 months after the EOT visit, subjects will have to undergo FU1, FU2, FU3, FU3a, and FU3b visits, respectively, to collect information on any SAE and/or pregnancy (follow-up) and on efficacy. The FU2, FU3, FU3a, and FU3b visits are conducted by phone and will occur 2, 3, 4 and 5 months after EOT, respectively. EOS should occur 6 months after the EOT visit.

The EOS at study level occurs at the time all subjects have completed their EOS visit, as described above.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal

from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study.

Subjects are considered as lost to follow-up if all repeated attempts by the investigator to communicate with the individual have failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as phone number, home address, e-mail address, person to be contacted if the subject cannot be reached). If the subject cannot be reached, the site must make reasonable repeated efforts to contact the subject. The following methods must be used: at least 3 attempts at contact (e.g., phone calls, or e-mails) must be placed to the last available phone number or e-mail address and 1 registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above he/she will be considered lost to follow-up.

The reason for premature withdrawal from the study must be recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator should make best efforts to schedule a last appointment / phone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / phone call will be recorded in the subjects' medical records but it will not be collected in the eCRF.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is prematurely suspended or terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and Health Authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator, in agreement with the sponsor, must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up, as described in Section 8.2. The sponsor may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from the sponsor, the investigator must promptly inform the sponsor personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval / favorable opinion of the study, the investigator must promptly notify the sponsor personnel and provide a detailed written explanation of the termination or suspension.

A potential restart of the study will be allowed only in agreement with Health Authorities and IRBs/IECs.

Study-specific subject's criteria for interruption / premature discontinuation of study treatment are described in Section 5.1.8. Hold of the clinical study may occur if a certain number of subjects are discontinued from study treatment due to study-specific criteria for interruption / premature discontinuation.

8.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local practice.

In the event of premature discontinuation from the study, WOCBP should be instructed to continue the use of contraception for at least 6 months after the last dose of study drug.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Safety definition

9.1.1 Definitions of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease if considered relevant.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study, even though it may have been present prior to the start of the study.

- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which were not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective of whether a clinical event occurs.

9.1.2 Definition of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least 1 of the following criteria:

- Fatal;
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe;
- Requiring in-patient hospitalization or prolongation of existing hospitalization;
- Resulting in persistent or significant disability or incapacity;
- Congenital anomaly or birth defect;
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered medically significant based upon appropriate medical judgment, as they may jeopardize the subject, and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons;
- Hospitalization for pre-planned (i.e., planned prior to signing the ICF) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

9.1.3 Definition of suspected unexpected serious adverse reactions

The expectedness of an SAE is determined by the sponsor according to the Reference Safety Information (RSI) section provided in the most recent version of the IB.

Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR.

9.1.4 Intensity of adverse events

The intensity of AEs is graded on a three-point scale — mild, moderate, severe — as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 9.1.2]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

9.1.5 Relationship to study treatment

Each AE/SAE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated.

9.1.6 Relationship to protocol-mandated procedure

An AE/SAE is defined as related to protocol-mandated procedure if it appears to have a reasonable possibility of a causal relationship to either the study design or to a protocol-mandated procedure.

The determination of the likelihood that a protocol-mandated procedure caused the AE/SAE will be provided by the investigator.

9.2 Time period and frequency for adverse event / serious adverse event assessment and follow-up

The occurrence of an AE/SAE may come to the attention of study personnel during study visits, phone calls or interviews of subjects presenting for medical care.

At each study visit (scheduled or unscheduled), the investigator will inquire about the occurrence of AE/SAEs since the last visit.

9.2.1 Follow-up of adverse events

AEs still ongoing at the EOS visit must be followed up until resolution, are no longer considered clinically relevant or until stabilization.

9.2.2 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution, stabilization, or until the event outcome is provided.

9.3 Reporting procedures

9.3.1 Reporting of adverse events

All AEs with an onset date after signing of the ICF and up to 6 months after study treatment discontinuation must be recorded on specific AE forms of the eCRF.

Information to be collected in an AE form in the eCRF includes seriousness, date of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable) and investigator's assessment of intensity, and relationship to study treatment, study design or protocol-mandated procedures.

Information on worsening of intensity will be collected on a new AE form. If the AE lessens in intensity, no change in the severity is required to be reported.

Follow-up information on ongoing AEs obtained after the subject's EOS visit will not be collected in the eCRF.

9.3.2 Additional reporting procedure for serious adverse events

All SAEs must be reported by the investigator to the sponsor's Global Drug Safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs occurring after signing of the ICF up to 6 months after study treatment discontinuation must be recorded on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

The SAE forms must be sent to the sponsor's Global Drug Safety department (see contact details on the SAE form). The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The sponsor's Global Drug Safety personnel may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than that of the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

New SAEs occurring after the 6-month follow-up period must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.4 Pregnancy

Women must not become pregnant during the study and up to 6 months after study drug discontinuation. The investigator must explain and remind female subjects of the importance of using methods of contraception at every study visit.

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.4.1 Reporting of pregnancy

Any pregnancy occurring in a female subject after signing of the ICF and up to 6 months following study treatment discontinuation must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the sponsor Pregnancy form, which is faxed to the sponsor's Global Drug Safety department (see contact details provided on the Pregnancy form).

9.4.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion, and its outcome must be reported to the sponsor's Global Drug Safety department.

Any AE associated with the pregnancy occurring during the follow-up period after study drug discontinuation must be reported on separate AE forms in the eCRF up to 6 months following study treatment discontinuation (EOS).

Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.3.2.

9.4.3 Reporting of study treatment overdose, misuse, abuse and medication errors

Study treatment overdose (defined as higher than the dose of study treatment prescribed), and study treatment errors will be reported as an AE when associated with signs or symptoms.

In addition, study treatment errors must be documented in the study drug log of the eCRF.

Misuse and abuse of the study treatment will be reported as an AE/SAE as determined.

9.5 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and project-specific labs/examinations as required) is monitored and reviewed on a continuous basis by the sponsor (in charge of ensuring subjects' safety as well as data quality). The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values).

In addition, an IDMC is periodically monitoring the study data [see Section 3.4.1].

10 STATISTICAL METHODS

10.1 Analysis sets

10.1.1 Screened Analysis Set

The Screened analysis set (SCR) includes all subjects who entered Screening and have a subject identification number.

10.1.2 Full Analysis Set

The Full analysis set (FAS) includes all subjects randomized to double-blind study treatment at the start of TP1. Subjects will be analyzed based on their assigned study treatment.

10.1.3 Full Analysis Set – TP2

The Full analysis set TP2 (FAS-TP2) includes all subjects from the FAS who have been randomized to double-blind study treatment at the start of TP2. Subjects will be analyzed based on their assigned study treatment.

10.1.4 Per-Protocol Analysis Set (PPS)

The Per-protocol set (PPS) includes all subjects from the FAS without clinically important protocol deviations occurring during TP1 which could affect the analysis of the primary endpoint variable.

The precise reasons for excluding subjects from the PPS will be fully defined and documented in the statistical analysis plan (SAP) before breaking the randomization blind.

The PPS will only be defined for the period TP1.

10.1.5 Safety Analysis Set

The Safety analysis set (SAF) includes all subjects who received at least one dose of double-blind study treatment during TP1. Subjects will be analyzed based on the treatment received.

10.1.6 Safety Analysis Set – TP2

The Safety analysis set TP2 (SAF-TP2) includes all subjects from the SAF who received at least one dose of double-blind study treatment during TP2. Subjects will be analyzed based on the treatment received.

10.1.7 Echocardiography Set

The Echocardiography set (ECS) includes subjects who were assigned to the Echocardiography sub-study by IRT with at least one post-baseline echocardiography assessment. Subjects will be analyzed based on the treatment received.

10.1.8 PK Analysis Set

The PK analysis set (PKS) includes all randomized subjects who received at least one cenerimod dose, had at least one blood sample for PK evaluation collected after cenerimod initiation, had evaluable plasma concentrations, and did not deviate from the protocol in a way that might affect the evaluation of the PK endpoint. Subjects will be analyzed based on actual dose taken, not the randomized dose.

10.1.9 Usage of the analysis sets

The analyses of efficacy endpoints including baseline and disease characteristics from TP1 will be performed using the FAS and the PPS for sensitivity analyses. FAS-TP2 will be used for specific analyses only including TP2 data.

The FAS will be used for analyses which combine TP1 and TP2 data (and FU data when applicable).

The Safety Set will be used for the analysis of safety endpoints (including study treatment exposure) from TP1. SAF-TP2 will be used for specific analyses only including TP2 data.

The Safety Set will be used for analyses which combine TP1 and TP2 data (and FU data when applicable).

Subject data will be listed using the SCR, unless otherwise specified.

10.2 Variables

Detailed description of study efficacy and safety endpoints can be found in Section 6.

10.3 Description of statistical analyses

All available data for each subject will be used in all statistical analyses unless otherwise specified.

10.3.1 Overall testing strategy

The Type I error rate will be controlled for the testing of multiple null hypotheses associated with the primary and secondary endpoints and the four dose levels included in this study: 0.5, 1, 2, and 4 mg.

The four statistical null hypotheses associated with the primary efficacy endpoint are:

Change of mSLEDAI-2K from Baseline to Month 6:

$H1_{mSLEDAI\text{-}2K}$: $cenerimod_{0.5\ mg}$ – placebo = 0

$H2_{mSLEDAI\text{-}2K}$: $cenerimod_{1.0\ mg}$ – placebo = 0

$H3_{mSLEDAI\text{-}2K}$: $cenerimod_{2.0\ mg}$ – placebo = 0

$H4_{mSLEDAI\text{-}2K}$: $cenerimod_{4.0\ mg}$ – placebo = 0

These hypotheses represent the difference in mean change from baseline to Month 6 in mSLEDAI-2K between the four doses of cenerimod and placebo.

The eight statistical null hypotheses associated with the secondary efficacy endpoints are:

SRI-4

$H1_{SRI\text{-}4}$: $cenerimod_{0.5\ mg}$ / placebo = 1

$H2_{SRI\text{-}4}$: $cenerimod_{1.0\ mg}$ / placebo = 1

$H3_{SRI\text{-}4}$: $cenerimod_{2.0\ mg}$ / placebo = 1

$H4_{SRI\text{-}4}$: $cenerimod_{4.0\ mg}$ / placebo = 1

and BILAG

$H1_{BILAG}$: $cenerimod_{0.5\ mg}$ / placebo = 1

$H2_{BILAG}$: $cenerimod_{1.0\ mg}$ / placebo = 1

$H3_{BILAG}$: $cenerimod_{2.0\ mg}$ / placebo = 1

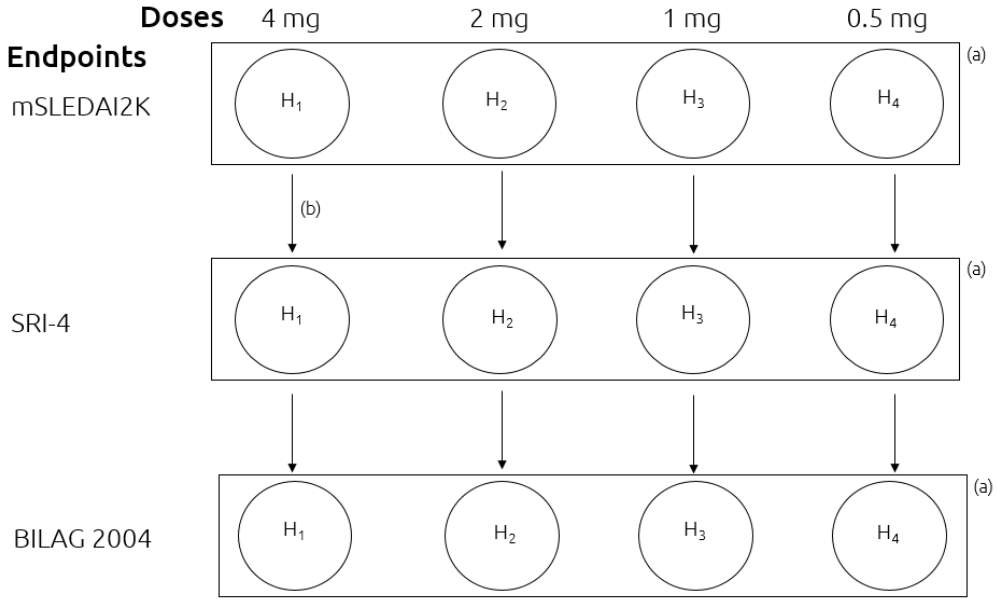
$H4_{BILAG}$: $cenerimod_{4.0\ mg}$ / placebo = 1

These eight hypotheses represent the odds ratios of the secondary endpoints SRI-4 and BILAG-2004 between the four doses of cenerimod and placebo.

Each null hypothesis will be tested against the alternative hypothesis that a difference exists between cenerimod and placebo, at a given dose, in mSLEDAI-2K, SRI-4, and BILAG-2004.

Within each primary and secondary endpoint analysis, the Hochberg procedure will be used to control the familywise error rate to ensure an overall two-sided Type I error rate of 5% for the four treatment group comparisons vs placebo. Further control of the study-wise error rate is conducted such that, for a given hypothesis to be rejected at a two-sided Type I error rate of 5%, the same dose-level hypothesis must have also been rejected for the previous endpoint(s), considering the above ordering of the endpoint hypotheses [see Figure 4].

Figure 4 Control of Type I error rate within each endpoint and treatment group



(a)The Hochberg procedure is used to control the familywise error rate for the four dose comparisons vs. placebo within each endpoint (grouped in rectangles).

(b) Further control of Type I error rate is ensured in a hierarchical manner for each dose comparison. To obtain statistical significance the p-value must be less than 0.05 for the hypothesis of interest and all previous hypotheses in the hierarchy (descending arrows).

1

10.3.2 Analysis of the primary efficacy variable

The primary efficacy variable, based on the mSLEDAI-2K [Section 6.1.1], is continuous in definition such that higher scores indicate more severe SLE disease.

10.3.2.1 Hypotheses

The hypothesis for the primary mSLEDAI-2K endpoint comparisons between the four doses of cenerimod and placebo are formulated in Section 10.3.1.

10.3.2.2 Primary statistical analysis

The primary statistical analysis will be performed on the FAS, according to the intent-to-treat approach.

The null hypotheses for the primary endpoint will be tested using a mixed model for repeated measures (MMRM) on all available changes from baseline in mSLEDAI-2K for post-baseline scores from Months 1 to 6. The following terms will be included in the model: baseline mSLEDAI-2K score, treatment group, month, treatment group by month interaction, baseline mSLEDAI-2K score by month interaction, and the single stratification factor OCS (from IRT). The stratification factor mSLEDAI-2K (from IRT) will not be included in the model as the continuous baseline value is already included. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject.

The treatment effect for each cenerimod dose vs placebo will be estimated from the Least Squares Mean (LSM) differences for each dose vs placebo at Month 6 and their corresponding 95% confidence intervals (CIs).

The hypothesis tests will be based on the associated p-values at the two-sided significance level of alpha of 5%, controlling for multiplicity using the Hochberg procedure as mentioned above.

10.3.2.3 Handling of missing data

Based on the Phase 2 study, AC-064A201, it is expected that 6% of subjects will have a missing mSLEDAI-2K result at Month 6. Missing data will not be imputed but will be handled by the MMRM assuming that the data are missing at random (MAR).

10.3.2.4 Sensitivity analyses for missing data

The impact of missing data on the MAR assumption from the MMRM will be assessed to check the robustness of the primary endpoint results and to ensure that missing data have not had an influence on the results.

An analysis based on a pattern-mixture model will be performed keeping a MAR imputation in the placebo arm while using a missing not at random (MNAR) approach in the cenerimod arms.

Multiple imputation analyses will be performed assuming a monotone missing data pattern, such that, if data are missing at a given visit, they are assumed to be missing at all remaining visits. Any non-monotone missing data, i.e., missing values which occur between non-missing values will first be imputed under MAR. This is considered reasonable because the proportion of non-monotone missing data is expected to be low.

Two control-based multiple imputation analyses will then be performed under MNAR using both Jump to Reference (J2R) and Copy Reference (CR) approaches [Carpenter 2013]. In these approaches, multiple imputation of missing values will be performed based on the assumption that subjects with missing data in the cenerimod groups follow the trajectory of the placebo arm, conditional on subject data available prior to discontinuation (baseline mSLEDAI-2K for the J2R approach; baseline as well as available post-baseline mSLEDAI-2K for the CR approach).

10.3.2.5 Supportive analyses

A series of additional analyses based on the mSLEDAI-2K are presented below and will support the primary endpoint results by analyzing the primary endpoint variable using various other methods and assumptions.

Impact of the use of different analysis sets

The primary endpoint analysis will be repeated on the PPS in order to assess the impact of important protocol deviations on the assessment of the primary endpoint. This analysis will address the issue of the lack of adherence to the protocol and lack of compliance to study treatment.

Examination of treatment effect over time

A supportive analysis using the above MMRM will be conducted to characterize the treatment effect over time such that the monthly changes from baseline in mSLEDAI-2K will be analyzed on all available data from all visits from Month 1 to Month 6 without replacement of missing values.

The model will enable:

- Estimation of the treatment differences (cenerimod dose vs placebo) in the mean changes from baseline to Month 6 along with the corresponding two-sided 95% CI.
- Characterization of the patterns of change over time in the mean change from baseline in mSLEDAI-2K by treatment group.
- No multiplicity adjustment is applied as this analysis is descriptive in nature.

Complete case analysis

To assess the impact of missing data on the primary endpoint analysis the MMRM analysis of the primary endpoint will be conducted on the subset of subjects with the complete monthly score data for Months 1 to 6.

Dose-response analysis

As a supportive analysis, the overall dose-response will be assessed using modeling and multiple comparison procedures. Details of this analysis will be described in the SAP.

10.3.2.6 Subgroup analyses

The aim of the subgroup analyses is to explore the consistency of treatment effect in relevant subgroups:

- Daily dose of OCS (< 7.5 mg or ≥ 7.5 mg prednisone equivalent) from IRT system
- mSLEDAI-2K (< 10 or ≥ 10) from IRT system
- Sex (male/female)
- Geographical region (Europe, US, Rest of World)
- Age (< 65 years vs ≥ 65 years) at Screening
- Belimumab treatment status ("treated" vs "not treated") at Screening
- Race (white, American Indian, Asian, and black)

Results of the subgroup analyses will be displayed in a forest plot and will include:

- An estimate of the treatment effect for each cenerimod dose vs placebo with corresponding 95% CI for each level of the subgroup. It will be calculated as the LSM difference vs placebo at Month 6 obtained separately for each subgroup level.
- A vertical reference line displayed at the level of the overall treatment effect.
- For the analyses of the OCS and mSLEDAI-2K subgroups, the corresponding subgroup will not be included as a stratification factor in the MMRM.

10.3.3 Analysis of the secondary efficacy variables

10.3.3.1 Response at Month 6 based on SRI-4

A repeated measurement generalized linear model will be fitted with the secondary endpoint SRI-4 as response (from Month 1 to Month 6). The model will include the treatment group, month, the treatment group by month interaction, and will be stratified by the OCS and mSLEDAI-2K stratification variables (from IRT).

The odds ratios and corresponding 95% CI for each treatment group comparison vs placebo will be provided along with the p-values from the Wald test.

10.3.3.2 Response at Month 6 based on BILAG-2004

The analysis will be performed based on the same repeated measurement model as described in Section 10.3.3.1.

10.3.4 Analysis of other efficacy variables

The analyses of all other efficacy variables will be described in detail in the SAP. Other efficacy endpoints will be analyzed at each relevant time point [see Section 6.1.3].

10.3.5 Analysis of the safety variables

The Safety Set will be used to perform all safety analyses.

Safety analysis may be split by treatment period [defined in Section 3.1.1.2]. This will be further detailed in the SAP.

If not otherwise stated, only treatment-emergent safety data will be considered in tables and figures. All safety data will be included in outputs, with flags for safety data not considered to be treatment-emergent.

10.3.5.1 Adverse events

10.3.5.1.1 Treatment-emergent adverse events and serious adverse events

Treatment-emergent AEs and SAEs will be tabulated by study treatment, system organ class (SOC), and preferred terms within each SOC: the number and percentage of subjects who experienced at least one (S)AE, at least one (S)AE within each SOC and at least one (S)AE within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term. (S)AEs will also be tabulated by maximum intensity and relationship to cenerimod dose or placebo.

10.3.5.1.2 Adverse events leading to premature discontinuation of study drug

(S)AEs leading to premature discontinuation of study drug will be summarized in a similar manner as that described in Section 10.3.5.1.1.

10.3.5.2 Vital signs

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute changes from baseline in HR, SBP, DBP, and body weight.

Treatment-emergent notable BP abnormalities will also be summarized descriptively.

10.3.5.3 Electrocardiography

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute changes from baseline in numeric 12-lead ECG values (HR, PR, QRS, QT, QTcB, QTcF).

Changes in 12-lead ECG variables (HR, PR, QRS, QT, QTcB, QTcF) from pre-dose to post-dose will be summarized.

Treatment-emergent notable abnormalities for 12-lead ECG variables (HR, PR, QRS, QT, QTcB, QTcF) will be summarized at all visits and pre-/post-dose time points.

In addition, summaries of treatment-emergent ECG abnormal findings that were not present before first study treatment intake (using data from the ECG provider) will be provided.

10.3.5.4 Laboratory data

10.3.5.4.1 Changes from baseline in laboratory variables

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute and percentage changes from baseline for laboratory tests (hematology, blood chemistry, urinalysis).

Data will be displayed in SI units whenever possible and graphical approaches will be applied for certain variables.

10.3.5.4.2 Treatment-emergent marked laboratory abnormalities

Laboratory abnormalities will be summarized descriptively by study treatment as categorical variables.

10.3.6 Analysis of other variables

A full description of all other analyses will be described in the SAP.

10.4 Study analyses

Three study analyses will be performed: the Month-6 analysis, the Month-12 analysis and the final EOS analysis.

10.4.1 Month-6 analysis

Month-6 analysis will be performed when all randomized subjects have completed TP1 or discontinued the study, using all data collected up to that time.

All analyses planned in the SAP will be performed including data beyond the Month-6 visit. This includes the analyses of the confirmatory efficacy endpoints described in Sections 10.3.2 and 10.3.3.

Prior to the database lock for Month-6 analysis, a full data cleaning will be performed. Thereafter, the data used for Month-6 analysis will not change and Type I error control will be maintained, as described in Section 10.3.1.

10.4.2 Month-12 analysis

Month-12 analysis will be performed when all randomized subjects have completed TP2 or discontinued the study, using all data collected up to that time.

All analyses planned in the SAP and including data beyond the Month-6 visit will be performed, including data beyond the Month-12 visit (i.e., analyses on TP2 data or on combined TP1 and TP2 [and FU when applicable] data). Analyses on TP1 data only, including analyses of the confirmatory efficacy endpoints, will not be repeated as the data used for Month-6 analysis will have been locked [see section 10.4.1]. Prior to the database lock for Month-12 analysis, a full data cleaning will be performed.

10.4.3 Final EOS analysis

Final EOS analysis will be performed when all randomized subjects have completed the posttreatment follow-up period or discontinued the study.

All analyses planned in the SAP will be performed, including all data collected.

10.5 Sample size

Assumptions used to calculate power are provided in Table 6.

Table 6 Statistical assumptions for endpoints at Month 6

Continuous endpoints	**Expected mean difference vs placebo**	**SD per treatment group**	**Effect size (mean/SD)**
mSLEDAI-2K	[redacted]	[redacted]	[redacted]
Response endpoint	**Placebo response rate**		**Expected difference vs placebo**
SRI-4	40%		20%
BILAG-2004	40%		20%

Effect size calculated as [redacted]
BILAG = British Isles Lupus Assessment Group-2004; mSLEDAI-2K = modified Systemic Lupus Erythematosus Disease Activity Index-2000; SD = standard deviation; SRI-4 = Systemic Lupus Erythematosus Responder Index 4.

Assumptions for the expected mean difference and corresponding between-subject standard deviation for the mSLEDAI-2K primary endpoint are based on the recently completed 12-week Phase 2 study, AC-064A201 conducted in SLE subjects receiving 0.5, 1, 2, or 4 mg of cenerimod or placebo. The resulting effect size of [redacted] is in line with that seen at higher doses of cenerimod at 12 weeks in AC-064A201. Such a difference is greater

than that seen in other treatments approved for the treatment of SLE [GlaxoSmithKline 2018].

Based on the above effect size assumption for the continuous mSLEDAI-2K primary endpoint, 10,000 simulations using analysis of covariance to test four doses vs placebo indicate that 325 subjects (65 per group) will provide 89.6% power at a two-sided 5% level of significance to reject at least one of the four treatment hypotheses.

Under the same conditions, for the response based secondary endpoints, this sample size provides 71.4% power to reject at least one of the four treatment hypotheses.

All power calculations provided account for multiplicity of the four comparisons vs placebo, using the Hochberg procedure.

With an increasing number of null hypotheses being tested the power to reject these hypotheses decreases, as shown in Table 7.

Table 7 Effect of testing multiple null hypotheses on power

Endpoint	Power (%) related to the number of hypotheses rejected			
	At least one	2 or more	3 or more	All 4
Primary	89.6	79.9	70.7	58.3
Secondary	71.4	57.4	45.2	29.8

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timelines of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture using the Rave system provided by Medidata Solutions, Inc., a web-based tool. The investigator and site staff will be trained to enter and edit the data via a secure network, with secure access features (username, password and identification – an electronic password system). A complete electronic audit trail will be maintained.

Physician-reported entries recorded in the PGA are considered source data.

Subject Screening and Enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who

fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to the sponsor and any vendors or CROs, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other personal identifier. The investigator/delegate must keep a subject identification code list at the site, showing the screening/randomization number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to the sponsor, any vendor or CROs, and must be kept in strict confidence by the investigator/delegate.

11.3 Database management and quality control

eCRFs will be used for all subjects. The investigator will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any timepoint during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by the sponsor on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of Health Authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database lock.

Laboratory samples, standard biomarkers, 12-lead ECG, 24-hour Holter ECG, echocardiography and spirometry will be processed through a central laboratory or vendor and the results of the randomized subjects will be electronically sent to the sponsor at pre-specified intervals with a final transfer prior to database lock. During the course of the study, the site staff and sponsor representatives can access the data in a view-only mode on the central server of the respective vendor.

AEs and medical history are coded according to the latest MedDRA™ version used by the sponsor or its delegate. Medications are coded according to the latest WHO Drug Dictionary version used by the sponsor or its delegate.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made as described in the appropriate sponsor QS docs. After database lock, the investigator will have read-only access to the site eCRF subject data, until receipt of an electronic copy of the site eCRFs (including the audit trail) on electronic media.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

The sponsor and the investigators will ensure that the study is conducted in full compliance with ICH GCP guidelines, the principles of the 'Declaration of Helsinki' and with the laws and regulations of the country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB/IEC. Approval from the committee/board must be obtained before starting the study and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations.

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation. If a study staff member was present during a meeting, it must be clear that this person did not vote.

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason without having to provide any justification.

The ICF will be provided in the country local language(s).

Site personnel authorized (according to local regulations) to participate in the consent process and/or to obtain consent from the subject and/or legal representative will be listed on a Sponsor Delegation of Authority form. A study physician must always be involved in the consent process.

The subject and/or legal representative and authorized site personnel must sign, personally date and time (if the first study-mandated procedure was performed on the same day informed consent was obtained, and as per local regulations) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) when the subject was first introduced to the sponsor's clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., subject family member), copy of the signed ICF given to the subject / legal representative.

In the event that the site would like to recruit a subject who would be considered as vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject rights are respected and the consent obtained is legally valid. The sponsor, the regulatory authorities (if applicable) and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before subjects are recruited.

12.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform the sponsor or its representative in a timely manner. The investigator/delegate must document and explain

any deviation from the approved protocol. Deviations considered to be a violation of ICH GCP must be reported to IEC/IRB and regulatory authorities according to the sponsor or (overruling) local requirements.

All protocol deviations will be reported in the Clinical Study Report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. A protocol amendment must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

12.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring and available when needed.

These records are to be classified into two different categories of documents: the investigator's file and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with the sponsor's requirements (e.g., as specified in the clinical study agreement) and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed

for verification by the CRA. The printouts must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject, regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per the sponsor's instructions. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies, therefore the site cannot be selected for the clinical study.

12.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after all the required approvals are obtained and the required essential study documents are approved by the sponsor. The study treatment will be shipped to the site upon approval of the required essential documents.

The principal investigator must ensure that all site personnel involved in the study will be present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the initiation visit.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the principal investigator and filed in the ISF.

During the study, the CRA will contact and visit the investigational site regularly and, on request, must be permitted to have access to trial facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered in the eCRFs and other protocol-related documents. The sponsor's monitoring standards require full verification that informed consent has been provided and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The principal investigator must ensure that the eCRF is completed after a subject's visit to the site and that all requested subject files (e.g., ICFs, medical notes/charts, other

documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site and when there are no more active subjects and after all study data have been accepted by medical review and all follow-up issues have been resolved. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database lock at the discretion of the sponsor.

12.9 Investigator Site File

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH GCP section 8.

The ISF will include a table of contents listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH GCP as well as instructions from the sponsor. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the principal investigator must inform the sponsor immediately.

If the principal investigator changes, or if the site relocates, the CRA must be notified as soon as possible.

12.10 Audit

The sponsor’s Global Quality Management representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator’s adherence to ICH GCP, the protocol, and applicable regulations; adherence to the sponsor’s requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

12.11 Inspections

Health Authorities and/or IECs/IRBs may also wish to conduct an inspection of the sponsor's clinical study (during the study or after its completion).

Should an inspection be requested by a Health Authority and/or an IEC/IRB, the investigator must inform the sponsor immediately (usually via the CRA) that such a request has been made.

The investigator and staff must cooperate with the inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

12.12 Reporting of study results and publication

The sponsor will post the key elements of this protocol and the summary of results within the required timelines on publicly accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by the sponsor's representatives and the Coordinating Investigator.

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria and be based on:

- Substantial contributions to: the conception or design of the study, or the acquisition, analysis or interpretation of data; and
- Drafting of the publication or critical review for important intellectual content; and
- Providing final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 30 days prior to submission for publication or presentation.

Upon review, the sponsor may provide comments and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

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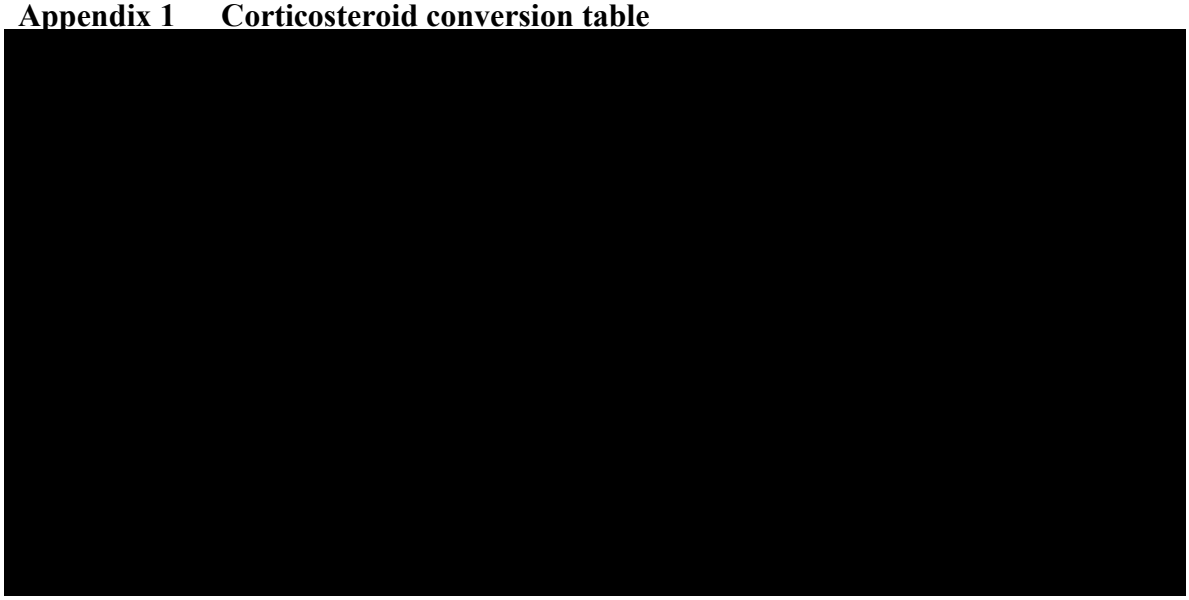
14 APPENDICES

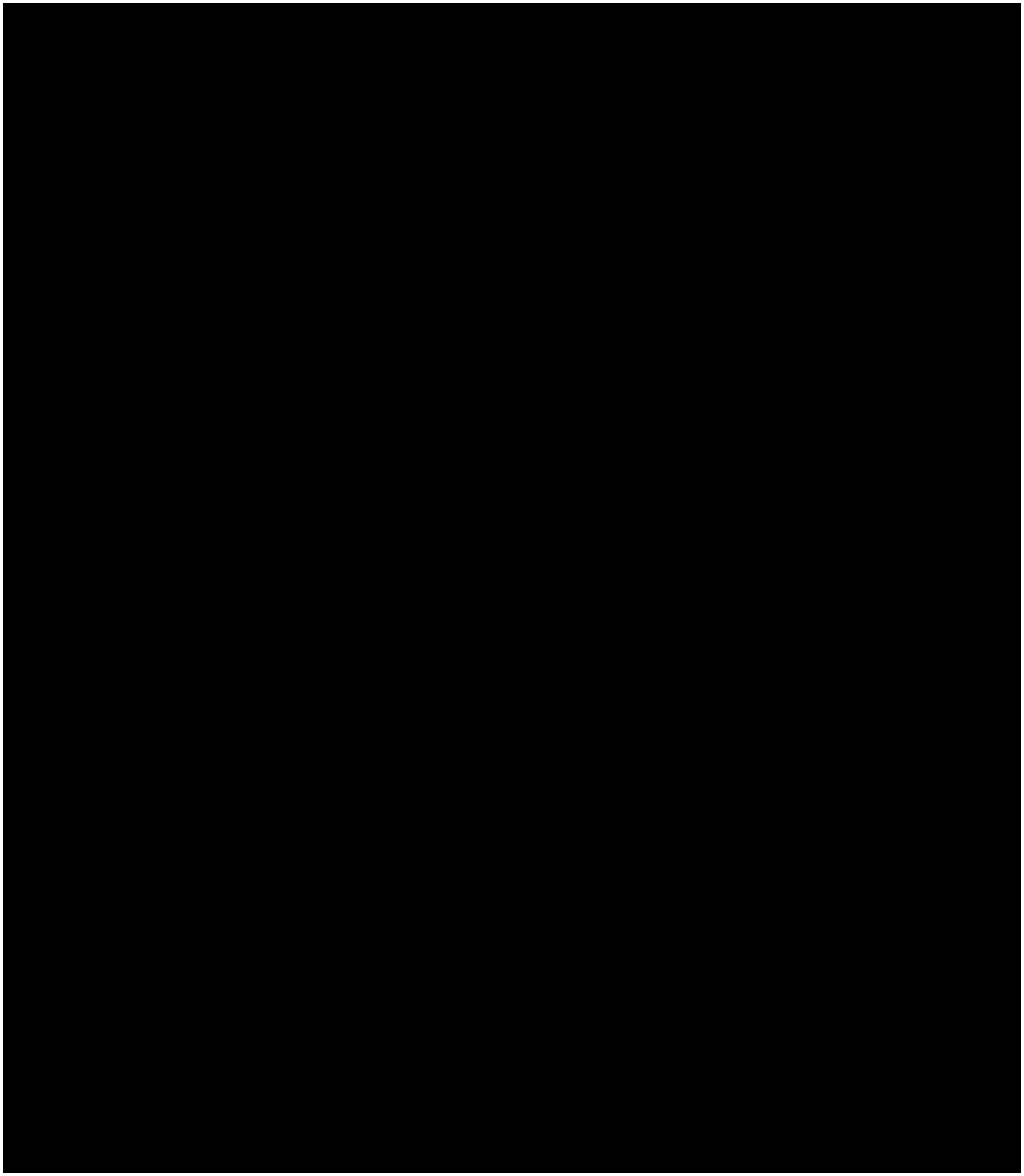
Appendix 1 Corticosteroid conversion table



[Dixon 1991, Meikle 1977, Webb 2005]

Appendix 2 American College of Rheumatology (ACR) Criteria for SLE

The ACR Criteria for the Classification of SLE [Tan 1982, Hochberg 1997].



Appendix 3 Forbidden anti-arrhythmic or heart rate lowering medications

The use of the following drugs at any time during the study is prohibited [see Section 5.2.4]:

- Adenosine
- Acebutolol
- Ajmaline
- Amiodarone
- Aprinidine
- Atenolol
- Azimilide
- Bepridil
- Bisoprolol
- Betaxolol
- Bretylium
- Bunaftine
- Cibenzoline
- Diltiazem
- Digoxin
- Disopyramide
- Dofetilide
- Dronedarone
- Encainide
- Esmolol
- Flecainide
- Ibutilide
- Ivabradine
- Lidocaine
- Lorajmine
- Lorcainide
- Metoprolol
- Mexiletine
- Moracizine
- Nadolol
- Phenytoin
- Pilocarpin
- Prajmalium
- Procainamide
- Propafenone
- Propranolol
- Quinidine
- Sotalol
- Sparteine
- Tedisamil
- Timolol
- Tocainide
- Verapamil
- Vernakalant

If, in the judgment of the investigator, it is in the best interests of the subject to receive any of the drugs listed above, study drug must be permanently discontinued.

Appendix 4 Forbidden medications with risk of torsade de pointes

The use of the following QT-prolonging medications with a known risk of torsade de pointes at any time during the study is prohibited [see Section 5.2.4]:

- Arsenic trioxide
- Astemizole
- Anagrelide
- Azithromycin
- Bepridil
- Chlorpromazine
- Cisapride
- Citalopram
- Clarithromycin
- Cocaine
- Domperidone
- Dronedarone
- Droperidol
- Erythromycin
- Escitalopram
- Flecainide
- Halofantrine
- Haloperidol
- Levomethadyl
- Mesoridazine
- Methadone
- Moxifloxacin
- Ondansetron
- Pentamidine
- Pimozide
- Probucol
- Sevoflurane
- Sparfloxacin
- Sulpiride
- Terfenadine
- Thioridazine
- Vandetanib

If, in the judgment of the investigator, it is in the best interests of the subject to receive any of the drugs listed above, study treatment must be permanently discontinued.

Appendix 5 Adverse events of special interest

AESIs will include the anticipated risks of treatment with cenerimod or the known class effects or the events that may be related to SLE comorbidities (e.g., cardiovascular AEs) and will address the following safety areas:

- Effect on HR and rhythm-related AEs
- Hypotension-related AEs
- Hypertension-related AEs
- Hepatobiliary disorders / liver enzyme abnormality-related AEs
- Pulmonary-related AEs
- Eye disorder-related AEs
- Infection-related AEs
- Skin malignancy-related AEs
- Malignancy- (non-skin) related AEs
- Cardiovascular-related AEs

A list of AESIs (MedDRA preferred terms) will be defined in the SAP.

Appendix 6 Criteria for discharge from monitored setting on Day 1 and on the first day of re-initiation following treatment interruptions

At the time of discharge (i.e., 6 h post-dose) on Day 1 and on the first day of re-initiation of study treatment following drug interruptions, the following criteria must be met:

- ECG-derived resting HR > 45 bpm; and if HR < 50 bpm it must not be the lowest value post-dose;
- SBP ≥ 90 mmHg;
  - For subjects with baseline pre-dose SBP < 90 mmHg: decrease in SBP of ≤ 5 mmHg from pre-dose SBP value;
- QTcF < 500 ms (females) or < 480 ms (males);
- No persistent ECG abnormality (e.g., AV block second degree or higher) or ongoing AE requiring continued hospitalization.

Should the subject not meet the criteria for discharge 6 h post-dose, he/she will be monitored until 12 h post-dose with 12-lead ECG and BP measurements performed hourly and may be discharged after any of the hourly measurements, provided that discharge criteria are met until 12 h post-dose. If at 12 h post-dose the subject does not meet discharge criteria, he/she must be permanently discontinued from study treatment. Subjects who are permanently discontinued should not be discharged from the monitored setting before vital signs return to near baseline values and until there are no persistent ECG abnormalities (e.g., AV block second degree or higher) or ongoing AE requiring continued hospitalization, or until a diagnosis is established.

Discharge criteria will be recorded in the eCRF.

Appendix 7 Notable abnormalities for ECG, BP and laboratory variables

Notable abnormalities for ECG and BP

Notable abnormalities for ECG and BP that are related to the potential effects of cenerimod will address the following variables:

- Morphological ECG findings (defined as any abnormal finding not present prior to start of treatment)
- HR outliers (bpm), based on ECG
- PR interval (ms)
- QT/QTc interval (ms), based on Bazett's or Fridericia's formula
- BP (mmHg)

The definition of the abnormal values to be reported will be described in the SAP.

Laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for "low", H for "high".

The term "marked abnormality" describes laboratory values above or below the thresholds, with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor in order to flag and/or communicate abnormal laboratory results from the central laboratory to the investigators, and for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events (CTCAE) grading system (2017 v5.0) and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known PD effect of the study drugs (e.g., LLL threshold for lymphocytes) [CTCAE 2017].

The term ALERT here corresponds to the protocol-defined test result threshold requiring action from the investigator as described in the protocol (e.g., repeat the test, interrupt or discontinue the study drug) and should not be confused with the term "call alert" used by the central laboratory for laboratory results, which will be communicated to the investigator. Not all ALERTs listed in this table will be "call alerts" from the central laboratory and vice versa.

PLEASE NOTE: Thresholds for abnormality of level L or H are not provided in this appendix but will be provided in the laboratory manual.

Thresholds for marked laboratory abnormalities for cenerimod

Parameter	LL	LLL	HH	HHH
Hemoglobin	< 100 g/L (< 10 g/dL; < 6.2 mmol/L)	< 80 g/L (< 8 g/dL; < 4.9 mmol/L)	Increase in > 20 g/L above ULN or above baseline (if baseline is above ULN)	Increase in > 40 g/L above ULN or above baseline (if baseline is above ULN)
MCH	ND	ND	ND	ND
MCV	ND	ND	ND	ND
MCHC	ND	ND	ND	ND
Hematocrit	< 28% (female) < 32% (male)	< 20%	> 60% (male) > 55% (female)	> 65%
Platelet count	< 75 × 10 e9/L (< 75,000/mm^3)	< 50.0 × 10 e9/L (< 50,000/mm^3)	> 600 × 10 e9/L	> 999 × 10 e9/L
RBC count	ND	ND	ND	ND
WBC count	ND	< 1.9 × 10e9/L	> 20.0 × 10e9/L (> 20 000/mm^3)	CTCAE (grade 3) > 100.0 × 10e9/L (>100,000/mm^3)
Lymphocyte	ND	< 0.2 × 10e9/L (< 200/mm^3) **ALERT*** **< 0.2 × 10e9/L (< 200/mm^3)**	> 4.0 × 10e9/L (> 4000/mm^3)	≥ 8 × 10e9/L (> 8000/mm^3)
Neutrophils	< 1.5 × 10e9/L (< 1500/mm^3)	< 1.0 × 10e9/L (< 1000/mm^3)	ND	ND
Eosinophils	ND	ND	> 5.0 × 10 e9/L or > 5% (> 5000 cells/mm^3)	ND
Monocytes	ND	ND	ND	ND
Basophils	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells	ND	ND	> 90%	> 95%
AST	ND	ND	≥ 3 ULN (U/L) **ALERT** **≥ 3 ULN**	≥ 5 ULN (U/L) **ALERT** **≥ 5 ULN** **≥ 8 ULN**
ALT	ND	ND	≥ 3 ULN (U/L) **ALERT** **≥ 3 ULN**	≥ 5 ULN (U/L) **ALERT** **≥ 5 ULN** **≥ 8 ULN**
Total bilirubin	ND	ND	≥ 2 ULN (umol/L) **ALERT** **≥ 2 ULN combined with ALT or AST ≥ 3 ULN**	≥ 5 ULN (umol/L)

Parameter	LL	LLL	HH	HHH
Alkaline Phosphatase	ND	ND	> 2.5 ULN (U/L)	> 5 ULN (U/L)
INR	ND	ND	≥ 1.5** or ≥ 1.5 times above baseline if on anticoagulation ALERT ≥ 1.5 combined with ALT or AST ≥ 3 ULN	≥ 2.5** or ≥ 2.5 times above baseline if on anticoagulation
aPTT	ND	ND	> 1.5–2.5 × ULN	> 2.5 × ULN
Lactate dehydrogenase	ND	ND	ND	ND
Creatinine	ND	ND	> 1.5 ULN (umol/L) or > 1.5 × baseline	> 3 ULN (umol/L) or > 3 × baseline
Creatinine Clearance (eGFR)	< 60 ml/min/1.73m^2	< 30 ml/min/1.73m^2	ND	ND
Urea	ND	ND	> 2.5 ULN (mmol/L)	> 5 ULN (mmol/L)
Uric acid	ND	ND	> 590 µmol/L (> 10 mg/dL)	> 720 µmol/L (> 12 mg/dL)
Proteinuria	ND	ND	≥ 1.0 g/24 h 2+ and 3+ proteinuria	≥ 3.5 g/24 h 4+ proteinuria
Protein/creatinine ratio	ND	ND	> 100 mg/mmol***	> 300 mg/mmol***
Albumin	< 30 (g/L)	< 20 (g/L)	ND	ND
Protein total	ND	ND	ND	ND
C-reactive protein	ND	ND	ND	ND
Glucose (non-diabetic Fasting)	< 3.0 (mmol/L) (< 55 mg/dL)	< 2.2 (mmol/L) (< 40 mg/dL)	> 8.9 (mmol/L) (> 160 mg/dL)	> 13.9 (mmol/L) (> 250 mg/dL)
Potassium	< 3.2 (mmol/L)	< 3.0 (mmol/L)	> 5.5 (mmol/L)	> 6.0 (mmol/L)
Sodium	ND	< 130 (mmol/L) (< 130 mEq/L)	> 150 (mmol/L) (> 150 mEq/L)	> 155 (mmol/L) (> 155 mEq/L)
Calcium (corrected for albumin)	< 2.0 (mmol/L) (< 8.0 mg/dL)	< 1.75 (mmol/L) (< 7.0 mg/dL)	> 2.9 (mmol/L) (> 11.5 mg/dL)	> 3.1 (mmol/L) (> 12.5 mg/dL)
Chloride	ND	ND	ND	ND
Triglyceride	ND	ND	> 3.42 (mmol/L)	> 11.4 (mmol/L)
Cholesterol	ND	ND	> 7.75 (mmol/L)	> 12.92 (mmol/L)

Parameter	LL	LLL	HH	HHH
Fibrinogen	< 0.75–0.5 LLN or 25– < 50% decrease from baseline	< 0.25 LLN or > 75% decrease from baseline or absolute value < 50 mg/dL	ND	ND
IgG	ND	ND	ND	ND
IgM	ND	ND	ND	ND
IgA	ND	ND	ND	ND
ANA	ND	ND	ND	ND
Anti-dsDNA	ND	ND	ND	ND
C3	ND	ND	ND	ND
C4	ND	ND	ND	ND
Anti-Sm	ND	ND	ND	ND
Anti-ribosomal P	ND	ND	ND	ND
Anti-cardiolipin IgA	ND	ND	ND	ND
Anti-cardiolipin IgG	ND	ND	ND	ND
Anti-cardiolipin IgM	ND	ND	ND	ND
Serum pregnancy test	ND	ND	ND	Positive **ALERT: Positive**

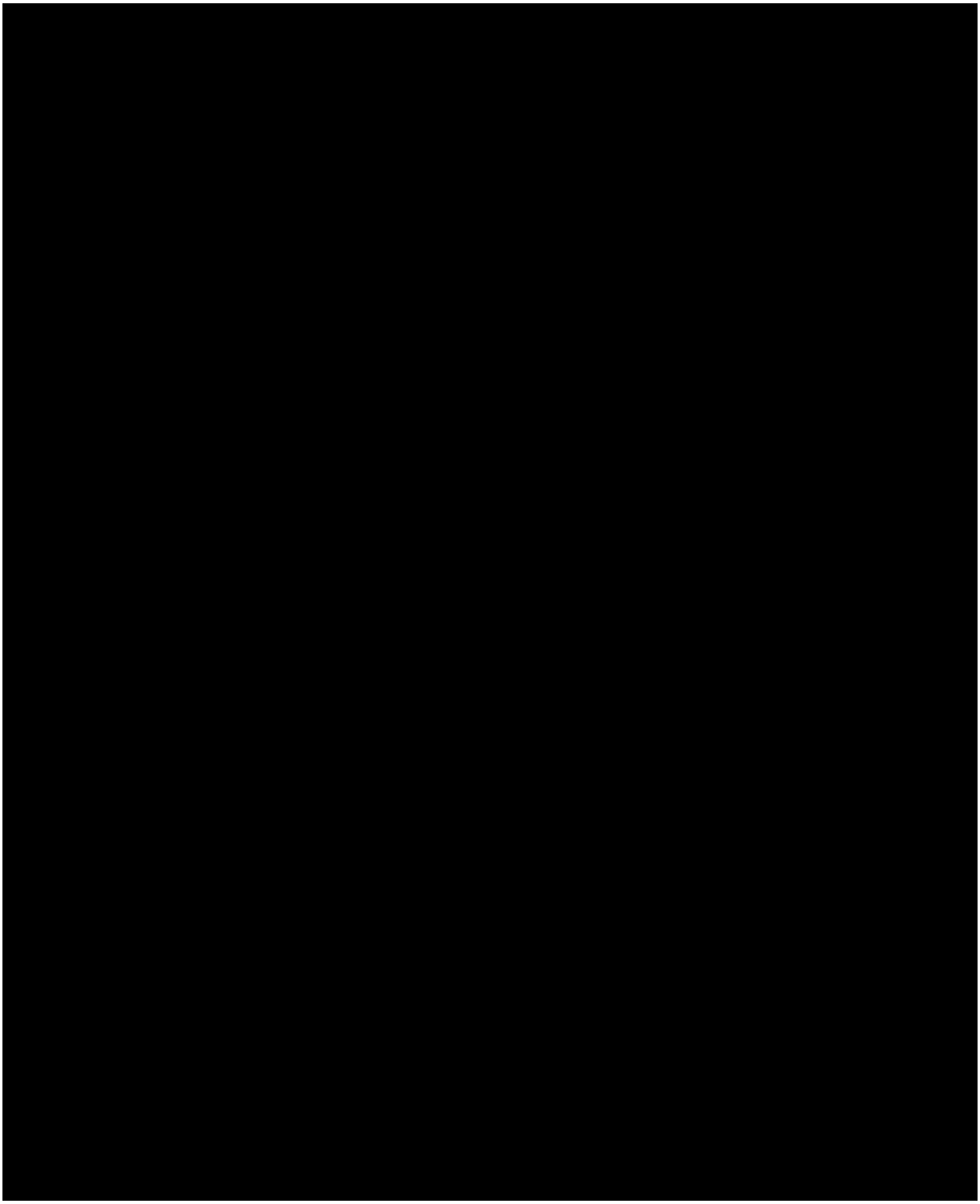
* If lymphocyte count < 800 cells/µl at EOS visit, an ALERT will be sent.
** HH and HHH based on CTCAE 2017 v5.0 [CTCAE 2017]. However, an ALERT will be sent when INR ≥ 1.5 based on the guidance for monitoring liver test abnormalities from Food and Drug Administration (FDA) [FDA 2009].
*** Source for protein/creatinine ratio thresholds: http://www renal.org/information-resources/the-uk-eckd-guide/proteinuria#sthash.jdT5cPIP.dpbs.
ALT = alanine aminotransferase; ANA = anti-nuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; anti-Sm = anti-Smith; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; eGFR = estimated glomerular filtration rate; EOS = End-of-Study; Ig = immunoglobulin; INR = international normalized ratio; LLN = lower limit of normal; MCH = mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; ND = not defined; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.

Appendix 8 American College of Cardiology / American Heart Association / American College of Physicians Training Requirements for Performance and Interpretation of Adult Transthoracic Echocardiography

[redacted]

Source: [Quiñones 2003].

Appendix 9 SLEDAI-2K: Data Collection Sheet



Note that leukopenia will not be evaluated for reasons of functional blinding [see Section 5.1.3.2] and CH50 will not assessed by central laboratory.

Hematuria, proteinuria and pyuria are evaluated by dipstick at each visit assessing SLEDAI-2K. If the dipstick results are positive, urine sample will be further analyzed as clinically indicated (i.e., microscopic analysis of WBC, RBC, casts, and protein quantification).

Appendix 10 Physician's Global Assessment Visual Analog Scale

ONLY ORIGINAL SHEETS DISTRIBUTED BY THE SPONSOR MUST BE USED

Source: [Petri 2005].

Appendix 11 BILAG-2004 INDEX

[redacted]

Appendix 12 SLE Flare Index

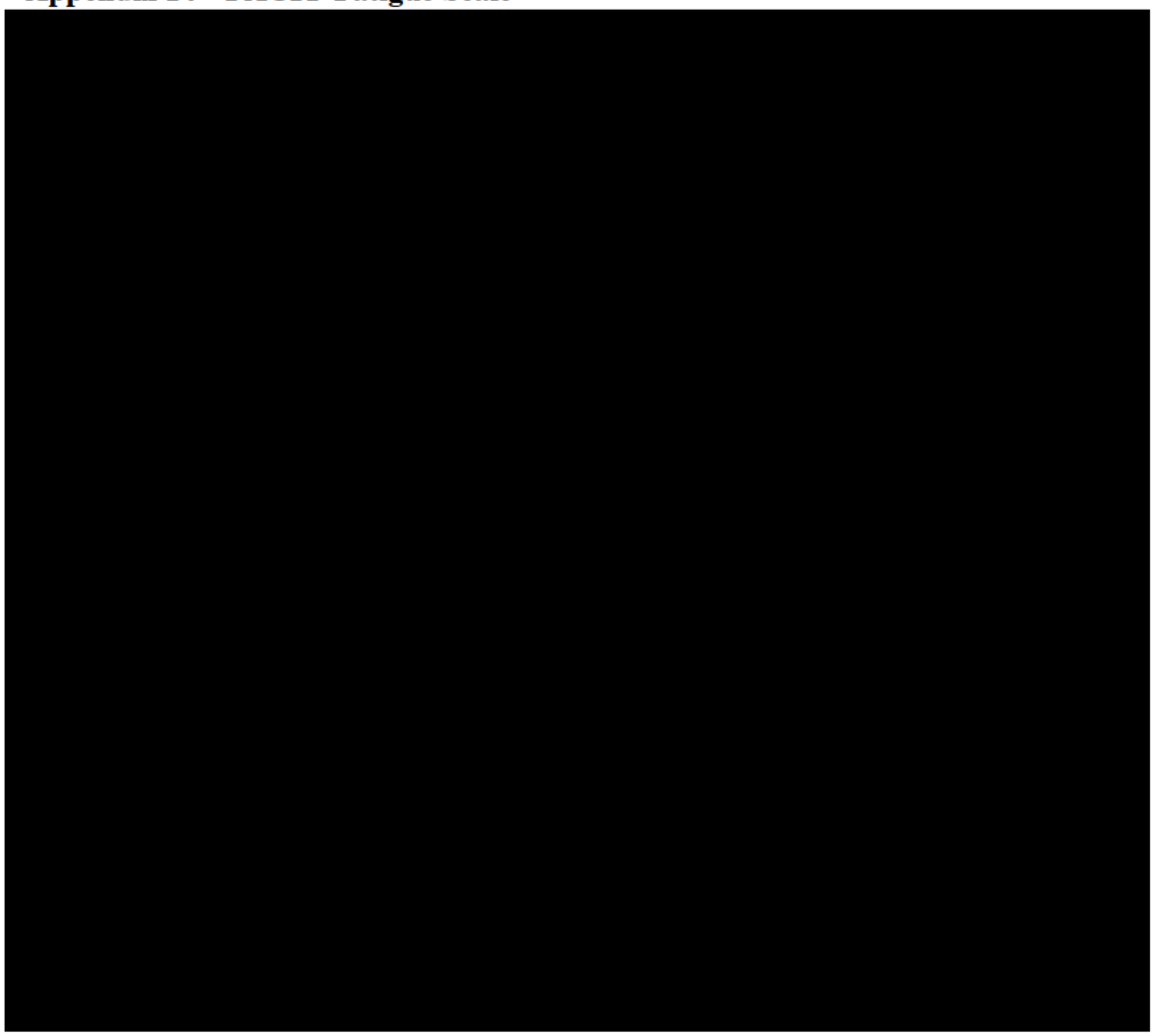
Source: [Petri 2005].

Appendix 13 SF-36v2™

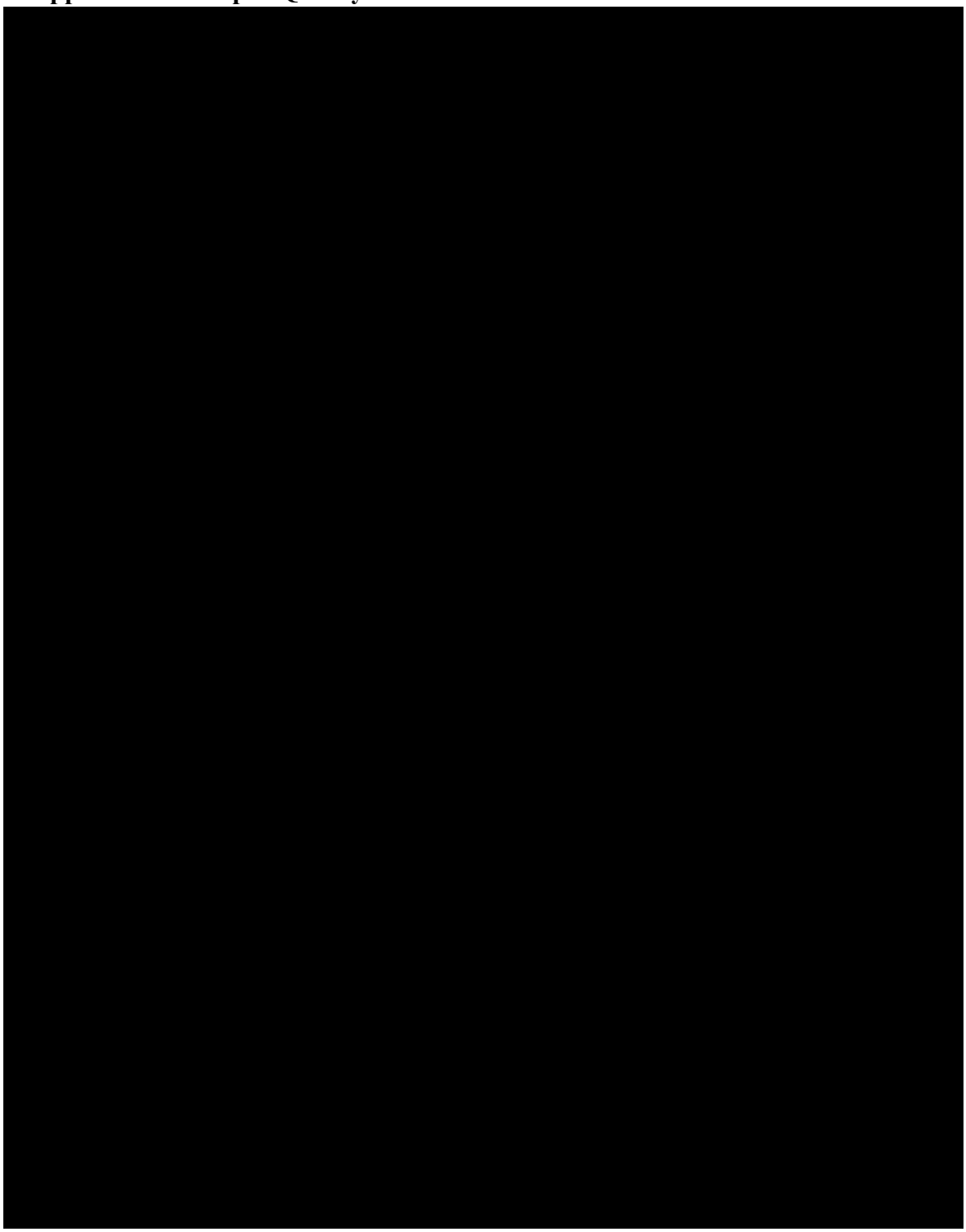
United States (English) SF-36v2™ Standard

Your Health and Well-Being

Appendix 14 FACIT-Fatigue Scale



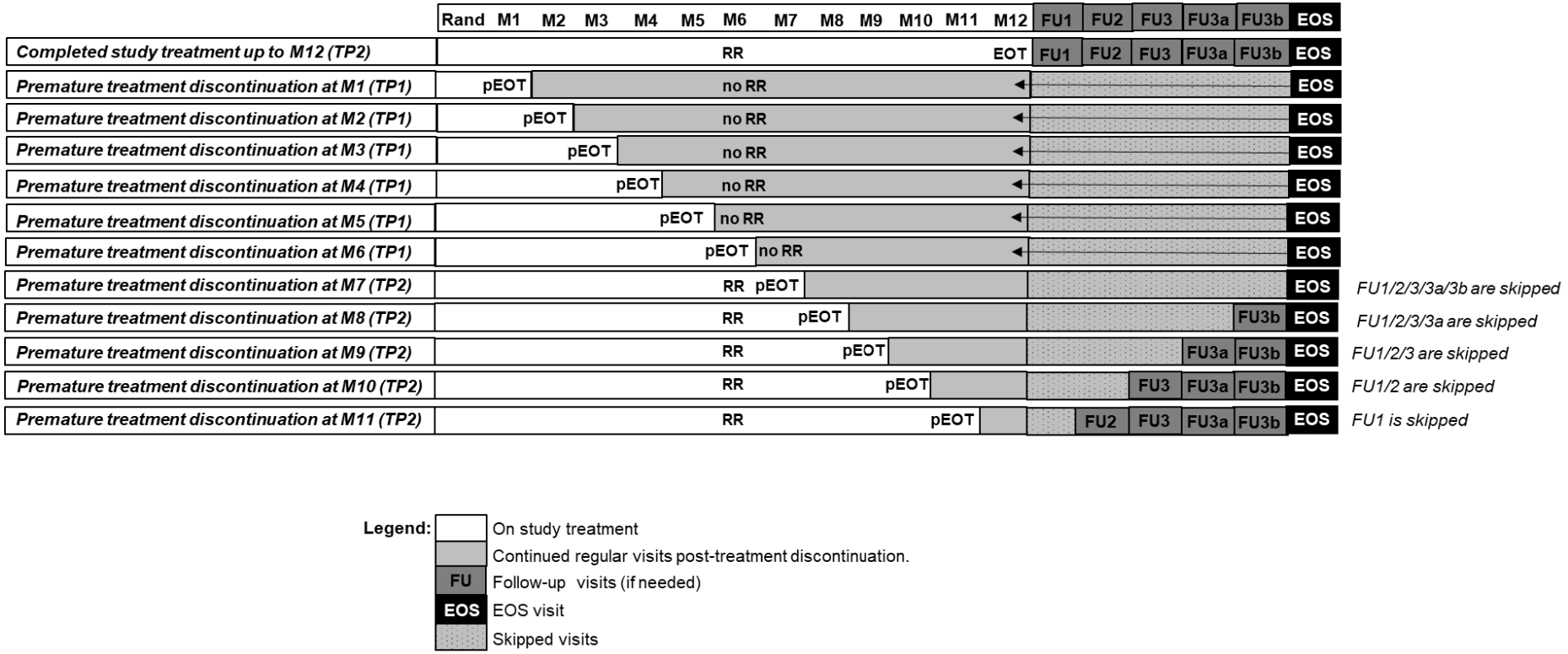
Appendix 15 Lupus Quality of Life



Appendix 16 Patient Global Impression of Severity – Fatigue

Appendix 17 Patient Global Impression of Change – Fatigue

Appendix 18 Premature study treatment discontinuation examples



Note: If pEOT occurs within the visit window of next scheduled visit, the next scheduled visit is to be replaced with the pEOT visit.
EOS = End-of-Study, EOT = End-of-Treatment, FU = Follow-up, M = month, pEOT = premature End-of-Treatment, Rand = Randomization, RR = re-randomization.