Cenerimod (ACT-334441)

Systemic lupus erythematosus

Protocol ID-064A204

A multicenter, open-label, single arm, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of cenerimod in adult Chinese participants with moderate-to-severe systemic lupus erythematosus (SLE) on top of background therapy

Study Phase:	2
EudraCT Number:	Not applicable
Status and version:	Final Version 3.0
Date:	16 Sep. 2025
Document type:	Clinical study protocol
Viatris Innovation document number (Doc No.):	V-25.095

SPONSOR CONTACT DETAILS

Sponsor	Viatris Innovation GmbH Gewerbestrasse 14 CH-4123 Allschwil Switzerland
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
Local Sponsor in China	Viatris Pharmaceuticals Co., Ltd. Units 1-2, 5-9, F10 (9F actual floor), 669 Xinzha Road, Jing'an District, Shanghai, China
Medical Emergency Hotline Toll Telephone Number	Site-specific toll telephone numbers and toll-free telephone numbers for the Medical Emergency Hotline can be found in the Investigator Site File

CONTRACT RESEARCH ORGANIZATION INFORMATION

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

Contract Research Organization Information	Frontage Laboratories (Shanghai) Co., Ltd. No. 13, Lane 67, Libing Road, Pilot Free Trade Zone, Shanghai, China
Central Laboratory	GOBROAD LABORATORIES CO., LTD. No. 6 Zhengwangfen South, Fengtai District, Beijing, China
	Q Squared Solutions (Beijing) Co., Ltd. Unit 302, Building 15, No. 8 Liangshuihe 2nd Street Han’s Enterprise Bay, BDA Beijing, 100176 China
	Frontage Laboratories (Suzhou) Co., Ltd. 3/F, Block C, 1336 Wuzhong Avenue, Wuzhong District, Suzhou

SIGNATURE PAGE FOR VIATRIS INNOVATION GmbH

Hereinafter called Sponsor

Compound name / number

Cenerimod / ACT-334441

Indication

Systemic lupus erythematosus

Protocol number, study acronym, study title

ID-064A204

A multicenter, open label, single arm, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of cenerimod in adult Chinese participants with moderate-to-severe systemic lupus erythematosus (SLE) on top of background therapy.

Name (Title)	Date	Signature
ZhiJun Zhang, Clinical Project Physician Sponsor Medical Expert	Zhi Jun Zhang	数字签名者：Zhi Jun Zhang DN：c=US, st=Pennsylvania, l=Canonsburg, 2.5.4.97=LEIXG-254900ZZTSW7NL773X71, o=Viatris Inc., cn=Zhi Jun Zhang, email=zhijun.zhang@viatris.com 原因：我正在审批本文档 日期：2025.09.17 10:04:53 +08'00'
Mark Liu Head of Clinical Pharmacology Statistics & Data Management Global Clinical Pharmacology Viatris	Mark Shiyao Liu	Digitally signed by Mark Shiyao Liu DN: c=US, st=Pennsylvania, l=Canonsburg, 2.5.4.97=LEIXG-254900ZZTSW7NL773X71, sn=Shiyao Liu, givenName=Mark, o=Viatris Inc., cn=Mark Shiyao Liu, email=shiyao.liu@viatris.com Reason: I am approving this document Date: 2025.09.16 15:55:25 -04'00'

INVESTIGATOR SIGNATURE PAGE

Compound name / number

Cenerimod / ACT-334441

Indication

Systemic lupus erythematosus

Protocol number, study acronym, study title

ID-064A204

A multicenter, open label, single arm, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of cenerimod in adult Chinese participants with moderate-to-severe systemic lupus erythematosus (SLE) on top of background therapy.

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 participants (other than those procedures necessary for the well-being of the participants).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, ICH GCP guidelines, and applicable local GCP guidelines, regulations and laws.

Principal Investigator	Location (Site number)	Date	Signature
		2025-9-17	

AMENDMENT DETAILS

Current Amendment

<table>
<tr><td>Amendment Number</td><td colspan="2">ID-064A204</td></tr>
<tr><td>Version No.</td><td colspan="2">V3.0</td></tr>
<tr><td>Version Date</td><td colspan="2">16 Sep. 2025</td></tr>
<tr><td>Number of participants enrolled</td><td colspan="2">Fifteen (15) participants to be enrolled and none enrolled at present</td></tr>
<tr><td>Reason(s) for Amendment</td><td>Primary Reason:
Select from the following (multiple selections allowed):
• Regulatory agency request to amend
• New regulatory guidance
• IRB/IEC feedback
• New safety information available
• Manufacturing change
• Adaptive clinical trial IMP addition
✓ Change in strategy: 3-month interim analysis and report submitted to CDE is not required
• Change in standard of care
• New data available (other than safety data)
• Investigator/site feedback
• Recruitment difficulty
• Inconsistency and/or error in the protocol
• Protocol design error
✓ Other: Change of sponsor information</td><td>Other:
Select from the following (multiple selections allowed):
• Regulatory agency request to amend
• New regulatory guidance
• IRB/IEC feedback
• New safety information available
• Manufacturing change
• Adaptive clinical trial IMP addition
• Change in strategy
• Change in standard of care
• New data available (other than safety data)
• Investigator/site feedback
• Recruitment difficulty
• Inconsistency and/or error in the protocol
• Protocol design error
✓ Other: A few updates for the scale in Appendix 6
Specify the exclusion criteria 18
Revision in section 2.4.3</td></tr>
<tr><td>Summary of the Amendment</td><td colspan="2">1) Deletion of contents about 3-month interim analysis;
2) Change of sponsor information;
3) Change of Appendix 6 in Protocol according to the scale to be used;
4) Specification of the varicella-zoster virus antibody type as IgG in exclusion criteria 18;</td></tr>
</table>

	5) Revision of the blood amount to be collected at each visit on average in section 2.4.3 Study procedures and associated potential risks.
Is this amendment likely to have a substantial impact on • Safety or rights of the participants, or • On the reliability and robustness of the data generated in the clinical trial?	**No**

Summary of Changes in the Current Amendment

Section and Name	Description of Change	Brief Rationale for Change
1.1 Protocol synopsis ID-064A204 1.2 Schema 2.3 Study rationale 3.1 List of objectives and endpoints – 9.3 Planned analyses	Delete content on "The Month-3 interim analysis will be performed when all enrolled participants have completed the 3-month treatment period or permanently discontinued the study" and "The Month-3 interim report will be submitted to CDE for decision to allow the continuation of this Phase 2 study and initiation of the Phase 3 study in China". In addition, "The safety of the participants will be closely monitored. Safety review will be conducted regularly and on demand during the study" is clarified for safety monitoring.	Based on the review comments on cenerimod data from CDE, the development strategy would be changed: The 3-month interim analysis and report submitted to CDE is not required. The safety of the participants will be closely monitored and further decision on the clinical studies would be based on periodical safety results.
COVER PAGE SPONSOR CONTACT DETAILS SIGNATURE PAGE FOR SPONSOR Protocol header	Delete information about Idorsia pharmaceuticals Ltd., and change the global sponsor to Viatris Innovation GmbH	Change global sponsor according to the transfer of the cenerimod development program
12 APPENDICES	Change of Appendix 6 SLEDAI-2K: Data collection sheet	A few description content updates to be consistent with the scale to be used
1.1 Protocol synopsis ID-064A204 5.3 Exclusion criteria	Clarify the varicella-zoster virus antibody type as IgG in exclusion criteria 18	Specify the requirement

Section and Name	Description of Change	Brief Rationale for Change
2.4.3 Study procedures and associated potential risks	Revise the blood amount to be collected at each visit on average	Update the planned blood amount to be collected according to the trial design and the requirement by the test laboratory

AMENDMENT DETAILS

Amendment Version 2.0

Amendment Number	ID-064A204	
Version No.	V2.0	
Version Date	11 Jul. 2025	
Number of participants enrolled	Fifteen (15) participants to be enrolled and none enrolled at present	
Reason(s) for Amendment	**Primary Reason:** Select from the following (multiple selections allowed): • Regulatory agency request to amend • New regulatory guidance • IRB/IEC feedback • New safety information available • Manufacturing change • Adaptive clinical trial IMP addition • Change in strategy • Change in standard of care • New data available (other than safety data) • Investigator/site feedback • Recruitment difficulty • Inconsistency and/or error in the protocol • Protocol design error ✓ **Other: details optimization**	**Other:** Select from the following (multiple selections allowed): • Regulatory agency request to amend • New regulatory guidance • IRB/IEC feedback • New safety information available • Manufacturing change • Adaptive clinical trial IMP addition • Change in strategy • Change in standard of care • New data available (other than safety data) • Investigator/site feedback • Recruitment difficulty • Inconsistency and/or error in the protocol • Protocol design error • Other: [Describe]
Summary of the Amendment	1) Protocol description optimization; 2) Update detailed operation as applicable.	
Is this amendment likely to have a substantial impact on • Safety or rights of the participants, or • On the reliability and robustness of the data generated in the clinical trial?		**No**

Summary of Changes in the Amendment Version 2.0

Section and Name	Description of Change	Brief Rationale for Change
Full text	Update "subject" to "participant" or "patient"	Update according to the latest Declaration of Helsinki and guidance e.g. ICH M11
SPONSOR CONTACT DETAILS	Add CRO and central lab unit information	Important unit information added
LIST OF ABBREVIATIONS AND ACRONYMS	Revision, adding and deleting as applicable	Update abbreviations as used actually in protocol
1.1 Protocol synopsis ID-064A204 5.2 Inclusion criteria	Delete the requirement "BILAG Grade B in ≥ 2 organ systems or a BILAG Grade A in ≥ 1 organ system" for enrollment on Day 1.	Based on the study objective, the limitation on BILAG for enrolled participants is not required
1.1 Protocol synopsis ID-064A204	Description of core protocol was deleted	There was no core protocol and the information not applicable was deleted
1.1 Protocol synopsis ID-064A204 9.1 Analysis sets	Update the abbreviation of safety analysis set to SS from SAF.	Update according to the domestic operation and guidance
1.1 Protocol synopsis ID-064A204	Add analysis of efficacy endpoints in STATISTICAL METHODOLOGY: **Analysis of efficacy endpoints** Efficacy data will be analyzed descriptively. These analyses are detailed in the statistical methods section.	List all endpoints and the statistical methods
1.3 Schedule of activities	Adjust the location of the superscript remarks: superscript remarks 3, 4, 5, and 6 were involved in table 1; all superscript remarks were involved in table 2;	Improve readability

Section and Name	Description of Change	Brief Rationale for Change
	superscript remarks 2 and 3 were involved in table 3.	
1.3 Schedule of activities	The SLE biomarkers in PAXgene samples was deleted in table 1.	The test results on Day 1 predose will be considered as baseline values
1.3 Schedule of activities 9.2.2 Analysis of pharmacokinetic endpoints	The timepoint of 24 h postdose for PK sampling was added at Month 2 visit.	To obtain more accurate PK results
1.3 Schedule of activities 7.2.3.3.2 Additional cardiac monitoring on Day 1	Clarify the hourly frequency of 12-lead ECGs monitoring within 12 hours postdose on Day 1 or the day of treatment re-initiation.	Clarify the operation to guide clinical implementation
1.3 Schedule of activities	Clarify the body weight should be measured under fasting conditions in the morning.	Clarify the operation to guide clinical implementation
2.4.2 Known and potential risks	Classify the embryo-fetal toxicity to potential risks.	Only pre-clinical data indicated the embryo-fetal toxicity and no human data was reported
2.4.3 Study procedures and associated potential risks	The CT scan is also allowed for eligibility to exclude latent TB in table 4	CT is more sensitive
5.8.1.4.1 Day 1 specific stopping criteria	Update the criteria of permanent discontinuation of study treatment on Day 1 and on the first day of re-initiation of study treatment	To better ensure participant safety
7.2.2.4 Physician's Global Assessment of disease	Clarify 1, 2, and 3 are indicative of SLE disease activity assessment and correspond to **upper limits** of "mild", "moderate", and "severe", respectively.	The upper limits of disease activity were clarified to avoid confusion
7.2.3.2 Weight and height	The participant body weight will be measured with heavy clothing removed rather than in underwear	To be more operable
7.2.3.3.1 Cardiac monitoring applicable to all participants	The ECG findings (e.g., rhythm, ectopy, conduction, and morphology) and the overall interpretation of the ECG (normal/abnormal) will	The ECG findings and interpretation will also be sent to sponsor in actual operation

Section and Name	Description of Change	Brief Rationale for Change
	be provided by the ECG central vendor to the study site and to sponsor.	
7.2.3.5 Ophthalmological examination 7.2.3.6 Optical coherence tomography	Update the results record from "Yes/No for abnormality" to "Normal, NCS abnormal and CS abnormal"	The latter is more conformed with the clinical assessment for the results in actual operation
7.2.5.1 Pharmacokinetic assessments	Add the allowed time window for PK sampling	Clarify the operation to guide clinical implementation
7.2.5.1 Pharmacokinetic assessments	Delete the description of "The plasma samples will be destroyed upon signature of the CSR"	The samples will be processed according to the actual agreement
8.2.2 Reporting serious adverse events 8.3.1 Reporting of pregnancy 8.3.2 Follow-up of pregnancy	AEs and pregnancy will be sent to sponsor's "Drug Safety department" rather than "Global Drug Safety department"	Update protocol to consistent with the actual operations
9.2.2 Analysis of pharmacokinetic endpoints	Delete the detailed rule for statistical description of "If more than 50% of the values at a given time point are BLQ, no mean (including 95% CI), SD, or SE will be calculated for this time point"; Update the software for PK calculation	The actual statistical analysis methods shall prevail
9.2.3 Analysis of PD endpoints	Clarify that PD parameters will be calculated and summarized based on Lymphocyte counts	Clarify the PD endpoint to be analyzed
10.12 Inspections	Delete the specific way in which the inspection should be inform to sponsor	The actual operation shall prevail
Appendix 1 Clinical laboratory tests	Revise "Blood urea nitrogen" to "Blood urea nitrogen or urea, urea (mg/dL) = urea nitrogen (mg/dL) * 2.14"; Delete "leukocyte esterase" in Urinalysis; clarify the items in urinalysis–blood (hemoglobin, white blood cells) and Microscopic examination-sediment (red blood cells, white blood cells and casts)	Update according to the actual items to be tested

Section and Name	Description of Change	Brief Rationale for Change
Appendix 2 2019 EULAR/ACR Classification criteria for SLE Appendix 6 SLEDAI-2K: Data collection sheet Appendix 7 BILAG-2004 index Appendix 8 SLE Flare Index Appendix 9 Physician's Global Assessment Visual Analog Scale Appendix 11 Tender/swollen joints count	Make notes to clarify that "The actual scale/assessment to be used will prevail"	The actual scale/assessment to be used will prevail
Appendix 10 CLASI	Update the scale	Update according to the actual scale to be used

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

ACR	American College of Rheumatology
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AI	Accumulation index
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
Anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
Anti-Sm	Anti-Smith
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{τ}	Area under the plasma concentration-time curve during a dose interval at steady state
AUC_{0-24}	Area under the plasma concentration-time curve from zero to 24 h after dosing
AV	Atrioventricular
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group-2004
BLQ	Below the limit of quantification
BP	Blood pressure
bpm	Beats per minute
CDE	Center for Drug Evaluation
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Corticosteroid(s)
CSR	Clinical study report

CT	Computed tomography
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EOS	End-of-Study
EOT	End-of-Treatment
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration (US)
FSV	Final study visit
FU	Follow-up
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HR	Heart rate
i.v.	Intravenous(ly)
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IFN-1	Type 1 interferon
Ig	Immunoglobulin
IGRA	IFN gamma release assay
IL	Interleukin
INR	International normalized ratio
IOSB	Independent Ophthalmology Safety Board
IRB	Institutional review board
IRT	Interactive Response Technology

ISF	Investigator Site File
MCP	Metacarpophalangeal
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRL/lpr	Murphy Roths large lymphoproliferation
mRNA	Messenger ribonucleic acid
mSLEDAI-2K	Modified Systemic Lupus Erythematosus Disease Activity Index-2000
NSAID	Nonsteroidal anti-inflammatory drug
o.d.	Once daily
OCS	Oral corticosteroid(s)
OCT	Optical coherence tomography
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic analysis set
pEOT	Premature End-of-Treatment
PGA	Physician’s Global Assessment
PIP	Proximal interphalangeal
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PT	Preferred Term
PTOP	Post-treatment observation period
QTcB	QT interval corrected according to Bazett’s formula
QTcF	QT interval corrected according to Fridericia’s formula
RBC	Red blood cell count
RNA	Ribonucleic acid
s.c.	Subcutaneousl(ly)
S1P	Sphingosine-1-phosphate
$S1P_1$	Sphingosine-1-phosphate receptor 1
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation

SE	Standard error
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SFI	SLE Flare Index
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
SRI	Systemic Lupus Erythematosus Responder Index
SS	Safety analysis set
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
TB	Tuberculosis
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum plasma concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
WoCBP	Women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Protocol synopsis ID-064A204

TITLE	A multicenter, open label, single arm, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of cenerimod in adult Chinese participants with moderate-to-severe systemic lupus erythematosus (SLE) on top of background therapy
OBJECTIVES	**Primary objectives** • To evaluate the safety and tolerability of cenerimod 4 mg in Chinese participants. • To evaluate the PK of cenerimod 4 mg in Chinese participants. • To evaluate the PD of cenerimod 4 mg in Chinese participants. **Other objective** • To preliminarily evaluate the efficacy of cenerimod 4 mg in Chinese participants.
ENDPOINTS	**Safety endpoints** The following endpoints will be evaluated. • Occurrence of treatment-emergent adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs) • Occurrence of AEs leading to permanent discontinuation of study treatment. • Changes in vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP]) and body weight from baseline to each post-baseline assessment. • Changes in hourly 12-lead electrocardiogram (ECG) variables (hear rate [HR] and the QTcB and QTcF intervals) and SBP/DBP assessments at Day 1 cardiac monitoring. • Changes in 12-lead ECG variables (HR and the PR, QRS, QTcB, and QTcF intervals) from baseline to each post-baseline assessment. • Treatment-emergent medically relevant ECG abnormalities from baseline to each post-baseline assessment.

	• Changes in laboratory variables (hematology, blood chemistry, and urinalysis) from baseline to each post-baseline assessment. • Treatment-emergent marked laboratory abnormalities from baseline to each post-baseline assessment. The treatment-emergent period for the study is defined as the time from first study treatment intake until the end of the safety follow-up period, i.e., up to last study treatment intake + 180 days. **PK endpoints** • Cenerimod plasma concentrations at all scheduled time points (see Table 2). • The plasma PK parameters of 4 mg cenerimod will be derived by non-compartmental analysis of the plasma concentration-time profiles and calculated based on the actual PK sampling time points. The following endpoints will be determined: – C_{max}, t_{max}, and AUC_{0-24} during the first dosing interval on Day 1, – C_{max}, t_{max}, and AUC_{τ} during a dosing interval at steady state (i.e., at Month 2), – Accumulation index (AI) between Day 1 and Month 2. **PD endpoints** • Change in total blood lymphocyte count from baseline to each post-baseline assessment. **Efficacy endpoints** • Response on SRI-4 from baseline to Month 12. • Response on mSLEDAI-2K from baseline to Month 12. • Response on BICLA from baseline to Month 12. • Response on CLASI from baseline to Month 12. • Change in tender and swollen joints from baseline to Month 12. • Changes in OCS dosage from baseline to Month 12.

DESIGN	This is a multicenter, single arm, open label, multiple dose, study in adult Chinese participants with moderate-to-severe SLE with cenerimod 4 mg being administered on top of background SLE therapy. The safety of the participants will be closely monitored. Safety review will be conducted regularly and on demand during the study.
PERIODS	The study comprises the following consecutive periods: **Screening period:** Lasts up to 30 days; starts with the full signature of the informed consent form (ICF; participant, investigator/delegate and/or any other applicable third party) and ends with the administration of the study treatment on Day 1 or screening failure. **Treatment period:** Starts with the administration of the first dose of study treatment and ends on the day of the last dose of study treatment. It is planned that participants will be treated for up to 12 months. **Post-treatment observation period** (PTOP; only applicable to participants who permanently discontinue study treatment): Starts the day after the last dose of study treatment and participants will complete visits until at least 6 months after last study treatment intake as follows: • Participants who permanently discontinue study treatment before or at Month 6 will complete study visits until Month 12 and the final study visit (FSV) will be at Month 12 (i.e., PTOP-Visit 14). • Participants who permanently discontinue study treatment between Month 7 and Month 12 (inclusive), will complete PTOP follow-up visit(s). The FSV will be one of the monthly PTOP FU visits, as applicable. **Follow-up period:** Starts on the day after the last dose of study treatment and ends 6 months, i.e., 180 days, thereafter with FSV. The visit schedule and protocol-mandated procedures are performed according to the schedule of activities (SoA) [see Table 1, Table 2, and Table 3].

	The study design is depicted in Figure 1.
PLANNED DURATION	Approximately 22 months from first participant first visit to last participant last visit.
SITES / COUNTRIES	Approximately 5 -10 sites in China.
PARTICIPANTS / GROUPS	Approximately 15 adult participants diagnosed with generalized moderate-to-severe SLE and concurrently receiving SLE background therapy will receive 4 mg of cenerimod once daily for 12 months.
INCLUSION CRITERIA	**Screening criteria** 1. Signed and dated ICF prior to any study-mandated procedure. 2. Male and female Chinese participants aged from 18 to 75 years old (inclusive) at the time of signing the ICF. 3. Diagnosis of SLE made at least 6 months prior to Screening, according to 2019 European League Against Rheumatism / American College of Rheumatology Criteria. 4. An mSLEDAI-2K score ≥ 6 and clinical mSLEDAI-2K score ≥ 4 with at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers). Note: The mSLEDAI-2K score does not include "leukopenia". The clinical mSLEDAI-2K is the mSLEDAI-2K assessment score without the inclusion of points attributable to hematuria, proteinuria, pyuria, urinary casts, low complement, increased DNA binding, and thrombocytopenia. 5. PGA score ≥ 1.0 on a 0 to 3 VAS. 6. Currently treated with one or more of the following SLE background medications: • Antimalarials: (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine), • Mycophenolate mofetil (≤ 2 g/day) / mycophenolic acid (≤ 1.44 g/day), • Azathioprine (≤ 2 mg/kg/day),

	• Methotrexate (≤ 25 mg/week), • Oral corticosteroid(s) (OCS): – If OCS is the only SLE background medication: ≥ 7.5 mg/day and ≤ 30 mg/day prednisone or equivalent. – If OCS is not the only SLE background medication: ≤ 30 mg/day prednisone or equivalent. • Belimumab (≤ 10 mg/kg every 4 weeks intravenously [i.v.] or ≤ 200 mg/week subcutaneously [s.c.]). • Telitacicept (≤ 240 mg/week subcutaneously). Treatment with antimalarials, mycophenolate mofetil, mycophenolic acid, azathioprine, methotrexate, belimumab, or telitacicept must have been started at least 90 days prior to Screening. Treatment with OCS must have been started at least 30 days prior to Screening. 7. For women of childbearing potential (WoCBP): • Negative serum pregnancy test at Screening. • Agreement to undertake monthly urine pregnancy tests from Day 1 up to 6 months after study treatment discontinuation. • Agreement to use a highly effective method of contraception from Screening (Visit 1) up to 6 months after study treatment discontinuation. **Day 1 pre-dose criteria** 8. A clinical mSLEDAI-2K score ≥ 4 with at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers). 9. PGA score ≥ 1.0 on a 0 to 3 VAS. 10. Presence of **at least one** of the following biomarkers of serological evidence of active SLE (in a Screening sample as measured by central laboratory): • Anti-dsDNA antibodies elevated above normal. • Antinuclear antibodies (ANA) with a titer of at least 1:160.

	• Anti-Smith (anti-Sm) antibody elevated above normal. 11. Currently treated with one or more of the following SLE background medications that must be stable for at least 30 days prior to Day 1 (except OCS, which must be stable for at least 15 days prior to Day 1): • Antimalarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine), • Mycophenolate mofetil (≤ 2 g/day) / mycophenolic acid (≤ 1.44 g/day), • Azathioprine (≤ 2 mg/kg/day), • Methotrexate (≤ 25 mg/week), • OCS: – If OCS is the only SLE background medication: ≥ 7.5 mg/day and ≤ 30 mg/day prednisone or equivalent. – If OCS is not the only SLE background medication: ≤ 30 mg/day prednisone or equivalent. • Belimumab (≤ 10 mg/kg every 4 weeks i.v. or ≤ 200 mg/week s.c.); • Telitacicept (≤ 240 mg/week subcutaneously). 12. WoCBP must have a negative urine pregnancy test.
EXCLUSION CRITERIA	**Pregnancy and breastfeeding** 1. Pregnant, planning to be become pregnant up to 6 months after the last dose of cenerimod in this study, or lactating women. **SLE and other immune diseases** 2. Active severe SLE-driven renal disease (within 90 days prior to Screening or during Screening) where, in the judgment of the investigator, protocol-specified SLE background therapy is insufficient and the use of a more aggressive therapeutic approach or other treatments not permitted in the protocol is indicated. 3. Urine protein/creatinine ratio > 3000 mg/g (i.e., > 339.45 mg/mmol) at Screening assessment based on central assessment.

	4. Severe active central nervous system lupus or active severe or unstable neuropsychiatric SLE including but not limited to: aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy); acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; or mononeuritis multiplex: • That would make the participant unable to fully understand the ICF. *or* • Where, in the opinion of the investigator/delegate, protocol-specified standard of care is insufficient and the use of a more aggressive therapeutic approach, such as adding i.v. cyclophosphamide and/or high dose i.v. pulse corticosteroid (CS) therapy or other treatments not permitted in the protocol is indicated. 5. Severe forms of vasculitis (e.g., retinal vasculitis, coronary vasculitis, pulmonary vasculitis, mesenteric vasculitis) requiring systemic immunosuppressive treatment within 90 days prior to Screening or during Screening. 6. A diagnosis of mixed connective tissue disease or any history of overlap syndromes of SLE with psoriasis, rheumatoid arthritis, erosive arthritis, scleroderma, autoimmune hepatitis, or uncontrolled autoimmune thyroid disease. **Cardiovascular** 7. History or presence of Mobitz type II or third-degree atrioventricular block, sick sinus syndrome, symptomatic bradycardia, or syncope associated with cardiac disorders. 8. Participants 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 Class III/IV (see Appendix 14) within 6 months prior to Screening.

	9. Resting HR < 50 beats per minute as measured by the 12-lead ECG at Screening or at Day 1 prior to study treatment administration. 10. An elevated QTcF interval of > 470 ms (females) / > 450 ms (males) at Screening or at Day 1 prior to study treatment administration. **Pulmonary** 11. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function, and chest X-ray (or CT scan as per local guidelines), performed at Screening or within 6 months prior to Screening. 12. History of clinically relevant bronchial asthma or chronic obstructive pulmonary disease that has required treatment with oral or parenteral CS for more than a total of 2 weeks within the last 6 months prior to Screening. **Infection and infection risk** 13. Have had household contact with a person with active Tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB. 14. Have evidence of active TB or latent TB a. Active TB: Have evidence of active TB, defined in this study as the following: • Medical history, clinical features, and abnormal chest X-ray at Screening indicating the presence of TB. • IFN gamma release assay (IGRA): participants are excluded from the study if the test is not negative and there is clinical evidence of active TB. Exception 1: participants with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a Screening chest X-ray with no evidence of active TB may be enrolled if other entry criteria met. Such participants would not be required to undergo the IGRA test, but must have a chest X-ray at Screening (i.e., chest imaging performed within the past 6 months will not be accepted).

	b. Latent TB: Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following: • An IGRA test which is not negative, no clinical features consistent with active TB, and a chest X-ray with no evidence of active TB at Screening; • If the IGRA test results are positive, the participant will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the participant will be considered to have latent TB (for purposes of this study). Exception 2: participants with a history of latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a Screening chest X-ray with no evidence of active TB may be enrolled if other entry criteria met. Such participants would not be required to undergo the IGRA test, but must have a chest X-ray at Screening (i.e., chest imaging performed within the past 6 months will not be accepted). 15. Ongoing bacterial, viral, parasitic, or fungal infection that is of clinical concern according to the investigator or any of the following: • Clinically significant chronic infection (e.g., osteomyelitis, bronchiectasis, etc.) within 8 weeks prior to Screening (chronic nail infections are allowed). • Any infection requiring hospitalization or treatment with i.v. anti-infectives not completed at least 4 weeks prior to Screening. 16. Positive results for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection: • Anti-hepatitis A virus (HAV) immunoglobulin M (IgM). • Hepatitis B surface antigen. • Anti-hepatitis C virus (HCV) IgG or IgM (if positive IgM and/or IgG, to be confirmed by HCV-RNA polymerase

	chain reaction assessment, and if this assessment is negative, participant can be enrolled). • Anti-hepatitis E virus (HEV) IgG or IgM (if positive IgM and/or IgG, to be confirmed by HEV-RNA polymerase chain reaction, and if this assessment is negative, participant can be enrolled). 17. Participants who have congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing. 18. Negative IgG antibody test for varicella-zoster virus. **Malignancy** 19. History or presence of malignancy (except for surgically excised and non-recurrent cutaneous basal cell carcinoma, squamous cell carcinoma, or cervical carcinoma), lymphoproliferative disease, or history of total lymphoid irradiation within 10 years prior to Screening. **Transplantation** 20. History or presence of homologous (allogenic) bone marrow or solid organ transplantation. **Ophthalmologic** 21. Presence of macular edema or active uveitis detected by optical coherence tomography (OCT) during Screening. **Metabolic** 22. Documented poorly controlled diabetes mellitus (i.e., glycated hemoglobin > 8.0% at Screening as reported by the central laboratory or unstable blood sugar control/treatment adherence as per investigator's judgment) or diabetes mellitus complicated with organ involvement, such as diabetic nephropathy or retinopathy as assessed by investigator. **Hepatic** 23. History of chronic liver or biliary disease (other than Gilbert's Syndrome) or participants with alanine aminotransferase or aspartate aminotransferase > 3 × upper

	limit of normal or total bilirubin > 1.5 × upper limit of normal (unless in the context of known Gilbert's Syndrome). **Hematology** 24. Significant hematology abnormality at screening assessment: • Lymphocyte count < 500 /μL (0.5×10^9/L); • Hemoglobin < 7 g/dL; • White blood cell count < 2000/μL (2.0×10^9/L) or • Platelets < 25,000/μL (25×10^9/L). **Renal** 25. Estimated glomerular filtration rate < 15 mL/min/1.73 m^2. **Medications** 26. Treatment with the following medications within 15 days or 5 half-lives of the medication (whichever is longer) prior to Day 1: • β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering systemic therapy. • QT-prolonging drugs with known risk of torsade de pointes irrespective of indication. 27. Treatment with the following medications within 30 days or 5 half-lives of the medication (whichever is longer) prior to Day 1: • Cyclophosphamide, cyclosporine, voclosporin, tacrolimus, sirolimus, etc. • Pulse methylprednisolone. • Vaccination with live vaccines. 28. Intra-articular, intramuscular or i.v. CS within 6 weeks prior to Day 1. 29. Treatment with the following medications within 90 days or 5 half-lives of the medication (whichever is longer) prior to Day 1: • Leflunomide.

	• i.v. immunoglobulins. 30. Treatment with any investigational agent within 90 days or 5 half-lives of the drug (whichever is longer) prior to Day 1. 31. Treatment with B cell-depleting biological agents (e.g., rituximab or ocrelizumab) or biological immunosuppressive agents (e.g., anti-tumor necrosis factor, anti-interleukin-[IL]1, anti-IL-6 therapies), within 12 months prior to Day 1. 32. Treatment with anifrolumab within 6 months prior to Day 1. 33. Treatment with any of the following medications any time prior to Screening: • Alemtuzumab. • Sphingosine-1-phosphate (S1P) receptor modulators (e.g., fingolimod). • Participants previously randomized to cenerimod or placebo in any trial involving cenerimod. **Other categories** 34. Recent clinically significant drug or alcohol abuse as per investigator's judgment. 35. Known allergy to S1P receptor modulators or any of the cenerimod formulation excipients. 36. Any other clinically relevant medical condition that would put the participant at risk if participating in the study, or any other diseases that may confound the disease activity assessments. 37. Participants with body weight < 40 kg at Screening or Day 1.
STUDY TREATMENTS	**Investigational treatment** Cenerimod is supplied as film-coated tablets at the dose of 4 mg. **Study treatment dosing and administration** One tablet of cenerimod will be taken orally once daily, irrespective of food intake. The tablet should be taken each day in the morning.
CONCOMITANT THERAPY	**Allowed background SLE therapy** See inclusion criteria 6 and 11.

	SLE background therapy (except OCS) Background SLE therapy must have been started at least 90 days prior to Screening and must be stable for at least 30 days prior to Day 1. Any post-Day 1 change of background medication has the potential to obviate the treatment effect and efforts should be made to adjust background medication during the screening period prior to Day 1. After Day 1 study treatment administration, SLE background medications and route of administration must not change. Dose must remain stable from Day 1 to the completion of Month 12 but may be decreased for toxicity reasons or to optimize management of an AE, such as infection. The toxicity/event must be reported as an AE and the change of dose entered in the electronic case report form (eCRF). The dose can be returned to the Day 1 level if the toxicity/event resolves and if clinically indicated. Antimalarials/immunosuppressants (including dose, frequency, and route of administration) should not be changed if a participant has increased SLE disease activity during the OCS tapering period. **OCS management** <u>OCS management and dose optimization during Screening (Visit 1 up to Visit 2):</u> Participants will be eligible if background OCS dose is ≤ 30 mg/day of prednisone or equivalent. If OCS is the only SLE background medication, OCS dose must be ≥ 7.5 mg/day and ≤ 30 mg/day of prednisone or equivalent (see inclusion criteria 6 and 11). Treatment with OCS must have been started at least 30 days prior to Screening and must be stable for at least 15 days prior to Day 1. Investigators are encouraged to enroll participants that have optimized OCS usage prior to Screening. Dose reductions are at the investigator's discretion. The OCS dose must be stable for 15 days prior to Day 1. For the purpose of standardization, background OCS therapy is recommended to be

	prednisone, methylprednisolone, or prednisolone during the study. At Day 1 When OCS is not the only SLE background medication, the OCS dose must be ≤ 30 mg/day background prednisone or equivalent (see inclusion criteria 6 and 11). When OCS is the only SLE background medication, the OCS dose must be between ≥ 7.5 mg/day and ≤ 30 mg/day prednisone or equivalent. During study treatment period Change in OCS dose should be restricted to: • medically justified safety reasons, and • protocol-specified rules (see below). The justification and nature of any change in OCS dose should be thoroughly documented in the participant's medical records. **Protocol-specified rules for changes in CS dose** ***From Visit 2 up to Visit 5: Recommended stable OCS dose*** The OCS dose should be kept stable. The investigator is encouraged to only change the OCS dose in the following situation: • In participants with SLE disease activity improvement for at least 4 consecutive weeks (i.e., between 2 consecutive visits), an OCS dose decrease is allowed using the tapering schedule detailed in the protocol but is not mandatory. SLE disease activity improvement is defined as the British Isles Lupus Assessment Group-2004 (BILAG) reduction of all A scores to B/C/D scores and the reduction of all B scores to C/D scores, and no worsening score in other organ systems, as defined by ≥ 1 new A score or ≥ 2 new B score. ***From Visit 5 up to Visit 10: Mandatory OCS tapering*** For participants with OCS dose ≥ 10 mg/day at Day 1, steroid tapering to an OCS dose of ≤ 7.5 mg/day MUST be attempted as per the algorithm in the protocol and started within 14 days after

	Visit 5. Tapering should not be attempted if at least 1 of the following criteria is met: • Worsening of SLE disease activity defined as ≥ 1 new BILAG A or ≥ 2 new BILAG B scores (except mucocutaneous and musculoskeletal domains). • Moderate-to-severe skin disease as reflected by a Cutaneous Lupus Erythematosus Disease Area and Severity Index activity score of ≥ 10. • Moderate-to-severe arthritis disease as reflected by an active joint count of ≥ 4 tender and/or swollen joints. If a participant fails tapering down on the first attempt, an increase of OCS dose up to the dose before the start of the forced tapering is allowed. Another attempt to taper down OCS might be done unless at least 1 of the above criteria is met. If steroid tapering is not attempted in an eligible participant, the sponsor must be contacted immediately. The recommended steroid tapering regimen is detailed in the protocol, but due to variability in participant responses to steroid treatment and tolerability of taper, investigators will have flexibility in how the OCS dose is reduced at each visit. Investigators will not be required, but may continue, to taper the OCS dose below 7.5 mg/day up to Visit 10. From Visit 2 to Visit 10, participants who experience an increase in SLE disease activity may receive *one* (and only one) CS burst as follows: • OCS increase up to a maximum daily dose of 40 mg/day prednisone or equivalent up to a total of 14 days. This OCS increase must be fully administered and tapered to less than or equal to the Day 1 (Visit 2) by no later than Visit 10. *or* • Intramuscular methylprednisolone (≤ 80 mg or equivalent) administered as a single dose. *or* • A maximum of 2 intra-articular / tendon sheath / bursal injections (for a total methylprednisolone ≤ 80 mg or equivalent) at the same visit.

	Steroid tapering will not be permitted after Visit 10. ***From Visit 10 to Visit 14: Mandatory stable OCS dosage*** OCS dosage must be stable unless medically justified by the investigator. No increase in OCS is allowed after Visit 10 except for managing AEs or as prophylaxis for adrenal insufficiency. **Other allowed concomitant therapies:** • Atropine (i.v.) in the event of symptomatic bradycardia. • Topical ocular therapy (e.g., chronic treatment for glaucoma, ocular inflammation, allergy), 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 (skin), inhaled, and nasal use of CS. • Nonsteroidal anti-inflammatory drugs (NSAIDs). – If used for treatment of SLE, NSAIDs must be stable for a period of at least 30 days prior to Day 1 and must remain stable throughout the study but can be reduced for reasons of toxicity but not efficacy. – Temporary use and/or dose change for treatment of non-SLE-related conditions (e.g., headache, menstrual cramps) is allowed. – NSAIDs cannot be used in combination with another NSAID at any dose, except low-dose aspirin (≤ 325 mg/day). – Topical NSAIDs may be used in combination with one oral NSAID. – On a given scheduled visit day, NSAIDs should not be taken until after all assessments have been completed. • Stable long-term use of low-dose aspirin (maximum of 325 mg/day) for cardiovascular disease is permitted. • Temporary use of pain medications (e.g., acetaminophen/paracetamol or other non-NSAID pain medication) may be used for pain as required, based on the investigator judgment for up to 1 week at a time and should not be taken on the day of a scheduled visit until all assessments have been completed.

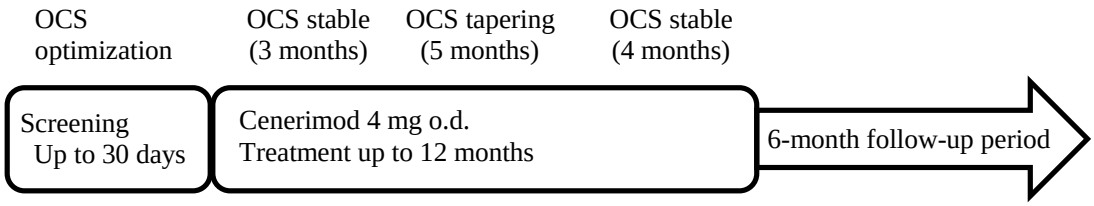
	• All other medications that are not forbidden. **Forbidden concomitant therapies:** • Immunosuppressive agents not listed as allowed concomitant medications, such as cyclophosphamide, cyclosporine, voclosporin, leflunomide, sirolimus, tacrolimus, etc. • Immunosuppressive or immunomodulatory biological agents (e.g., i.v. immunoglobulin, anifrolumab, rituximab, etc.). • 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, cyclosporine, eltrombopag, elacridar, gefitinib, teriflunomide. • Cannabidiol and other derivatives of marijuana. • Investigational agents.
STATISTICAL METHODOLOGY	**Analysis of safety endpoints** Descriptive analysis of safety endpoints will be performed using the safety analysis set (SS). The SS includes all participants who received at least 1 dose of study treatment. ***Adverse events*** AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). The number (%) of participants experiencing a treatment-emergent AE (including SAEs, AESIs, and AEs leading to premature discontinuation of the study treatment) will be summarized by system organ class (SOC) and/or preferred term (PT), and maximum intensity. A participant with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT). ***Vital signs and electrocardiograms during post-dose cardiac monitoring on Day 1*** Observed values and changes in vital signs (SBP and DBP) and 12-lead ECG variables, including HR and QTcB and QTcF intervals, from baseline to all post-dose assessments will be

	summarized. The number (%) of participants with a marked ECG abnormality will be tabulated. The number of participants discharged at 12 h will be summarized. For participants not discharged, reasons for not being discharged will be summarized. ***Vital signs and body weight*** Observed values and changes in vital signs (SBP and DBP) and body weight from baseline to all scheduled post-baseline visits will be summarized. ***Electrocardiograms*** Observed values and changes for each 12-lead ECG variable (HR and the PR, QRS, QTcB, and QTcF intervals) from baseline to all scheduled post-baseline visits will be summarized. The number (%) of participants with a marked ECG abnormality will be tabulated. ***Laboratory data*** Observed values for all scheduled post-baseline visits in hematology, blood chemistry, and urinalysis laboratory variables will be summarized. The number (%) of participants with a marked laboratory abnormality will be tabulated. **Analysis of PK and PD endpoints** PK and PD data will be analyzed descriptively. These analyses are detailed in the statistical methods section. **Analysis of efficacy endpoints** Efficacy data will be analyzed descriptively. These analyses are detailed in the statistical methods section.
STUDY COMMITTEE	An Independent Ophthalmology Safety Board (IOSB) will receive all information related to suspected cases of macular edema and will perform a central review of OCT images and participants' data of suspected cases of macular edema as per the IOSB charter.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study design



OCS = oral corticosteroid(s)

1.3 Schedule of activities

The visit schedule and protocol-mandated activities are performed according to the SoA [Table 1, Table 2, and Table 3] and are described in Section 7.

Table 1 Schedule of activities at Screening

PERIODS	**Name**	**SCREENING**
	Duration	**Up to 30 days**
VISITS	**Number**	**1**
	Time window	**Day –30 to Day –1**
Contact IRT		X
Informed consent and participant's lupus history		
Informed consent		X
Eligibility		X
Demographics		X
Medical history and SLE history (including 2019 EULAR/ACR criteria questionnaire)		X
SLE and previous/concomitant therapies		X
Medical examination and SLE disease activity		
Physical examination[1], body weight [2] and height		X
Vital signs[3]		X
12-lead ECG[3]		X
Ophthalmological examinations		X
OCT		X
Chest X-ray / CT scan [4]		X
SAEs / AEs		X
SLE disease activity		
mSLEDAI-2K		X
SFI		X
PGA		X
CLASI		X
Tender/swollen joint count		X
BILAG		X
Laboratory tests		
Serum pregnancy test [5]		X
Labs (hematology/serum chemistry, coagulation and urine analyses)[6,]		X
HbA1c		X
Anti b2GP1		X
Blood test for TB		X
Hepatitis A, B, C, E		X
Varicella-zoster virus		X
HIV test		X
Anti-dsDNA, complement (C3, C4, CH50), ANA, anti-Smith		X

[1] Physical examination 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 to capture assessments needed for the SLEDAI-2K, the PGA, the CLASI and the SFI.

[2] Body weight (measured under fasting conditions in the morning) should be recorded in the BILAG assessment page in the paper sheets at all visits in which this assessment is performed. It should also be recorded in the eCRF at Visits 1, 14, and 20.

[3] At all visits, a single pre-dose 12-lead ECG will be performed and transmitted to the central reader. A pre-dose SBP/DBP will be performed at all visits (including Screening) in duplicate and both values, including the arm and position used, will be entered into the eCRF.

[4] If a chest X-ray or CT scan has been performed within 6 months prior to Screening and the results are available, there is no need to repeat the chest X-ray or CT scan at Screening.

[5] Only applicable for WoCBP. The serum pregnancy test at Visit 1 must be performed at least 3 weeks before the urine dipstick pregnancy test performed at Visit 2 prior to cenerimod intake.

[6] A central laboratory will be used for all protocol-mandated laboratory tests, including retests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Local laboratory tests may be required under exceptional circumstances and results should be recorded as unscheduled local laboratory in eCRF.

AE = adverse event; ANA = antinuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; BILAG = British Isles Lupus Assessment Group-2004; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CT = computed tomography; ECG = electrocardiogram; EULAR/ACR = European League Against Rheumatism/American College of Rheumatology; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; IRT = Interactive Response Technology; mSLEDAI-2K = Modified Systemic Lupus Erythematosus Disease Activity Index-2000; OCT = Optical coherence tomography; PGA = Physician's Global Assessment; SAE = serious adverse event; SFI = SLE Flare Index; SLE = systemic lupus erythematosus; TB = tuberculosis.

Table 2 Schedule of activities after Screening

PERIODS	Name	TREATMENT				
	Duration	**12 months**				
VISITS	**Number**	**2**	**3**	**4, 6, 7, 9, 10, 12, 13**	**5, 8, 11**	**14**
	Name	**1st study drug administration**	**Month 1**	**Months 2, 4, 5, 7, 8, 10, 11**	**Months 3, 6, 9**	**Month 12 (EOT) / Premature EOT (pEOT)[12, 13]**
	Time window	**Day 1**	**Day 30 (±2 days)**	**Days 60, 120, 150, 210, 240, 300, 330 (±7 days)**	**Days 90, 180, 270 (±7 days)**	**Day 360 (±7 days) / pEOT (from next day up to 7 days after last study treatment intake)**
To be performed at Day 1 only						
Eligibility		X				
Day 1 cardiac monitoring [1]		X				
To be performed at all visits						
SLE and previous/concomitant therapies		X	X	X	X	X
Physical examination[2]		X	X	X	X	X
Body weight [3]		X	X	X	X	X
mSLEDAI-2K, BILAG, SFI, PGA, CLASI, Tender/swollen joint count [2]		X	X	X	X	X
Vital signs, 12-lead ECG [4, *]		X[1]	X	X	X	X
Labs (hematology/serum chemistry[5], coagulation and urine analyses)[6, *]		X	X	X	X	X
BILAG associated blood and urine samples (anti-cardiolipin, lupus anticoagulant haptoglobin, and Coombs) [7]		X	X	X	X	X
Urine pregnancy test [8]		X	X	X	X	X
Contact IRT		X	X	X	X	X
Study treatment dispensing/return and accountability		X	X	X	X	X
SAEs/AEs[9]		X	X	X	X	X

PERIODS	**Name**	**TREATMENT**				
	Duration	**12 months**				
VISITS	**Number**	**2**	**3**	**4, 6, 7, 9, 10, 12, 13**	**5, 8, 11**	**14**
	Name	**1st study drug administration**	**Month 1**	**Months 2, 4, 5, 7, 8, 10, 11**	**Months 3, 6, 9**	**Month 12 (EOT) / Premature EOT (pEOT)[12, 13]**
	Time window	**Day 1**	**Day 30 (±2 days)**	**Days 60, 120, 150, 210, 240, 300, 330 (±7 days)**	**Days 90, 180, 270 (±7 days)**	**Day 360 (±7 days) / pEOT (from next day up to 7 days after last study treatment intake)**
To be performed at specific visits						
Site visit study treatment administration[10]		X	X	X	X	
Ophthalmological examinations[11]					X (Months 3, 6 only)	X
OCT[11]					X (Months 3 and 6 only)	X
PK sampling		Pre-dose*, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h after the first dose	Pre-dose*	Pre-dose*, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h after dosing (Month 2 only); Pre-dose* (Month 4 only)	Pre-dose* (Month 6 only)	X
SLE biomarkers in PAXgene samples		X			X (Month 6 only)	X
Anti-dsDNA, complement (C3, C4, CH50)		X	X	X	X	X
ANA		X			X	X
Anti-Smith		X				
IFN-alpha sample		X			X (Month 6 only)	X

PERIODS	Name	FOLLOW-UP[6]			UNSCHEDULED	
	Duration	6 months			NA	
VISITS	Number	15	16, 17, 18, 19	20 (FSV)	U1, U2, …	RI
	Name	FU1	FU2, FU3, FU4, FU5 Phone call	Final study visit	Unscheduled[15]	Re-initiation
	Time window	1 month after last study treatment intake (±7 days)	Monthly after FU1 (±7 days)	6 months after last study treatment intake (±7 days)	Any day between ICF signature and FSV (assessments to be performed as applicable)	Re-initiating study treatment after interruption lasting more than 7 days between Day 1 and Day 14
To be performed at all visits						
SAEs/AEs[9]		X	X	X	X	X
To be performed at specific visits						
SLE and concomitant therapies		X	X	X	X	X
Physical examination[2]		X		X	X	X
Body weight[3]				X	X	
mSLEDAI-2K, BILAG, SFI, PGA, CLASI, Tender/swollen joint count					X	
Vital signs, 12-lead ECG[4]		X		X	X	X[1]
Ophthalmological examinations				X	X	
OCT					X	
Labs (hematology/blood chemistry[5], urine analyses)[6]		X		X	X	
Labs (coagulation)[6]					X	
BILAG associated blood and urine samples (anti-cardiolipin, lupus anticoagulant, haptoglobin, and Coombs)[7]					X	
Serum pregnancy test[8]				X	X	
Urine pregnancy test[14]		X	X			
Viral serology / TB test					X	
PK sampling				X		

PERIODS	Name	FOLLOW-UP[6]			UNSCHEDULED	
	Duration	6 months			NA	
VISITS	Number	15	16, 17, 18, 19	20 (FSV)	U1, U2, …	RI
	Name	FU1	FU2, FU3, FU4, FU5 Phone call	Final study visit	Unscheduled[15]	Re-initiation
	Time window	1 month after last study treatment intake (±7 days)	Monthly after FU1 (±7 days)	6 months after last study treatment intake (±7 days)	Any day between ICF signature and FSV (assessments to be performed as applicable)	Re-initiating study treatment after interruption lasting more than 7 days between Day 1 and Day 14
SLE biomarkers in PAXgene samples				X	X	
IFN-alpha sample				X	X	
Anti-dsDNA, complement (C3, C4, CH50)				X	X	
ANA				X	X	
Anti-Smith				X	X	
Study treatment dispensing/return and accountability						X

One month is considered to be 30 days.
Day 1 is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).
* Study treatment should not be taken before the assessment (i.e., SBP/DBP, ECGs, laboratory tests and PK sampling).
[1] The post dose 12-lead ECGs assessments will be measured once at each hourly time point within 12 hours post-dose, while SBP/DBP assessments will be measured once at each hourly time point within 6 hours post-dose and at 12 hours post-dose at Visit 2 (Day 1) and at study treatment re-initiation. At the 12-hour post-dose timepoint, participants may be discharged from the monitored setting if they meet the pre-specified discharge criteria. For discharge criteria see Appendix 5.
[2] Physical examination 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 to capture assessments needed for the SLEDAI-2K, the PGA, the BILAG, the CLASI and the SFI.
[3] Body weight (measured under fasting conditions in the morning) should be recorded in the BILAG assessment page in the paper sheets at all visits in which this assessment is performed. It should also be recorded in the eCRF at Visits 1, 14, and 20.
[4] At all visits, a single pre-dose 12-lead ECG will be performed and transmitted to the central reader. A pre-dose SBP/DBP will be performed at all visits (including Screening) in duplicate and both values, including the arm and position used, will be entered into the eCRF.
[5] Aldolase to be measured only at investigator's request.
[6] A central laboratory will be used for all protocol-mandated laboratory tests, including retests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Local laboratory tests may be required under exceptional circumstances and results should be recorded as unscheduled local laboratory in eCRF.

[7] For some tests associated with BILAG, samples will be collected and sent to the central laboratory. The analysis of the sample will only be done upon request of the investigator. The following blood tests must be performed at Day 1 pre-dose but are optional at all other visits: cardiolipin IgA, IgG and IgM antibodies and lupus anticoagulant. Haptoglobin is optional at all visits.

[8] Only applicable for WoCBP. The serum pregnancy test at Visit 1 must be performed at least 3 weeks before the urine dipstick pregnancy test performed at Visit 2.

[9] All AEs and SAEs that occur after signing the informed consent form and up to 6 months after study treatment discontinuation must be reported.

[10] Study treatment should be administered at the site from study treatment dispensed on the day of the visit, after study assessments have been performed.

[11] Ophthalmological examination and OCT may be performed up to 7 days prior to the visit date but no later than 7 days after the visit.

[12] All participants will be asked to return for an EOT visit. For participants who permanently discontinued study treatment, the pEOT visit will occur within 7 days of last intake of study treatment and participants will thereafter attend PTOP visits [see Table 3]. If a pEOT visit occurs within 7 days of a scheduled PTOP visit, this PTOP visit should be skipped. For all other participants, the EOT visit will coincide with Visit 14.

[13] After completion of the Month 12 visit, participants will be asked to complete the follow-up period.

[14] For Visits 16–19, the site will dispense urine pregnancy kits to WoCBP and collect the results during the scheduled phone call. If a urine test is positive, the participant will be instructed to return to the site for a serum pregnancy test.

[15] During unscheduled visits, any additional assessments considered necessary by the investigator may be performed.

AE = adverse event; ANA = antinuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; BILAG = British Isles Lupus Assessment Group-2004; bpm = beats per minute; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; DBP = diastolic blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; EDTA = ethylenediaminetetraacetic acid; EOT = End-of-Treatment; FSV = final study visit; FU = follow-up; IFN-1 = Type 1 interferon; IRT = Interactive Response Technology; mSLEDAI-2k = modified Systemic Lupus Erythematosus Disease Activity Index-2000; OCT = optical coherence tomography; pEOT = premature End-of-Treatment or permanent discontinuation of study treatment; PGA= Physician's Global Assessment; PK = pharmacokinetic; PTOP = post-treatment observation period; RI = re-initiation; SAE = serious adverse event; SBP = systolic blood pressure; SFI = SLE Flare Index; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; TB = tuberculosis, WoCBP = women of childbearing potential.

Table 3 Schedule of activities: PTOP (applicable to participants who permanently discontinue study treatment

PERIODS	Name			POST-TREATMENT OBSERVATION		
	Duration	Up to 12 months[1]		Up to 6 months[1]		
PTOP VISITS[1]	Number	PTOP 3, 4, 6, 7, 9, 10, 12, 13[1]	PTOP 5, 8, 11, 14[1]	PTOP 15[1]	PTOP 16, 17, 18, 19[1]	PTOP 20 / FSV[1]
	Name	Months 1, 2, 4, 5, 7, 8, 10, 11	Months 3, 6, 9, 12	FU Month 1	FU Months 2, 3, 4 and 5 Phone call	FU Month 6
	Time window	Days 30, 60, 120, 150, 210, 240, 300, 330 (±7 days)	Days 90, 180, 270, 360 (±7 days)	1 month after last dose (±7 days)	Monthly after PTOP FU1 (±7 days)	6 months after last dose (±7 days)
To be performed at all visits						
Pregnancy test [2]	X	X	X	X	X	
SAEs/AEs	X	X	X	X	X	
SLE concomitant therapies	X	X	X	X	X	
To be performed at specific visits						
Physical examination	X	X	X		X	
Body weight[3]	X	X (Month 12)			X	
mSLEDAI-2K, BILAG, SFI, PGA, CLASI, tender/swollen joint count,	X	X				
Vital signs, 12-lead ECG	X	X	X		X	
Ophthalmological examinations		X (Months 3, 6, 12)			X	
OCT		X (Months 3, 12)				
Labs (hematology/blood chemistry, urine analyses)[4]	X	X	X		X	
Anti-dsDNA, complement (C3, C4, CH50)	X	X			X	
ANA		X			X	
Anti-Smith					X	

[1] Participants who permanently discontinue study treatment will attend PTOP visits starting at the visit following the permanent treatment discontinuation as follows:

- Participants who permanently discontinue before or at Month 6 will complete study visits until Month 12 and the FSV will be at Month 12 (i.e., PTOP Visit 14).
- Participants who permanently discontinue between Month 7 and Month 12 (both inclusive), will complete PTOP FU visits until at least 6 months after last study treatment intake and the FSV will be one of the monthly PTOP FU visits, as applicable.

[2] Only applicable for WOCBP. A serum pregnancy test for participants who permanently discontinue study treatment before or at Month 6 will be performed and analyzed centrally at Month 12 (i.e., PTOP Visit 14). A serum pregnancy test for participants who permanently discontinue study treatment between Month 7 and Month 12 (both inclusive) will be performed and analyzed centrally at FSV, i.e., 6 months after last study treatment intake. Urine pregnancy tests will be performed at all other visits with kits provided by the site.

[3] Body weight should be measured as part of BILAG assessment at each applicable visit and recorded in the source documentation. It should also be recorded in the eCRF at PTOP 14 and 20.

[4] A central laboratory will be used for all protocol-mandated laboratory tests, including retests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

AE = adverse event; ANA = antinuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; BILAG = British Isles Lupus Assessment Group-2004; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; ECG = electrocardiogram; eCRF = electronic case report form; FU = follow-up; FSV = final study visit; mSLEDAI-2k = modified Systemic Lupus Erythematosus Disease Activity Index-2000; OCT = optical coherence tomography; PGA = Physician's Global Assessment; PTOP = post-treatment observation period; SAE = serious adverse event; SFI = SLE Flare Index; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; WoCBP = women of childbearing potential.

2 INTRODUCTION

2.1 Indication

Systemic lupus erythematosus

SLE is an autoimmune disease of unknown etiology, characterized by the production of pathogenic autoantibodies, tissue deposition of immune complexes, and tissue damage across multiple organ systems. This heterogeneous, chronic, debilitating, autoimmune inflammatory disorder characterized by diverse clinical manifestations can affect any organ or system in the body simultaneously or sequentially [Kaul 2016]. The adaptive T and B cells and the innate immune system are considered to play a major pathophysiological role in this disease [Carroll 2004, Kaul 2016].

Despite many treatment advances and improved diagnostics, SLE continues to cause substantial morbidity and premature mortality. Current management strategies are limited by high failure rates and toxicity. An overreliance on CS therapy contributes to much of the long-term organ damage [Durkan 2019].

Medical need for new targeted therapies

The current treatment of SLE comprises NSAIDs, antimalarials, CS, and immunosuppressive drugs, often prescribed in that order as the disease progresses [Xiong 2014]. Belimumab (an inhibitor of soluble B-cell-activating factor), approved by the FDA in 2011, anifrolumab (an IFN-1 receptor antagonist), approved by the FDA in 2021, and telitacicept (a novel human recombinant fusion protein) conditionally approved in China in 2021 are the only treatments approved for SLE in over 60 years [Furie 2019, Morand 2020, Navarra 2011, Dhillon 2021]. Clinical experience with anifrolumab and telitacicept is limited to date. Other medications currently used to treat SLE, such as azathioprine, cyclophosphamide, and mycophenolate mofetil / mycophenolic acid, have not been approved for the disease by regulatory authorities. Antimalarials and CS are also used to control some manifestations of lupus (e.g., arthralgia, arthritis, and rashes). All these drugs have well-documented and substantial safety profiles and are not effective in all patients and/or on all SLE manifestations. Furthermore, it is difficult to taper participants with moderate or severe disease completely off CS, which cause long-term morbidity and may contribute to early cardiovascular mortality [Petri 2001, Urowitz 1976]. Even small daily doses of 5 to 10 mg prednisone used long term carry increased risks of side effects such as cataracts, osteoporosis, and coronary artery disease [Petri 2001].

In China there is a large population of SLE patients with a clinical presentation that may differ from that reported in other ethnicities [Tian et al 2022]. Guidelines developed by Chinese rheumatologists and other experts have made several recommendations for the diagnosis, treatment and follow-up of disease activity, including disease monitoring using the SLEDAI-2K which will be used in this clinical study [Li et al 2020]. It has been shown

that Chinese SLE patients that experience severe flares have associated costs 5 times greater than those with non-severe flares [He et al 2023]. This suggests that aside from the medical rational to reduce flares and thus subsequent organ damage there is also an economic reason.

There is thus a medical need to identify new targeted therapies, particularly agents that may reduce the requirement for CS and cytotoxic agents.

Though recent improvements in care have dramatically enhanced the survival of patients with SLE, increased morbidity and mortality remain a major concern. Many patients have partially controlled disease and progression to end-stage organ involvement continues, and the therapies carry risks of debilitating side effects [Lateef 2012]. Therefore, it is important to continue the development of medical products that have the potential to be more effective and/or less toxic.

2.2 Investigational treatment

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 PD effect, observed in both healthy volunteers and SLE patients, is sustained with continued daily oral dosing. After study treatment discontinuation, a gradual return towards baseline levels in lymphocyte counts was observed [Cenerimod IB, Hermann 2019]. The compound was selected based on its potential for o.d. oral administration, its long $t_{½}$ allowing a built-in natural up titration, and its high selectivity for the $S1P_1$ receptor [Juif 2016, Juif 2017].

Cenerimod has unique $S1P_1$ receptor-signaling properties, and an improved safety profile compared to other S1P modulators. For instance, the absence of broncho- and vaso-constrictor effects ex vivo and in vivo was notable [Piali 2017]. Cenerimod dose-dependently lowered circulating lymphocyte counts in animal models (mice, rats, dogs) and in human participants, leaving Natural Killer cell and monocyte counts unaffected. Cenerimod effectively attenuated disease variables in a mouse experimental autoimmune encephalitis model and was effective in the treatment of lupus-like disease in the MRL/lpr mouse model of SLE [Cenerimod IB, section 1.3.1].

The PK of cenerimod in healthy participants were characterized by a slow absorption (median t_{max}: 5–6 and 6–7 h after single- and multiple-dosing, respectively) and elimination ($t_{½}$ approximately 33 days measured after the last dosing under steady-state conditions), dose-proportional exposure in the range of 0.5–4 mg, and steady-state conditions reached within 50 days. Cenerimod showed an accumulation of approximately 8-fold at steady state when compared to the first day of treatment. The PK of cenerimod support o.d. dosing and no dose adjustment is required for sex, ethnicity, or fed/fasted state. Cenerimod can be concomitantly administered with drugs that are inhibitors, inducers, or substrates of

cytochrome proteins without dose adjustment. Further details on the PK characteristics of cenerimod are provided in the IB [Cenerimod IB].

The first study performed in adult participants with moderate-to-severe SLE (AC-064A201) 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 significantly reduced lymphocyte counts in a dose-dependent manner ($p < 0.01$) as expected from its primary mode of action [Cenerimod IB, sections 1.4.2.2 and 5.3.1.1]. The exploratory analysis of efficacy suggested clinical improvement, particularly with the higher cenerimod doses [Cenerimod IB, section 5.3.1.1]. Cenerimod treatment was well tolerated in patients with SLE at all doses tested [Cenerimod IB, section 5.3.2.2].

In adult participants with moderate-to-severe SLE (Phase 2b study ID-064A202), cenerimod 4 mg showed a clinically significant reduction in disease activity characterized by an improvement in the mSLEDAI-2K score from baseline to Month 6 (the primary efficacy endpoint). [Cenerimod IB, sections 1.4.3 and 5.3.1.2]. The subgroup analyses of change from baseline to Month 6 in mSLEDAI-2K in participants with a more severe or more active disease categorized by daily dose of CS ($\geq$ 7.5 mg/day) and by mSLEDAI-2K score ($\geq$ 10) at baseline revealed that efficacy of the 4 mg dose appeared to be greater (vs placebo and lower doses) in participants receiving higher doses of prednisone or with a more active disease. [Cenerimod IB, section 5.3.1.2]. The cenerimod safety profile did not show any unexpected findings and safety areas of special interest related to class did not raise any concerns with any dose, up to and including 4 mg [Cenerimod IB, section 5.3.2.3].

Post-hoc analyses were made by immunological status at baseline with regards to IFN-1, anti-dsDNA, and complement C4 and C3 levels at baseline. The placebo-corrected changes in mSLEDAI-2K score for the cenerimod 4 mg dose were consistently larger compared to placebo in participants with high disease activity assessed by the immunological variables. Based on these data, the same analytes will be measured in this clinical study to compare the results with previous studies.

In participants with high IFN-1 status at entry, representing 50.7% of the overall study population, the placebo-corrected mSLEDAI-2K change from baseline to Month 6 in participants on cenerimod 4 mg was greater than that observed in the overall population.

2.3 Study rationale

Despite recent improvements in treatment regimens and medical care in reducing mortality and morbidity, many patients have partially controlled disease and progression to end-stage organ involvement, and the therapies carry risks of side effects [Lateef 2012]. Effective control of SLE is still difficult due to disease heterogeneity and variability in disease manifestations among individuals.

Results of recently conducted clinical studies in SLE patients have demonstrated a favorable effect of cenerimod on mediators of inflammation and on lupus efficacy clinical outcome measures [see Section 2.2]. In the Phase 2b dose-finding study (ID-064A202), cenerimod 4 mg was well tolerated over a treatment period of 6 months with limited side effects vs placebo.

The nonclinical safety data and the resulting safety margins / exposure ratios are considered adequate to support the safe use of cenerimod in humans at the dose of 4 mg selected for the ID-064A204 study.

Cenerimod exposure in the Chinese population has not yet been evaluated and, while differences in drug response due to intrinsic or extrinsic factors in the Chinese ethnic population are not expected based on cenerimod properties, it should be assessed. For Chinese participants, a staggered approach will therefore be implemented with the limited ID-064A204 study started first to mitigate the risk of exposing a large number of Chinese patients to cenerimod 4 mg. Study ID-064A204 will evaluate the safety, tolerability, PK and PD of cenerimod in Chinese participants.

The safety of the participants will be closely monitored and safety review will be conducted regularly and on demand.

2.4 Benefit/risk assessment of cenerimod

Currently there is limited clinical data to assess the benefit/risk ratio of cenerimod. In the following sub-sections, the potential and known risks and potential benefits of treatment with cenerimod are discussed.

2.4.1 Potential benefits

In the Phase 2b study (ID-064A202), the primary analysis of efficacy at 6 months revealed a clinically and nominally statistically significant improvement ($p = 0.029$) in mSLEDAI-2K score from baseline to Month 6 in cenerimod 4 mg vs placebo. From Month 4 onwards, the change from baseline and the difference to placebo was consistently larger in the cenerimod 4 mg group than for lower doses and placebo. For the secondary endpoints, a numerically greater response in SRI-4 was observed at Month 6 in the 4 mg group than in the placebo group. The effect was greater in participants with more serologically or clinically active disease. The selection criteria for the population in the current study are aimed at enrolling a population with a clinically and serologically active disease, as this population will potentially derive greater benefit from treatment.

Based on available data, cenerimod may have the potential to be a new oral therapeutic approach for patients with SLE [see Cenerimod IB, section 5.3].

2.4.2 Known and potential risks

Safety areas of special interest were identified in the nonclinical program and were considered in the clinical development of cenerimod. Compared to other S1P receptor modulators, the $S1P_1$-selective cenerimod did not show a negative effect on bronchoconstriction or vasoconstriction, which are known class effects; the spirometry data showed no significant worsening of the pulmonary function in participants treated with cenerimod compared to placebo. Nonclinical pharmacological studies concluded that the QT prolongation potential of cenerimod is low; this was later confirmed in humans [Cenerimod IB, section 5.3.2.1.3]. Furthermore, the results of the ECG monitoring and echocardiography sub-study performed during the ID-064A202 study were not suggestive of any clinically relevant effect in humans.

Accordingly, and taking into consideration the safety results from the Phase 2b study (ID-064A202), the following risk-minimization measures for identified and potential risks will be implemented for participants participating in this study:

Identified risks:

- Cardiovascular variables: cenerimod shows a transient effect on HR at the time of first dose intake, with a maximum decrease of 9 beats per minute (bpm) observed 6 h post-dose. To mitigate the risk of cardiac events, participants will be excluded from this Phase 2 study if they have certain cardiac rhythm disorders, ECG abnormalities indicative of increased risk for arrhythmia, and/or low resting HR [see Section 5.3]. Participants will be excluded or discontinued if receiving medications likely to reduce HR (e.g., beta-blockers) or to increase the risk of cardiac arrhythmia [see Sections 5.3 and 6.2.3]. All participants in this clinical study will undergo cardiac monitoring on Day 1 for 12 hours. Since the effects on HR are expected to be transient and related to initial dosing, no treatment of sinus bradycardia and/or atrioventricular (AV) block is anticipated, unless the symptoms or the seriousness of the condition mandate therapeutic intervention in the view of the treating physician.

Potential risks:

- Embryo-fetal animal toxicity studies showed that cenerimod is embryotoxic and teratogenic in rats and rabbits. Therefore, pregnant women are excluded from this study [see Section 5.3]. Cenerimod should be given to WoCBP only when the absence of pregnancy has been verified, appropriate advice on contraception has been provided, and highly effective contraception is practiced [see Section 5.5]. Women should not become pregnant while on treatment and for 6 months after discontinuation of cenerimod. During these periods, the absence of pregnancy is monitored monthly [see Table 2]. Occurrence of pregnancy will result in immediate discontinuation of the study treatment and monitoring of the pregnancy [see Section 5.8.1.2].

- Liver: a slightly higher incidence of hepatic AEs (mostly denoting liver enzyme increase) and liver enzyme marked abnormalities with no dose-related trends were observed in participants treated with cenerimod compared to placebo in the ID-064A202 study [Cenerimod IB, section 5.3.2.3]. Overall, the incidence of hepatobiliary disorders was lower than seen with other S1P receptor modulators. Participants with signs of ongoing liver disease will not be enrolled into this study and monitoring/discontinuation criteria are applied [see Sections 5.3 and 5.8.1.7].
- Abnormal Immunomodulation: cenerimod reduces the number of circulating lymphocytes. Because of reduced immune surveillance, the risk of infections and malignancy may be increased. Participants with low lymphocytes and/or presenting certain types of malignancies at Screening are excluded from this study [see Section 5.3]. Monitoring/discontinuation criteria are applied [see Section 5.8.1.6].
- Infections: heightened vigilance is required for opportunistic infections, particularly for potentially serious viral infections with neurological symptoms, such as reactivation of human herpes viruses, and of John Cunningham polyoma virus, the causative agent of progressive multifocal leukoencephalopathy. If findings raise suspicion of an opportunistic infection, the participant must discontinue the study treatment. Study -specific eligibility/discontinuation criteria and proper clinical monitoring are applied in the study [see Sections 5.3 and 5.8.1.5]. Results from the ID-064A202 study did not reveal an increased rate of infection in participants treated with cenerimod compared to placebo [Cenerimod IB, section 5.3.2.3].
- Vaccination: no clinical data are currently available on vaccination efficacy under cenerimod. The currently registered S1P receptor modulators (i.e., fingolimod, siponimod, ozanimod, ponesimod) may reduce vaccine effectiveness [Gilenya® SmPC, Mayzent® SmPC, Ponvory® SmPC, Zeposia® SmPC]. Patients with SLE hospitalized because of COVID-19 have significantly higher risks of death and poor outcomes than patients without comorbidities and patients with other comorbidities [Bertoglio 2021]. COVID-19 vaccination induced humoral and cellular responses against SARS-CoV-2 variants in SLE [Moyon 2021] and appears well tolerated in patients with SLE, with only a minimal risk of flare, if any, including after the mRNA vaccines [Felten 2021]. Altogether, vaccination of participants participating in this study may be recommended by the investigator, except for vaccination with live vaccines, which is not allowed within 30 days prior to Day 1 and up to 6 months post last study dose.
- Macular edema: clinical experience with other S1P receptor modulators indicates that participants treated with these drugs may be at increased risk of developing macular edema. Participant safety is ensured by implementation of appropriate eligibility and discontinuation criteria as well as monitoring during this study [see Sections 5.3 and 5.8.1.8]. Participants presenting with a suspicion of macular edema, as reported by

investigators, will be temporarily discontinued from study treatment while an IOSB reviews and assesses the suspected cases [see Section 4.4].

2.4.3 Study procedures and associated potential risks

The following procedures shown in Table 4 will be performed during the study, with their associated potential risks.

Table 4 Study procedures and associated potential risks

Procedure	Standard of Care	Associated potential risk
Physical exam	Yes	No associated potential medical risks.
Blood sampling	No	On average between 7 and 63.5 mL of blood will be sampled (planned) at each monthly visit for the different assessments. The amount of blood drawn at each visit and in total (19 months) is considered acceptable. Potential medical risks include bruising. Additional blood sample maybe required for AE re-test or unscheduled visit.
Urine sampling	Yes	No associated potential medical risks.
12-lead ECG	No	Possible discomfort and transient erythema of ECG patches.
Vital signs	Yes	No associated potential medical risks.
Ophthalmological exam and OCT	No	No associated potential medical risks.
Chest X-ray (or CT scan) for eligibility to exclude latent TB	No	Single low radiation exposure. Performed only at Screening.

ECG = electrocardiogram; OCT = optical coherence tomography; TB = tuberculosis.

2.4.4 Assessment of benefit -risk

In the ID-064A202 study, there was no participant discontinuation due to low HR on Day 1, no relevant findings in the echocardiography sub-study, no difference in pulmonary function tests compared to placebo. Three cases of macular edema were reported but none were related to cenerimod with one each being present at baseline, due to retinitis pigmentosa or related to chloroquine therapy, and considered to be due to a branch retinal vein occlusion (refer to Investigator Brochure). Second-degree AV block Mobitz I was reported in 2 participants; all AV blocks were transient, asymptomatic, resolved within 24 h without therapeutic intervention, and did not require study treatment discontinuation. Finally, there was no imbalance in AEs compared to placebo denoting infections and no consistent or dose-dependent change in SBP or DBP over time. Although 4 mg cenerimod was administered for a total of 6 months only, followed by either placebo or 2 mg for another 6 months, there is currently no indication that prolonged use of 4 mg cenerimod

(12 months of 4 mg) would create further risks. However, caution is advised for the longer-term treatment at this dose in study ID-064A204 due to the limited data generated so far.

Safety data (AEs, SAEs, laboratory assessments, ECGs, vital signs, and other study-specific examinations) will be monitored on a regular basis by the sponsor.

It is the investigator/delegate's responsibility to monitor the benefit -risk ratio of study treatment administration, as well as the degree of distress caused by study procedures, at an individual participant level, and to discontinue study treatment or the study for that individual if, on balance, they believe that continuation would be detrimental to the participant's wellbeing.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 List of objectives and endpoints –

The objectives are:

Primary objectives

- To evaluate the safety and tolerability of cenerimod 4 mg in Chinese participants.
- To evaluate the PK of cenerimod 4 mg in Chinese participants
- To evaluate the PD of cenerimod 4 mg in Chinese participants.

Other objective

- To preliminarily evaluate the efficacy of cenerimod 4 mg in Chinese participants.

All endpoints and their relationship to the objectives are shown in Table 5. Baseline is defined as the last available measurement before the start of treatment. These endpoints will be evaluated according to the protocol once the last participant completes the 6-month safety follow-up visit or withdraws from the study.

Table 5 Objectives and endpoints

Objectives	Endpoints
To evaluate the safety and tolerability of cenerimod 4 mg in Chinese participants	• Occurrence of TEAEs[1], SAEs and AESIs up to FSV. • Occurrence of AEs leading to permanent discontinuation of study treatment. • Changes in vital signs (SBP, DBP) and body weight from baseline to each post-baseline assessment. • Changes in hourly 12-lead ECG variables (HR and the intervals: QTcB, and QTcF) and in SBP/DBP assessments at Day 1 cardiac monitoring.

Objectives	Endpoints
	• Changes in 12-lead ECG variables (HR and the intervals: PR, QRS, QTcB, and QTcF) from baseline to each post-baseline assessment. • Treatment-emergent medically relevant ECG abnormalities from baseline to each post-baseline assessment. • Changes in laboratory variables (hematology, blood chemistry, and urinalysis) from baseline to each post-baseline assessment. • Treatment-emergent marked laboratory abnormalities from baseline to all assessed time points.
To evaluate the PK of cenerimod 4 mg in Chinese participants.	**PK endpoints** • Cenerimod plasma concentrations at all scheduled time points (see Table 2). • The plasma PK parameters of 4 mg cenerimod will be derived by non-compartmental analysis of the plasma concentration-time profiles and calculated based on the actual PK sampling time. The following endpoints will be determined: – C_{max}, t_{max}, and AUC_{0-24} during the first dosing interval on Day 1, – C_{max}, t_{max}, and AUC_{τ} during a dosing interval at steady state (i.e., at Month 2), – AI between Day 1 and Month 2.
To evaluate the PD of cenerimod 4 mg in Chinese participants.	**PD endpoints** • Change in total blood lymphocyte count from baseline to each post-baseline assessment.

Objectives	Endpoints
To preliminarily evaluate the efficacy of cenerimod 4 mg in Chinese participants.	**Efficacy endpoints** • Response on SRI-4 from baseline to Month 12 • Response on mSLEDAI-2K from baseline to Month 12. • Response on BICLA from baseline to Month 12 • Response on CLASI from baseline to Month 12 • Change in tender and swollen joints from baseline to Month 12 • Changes in OCS dosage from baseline to Month 12

[1] A TEAE is any AE temporally associated with the use of study treatment (from study treatment start until 180 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AE = adverse event, AESI = adverse event of special interest, AI = Accumulation index, BICLA = BILAG-based Composite Lupus Assessment, CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, DBP = diastolic blood pressure, ECG = electrocardiogram, FSV = final study visit, HR = heart rate, mSLEDAI = Modified Systemic Lupus Erythematosus Disease Activity Index, OCS= oral corticosteroids, PK = pharmacokinetic(s), QTcB = QT corrected for heart rate using Bazett's formula, QTcF = QT corrected for heart rate using Fridericia's formula, SAE = serious adverse event, SBP = systolic blood pressure, SRI = Systemic Lupus Erythematosus Responder Index, TEAE = treatment-emergent adverse event.

3.2 Appropriateness of endpoints

The safety endpoints are well established and typically reported in studies at this stage of clinical development, such as safety laboratory data, ECGs and vital signs. Due to the known class effects of S1P receptor modulators, ophthalmology examinations and OCT assessments are being performed at regular intervals during the clinical study.

S1P receptor modulators, including cenerimod, have been shown to have an effect on HR. In Phase 2 studies, cenerimod has been shown to have a clinically non-significant decrease in HR at the first dose. In the current study, all participants will have HR, BP and ECG monitored at the first dose to determine if cenerimod has the same effect in Chinese SLE patients.

The PK endpoints are well established for evaluating the extent of systemic exposure (AUC) and rate of systemic absorption (C_{max} and t_{max}) of a drug [FDA 2014b]. Obtaining a plasma concentration-time profile at Month 2 will allow to assess the PK endpoints at steady-state conditions and, thus, to evaluate the accumulation of cenerimod.

The efficacy endpoints are based on previous clinical studies conducted in SLE and have regulatory precedent. Due to the open-label nature of this clinical study, no placebo group will be available for comparison, and the post-dose values of these endpoints will be compared to the baseline values. Multiple efficacy endpoints are included to allow

comparison between other studies and to act as an internal control between the disease assessments, e.g., the CLASI rash is a detailed evaluation of rash on the body and therefore can be used to determine if the rash reported in the mSLEDAI is correct.

4 STUDY DESIGN AND PLAN

4.1 Study design

This is a multicenter, open label, single arm, multiple-dose study in adult Chinese participants with moderate-to-severe SLE on top of background therapy.

It is planned that approximately 15 adult Chinese participants concurrently receiving SLE background therapy will receive cenerimod 4 mg o.d. for 12 months.

The study will be conducted at approximately 5-10 sites in China.

4.1.1 Study periods for an individual participant

The screening period will last up to 30 days. Participants will receive cenerimod for a maximum of 12 months. For participants that permanently discontinue study treatment, they will enter the post-treatment observation period. Participants that complete the 12-month treatment period will enter a 6-month safety follow-up period until FSV.

Post-treatment observation period (only applicable to participants who permanently discontinue study treatment): starts the day after the last dose of study treatment and participants will complete visits until at least 6 months after last study treatment intake as follows:

- Participants who permanently discontinue study treatment before or at Month 6 will complete study visits until Month 12 and the FSV will be at Month 12 (i.e., PTOP Visit 14).
- Participants who permanently discontinue study treatment between Month 7 and Month 12 (inclusive) will complete PTOP FU visit(s) until 6 months after last study treatment intake and the FSV will be one of the monthly PTOP FU visits, as applicable.

Follow-up period: Starts on the day after the last dose of study treatment and ends 6 months, i.e., 180 days, thereafter with FSV.

A participant's participation in the study ends with the completion of the FSV. The participant will participate in the study for a duration of up to 19 months.

The visit schedule and protocol-mandated procedures are performed according to the SoA [Table 1, Table 2, and Table 3] and are described in Section 7.2.

The study design is depicted in Figure 1.

4.2 Study duration and End-of-Study definition

The study starts with the recruitment of the first participant. A participant is considered recruited when the participant's ICF has been fully signed.

The study's primary completion date is the date of the last participant's FSV (i.e., completion of the 6-month safety follow-up).

The End-of-Study (EOS) is defined as completion of the last FSV. The study is expected to last approximately 22 months.

4.3 Study design rationale

This study is a multicenter, open label, single arm, multiple-dose study evaluating the safety, PK and PD of cenerimod 4 mg in adult Chinese patients with moderate-to-severe SLE in addition to background SLE therapy.

A treatment period of 12 months is an appropriate study duration to evaluate cenerimod's long-term safety profile.

Open label treatment is considered adequate to evaluate the PK of cenerimod in Chinese participants based on the quantitative nature of these measurements. As cenerimod has been evaluated in a number of other clinical studies, the safety endpoints can also be evaluated in an open label manner to avoid treating SLE patients with a placebo for 12 months.

To ensure adequate treatment, all participants will receive SLE standard of care treatment with at least 1 of the following: OCS, antimalarial, or immunosuppressants, in addition to study treatment [see Sections 5.2 and 6.2]. This is consistent with the Chinese guidelines for the treatment of moderate-to-severe SLE [Li et al 2020].

Given the associated side effects of OCS, an important goal of new therapies is to reduce the chronic use of CS. In this study OCS tapering is mandatory to investigate if cenerimod can reduce the usage of OCS in Chinese patients. Tapering will start after the Month 3 visit (see section 6.2.1.2.3for details), when cenerimod is expected to have a clinical effect but is not allowed after Month 9 to allow interpretation of the efficacy measurements.

Overexpression of IFN-1, IFN-1 gene signature, and proteins induced by Type 1 IFNs have all been associated with greater disease activity and organ system involvement in SLE. Recent clinical studies have demonstrated that between 50 and 90% of SLE patients show the consistent presence of an IFN-1 high signature based on blood analyses, and that this signal is stable over time [Kirou 2004, Northcott 2022, Oke 2019, Ronnblom 2019].

Therefore, in this study, we will evaluate the IFN-1 gene signature in participants at baseline, during and after treatment.

4.4 Study committees

An IOSB will receive all information related to suspected cases of macular edema and will perform a central, review of OCT images and participants' data of suspected cases of macular edema as per the IOSB charter.

5 STUDY POPULATION

5.1 Participant population description

The target population of this study is adult participants diagnosed with generalized moderate-to-severe SLE who are receiving SLE background therapy.

5.2 Inclusion criteria

Participants must meet all the following inclusion criteria:

Screening criteria

1. Signed and dated ICF prior to any study-mandated procedure.
2. Male or female Chinese participants aged from 18 to 75 years old (both inclusive) at the time of signing the ICF.
3. Diagnosis of SLE made at least 6 months prior to Screening, according to 2019 EULAR/ACR Criteria [see Appendix 2].
4. An mSLEDAI-2K score ≥ 6 and clinical mSLEDAI-2K score ≥ 4 with at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers) [see Appendix 6].

Note: The mSLEDAI-2K score does not include "leukopenia". The clinical mSLEDAI-2K is the mSLEDAI-2K assessment score without the inclusion of points attributable to hematuria, proteinuria, pyuria, urinary casts, low complement, increased DNA binding, and thrombocytopenia.

5. PGA score ≥ 1.0 on a 0 to 3 VAS [see Appendix 9].
6. Currently treated with one or more of the following SLE background medications:
    - Antimalarials: (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine)
    - Mycophenolate mofetil (≤ 2 g/day) / mycophenolic acid (≤ 1.44 g/day)
    - Azathioprine (≤ 2 mg/kg/day)
    - Methotrexate (≤ 25 mg/week)
    - OCS
        – if OCS is the only SLE background medication: ≥ 7.5 mg/day and ≤ 30 mg/day prednisone or equivalent

  - if OCS is not the only SLE background medication: ≤ 30 mg/day prednisone or equivalent
- Belimumab (≤ 10 mg/kg every 4 weeks i.v. or 200 mg/week s.c.).
- Telitacicept (≤ 240 mg/week subcutaneously).

Treatment with antimalarials, mycophenolate mofetil, mycophenolic acid, azathioprine, methotrexate, belimumab, or telitacicept must have been started at least 90 days prior to Screening.

Treatment with OCS must have been started at least 30 days prior to Screening.

7. For WoCBP [see definition in Section 5.5.1]:
   - Negative serum pregnancy test at Screening.
   - Agreement to undertake monthly urine pregnancy tests from Day 1 up to 6 months after study treatment discontinuation.
   - Agreement to use a highly effective method of contraception as described in Section 5.5.2 from Screening (Visit 1) up to 6 months after study treatment discontinuation.

Day 1 pre-dose criteria

8. A clinical mSLEDAI-2K score ≥ 4 with at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers).
9. PGA score ≥ 1.0 on a 0 to 3 VAS.
10. Presence of **at least one** of the following biomarkers of serological evidence of active SLE (in a Screening sample as measured by central laboratory):
    - Anti-dsDNA antibodies elevated above normal.
    - ANA with a titer of at least 1:160.
    - Anti-Sm antibody elevated above normal.
11. Currently treated with one or more of the following SLE background medications that must be stable for at least 30 days prior to Day 1 (except OCS that must be stable for at least 15 days prior to Day 1):
    - Antimalarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine),
    - Mycophenolate mofetil (≤ 2 g/day) / mycophenolic acid (≤ 1.44 g/day),
    - Azathioprine (≤ 2 mg/kg/day),
    - Methotrexate (≤ 25 mg/week),
    - OCS:

  - if OCS is the only SLE background medication: ≥ 7.5 mg/day and ≤ 30 mg/day prednisone or equivalent
  - if OCS is not the only SLE background medication: ≤ 30 mg/day prednisone or equivalent
- Belimumab (≤ 10 mg/kg every 4 weeks i.v. or 200 mg/week s.c.),
- Telitacicept (≤ 240 mg/week subcutaneously).

12. WoCBP must have a negative urine pregnancy test.

5.3 Exclusion criteria

Participants must not meet any of the following exclusion criteria:

Pregnancy and breastfeeding

1. Pregnant, planning to be become pregnant up to 6 months after the last dose of cenerimod in this study, or lactating women.

SLE and other immune diseases

2. Active severe SLE-driven renal disease (within 90 days prior to Screening or during Screening) where, in the judgment of the investigator, protocol-specified SLE background therapy is insufficient and the use of a more aggressive therapeutic approach or other treatments not permitted in the protocol, is indicated.
3. Urine protein/creatinine ratio > 3000 mg/g (i.e., > 339.45 mg/mmol) at screening assessment based on central assessment.
4. Severe active CNS lupus or active severe or unstable neuropsychiatric SLE including but not limited to aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy); acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; and mononeuritis multiplex.
   - That would make the participant unable to fully understand the ICF.

     or
   - Where, in the opinion of the investigator/delegate, protocol-specified standard of care is insufficient and the use of a more aggressive therapeutic approach, such as adding i.v. cyclophosphamide and/or high dose i.v. pulse CS therapy or other treatments not permitted in the protocol, is indicated.
5. Severe forms of vasculitis (e.g., retinal vasculitis, coronary vasculitis, pulmonary vasculitis, mesenteric vasculitis) requiring systemic immunosuppressive treatment within 90 days prior to Screening or during Screening.

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

Cardiovascular

7. History or presence of Mobitz type II or third-degree AV block, sick sinus syndrome, symptomatic bradycardia, or syncope associated with cardiac disorders.
8. Participants 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 Class III/IV within 6 months prior to Screening.
9. Resting HR < 50 bpm as measured by the 12-lead ECG at Screening or at Day 1 prior to study drug administration.
10. An elevated QTcF interval of > 470 ms (females) / > 450 ms (males) at Screening or at Day 1 prior to study drug administration.

Pulmonary

11. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function, and chest X-ray (or CT scan as per local guidelines) performed at Screening or within 6 months prior to Screening.
12. History of clinically relevant bronchial asthma or chronic obstructive pulmonary disease that has required treatment with oral or parenteral CS for more than a total of 2 weeks within the last 6 months prior to Screening.

Infection and infection risk

13. Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.
14. Have evidence of active TB or latent TB

    a. Active TB: Have evidence of active TB, defined in this study as the following:

    Medical history, clinical features, and abnormal chest x-ray at screening indicating the presence of TB.

    IFN gamma release assay (IGRA): Participants are excluded from the study if the test is not negative and there is clinical evidence of active TB.

    Exception 1: participants with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such participants would not be required to undergo the IGRA test but must have a chest x-

ray at screening (i.e., chest imaging performed within the past 6 months will not be accepted).

b. Latent TB: Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:
An IGRA test which is not negative, no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening;
If the IGRA test results are positive, the participant will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the participant will be considered to have latent TB (for purposes of this study).

Exception 2: participants with a history of latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such participants would not be required to undergo the IGRA test, but must have a chest x-ray at screening (i.e., chest imaging performed within the past 6 months will not be accepted

15. Ongoing bacterial, viral, parasitic, or fungal infection that is of clinical concern according to the investigator or history of any of the following:
    - Clinically significant chronic infection (e.g., osteomyelitis, bronchiectasis, etc.) within 8 weeks prior to Screening (chronic nail infections are allowed).
    - Any infection requiring hospitalization or treatment with i.v. anti-infectives not completed at least 4 weeks prior to Screening.
16. 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 (if positive IgM and/or IgG, to be confirmed by HCV-RNA PCR assessment, and if this assessment is negative, participant can be enrolled).
    - Anti-HEV IgG or IgM (if positive IgM and/or IgG, to be confirmed by HEV-RNA PCR assessment and if this assessment is negative participant can be enrolled).
17. Participants who have congenital or acquired severe immunodeficiency or known HIV infection or positive HIV testing.
18. Negative IgG antibody test for varicella-zoster virus.

Malignancy

19. History or presence of malignancy (except for surgically excised and non-recurrent cutaneous basal cell carcinoma, squamous cell carcinoma, or cervical carcinoma), lymphoproliferative disease, or history of total lymphoid irradiation within 10 years prior to Screening.

Transplantation

20. History or presence of homologous (allogenic) bone marrow or solid organ transplantation.

Ophthalmologic

21. Presence of macular edema or active uveitis detected by OCT during Screening.

Metabolic

22. Documented poorly controlled diabetes mellitus (i.e., HbA1c > 8.0% at Screening as reported by the central laboratory or unstable blood sugar control/treatment adherence as per investigator's judgment) or diabetes mellitus complicated with organ involvement, such as diabetic nephropathy or retinopathy as assessed by investigator.

Hepatic

23. History of chronic liver or biliary disease (other than Gilbert's Syndrome) or participants with ALT or AST > 3 × ULN or TBIL > 1.5 × ULN (unless in the context of known Gilbert's Syndrome).

Hematology

24. Significant hematology abnormality at screening assessment:
    - Lymphocyte count < 500 /μL (0.5×10^9/L);
    - Hemoglobin < 7 g/dL;
    - WBC count < 2000/μL (2.0×10^9/L) or
    - Platelets < 25,000/μL (25×10^9/L).

Renal

25. eGFR < 15 mL/min/1.73 m^2.

Medications

26. Treatment with the following medications within 15 days or 5 half-lives of the medication (whichever is longer) prior to Day 1:
    - β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering systemic therapy [list of drugs provided in Appendix 3].

- QT-prolonging drugs with known risk of torsade de pointes irrespective of indication [list of drugs provided in Appendix 4].

27. Treatment with the following medications within 30 days or 5 half-lives of the medication (whichever is longer) prior to Day 1:
    - Cyclophosphamide, cyclosporine, voclosporin, tacrolimus, sirolimus, etc.
    - Pulse methylprednisone.
    - Vaccination with live vaccines.
28. Intra-articular, intramuscular, or i.v. CS within 6 weeks prior to Day 1.
29. Treatment with the following medications within 90 days or 5 half-lives of the medication (whichever is longer) prior to Day 1:
    - Leflunomide.
    - i.v. immunoglobulins.
30. Treatment with any investigational agent within 90 days or 5 half-lives of the drug (whichever is longer) prior to Day 1.
31. Treatment with B cell-depleting biological agents (e.g., rituximab or ocrelizumab) or biological immunosuppressive agents (e.g., anti-TNF, anti-IL1, anti-IL6 therapies) within 12 months prior to Day 1.
32. Treatment with anifrolumab within 6 months prior to Day 1.
33. Treatment with any of the following medications any time prior to Screening:
    - Alemtuzumab.
    - S1P receptor modulators (e.g., fingolimod).
    - Participants previously randomized to cenerimod or placebo in any trial involving cenerimod.

Other categories

34. Recent clinically significant drug or alcohol abuse as per investigator's judgment.
35. Known allergy to S1P receptor modulators or any of the cenerimod formulation excipients.
36. Any other clinically relevant medical condition that would put the participant at risk if participating in the study, or any other diseases that may confound the disease activity assessments.
37. Participants with body weight < 40 kg at Screening or Day 1.

5.4 Rationale for the selection of the study population

The target population of this study is similar to the participant population from the Phase 2b ID-064A202 study as it consists of adult participants with generalized SLE who are receiving background therapy.

Participants must have at least a 6-month history of SLE and must be classified as SLE according to 2019 EULAR/ACR criteria [Aringer 2019]. This study is being performed in patients with SLE in order to evaluate the PK and PD effects in the target population which may benefit from cenerimod. Healthy volunteers would not allow for the same evaluation, as for example lymphopenia is often more prevalent in SLE as compared to healthy people.

Participants will be included in the study if they have a sufficient level of disease activity to justify therapeutic intervention.

However, since only limited efficacy data are available to date, it is premature to test cenerimod in the most severe spectrum of the disease. In line with our exclusion criteria, participants with active lupus nephritis and CNS lupus requiring additional immunosuppressive therapies are excluded [see Section 5.3].

Given the heterogeneity in SLE disease manifestations, treatment is often not standardized. In order not to confound the results of the study, participants should have initiated SLE background treatment (except OCS) at least 3 months prior to Screening and need to have stable doses at least 30 days prior to Day 1 and throughout the study. Background OCS therapy should have been initiated at least 30 days prior to Screening and the dose must be stable at least 15 days prior to Day 1 [see Section 5.2 and 6.2.1.2]. The inclusion of participants with background therapies commonly used to treat SLE in China will allow the evaluation of safety in a smaller number of patients prior to starting a large clinical study in China.

5.5 Contraception requirements for women of childbearing potential

5.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential, 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).

5.5.2 Methods of contraception

Cenerimod is embryotoxic and teratogenic in animal studies. WoCBP [see definition in Section 5.5.1] must use an **uninterrupted highly effective** method of contraception from Screening (Visit 1) up to at least 6 months after study treatment discontinuation due to the long half-life of the study treatment (33 days).

Contraceptive methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the study.

Highly effective methods of contraception are defined as those, alone or in combination, resulting in a failure rate of < 1% per year when used consistently and correctly. Such methods include:

- Hormonal contraceptives: Combined (containing estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation using one of the following routes of administration:
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
  - Implantable (low user dependency)

If a hormonal contraceptive is chosen from this group, it must be taken for at least 30 days prior to administration of the first study treatment dose. If, during the study treatment period, a participant switches or starts a hormonal contraceptive method, caution must be taken to ensure a highly effective method of contraception is used without discontinuation in order to ensure continued effective contraception.

- Intrauterine device (low user dependency).
- Intrauterine hormone-releasing system (low user dependency).
- Bilateral tubal occlusion/ligation at least 6 weeks prior to Screening (low user dependency).
- Vasectomized partner: this is a highly effective birth control method, provided that the partner is the sole sexual partner of the participant and that the vasectomized partner has received a medical assessment of the surgical success.
- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study; whether it is the preferred and usual lifestyle of the participant; and whether it is locally accepted as a highly effective method of contraception.

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

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

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

- Progestogen-only oral hormonal contraception (except if inhibition of ovulation is 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 must explain and remind female participants of the importance of using methods of contraception **at every study visit**.

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 participant to follow the protocol-mandated method of contraception up to at least 6 months after study treatment discontinuation.

If the investigator/delegate finds that the protocol-mandated highly effective method of contraception is not consistently and correctly followed by the participant, the study treatment **must** be permanently discontinued [see Section 5.8.1.3].

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

5.6 Contraception for male participants with a partner who is of childbearing potential

Cenerimod is neither genotoxic nor mutagenic [see section 4.3.8.7 of the Cenerimod IB]. Thus, no contraceptive methods are needed for male participants participating in this clinical study. 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 very low.

5.7 Screen failures and re-screening

Screen failures are defined as participants recruited in the clinical study (i.e., ICF fully signed) who are not subsequently enrolled in the study. Participants may have a laboratory assessment repeated once during the screening period, if, in the investigator's medical opinion, the value leading to ineligibility is transient and not clinically significant, prior to the participant being screen failed.

A minimal set of screening failure information is required to ensure compliant reporting of screening failure participants. For participants who failed Screening, the following data will be recorded in the eCRF:

- ICF signature date;
- Age, sex, and race;
- Inclusion criteria not met and/or exclusion criteria met;
- SAEs.

Re-screening of participants after screen failure is not allowed.

5.8 Criteria for withdrawal of participants

A participant has the right to permanently discontinue the study treatment at any time by withdrawing from the study treatment only or by withdrawing from the study treatment **and** any further participation in the study (i.e., premature withdrawal from the study). It is recommended that the investigator/delegate makes a reasonable effort to maintain participants on treatment, as medically appropriate, and follow the schedule of visits, as data robustness depends on such compliance. Should a participant stop treatment or withdraw from the study, the investigator/delegate should ascertain the reason(s), while fully respecting the participant's rights.

5.8.1 Study treatment interruption and permanent discontinuation of study treatment

5.8.1.1 Principles

The decision to permanently discontinue the study treatment can be made by the participant, the investigator/delegate, or the sponsor personnel.

The investigator/delegate has the option of temporarily interrupting or permanently discontinuing the study treatment for a given participant in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. If the

study treatment is interrupted by the participant for any reason, he/she must inform the investigator/delegate as soon as possible. Any study treatment interruptions (i.e., for a day or more) must be recorded in the eCRF.

The investigator/delegate must permanently discontinue the study treatment for a given participant if, on balance, he/she believes that continued administration would be contrary to the best interests of the participant.

Study-specific criteria for temporary interruption and permanent discontinuation of the study treatment are described in Sections 5.8.1.2 to 5.8.1.11.

The main reason for permanent discontinuation of the study treatment (e.g., due to pre-specified study treatment discontinuation criteria, an AE, lack of efficacy, study termination) must be documented in the eCRF.

A participant who permanently discontinues the study treatment is **NOT** considered withdrawn from the study. The participant will be asked to return for a pEOT visit within 7 days after the last dose of study treatment intake, and thereafter to attend further planned visits as defined in the SoA [Table 2 and Table 3] and in Section 7.2.

All participants withdrawn from study treatment are encouraged to continue the planned study procedures (e.g., visits and questionnaire completion [Table 3]) until planned FSV, provided that the participant's consent for this further limited participation in the study has not been withdrawn. This will decrease the amount of missing data, which is important to maintain the integrity of the study.

5.8.1.2 Pregnancy

If a participant becomes pregnant while on study treatment, the study treatment **must** be permanently discontinued. The investigator/delegate must counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. For reporting of pregnancies, refer to Section 8.3.1.

If a participant has a positive urine pregnancy test, the study treatment must be interrupted immediately. A serum pregnancy test must be performed as soon as possible. If the pregnancy is confirmed, the study treatment **must** be permanently discontinued. If the result of the serum pregnancy test is negative, the study treatment may be resumed.

5.8.1.3 Lack of compliance with methods of contraception

If the investigator/delegate considers that the participant is not compliant with the protocol methods of contraception instructions, the study treatment **must** be permanently discontinued.

5.8.1.4 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 8.1.1].

5.8.1.4.1 Day 1 specific stopping criteria

Cardiac monitoring on the first dose on Day 1 and on the first day of re-initiation of study treatment will be required for participants.

Participants **must** be permanently discontinued from study treatment if any of the following occurred on Day 1 or on the day of re-initiation:

- 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 participants 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 participant does not meet the criteria for discharge from the monitored setting at 12-hour post-dose.

Close monitoring (ECG or BP, as appropriate) is recommended for participants who meet study treatment discontinuation criteria as detailed in Appendix 5.

5.8.1.4.2 Other cardiovascular stopping criteria

- If participant presents with a QTcF of > 500 ms (females) or > 480 ms (males) at any time throughout the study, as measured and documented by 12-lead ECG, a re-test should be performed at the same visit. If at re-test, QTcF is confirmed > 500 ms (females) or > 480 ms (males), the participant must be permanently discontinued from study treatment. Participants 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.

If any of those criteria are met, it will be recorded as an AE/SAE, and follow-up monitoring will have to be provided until the AE resolves and the participant's condition is stable.

5.8.1.5 Infections

In the event of a serious infection as per the investigator's opinion (e.g., opportunistic infection or serious infection requiring i.v. medication or hospitalization), the participant should be adequately treated and monitored until resolution of the infection. The investigator should consider permanent discontinuation of study treatment. The decision to

permanently discontinue study treatment should be made after evaluation of all available information concerning all potential causes of infection and based on the clinical status of the participant and response to the treatment of the infection. 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.

These AEs must be reported in the eCRF [see Section 8.2]. Concomitant immunomodulatory medications may also be discontinued at the discretion of the investigator.

Note: Participants should not receive any of the per-protocol prohibited systemic treatments during 6 months after last study treatment intake, unless clinically indicated and justifiable in the opinion of the investigator.

5.8.1.6 Lymphocyte count monitoring

Lymphocytes are assessed by the central laboratory at each scheduled visit.

Alert for total lymphocyte < 200 cells/µL (i.e., 0.2 × 10^9 cells/L or 0.2 × 10^3 cells/µL)

At any time throughout the study, when total lymphocyte count is < 200 cells/µL, an alert including the lymphocyte count results will be generated by the central laboratory. This alert will be distributed to the investigator and to the sponsor. The sponsor will ensure that the investigator/delegate has received the alert. The investigator/delegate will take appropriate action to ensure the safety of the participant [see Figure 2]. The investigator must closely follow up with the participant, especially focusing on signs or symptoms of infection. The participant must be instructed to contact the study site if symptoms of infection occur [see Section 5.8.1.5].

Upon receipt of the first alert, the investigator/delegate will rapidly contact the participant to schedule a visit at study site as detailed below, while asking the participant to continue taking the study treatment.

At this visit, a lymphocyte count re-test and necessary clinical assessments will be performed. The central laboratory must be used for assessments of the re-test lymphocyte count.

Re-test result is ≥ 200 cells/µL (i.e., 0.2 × 10^9 cells/L or 0.2 × 10^3 cells/µL)

The participant can continue taking study medication and can resume the regular schedule of visits as per protocol.

Re-test result is 100 to < 200 cells/µL

The participant must be retested within 2 weeks, while continuing to take study treatment.

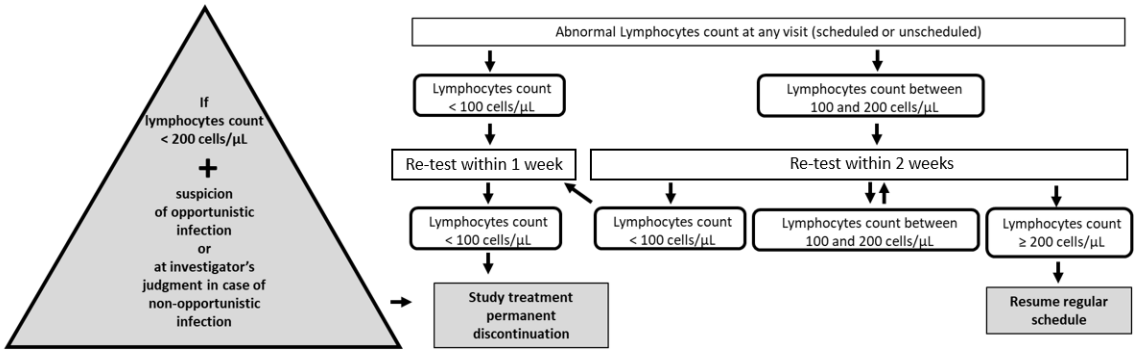
Re-test result is < 100 cells/µL (i.e., 0.1 × 10^9 cells/L or 0.1 × 10^3 cells/µL)

The participant must be permanently discontinued from study treatment, except at the first occurrence of a total lymphocyte count at re-test < 100 cells/µL, in which case the participant must be re-tested within 1 week. Then, based on the results:

- If the lymphocyte count at 1-week re-test is confirmed < 100 cells/µL, the participant must be permanently discontinued from study treatment. For results of 100 to < 200 cells/µL or ≥ 200 cells/µL, see instructions above.

Note: If the lymphocyte count < 200 cells/µL is accompanied by signs of opportunistic infection or severe infection (as per investigator's judgment), the study treatment will be permanently discontinued. The participant will be medically followed [see Section 5.8.1.5].

Figure 2 Guidance for re-test results of lymphocytes < 200 cells/µL



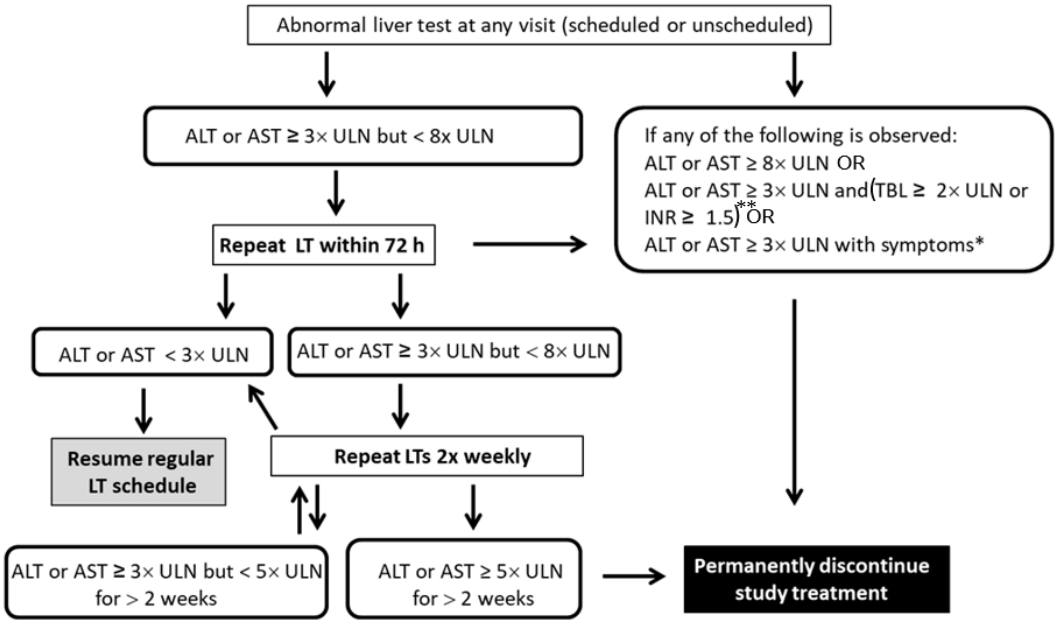
Total lymphocyte count at final study visit

If the lymphocyte count is < 500 cells/µL at FSV (i.e., after 6 months FU period or at the end of PTOP/FU period for participants who permanently discontinued study treatment), monitoring of clinical status and total lymphocyte count in local laboratory should be performed on a regular basis (e.g., every 2–4 weeks) until the lymphocyte count has returned to ≥ 500 cells/µL.

5.8.1.7 Liver enzyme abnormalities

In the event of elevated transaminase > 3 × ULN, the participant will be closely observed, liver tests 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%).
** See details below for participants receiving or not receiving anticoagulants.
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 INR are reached as indicated in Figure 3, an alert will be sent by the central laboratory to the site/investigator and the sponsor. If a participant has ALT or AST ≥ 3 × ULN and is not receiving an anti-coagulant, then the threshold to permanently discontinue study treatment is 1.5 × ULN for INR. If a participant has ALT or AST ≥ 3 × ULN and is receiving an anti-coagulant (e.g., coumadin), then the threshold for INR is 1.5 × the upper INR target set for the participant (for example, if a participant is receiving coumadin with an INR target of 2 to 3, the marked abnormality for the INR would be 4.5 for this participant). The sponsor will contact the site/investigator to ensure that he/she will immediately contact the participant to enquire about symptoms and ask the participant to permanently discontinue study treatment or to return to the site within 72 h at the latest to repeat the test at the central laboratory (unless the clinical situation mandates immediate local testing) as applicable.

In the event of repeated abnormal liver tests within 72 h, the participant will be closely monitored, 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. Preferably, the central laboratory should be used. If the local laboratory is used for testing in some situations (e.g., laboratory result needed immediately by treating physician), please ensure that an additional sample is sent to the central laboratory at the same time.

In all cases of permanent study treatment discontinuation, follow-up monitoring must be conducted until abnormalities in the liver assessments have resolved or are steadily improving.

5.8.1.8 Ocular abnormalities

Suspected macular edema cases will be submitted to the IOSB [see Section 4.4].

The study treatment must be temporarily interrupted during the case assessment. If the IOSB confirms or suspects macular edema, study treatment must be permanently discontinued. If the IOSB assesses the case as not being a macular edema, the study treatment can be re-started. The participant must be followed up until resolution or until the condition is considered not clinically significant by the investigator.

5.8.1.9 Initiation of forbidden concomitant medication during the study

At any time throughout the study, study treatment will be permanently discontinued if the participant starts taking a forbidden concomitant therapy [see Section 6.2.3].

5.8.1.10 Other potential permanent treatment discontinuation

In the event of malignancy, study treatment will be permanently discontinued and the participant must be medically followed up as appropriate.

5.8.1.11 Other study-specific criteria for re-initiation after temporary treatment interruption

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

A study visit to re-initiate treatment is only required after a study treatment interruption lasting more than 7 consecutive days and occurring between Day 1 and Day 14 of the study.

- During the period between Day 1 and Day 14, if the participant fails to take the dose for more than 7 consecutive days, the participant must inform the 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 [see Appendix 5].

- If, at any visit (scheduled or unscheduled), the participant 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 study treatment interruption should be collected. The participant should be counseled on the risks of non-compliance. Information on the treatment interruption must be recorded in the eCRF. No re-initiation visit needs to be performed in such a case.

If the participant misses 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 participant should be counseled on the risks of non-compliance. Information on the treatment interruption must be recorded in the eCRF. Participants must be instructed to contact the investigator immediately if they experience any symptoms that may be related to bradycardia (e.g., dizziness, vertigo, syncope).

5.8.2 Measures for participant retention

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

In order to ensure study data integrity and completeness, participants that are prematurely discontinued from study treatment should perform the subsequent visits as per PTOP schedule [see Table 3].

The investigator is encouraged to explain to the participants 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 participant's data.

5.8.3 Withdrawal from the study

Participants may voluntarily withdraw from the study without justification for any reason at any time. Participants 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 [see Section 5.8.4]. If a participant withdraws consent for further study participation, no further data will be collected in the eCRF from the date of withdrawal onward.

If, for whatever reason (except death or lost to follow-up), a participant withdraws from the study, the investigator/delegate should make their best effort to schedule a last appointment / telephone call to assess the safety and wellbeing of the participant, collect unused study treatment, and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the participant's medical records but will not be collected in the eCRF.

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

The investigator must provide follow-up medical care for all participants who withdraw from the study, or must refer them for appropriate ongoing care, as described in Section 6.3.

5.8.4 Lost to follow-up

A participant will be considered as lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The site must take preventive measures to avoid a participant being lost to follow-up (e.g., document different ways of contact, such as telephone number, home address, email address, contact person if the participant cannot be reached).

The following actions must be taken if a participant fails to return to the site for a scheduled study visit:

- The site staff must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- If the participant cannot be reached, the site must make a reasonable effort to contact the participant and document all attempts in the participant's medical chart. Reasonable efforts include, when possible, 3 telephone calls to the last available telephone number and 1 registered/certified letter to the participant's last known mailing address or local equivalent methods.
- If the participant is still unreachable after all contact attempts listed above, he/she will be considered lost to follow-up.

The date of last successful contact with the participant will be collected in the eCRF.

6 TREATMENTS

6.1 Study treatment

6.1.1 Investigational treatment

Cenerimod is supplied as film-coated tablets at a 4 mg dose.

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.

6.1.2 Study treatment dosing and administration

One tablet of cenerimod 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.

Participants 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., vital signs, ECGs, laboratory tests, and PK sampling). The dose prior to the Month 2 visit must be administered by the participant 24 h (±3 h) prior to the anticipated dosing at the Month 2 visit. Date and time of study treatment intake will be recorded in the eCRF for Day 1, the day before Month 2, and Month 2.

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

6.1.2.1 Study treatment dose adjustments

Study treatment dose adjustments are not permitted.

Note that under **no circumstances** should a participant take more than 1 tablet per day.

6.1.3 Justification for dose

The selection of a 4 mg (o.d.) dose of cenerimod for this study is based on the safety and efficacy results from the Phase 2b study (ID-064A202), where cenerimod did not show any safety signals/concerns at any tested dose (0.5, 1, 2, and 4 mg), and was not associated with any clinically relevant safety findings. In that study, cenerimod 4 mg was well tolerated and was the only dose to show a clinically significant reduction on the primary endpoint (change from baseline to Month 6 in mSLEDAI-2K score) [Cenerimod IB, section 5.3.1.2]. These results are in line with those of the anifrolumab Phase 3 study (TULIP-1) conducted in SLE patients and using similar endpoints [Furie 2019].

6.1.4 Treatment assignment

All participants will receive cenerimod. An IRT system will be used to assign the kit numbers to the individual participants.

6.1.5 Study treatment handling/preparation/storage/accountability

Manufacture, labeling, packaging, and supply of study treatments is conducted according to Good Manufacturing Practice.

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

6.1.5.1 Study treatment packaging and labeling

Study treatment is provided as tablets and supplied in childproof bottles.

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

6.1.5.2 Study treatment distribution and storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label. The storage conditions must be explained to the participant.

6.1.5.3 Study treatment dispensing

The participants will receive sufficient study treatment to cover the period up to the next scheduled visit. Participants 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.

Protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. In exceptional circumstances (e.g., if the participant lost the study treatment between 2 visits, or if the participant is unable to return to the site due to a medical emergency / hospitalization at another hospital / long distance to travel / pandemic restrictions), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit.

An accurate record of the date and amount of study treatment dispensed to each participant must be available for inspection at any time.

6.1.5.4 Study treatment accountability

The inventory of study treatment dispensed to and returned by the participant (i.e., study treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. The inventory is to be recorded by site personnel in the site documentation and in the eCRF. The study treatment accountability log in the eCRF will include the following information for each study treatment bottle dispensed to the participant:

- Dispensed bottles number.
- Date dispensed / number of tablets dispensed.
- Date returned / number of tablets returned.

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

If the participant forgets to bring the remaining study treatment 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 the next visit.

6.1.5.5 Study treatment return and destruction

On an ongoing basis and/or upon termination of the study, the CRA will collect used and unused treatment kits, which will be sent to the warehouse, where the sponsor / depot personnel or a deputy will check treatment reconciliation.

In certain circumstances (e.g., local hospital procedures), used and unused study treatment containers may be destroyed at the site. In general, this can only be done once study treatment accountability is finalized and has been checked by the sponsor personnel representative, and written permission for destruction has been obtained from the sponsor. Exceptions might occur if a local process requires immediate destruction of the study treatment. Such local study treatment destruction processes must be provided and approved by the sponsor.

6.1.6 Study treatment compliance

Study treatment compliance with the prescribed study treatment dose regimen is based on study treatment accountability. Study treatment compliance will be calculated by site personnel at each monthly visit during the study treatment period using the formula below:

Compliance = [(number of tablets dispensed – number of tablets returned) / total number of tablets that should have been taken during the period[*]] × 100

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

During the entire study treatment period, the study treatment compliance is expected to be 80% or above. At each monthly visit during the study treatment period, the study treatment compliance is also 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/delegate must discuss the non-compliance with the participant to clarify the reason(s) and to take appropriate actions to avoid re-occurrence. This discussion and its outcome must be documented in the source documents.

6.2 Previous and concomitant medications

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 FSV. 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 FSV), route, dose, frequency, and indication for use will be recorded in the eCRF.

6.2.1 Auxiliary medicinal products

An auxiliary medicinal product is a medicinal product used for the purpose of the clinical study but not as an Investigational Medicinal Product (e.g., a mandatory background therapy or a medicinal product used for a study-mandated procedure).

Auxiliary therapy includes background SLE therapy as requested for a participant to be eligible in the study. Any post-Day 1 change of background medication has the potential to obviate the treatment effect and efforts should be made to adjust background medication during the screening period.

Allowed auxiliary therapy	**Conditions of use**
Antimalarials (hydroxychloroquine, chloroquine, quinacrine)	See Section 6.2.1.1
Mycophenolate mofetil / mycophenolic acid	
Azathioprine	
Methotrexate	
Belimumab	
Telitacicept	
OCS background therapy	See Section 6.2.1.2

6.2.1.1 SLE background therapy (except OCS background therapy) conditions of use

For eligibility, SLE background medication must have been started at least 90 days prior to Screening.

Dose, frequency, and route of administration must be stable for at least 30 days prior to Day 1.

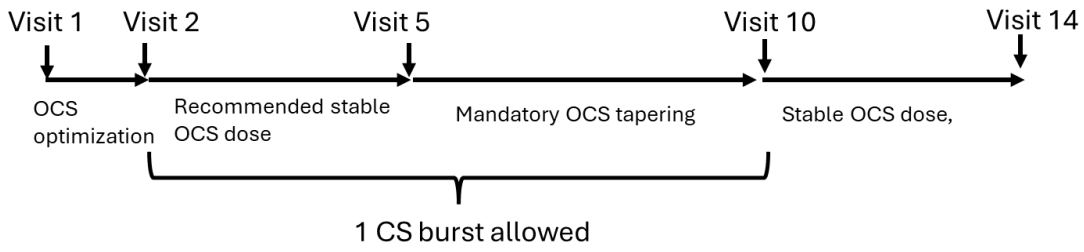
Treatment, dose, and route of administration should remain identical from Day 1 to the completion of Visit 14 (Month 12).

The dose may be decreased by the investigator/delegate for toxicity reasons, or to optimize management of an AE, such as an infection. The toxicity/event must be reported as an AE and the change of dose entered in the eCRF. The dose can be returned to the Day 1 level if the toxicity/event resolves and as clinically indicated.

Antimalarials/immunosuppressants (including dose, frequency, and route of administration) should not be changed if a participant has increased SLE disease activity during the OCS tapering period.

6.2.1.2 OCS background therapy conditions of use

Figure 4 OCS management overview



CS = corticosteroid(s); OCS = oral corticosteroid(s).

6.2.1.2.1 OCS eligibility criteria

- OCS must have been started at least 30 days prior to Screening.
- Participants will be eligible at Screening and Day 1 under the following conditions:
  - when OCS is the only SLE background medication: ≥ 7.5 mg/day and ≤ 30 mg/day prednisone or equivalent.
  - when OCS is not the only SLE background medication: ≤ 30 mg/day prednisone or equivalent.

6.2.1.2.2 OCS management and dose optimization during Screening (Visit 1 up to Visit 2)

For the purpose of standardization, it is recommended to use either prednisone, methylprednisolone, or prednisolone during the study [see Appendix 12]. If a participant is treated with another background OCS therapy, it is recommended to switch to 1 of the 3 OCS mentioned above during the Screening period.

For participants treated with OCS prior to enrollment, it is recommended to optimize the background OCS therapy during the Screening period to the minimal effective dose by performing a cautious tapering [Table 6]. This will allow for minimal OCS changes during the treatment period outside of the mandatory OCS tapering period (Visit 5 up to Visit 10), which is the preferred approach.

Dose reductions are at the investigator's discretion; however, the OCS dose must be kept stable for 15 days prior to Day 1.

6.2.1.2.3 OCS management during treatment period

The OCS dose should be kept stable. Any change in the OCS dose should be restricted to 2 different situations: a) medically justified safety reason and b) protocol-specified rules (see below). The justification and nature of any change should be thoroughly documented in the participants' medical records.

Protocol-specified rules for changes in OCS dose

From Visit 2 up to Visit 5: Recommended stable OCS dose

The OCS dose should be kept stable. The investigator is encouraged to only change the OCS dose in the following situation:

- OCS dose decrease is allowed for participants with SLE disease activity improvement for at least 4 consecutive weeks (i.e., between 2 consecutive visits), but is not mandatory. Table 6 describes a recommended tapering schedule. SLE disease activity improvement is defined as BILAG reduction of all A scores to B/C/D scores and reduction of all B scores to C/D scores, and no score worsening in other organ systems, as defined by ≥ 1 new A score or ≥ 2 new B score.

From Visit 5 up to Visit 10: Mandatory OCS tapering

For participants with an OCS dose ≥ 10 mg/day at Day 1, steroid tapering to an OCS dose of ≤ 7.5 mg/day MUST be attempted [see the recommended tapering schedule in Table 6] and started within 14 days after Visit 5.

Tapering should not be attempted if at least 1 of the following criteria is met:

- Worsening of SLE disease activity defined as ≥ 1 new BILAG A or ≥ 2 new BILAG B scores (except mucocutaneous and musculoskeletal domains).
- Moderate-to-severe skin disease as reflected by a CLASI activity score of ≥ 10.
- Moderate-to-severe arthritis disease as reflected by an active joint count of ≥ 4 tender and/or swollen joints.

If a participant fails tapering down at the first attempt, an increase of the OCS dose up to the dose before the start of the forced tapering is allowed. Another attempt to taper down OCS might be done unless at least 1 of the above criteria is met.

If steroid tapering is not attempted in an eligible participant, the sponsor must be contacted immediately. The recommended steroid-tapering regimen is provided in Table 6, but due to variability in participant responses to steroid treatment and tolerability of taper, investigators will have flexibility in how the OCS dose is reduced at each visit.

Investigators will not be required but may continue to taper OCS dose beyond 7.5 mg/day up to Visit 10.

Steroid tapering will not be permitted after Visit 10. The dose may be optimized for 14 days after Visit 9 but the OCS dose must be stable for 14 days prior to the scheduled Visit 10.

Table 6 Example of background OCS therapy forced tapering schedule

Initial stable OCS dose at randomization[1]		30	25	20	15	10
Days of corticosteroid tapering down	0 - 14[2]	20	20	15	12.5	7.5
	15 - 29	15	15	12.5	10	5
	30 - 44	12.5	12.5	10	7.5	
	45 - 59	10	10	7.5	5	
	60 - 74	7.5	7.5	5		
	75 - 90	5	5			

[1] OCS dose in [mg/day] prednisone equivalent.
[2] Day 0 = first day of OCS tapering.
OCS = oral corticosteroid(s).

Participants who experienced increased SLE disease activity may receive *one* CS burst (after study visit assessments) during the first 8 months of treatment [see Section 6.2.2.1].

From Visit 10 to Visit 14: Mandatory stable OCS dosage

OCS dosage must be stable unless medically justified by the investigator.

No increase in OCS is allowed after Visit 10 except for managing AEs or as prophylaxis for adrenal insufficiency.

6.2.2 Allowed concomitant therapy

Allowed concomitant therapy include medications allowed under certain conditions.

Allowed medication	Conditions of use
CS burst	See Section 6.2.2.1.
NSAIDs	See Section 6.2.2.2.
Low-dose aspirin	Stable long-term use of low-dose aspirin (maximum of 325 mg/day) for cardiovascular disease is permitted.
Non-NSAIDs pain medications	Temporary use of pain medications (e.g., acetaminophen/paracetamol or other non-NSAID pain medication) may be used for pain management as required, based on Investigator judgment for up to 1 week at a time and should not be taken on the day of a scheduled visit until all assessments have been completed.
Topical therapy	Topical ocular therapy (e.g., chronic treatment for glaucoma, ocular inflammation, allergy), including dilating eye drops, mydriatics, parasympathetic antagonists (e.g., tropicamide) or sympathetic agonists (e.g., phenylephrine). Topical skin therapy, inhaled and nasal therapy, including topical use of CS.
Atropine	Permitted i.v. in the event of symptomatic bradycardia.
Vaccination	Only non-live vaccines.

6.2.2.1 CS burst conditions of use

From Visit 2 to Visit 10

Participants who experienced increased SLE disease activity may receive *one* CS burst (after study visit assessments). Only one burst can be administered between Visit 2 and Visit 10, as follows:

- OCS dose increase up to a maximum daily dose of 40 mg/day prednisone or equivalent [see Appendix 12] up to a total of 14 days. This OCS increase must be fully administered and tapered to less than or equal to the Day 1 (Visit 2) dose by no later than Visit 10.

  or

- Intramuscular methylprednisolone (≤ 80 mg or equivalent) administered as a single dose.

  or

- A maximum of 2 intra-articular / tendon sheath / bursal injections (for a total methylprednisolone ≤ 80 mg or equivalent) at the same visit.

From Visit 10 to Visit 14

No CS burst allowed.

6.2.2.2 NSAIDs conditions of use

For the treatment of SLE, NSAIDs dose and frequency must be stable for at least 30 days prior to Day 1 and must remain stable throughout the study. The dose may be reduced for reasons of toxicity but not efficacy.

For the treatment of non-SLE-related conditions (e.g., headache, menstrual cramps), temporary use and/or dose change is allowed.

Of note, NSAIDs cannot be used in combination with another NSAID at any dose, except low-dose aspirin (≤ 325 mg/day) and topical NSAIDs may be used in combination with 1 oral NSAID.

On a given visit day, NSAIDs should not be taken until after all assessments have been completed.

6.2.3 Forbidden concomitant therapy

The following concomitant therapies are forbidden during the treatment period and until 6 months after last study treatment intake. Initiation of any of these medications will result in the permanent discontinuation of study treatment.

- Immunosuppressive agents not listed in allowed concomitant medications, such as cyclophosphamide, cyclosporine, voclosporin, leflunomide, sirolimus, tacrolimus, etc.
- Immunosuppressive or immunomodulatory biological agents (e.g., i.v. immunoglobulin, anifrolumab, rituximab).
- S1P receptor modulators other than cenerimod.
- β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering therapy [list of drugs provided in Appendix 3].
- QT-prolonging drugs with known risk of torsade de pointes [list of drugs provided in Appendix 4].
- Vaccination with live vaccines.
- Inhibitors of the breast cancer resistance protein transporter: curcumin, cyclosporine, eltrombopag, elacridar, gefitinib, teriflunomide.
- Cannabidiol and other derivatives of marijuana.
- Investigational agents.

Note: due to the long half-life of cenerimod, in the event of permanent discontinuation from study treatment for any reason, participants should not receive any of the forbidden

therapies during the follow-up period of 6 months after last study treatment intake, unless clinically indicated in the judgment of the investigator.

6.3 Medical care of participants after study completion / withdrawal from study

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

Female participants of childbearing potential must be reminded of the contraception requirements as described in Section 5.5.2. In the event of premature discontinuation from the study, WoCBP must be instructed to continue the use of contraception for at least 6 months after the last dose of study treatment to prevent any pregnancy. These reminders and instructions must be documented in the source documents of these female participants.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS AND PROCEDURES

7.1 General information

The study visits and their respective time windows are listed in the SoA [Table 1, Table 2, and Table 3]. If it is not possible to complete all assessments on the same day, a visit may extend over more than 1 day within the permitted time window.

All efforts should be made to keep participants on schedule based on the date of their Day 1 (Visit 2), which is the day of the first study drug treatment.

When scheduling the different assessments for a study site visit, the following should be considered:

- The participant must come to the clinic in a fasted condition for all protocol scheduled visits.
- Participants should be instructed not to take the study medication in the morning of the day of the visit.
- At Visit 2 (i.e., Day 1) and at the re-initiation visit if applicable [see Section 5.8.1.11], assessments during the visits will be divided into 2 parts: before (pre-dose) and after (post-dose) the administration of the study treatment, which will be taken at the site.
- Resting time:
  - When a participant must perform a specific protocol-mandated test at another department within the hospital, sufficient time should be allowed for the participant 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. Blood drawing should preferably be done after cardiac assessments.
- All PK samples are to be collected at the time points outlined in Table 2. The actual date and time of each PK sample collection will be collected in the eCRF.
- Follow-up information will be collected during the FU1 visit; FU2, FU3, FU4, and FU5 visits (telephone call visits), and at the FSV visit (6 months after last study treatment intake).
- To minimize the risk of non-compliance with contraception requirements, the study personnel must remind WoCBP at each visit to use the methods of contraception defined for this study.

Calibration certificates or evidence of equipment maintenance for the below-listed equipment used to perform study assessments will be collected for the study trial master file by the sponsor:

- OCT machine.
- BP device.

Calibration certificates or evidence of equipment maintenance of other equipment must be available as per local requirements.

7.1.1 Screening

A participant who agrees to be part of the study and the investigator/delegate must both sign the ICF prior to participation in the study. The ICF must be fully signed [see Section 10.2 for informed consent procedure] on the day of Screening.

A dated and timed signature must be available prior to any study-specific procedures are performed.

Procedures or assessments conducted as part of the participant's routine clinical management (e.g., laboratory sample, vital signs) obtained before signing the ICF may be used for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA [Table 1, Table 2, and Table 3]. 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.

After the ICF has been fully signed, the investigator/delegate contacts the IRT system to get a participant identification number allocated to the participant.

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

For participants who are being treated with CS prior to enrollment in this study, an optimization period aiming to reduce the doses of background OCS therapy to (or as close as possible to) the minimum effective dose, should be considered during the screening period [see Section 6.2.1.2].

Once the enrollment target (defined as completed Day 1 and received cenerimod) has been met, participants who have signed the ICF may not be allowed to enroll.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study and will be recorded in the eCRF. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the SoA [Table 2].

7.1.3 Study completion

A participant who completes 12 months of treatment and the follow-up period is considered to have completed the study. A participant who permanently discontinued the study treatment and who agreed to still follow planned study procedures thereafter [see Section 5.8.1] or was withdrawn from the study because of study closure or study premature termination or suspension of the study [see Section 10.10] is also considered to have completed the study.

7.2 Study assessments and procedures

The study assessments and procedures and their timing are summarized in the SoA [Table 1, Table 2, and Table 3]. All study assessments performed during study visits (scheduled or unscheduled) are carried out by the investigator/delegate physician or a healthcare professional with an advanced practice role, if allowed by local regulations, and are recorded in the eCRF, unless otherwise specified.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected in the eCRF for all participants that received study medication include age, sex, and race. Relevant medical history and/or current medical conditions based on the investigator/delegate's judgment (e.g., chronic and ongoing acute conditions, serious past conditions) present before and/or at the time of signing informed consent will be recorded in the eCRF. Where possible, diagnoses and not symptoms will be recorded.

The following medical history and/or current medical conditions are considered relevant for this study and must always be reported 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 New York Heart Association 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.
- Chronic medical conditions including pulmonary, CNS, liver function, renal function, eye disorder, and skin conditions at any time in the past.
- New acute medically relevant conditions in the past 6 months including any serious infection defined as life-threatening or requiring i.v. antibiotics or hospitalization.
- Exposure to healthcare settings in the past 3 months (e.g., hospitalization, emergency care admissions, visit to emergency medical services facility).
- Any history of pregnancy morbidity (e.g., fetus loss, spontaneous abortion, premature birth).
- Previous and concomitant therapy [see Section 6.2].
- Any history of chemotherapy, radiotherapy, operations, immunosuppression, or any other relevant medical treatment.

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

- Date of SLE diagnosis.
- SLE symptoms according to 2019 EULAR/ACR Criteria [see Appendix 2].

For women, the reason for not being of childbearing potential will be recorded in the eCRF.

7.2.2 Disease activity assessments

Unless otherwise specified, the date of each assessment will be collected in the eCRF.

Investigators and designated site personnel must be trained and certified for all the assessments required in this study prior to participants entering Screening at their respective sites. If there is a change in site personnel over the course of the study, new investigators or physicians must be trained and certified prior to performing these assessments.

The investigator/delegate will record data for the disease assessment scores on the paper scoring sheets which replicate those contained in the appendices. Data from the physical examination, weight, clinical symptoms, and the medical evaluation of the participant will also be collected by the investigator or delegate. These data will be used to complete relevant aspects of the disease assessment scores.

The instructions for the scoring of the disease activity assessments will be provided in form of instructions manual.

7.2.2.1 Systemic Lupus Erythematosus Disease Activity Index-2000

The SLEDAI-2K [see Appendix 6] will be assessed by the investigator or delegate as per the schedule of assessments [see Section 1.3].

The SLEDAI-2K is a validated clinical index for the measurement of disease activity in SLE. It was developed as a modification of SLEDAI to reflect persistent, active disease in descriptors (i.e., proteinuria, rash, alopecia, and mucous membrane lesions) that were previously only considered if new or recurrent.

The investigator will perform physical examinations, question the participant on his/her current state and about any potential SLE symptoms and/or manifestations that were "present" or "absent" during the last 10 days, and collect all laboratory variables 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). If the participant reports symptoms of myositis, the investigator should request aldolase analysis to be performed from the collected blood sample.

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 consider "leukopenia".)
- The clinical mSLEDAI-2K score is only used to evaluate inclusion criteria for eligibility, as visit laboratory assessment from central laboratory will not be available at the time of Day 1. The clinical mSLEDAI-2K excludes points attributable to any urine or laboratory results including immunologic measures.

7.2.2.2 British Isles Lupus Assessment Group

The BILAG will be assessed by the investigator or delegate as per the schedule of assessments [see Section 1.3].

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 investigator will record clinical features covered by the BILAG index of lupus disease activity and relevant data will be recorded in the BILAG form. There are 9 systems: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological. Immunological data do not contribute to BILAG scores, but basic hematology and assessment of renal function determine the scores of the relevant systems [see Appendix 7]. As cenerimod causes a reduction in the peripheral blood lymphocyte count, and hence the complete WBC count, these data will not contribute to the scoring.

A score is calculated for each system depending on the clinical features present and whether they are "not present", "new", "worse", "the same" or "improving" in the last 4 weeks compared to previous assessment. Of note, the "improving" score MUST respect the following definition:

- The amount of improvement is sufficient for consideration of reduction in therapy and would not justify escalation in therapy,

  and
- Improvement must be **present currently and for at least 2 weeks** out of the last 4 weeks,

  or
- The manifestation has **completely resolved and remained absent over the whole last 1 week**.

The scoring categorizes disease activity into 5 different grades from A to E:

- Grade A represents very active disease requiring a prednisone dose of > 20 mg/day or equivalent and/or immunosuppressive drugs.
- Grade B represents moderate disease activity requiring a prednisone dose of < 20 mg/day or equivalent, topical steroids, topical immunosuppressives, antimalarials, or NSAIDs.
- Grade C represents mild stable disease.
- Grade D represents no current disease activity, but the system has been previously affected.
- Grade E represents no current or previous disease activity.

Important extensions of selected BILAG glossary and SLEDAI-2K clinical variable definitions are detailed below. Of note, protocol-specific extensions for BILAG are highlighted in italic below:

- BILAG A or B score in the musculoskeletal organ system due to active polyarthritis, defined as follows:
  - "BILAG-2004 A": severe arthritis (BILAG #41) with observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living (ADL), that has been present on several days cumulatively over the past 4 weeks, including at the time of the Screening visit. *Basic ADLs are defined as the following activities which require assistance or assistive devices (at least 1 must be present and documented in source): ambulation, dressing, eating, toileting, grooming including bathing*.
  - "BILAG-2004 B": moderate arthritis or tendonitis or tenosynovitis (BILAG #42) defined as tendonitis/tenosynovitis or active synovitis in ≥1 joint (observed or through history) with some loss of functional range of movements *which leads to some loss of functional range of motion as manifested by effects on instrumental ADLs (including cooking, driving, using the telephone or computer, shopping, cleaning, etc.), which has been present on several days over the last 4 weeks, including at the time of the Screening visit.*
- BILAG and SLEDAI-2K "lupus headache": lupus headache is rare and is considered a manifestation of lupus cerebritis. Migraine, tension, or cluster headaches should not be recorded as a lupus headache. Lupus headache should only be recorded if it is disabling, lasts at least 3 days, and does not respond to narcotics. It is expected that its severity would prompt formal testing (lumbar puncture, magnetic resonance imaging, CT, etc.) and require CS and/or immunosuppressants and potentially hospitalization for treatment.

7.2.2.3 SLE Flare Index

The SFI will be assessed by the investigator or delegate as per the schedule of assessments [see Section 1.3], using paper sheets.

The classic SELENA-SLEDAI Flare Index 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 classic SELENA-SLEDAI Flare Index.

The SFI assessment [see Appendix 8] will be scored by the investigator/delegate in comparison to the participant's previous visit (i.e., over the past 28 days) and will only include findings which are due to SLE disease activity within that timeframe and as per investigator opinion. Flare will be defined as any 1 criterion present in either the Mild/Moderate Flare or Severe Flare categories. New or worsened manifestations should only be reported for manifestations of SLE. The increase in SLEDAI score used to determine the SFI will be evaluated in comparison with the previous visit.

7.2.2.4 Physician's Global Assessment of disease

The PGA will be assessed by the investigator or delegate as per the schedule of assessments [see Section 1.3] using paper sheets.

The PGA is a visual 100 mm analog scale for assessment of disease activity by the physician ranging from 0 to 100, with 0 indicating inactive disease and 100 indicating severe disease [see Appendix 9]. Pre-defined vertical marks with numbers 0, 1, 2, and 3 are indicative of SLE disease activity assessment and correspond to "none", upper limits of "mild", "moderate", and "severe", respectively. These marks aim to guide the evaluator in his/her assessment.

The investigator will rate the overall state of the participant and make a vertical mark on the scale that will automatically be translated into a length in mm. When scoring the PGA, the score from the last visit should be reviewed and the mark should be moved relative to the score from the last visit. The PGA is a global assessment for the participant's lupus disease activity. It should not consider non-lupus medical conditions.

7.2.2.5 Cutaneous Lupus Erythematosus Disease Area and Severity Index

The CLASI will be assessed by the investigator or delegate as per schedule of assessments [see Section 1.3] using paper sheets.

The CLASI consists of 2 scores: the first summarizes the activity of the disease and the second measures the damage done by the disease [see Appendix 10]. Activity is scored based on erythema, scale / hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. Damage is scored based on dyspigmentation and scarring, including scarring alopecia. The scores are calculated by simple addition based on the extent of the symptoms. The CLASI is designed as a table where the rows denote anatomical areas, and the columns score major clinical symptoms. The extent of involvement for each of the skin symptom is documented according to specific anatomic areas that are scored according to the worst affected lesion within that area for each symptom [Albrecht 2005].

7.2.2.6 Tender/swollen joints count

The tender/swollen joint count will be assessed by the investigator or delegate with adequate experience (minimum of 1 year) and training qualifications as per schedule of assessments [see Section 1.3] using paper sheets.

The tender/swollen joint count was originally proposed for rheumatoid arthritis patients. Because joint involvement is a common manifestation of SLE, it was later validated and used to assess the joint disease activity in SLE patients.

The tender/swollen joint count is based on left and right shoulder, elbow, wrist, MCP1, MCP2, MCP3, MCP4, MCP5, PIP1, PIP2, PIP3, PIP4, PIP5 joints of the upper extremities and left and right knee of the lower extremities [see Appendix 11]. Each of 28 joints will be evaluated separately for tenderness (by palpating the joint) and swelling. Joints with intra-articular injection within 4 weeks are not evaluable for the assessment.

7.2.3 Safety assessments

Unless otherwise specified, the date of each assessment will be collected in the eCRF.

The definitions, reporting, and follow-up of AEs, SAEs, and pregnancies are described in Section 8.

7.2.3.1 Physical examination

A full and complete physical examination will be performed at Visits 1, 2, 3, 5, 8, 11, 14, and 15. Full and complete physical examination includes the examination of the following body parts/systems:

- Head, ear, nose, mouth, and throat
- Eyes
- Neck
- Cardiovascular system
- Respiratory system
- Abdomen
- Skin
- Extremities
- Neurological system
- Musculoskeletal system

Other exams will be performed if indicated, based on medical history and/or symptoms.

For all other visits, a symptom-driven abbreviated physical examination will be performed to capture assessments needed for the SLEDAI-2K, the PGA, the BILAG, and the SFI.

For details on skin examination, please refer to Section 7.2.3.9.

Information for all physical examinations must be included in the source documentation at the study site.

All findings, including clinically not relevant findings that are present prior to signing the ICF, must be recorded as medical history or SLE-relevant disease history in the eCRF.

Physical examination findings after signing the ICF which meet the definition of an AE [Section 8.1.1] must be recorded as an AE in the eCRF.

7.2.3.2 Weight and height

Height will be measured and recorded in the eCRF at Visit 1 (Screening). Participant body weight will be measured (heavy clothing should be removed) and recorded in the eCRF at Visit 1 (Screening), Visit 14 (EOT), and Visit 20 (FSV). For further body weight measurements as part of the BILAG assessment at each applicable visit [see Section 7.2.2.2], the weights will be recorded in the source documentation and if clinically relevant, the body weight collected outside Visit 1 (Screening), Visit 14 (EOT) and Visit 20 (FSV) may be reported as an unscheduled assessment in the eCRF.

7.2.3.3 Electrocardiograms

7.2.3.3.1 Cardiac monitoring applicable to all participants

ECGs will be performed at pre-dose for all participants at all scheduled visits with the participant in a fully rested supine position after the participant has been allowed to rest for a minimum of 5 minutes prior to the measurement. Single digital 12-lead ECG will be performed using the ECG machine provided by the central ECG vendor. The date and actual time of ECGs will be recorded in the eCRF.

A central ECG vendor (see ECG manual for contact details) will be used for the evaluation of all protocol-mandated ECGs, including re-tests due to ECG abnormalities and ECGs performed at unscheduled visits. The site personnel will electronically transmit the ECGs to the central ECG vendor for central reading as soon as possible after the examinations.

The 12-lead ECG measurements will evaluate the following variables: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. The QTc (ms) will be calculated according to Bazett's and Fridericia's formula ($QTcB = QT/(RR)^{½}$ and $QTcF = QT/(RR)^{⅓}$, respectively). The ECG findings (e.g., rhythm, ectopy, conduction, and morphology) and the overall interpretation of the ECG (normal/abnormal) will be provided by the ECG central vendor to the study site and to sponsor.

At Visit 2 Day 1, the pre-dose ECG must be performed for all participants and interpreted by the investigator/delegate prior to study drug administration. The applicable cardiac exclusion criteria 7, 8, 9 and 10 must be ruled out.

In addition to transmitting the ECG to the central reader, an ECG record at the Visit 2 must be printed, signed, and dated by the person interpreting the ECG and determining that the relevant exclusion criteria were not met.

ECG reports will be provided by the central ECG vendor to the investigator/delegate. If specific (pre-defined in the ECG manual) ECG abnormalities are observed, the central ECG vendor will alert the sponsor and the investigator/delegate.

All ECG reports obtained from the central ECG vendor must be reviewed, signed, and dated by the investigator/delegate within 10 calendar days of receipt and filed with the source documentation. The investigator/delegate must indicate on the ECG report whether abnormal values or findings 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 medical history page in the eCRF. Any clinically relevant ECG abnormalities detected after signing the ICF must be reported as an AE or SAE as appropriate [see Section 8.2] and must be followed until the finding returns to normal, is considered stable, or until the change is no longer clinically relevant. Notable abnormalities are detailed in Appendix 13 and marked abnormalities will be detailed in the SAP.

Details on ECG procedures (recording, transfer of data and reporting) will be provided in the ECG manual.

7.2.3.3.2 Additional cardiac monitoring on Day 1

To evaluate the possible transient effects on BP and HR after study treatment initiation with S1P receptor modulators, 12-lead ECGs and BP assessments will be additionally performed as post-dose cardiac monitoring for all participants on Day 1 and at study treatment re-initiation visit(s).

The post-dose cardiac monitoring will consist of post-dose 12-lead ECGs, performed hourly within 12 hours post dose, and BP assessments, performed hourly within 6 hours post dose and at 12 hours post dose as per the SoA. At 12 hours the participant may be discharged from monitored setting if they meet the discharge criteria [see Appendix 5] If the participant does not meet the discharge criteria at 12 h post-dose, the participant will be permanently discontinued from the study treatment and will be kept in the monitored setting for observation.

Any cardiac events of potential clinical concern on Day 1 and on the first day of re-initiation visit must be assessed by the investigator or their delegate for seriousness. In addition, the investigator or their delegate should determine the need for medical management and decide what actions should be taken on study treatment, if any. The investigator or their delegate may consult with a cardiologist. In cases of acute cardiac events, and if they are not adequately trained and experienced in cardiology and are not equipped to provide emergency treatment, she/he will refer the participant to a cardiologist to receive emergency care and treatment.

7.2.3.4 Clinical laboratory assessments

See Appendix 1 for the list of clinical laboratory tests to be performed. See the SoA [Table 1, Table 2, and Table 3] for the timing and frequency.

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 7.2.6].

Blood samples will be drawn in the morning under fasted conditions (i.e., before breakfast) and when applicable before the morning administration of the study treatment at all scheduled and unscheduled visits. However, it is not permitted to request that participants are in a fasted state (for the study) at Screening unless the ICF has already been fully signed.

A midstream, clean-catch urine specimen will be collected according to the SoA [Table 1, Table 2, and Table 3] and sent to the central laboratory for analysis using urine dipsticks . If the dipstick results are positive for protein, leukocytes, or blood, the urine sample will be subject to further analysis (i.e., microscopic analysis). The results will be used for assessment of the mSLEDAI-2K and BILAG scores.

Urine protein-to-creatinine ratio is to be determined using urine samples sent to the central laboratory for analysis of protein and creatinine. 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, KDIGO 2012, Price 2005, Ruggenenti 1998]. For this reason, the result from urine protein-to-creatinine ratio can be used in this study for assessment of both the mSLEDAI-2K and BILAG scores. The relationship among these laboratory tests for proteinuria is provided below in Table 7 [KDIGO 2012]. If the results of the protein-to-creatinine ratio are below the lower limit of quantification, this must be recorded as "not determined" in the questionnaires and justification has to be provided.

Table 7 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.

A serum pregnancy test for WoCBP will be performed at Screening (Visit 1) and a urine pregnancy test prior to study drug administration Visit 2. Both must be negative and performed at least 3 weeks apart. A second serum pregnancy test is performed at Visit 20 (FSV). Serum pregnancy tests will be sent to the central laboratory for analysis and the result will be sent to the investigator/delegate.

Urine pregnancy tests will be performed at all other visits with kits provided by the central laboratory. Urine pregnancy kits will be provided to WoCBP at follow-up Visit 15 for use by the participant during the follow-up phone call Visits 16, 17, 18, 19, and the results collected during the scheduled phone calls. The results of the urine pregnancy tests, including those performed at home by the participants, will be collected in the eCRF. If pregnancy is suspected during the study, i.e., in each case of delayed menstrual period (e.g., over 1 month between menstruations), positive urine pregnancy test, etc., a serum pregnancy test must be performed as soon as possible. Reporting procedures of pregnancy are described in Section 8.3.1.

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including retests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

Exceptional circumstances that may require recording of local laboratory results of the variables described in Appendix 1 include hospitalization of the participant due to a medical emergency, inability to travel to the study site due to reasonable reasons judged by investigators and missing central laboratory results from a scheduled or unscheduled visit. The local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF.

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

Central laboratory reports will be sent to the investigator/delegate. In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the sponsor personnel and the concerned site personnel. Alert flags that trigger such notifications will be displayed in the laboratory manual.

All laboratory reports must be reviewed, signed and dated by the investigator/delegate within 10 calendar days of receipt and filed with the hospital chart. 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 signing the ICF must be recorded on the Medical History page in the eCRF. Any clinically

relevant laboratory abnormalities detected after signing the ICF must be reported as an AE or SAE as appropriate [see Section 8] and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant. Notable abnormalities are detailed in Appendix 13.

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

7.2.3.5 Ophthalmological examination

The purpose of the ophthalmology assessment prior to cenerimod treatment is to document a baseline assessment as well as to exclude participants with macular edema, retinal vasculitis, or active uveitis from the study. Assessments at other visits will ensure that any new ophthalmological abnormality is detected and treated at an early stage.

An ophthalmological examination will be performed by an ophthalmologist at any time during the screening period, but results must be available prior to Visit 2. Examinations after Screening will be performed as per schedule of assessments [see Table 2].

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

In the eCRF, the date of the ophthalmological examination and the presence/absence of any abnormality and clinical assessment results (i.e., Normal, NCS abnormal and CS abnormal) will be recorded. 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 8.1.1] and must be followed until the value returns to within the normal range or is steadily improving.

For participants with suspected macular edema or retinal vasculitis, the diagnosis should be confirmed by diagnostic work-up as recommended by local guidelines (e.g., OCT or fluorescence angiography).

7.2.3.6 Optical coherence tomography

OCT will be performed at as per the SoA. Testing at Visit 1 can be performed at any time during the screening period. At all other visits, 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 must be performed 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 an ophthalmologist.

The purpose of the assessment prior to Visit 2 is to exclude participants 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 certificate or evidence of equipment maintenance performed prior to the assessment must be stored as source documents at the site. To the extent that is logistically feasible, the same OCT machine is recommended to be used for each individual participant throughout the study.

In the eCRF, the date of the OCT assessment and the presence/absence of any abnormality and clinical assessment results (i.e., Normal, NCS abnormal and CS abnormal) will be recorded. Any clinically relevant abnormalities detected after signature of the ICF must be reported as an AE or SAE as appropriate [see Section 8.1.1].

7.2.3.7 Chest X-ray or CT scan

A chest X-ray or CT scan will be performed at Visit 1 (Screening) and assessed by the local radiologist to support the assessment of eligibility criteria (e.g., exclude any participant with active or latent TB). Chest X-ray or CT scan testing can be performed at any time during the screening period. If results of a chest X-ray or CT scan that has been performed within 6 months prior to Screening do not demonstrate active or latent TB, there is no need to repeat the chest X-ray or CT scan at Screening. The report of the chest X-ray or CT scan must be recorded in the participant's file.

7.2.3.8 Test for tuberculosis

An IGRA will be performed at Visit 1 (Screening) to screen for active or latent TB, unless one of the exceptions as detailed in the exclusion criterion have been met. The test will be analyzed and interpreted at the central laboratory and transferred to the investigator.

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

7.2.3.9 Skin examination

Each physical examination must include a complete skin examination performed by the investigator/delegate. In the event of findings other than skin findings relevant to SLE, a dermatologist will conduct further examination per local standard practice, including performing skin biopsies if required to rule out or confirm a diagnosis.

7.2.4 Blood pressure assessments

The investigator/delegate is responsible for BP measurements, including SBP and DBP. BP will be assessed as per the SoA.

For a given participant, BP measurements will be performed using the same type of device throughout the study on the same arm with the participant in a fully rested supine position after the participant has been allowed to rest for a minimum of 5 minutes prior to the measurement. At all visits (including Visit 1/Screening visit), SBP and DBP will be measured twice. The SBP/DBP assessment will be performed pre-dose at all visits during the study treatment period. Each of the 2 obtained measurements (i.e., 2 SBP measurements and 2 DBP measurements) and the position and arm used are to be recorded in the eCRF. The means of the 2 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 8.2].

At Visit 2 (Day 1) and at study treatment re-initiation, the post-dose SBP/DBP assessments will be performed in parallel to 12-lead ECGs.

The post-dose SBP/DBP assessments will only be measured once at each hourly time point until 6 h post-dose and at hour 12 post-dose. At the 12-hour post-dose timepoint, participants may be discharged from the monitored setting if they meet the pre-specified discharge criteria [see Appendix 5]. Refer to Appendix 5 regarding participant discontinuation and monitoring if discharge criteria not met.

7.2.5 Pharmacokinetic and pharmacodynamic assessments

7.2.5.1 Pharmacokinetic assessments

PK samples will be collected at the times indicated in the SoA [Table 2].

The date and actual time of collection of each blood sample will be entered in the eCRF. In addition, the food status will be recorded in the eCRF for study treatment intake on Day 1 and at Month 2.

The allowed time deviation from scheduled post dose PK sampling time points is listed as follows:

Time point	Allowed time window
1-12 hours post dose	±3 min
24 hours post dose	+18 min (Must obtained before the next dosing)

Details about the collection, sampling, storage, and shipment procedures can be found in the laboratory manual.

The analysis of cenerimod in plasma will be performed by a laboratory approved by the Sponsor using a validated bioanalytical method.

The PK data generated from this study may be used for PPK modeling in future.

7.2.5.2 Pharmacodynamic assessments

The PD marker is total lymphocyte counts, which will be measured as part of the hematology tests [see Section 7.2.3.4].

7.2.6 Biomarker assessments

7.2.6.1 Disease activity biomarkers

Serum, EDTA plasma, and whole blood (PAXgene) samples will be drawn at the indicated visits [Table 1, Table 2, and Table 3]. 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 following biomarkers will be measured at a central laboratory as per the SoA:

- Whole blood will be collected in PAXgene tubes to measure the overexpression of mRNA of specific IFN-1 inducible genes. Other gene expression signatures will be reported to examine T and B cell function, metabolism, and mRNA production.
- In serum samples: ANA, anti-dsDNA, anti-Sm, CH-50, and complement C3 and C4.
- In EDTA plasma samples: IFN alpha levels.

Details of the collection, labeling, and shipment of the samples can be found in the laboratory manual provided to the investigator.

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Safety definitions

8.1.1 Definition 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 participant during the study, whether or not considered by the investigator/delegate as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease if considered medically relevant.
- Exacerbation of a pre-existing disease except for efficacy endpoints and associated symptoms.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the study after signing the ICF, 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 after the start of the study.
- Abnormal change in physical examination or ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the study as per investigator medical assessment.
- Laboratory test abnormalities if they represent a clinically significant finding (symptomatic or not) that was not present at study start or worsened during the study as per investigator judgment, led to interruption or permanent discontinuation of study treatment.

8.1.2 Definition of adverse events of specific 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
- Cardiovascular-related AEs
- Hepatobiliary disorders / liver enzyme abnormality-related AEs
- Pulmonary-related AEs
- Eye disorder-related AEs
- Infection-related AEs

- Skin malignancy-related AEs
- (Non-skin) malignancy-related AEs

A list of AESIs (MedDRA preferred terms) will be defined in the SAP.

8.1.3 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 participant 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 (i.e., the AE required admission to hospital) 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 SAEs based upon appropriate medical judgment, as they may jeopardize the participant, and/or may require medical or surgical intervention to prevent 1 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 participant with stable angina pectoris.

8.1.4 Intensity of adverse events

The intensity of AEs is graded on a 3-point scale—mild, moderate, severe—as follows:

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

  - The event may make the participant 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 participant 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 8.1.2]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

8.1.5 Relationship to study treatment

Each AE/SAE must be assessed by the investigator/delegate as to whether there is a reasonable possibility of causal relationship to the study treatment and reported as either related or unrelated.

8.1.6 Relationship to study design or protocol-mandated procedure

An AE/SAE is defined as related to the study design or 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.

Determining the likelihood that a protocol-mandated procedure caused the AE/SAE will be provided by the investigator/delegate.

8.1.7 Definition of study treatment overdose, misuse, and abuse

Study treatment overdose is defined as higher than the dose of study treatment prescribed.

Study treatment misuse is defined as any intentional and inappropriate use of the study treatment which is different from the instruction provided in the protocol.

Study treatment abuse is defined as any intentional and excessive use of the study treatment, with harmful physical or psychological effects.

In the event of a study treatment overdose, abuse, or misuse, the investigator/delegate must contact the sponsor and closely monitor the participant for any AEs/SAEs.

8.2 Reporting procedures

8.2.1 Reporting adverse events

The occurrence of an AE may come to the attention of study personnel during study visits, telephone calls, or interviews with participants presenting for medical care.

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

All AEs with an onset date after signing the ICF and up to 6 months after study treatment discontinuation must be recorded in the eCRF.

The AE should be reported as a final diagnosis (if possible) rather than a list of symptoms.

Information to be collected on an AE form in the eCRF includes date of onset, action taken with the study treatment (e.g. dose reduction or suspension), outcome of AE, date of resolution (if applicable), and investigator/delegate's assessment of intensity as well as 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.

AEs still ongoing after study treatment discontinuation must be followed up until resolution, until they are no longer considered clinically relevant, or until stabilization.

8.2.2 Reporting serious adverse events

All SAEs must be reported by the investigator/delegate to the sponsor's Drug Safety department within 24 h of site staff first becoming aware of the event.

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

The SAE forms must be sent to the sponsor's Drug Safety department (see contact details on the SAE form). The investigator/delegate 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 be promptly reported. The sponsor's Drug Safety personnel may contact the investigator/delegate to obtain further information.

If the participant is hospitalized in a hospital other than that of the study site, it is the investigator/delegate'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 Drug Safety department within 24 h of site staff first awareness/knowledge of the event, **only** if considered by the investigator/delegate to be causally related to previous exposure to the study treatment.

SAEs still ongoing after study treatment discontinuation must be followed up until resolution, stabilization, or until the event outcome is provided.

8.2.3 Reporting procedure for SUSARs

The expectedness of an SAE is determined by the sponsor according to the reference safety information section provided in the Investigator's Brochure.

Any SAE that is assessed as related and unexpected against the reference safety information is considered a SUSAR.

Any SUSAR must be reported by the sponsor/CRO to relevant health authorities, and investigators. Submission to central/local IECs/IRBs will be done as per their requirements.

8.2.4 Reporting medical or surgical intervention

At each study visit (scheduled or unscheduled), the investigator/delegate will inquire about any medical or surgical intervention performed on the participant.

All medical or surgical intervention with an onset date after signing the ICF and up to 6 months after study treatment discontinuation must be recorded in the eCRF.

8.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued [see Section 5.8.1.2]. The investigator/delegate must counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

8.3.1 Reporting of pregnancy

Any pregnancy occurring in a female participant after signing of the ICF and up to 6 months following study treatment discontinuation must be reported to the sponsor's Drug Safety department within 24 h of site staff first becoming aware of the event.

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

The investigator/delegate must complete the Pregnancy form in English.

8.3.2 Follow-up of pregnancy

Any pregnancies must be followed up to their conclusion and the outcome must be reported to the sponsor's Drug Safety department. If local regulations or IRB/EC decisions mandate the reporting of the baby's health after delivery, this will be performed using the same procedure in Section 8.3.1. Any AE associated with the pregnancy of a female participant occurring during the AE reporting time must be reported on separate AE forms in the eCRF as described in Section 8.2.1.

Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 8.2.2.

9 STATISTICAL METHODS

All statistical analyses will be conducted by the sponsor/CRO.

The SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

9.1 Analysis sets

9.1.1 Screened set

The screened set includes all participants who provided informed consent and participated in any screening procedures.

9.1.2 Safety Analysis Set (SS)

The SS includes all participants who received at least 1 dose of study treatment.

9.1.3 Pharmacokinetic Analysis Set (PKS)

The PKS includes all participants from the SS who, after initiation of cenerimod treatment, have at least one PK sample collected, had evaluable plasma concentrations, and did not deviate from the protocol in a way that might affect the evaluation of the PK endpoint.

9.1.4 Pharmacodynamic Analysis Set (PDS)

The PDS includes all participants from the SS who, after initiation of cenerimod treatment, have at least one PD sample collected, had evaluable total lymphocyte counts, and did not deviate from the protocol in a way that might affect the evaluation of the PD endpoint.

9.2 Description of statistical analyses

All available data (regardless of whether collected during scheduled or unscheduled visits) for each participant will be used in all statistical analyses unless otherwise specified.

9.2.1 Analysis of safety endpoints

Descriptive analysis of safety endpoints will be performed using the SS (see definition in Section 9.1.2).

If not otherwise stated, only treatment-emergent safety data will be considered in tables and figures. Treatment-emergent safety data will be defined as assessments (or events) that were performed (or started) on or after the first study treatment intake (inclusive) up to the last study treatment intake + 180 days (inclusive).

Analyses on marked abnormalities for ECG and laboratory variables and Notable BP abnormalities will be specified in the SAP.

Adverse events

AEs will be coded using MedDRA. The number (%) of participants experiencing a TEAE (including SAEs, AESIs, and AEs leading to premature discontinuation of study treatment) will be summarized by SOC and/or PT, and maximum intensity. A participant with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT).

Vital signs and electrocardiograms during post-dose cardiac monitoring on Day 1

On Day 1, observed values and changes from baseline to all post-dose assessments in vital signs (SBP and DBP) and for 12-lead ECG variables, including HR and QTcB and QTcF intervals will be summarized by hourly timepoint. The number (%) of participants having a marked ECG abnormality will be tabulated on Day 1. The number of participants discharged at 12 h will be summarized for Day 1. For participants not discharged, reasons for not being discharged will be summarized.

The number of participants who discontinue study treatment after 12 h will also be summarized.

Vital signs and body weight

Observed values and changes from baseline to all scheduled post-baseline visits in vital signs (SBP and DBP) and body weight will be summarized. Treatment-emergent notable BP abnormalities will be summarized.

Electrocardiograms

Observed values and changes from baseline to all scheduled post-baseline visits for each 12-lead ECG variable (HR and the PR, QRS, QTcB, and QTcF intervals) will be summarized. The number (%) of participants with a marked ECG abnormality will be tabulated.

Laboratory data

Observed and change from baseline laboratory variables for hematology, blood chemistry, and urinalysis for all scheduled post-baseline visits will be summarized. The number (%) of participants with a marked laboratory abnormality (see Appendix 13) will be tabulated.

9.2.2 Analysis of pharmacokinetic endpoints

PK analyses will be performed using the PKS.

Plasma concentrations of cenerimod will be listed by participant and scheduled time point of blood sampling. For samples collected on Day 1/2 and at Month 2, when PK profiles are obtained, elapsed actual times will be displayed, too. Elapsed actual time in hours is defined as the number of hours elapsed from date and time of last study treatment intake to actual date and time of sampling recorded in the eCRF.

Cenerimod plasma concentrations will be summarized per scheduled timepoint by using the number of observations, arithmetic mean, minimum, median, maximum, SD, etc.. Concentrations reported as BLQ will be set to zero.

The arithmetic mean ± SD for the cenerimod plasma concentrations will be represented graphically over time for the PK profiles obtained during the first dosing interval (i.e., pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h after dosing on Day 1) and at Month 2 (i.e., pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h after the dosing at Month 2). In addition, the arithmetic mean ± SD for all pre-dose (trough) cenerimod plasma concentrations will be displayed graphically per visit.

PK parameters of cenerimod (AUC, C_{max}, t_{max}*, and AI) will be determined by non-compartmental methods by the responsible Clinical Pharmacologist using Professional WinNonlin version 8.4 or higher, Certara USA Inc and calculated based on the actual blood sampling time points. It is assumed that AUC and C_{max} are log-normally distributed [Julious 2000]. PK parameters will be listed by participant displaying the dosing interval (i.e., Day 1/2: first dosing interval, Month 2: dosing interval at steady-state conditions) and summarized by dosing interval, with arithmetic mean, minimum, median, maximum, SD, SE, geometric mean, coefficient of variation between participants in %, and 95% CIs of arithmetic and geometric means.

*For t_{max}, the geometric mean and its 95% CI and coefficient of variation will not be calculated.

If appropriate, the steady-state PK parameters such as $C_{min,ss}$, etc. will be derived and analyzed similarly as above.

Further details of these analyses will be provided in the SAP.

9.2.3 Analysis of PD endpoints

Lymphocyte count analyses will be performed using the PDS. Observed and change from baseline values for all scheduled post-baseline visits will be summarized. PD parameters will be calculated and summarized based on Lymphocyte counts, the details of which will be provided in the SAP.

A listing of lymphocyte counts by participant will be produced using the PDS.

9.2.4 Analysis of efficacy endpoints

The following variables will be descriptively analyzed and summarized by month using the SS.

- The observed mSLEDAI-2K total score and change from baseline
  Please refer to Appendix 6 for the detailed information.

- Observed SRI-4 response.
  A participant will be assessed as a SRI-4 responder if they meet ALL the below criteria:

  1. Reduction from baseline of at least 4 points in the mSLEDAI-2K;

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

  and
  3. No increase of more than 0.3 points on the PGA Score since baseline;

If 1 of the 3 components is missing, the SRI-4 response will be missing for this assessment, unless 1 of the non-missing components is not met. In that case, the participant will be assigned a non-response status for SRI-4.

- Observed BICLA response.
  A participant will be assessed as a BICLA responder if they meet ALL the below criteria:

1) Improvement from baseline in disease activity as measured by BILAG-2004. Improvement is defined as a reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D and no BILAG-2004 worsening in other organ systems, where worsening is defined as ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B.

2) No worsening from baseline in mSLEDAI-2K score, where worsening is defined as an increase from baseline of > 0 points.
3) No worsening from baseline in the participant's lupus disease activity, where worsening is defined as an increase of 0.3 points or more on a 3-point PGA VAS score.
4) No discontinuation of study treatment.

If 1 of the 4 components is missing, the BICLA response will be missing for this assessment, unless 1 of the non-missing components is not met. In that case, the participant will be assigned a non-response status for BICLA.

- Response on CLASI from baseline to Month 12.
  Please refer to Appendix 10 for the detailed information.

- Change from baseline in tender and swollen joints.

The total tender joint count will be derived at each assessment, by summing the number of tender joints (= 1) as derived above. The total tender joint count values range from 0 to 28. If at least one joint was not assessed for tenderness or was not evaluable, the total tender joint count will be missing.

The total swollen joint count will be derived at each assessment in the same manner as for tender joint count. The total swollen joint count values range from 0 to 28.

- Changes in OCS dosage from baseline to Month 12.

9.3 Planned analyses

The EOS analysis will be performed when all enrolled participants have completed the post-treatment follow-up period or discontinued the study.

9.4 Sample size

A total of approximately 15 Chinese patients with SLE are planned to be enrolled.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Regulatory and ethical considerations

The sponsor personnel 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.

The investigator and/or sponsor/CRO will submit this protocol and any related documents provided to the participant (such as the ICF) to an IEC/IRB and to the health authority (as applicable). Approval from both the IEC/IRB and the health authority must be obtained

before starting the study and must be documented in a dated letter to the investigator and/or sponsor/CRO, clearly identifying the study, the documents reviewed, and the date of approval.

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

10.2 Informed consent process

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study. The investigator/delegate must explain to participants that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention must be paid to the information needs of specific participant populations and of individual participants, as well as to the methods used to deliver the information. Adequate time must be given for the participant to consider his or her decision to participate in the study and it must be verified that the participant has understood the information (e.g., by asking the participant to explain what is going to happen).

If a revised version of the ICF is approved by health authorities (if applicable) and IRBs/IECs:

- Newly recruited participants must provide consent using the most current version of the ICF(s).
- Participants who are already participating in the study (e.g., already recruited) must re-consent using the most current version of the ICF(s), if necessary (e.g., additional study procedure, new safety information) and/or requested (e.g., as per IRB/IEC requirements).

The ICF will be provided, at a minimum, in the country's official local language(s) and as requested by health authorities (if applicable) and IRBs/IECs.

Site personnel authorized (according to local regulation) to participate in the consent process and/or to obtain consent from the participant will be listed on the Delegation of Authority form. A study physician or a healthcare professional with advanced practice, if allowed by local regulations must always be involved in the consent process.

The participant and authorized site personnel listed on the Delegation of Authority form must sign, personally date, and time the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. If the time is not included on the ICF due to

local regulations, the time of the ICF signature of the participant and investigator/delegate must be documented in the participant's medical charts.

A copy of the signed and dated ICF is given to the participant; the original is filed in the site documentation. The informed consent process must be fully documented in the participant's medical records. This must include, at a minimum, the study reference, the participant identification number, the date and, if applicable, time when the participant was first introduced to the study, the language in which the study was explained, the date, the time of consent, who participated in the consent discussion, who consented the participant, and any additional persons present during the consent process (e.g., participant's family member[s]), and the information that a copy of the signed ICF was given to the participant.

If a participant becomes pregnant during the study, she will be asked to sign a specific ICF to allow the collection of her health information during her pregnancy and from the baby(ies) following delivery. The father of the baby, if possible, will also be asked to sign the ICF.

If the site intends to recruit participants who are considered vulnerable (e.g., participant cannot read or write, does not speak or understand the ICF language), additional measures must be implemented to ensure the participant's 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 participants are recruited.

10.3 Data protection and privacy

Participant data confidentiality and privacy are strictly held in trust by the investigators, their staff, and the sponsor or delegate.

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, participants 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 participant identification code list at the site. Documents identifying the participants (e.g., signed ICFs) must not be sent to the sponsor or any vendors or CROs, and must be kept in strict confidence by the investigator/delegate.

The participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection laws.

The participants must be informed that their medical records may be inspected by the sponsor or sponsor's delegate, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4 Indemnification, compensation, and refund of expenses to participants 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 indemnification of the participants in the event of study-related injuries will comply with applicable regulations.

10.5 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. Several attributes are considered to be 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 a certified copy), attributable, complete, consistent, enduring, and available when needed.

These records will be classified into 2 different categories of document: ISF and participants' source documents.

These records must be kept by the investigator/site for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), ICH GCP and national and/or international regulations, whichever is the longest period. If the investigator/site cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator/site and the sponsor to store these documents off site, so that they can be retrieved in the event of a regulatory inspection. Study documents must not be destroyed without prior written approval from the sponsor. If the site needs to transfer the study records to another location and/or if the site facility can no longer store the study records, the investigator/site must immediately inform the sponsor.

10.5.1 Investigator Site File

Each site will maintain an ISF. It will contain all the essential documents that are required to be up-to-date and filed at the site as per ICH GCP section 8.

The ISF must be stored in a secure and access-restricted area during and after the study.

10.5.2 Source documents

All source documents should be completed in a neat and legible manner to ensure accurate interpretation and traceability of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

If the site is using electronic/computerized system(s) to store participants' 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 access to participants' medical records in order to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using electronic/computerized system(s) to store participant medical records but it cannot be confirmed that the system(s) is/are validated or if the CRA cannot be provided access to the system(s), the site is requested to print the complete set of source data needed for verification by the CRA. These printouts need to be produced via a controlled process in order to be considered as certified copies as defined in the ICH GCP (e.g., printout numbered, stapled together with a cover sheet, signed, and dated by the investigator / member of site staff to confirm that these certified copies are exact copies containing the same information as the original source data). The printouts will be considered as the official clinical study records. Once printed and certified, the document must not be edited/changed (e.g., manual notes added, clinical value changed) in order not to impact the validity of the certification. If the data need to be changed (e.g., correction of a mistake) the change(s) must be done in a traceable fashion and a new copy must be printed and certified.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA periodically requests that a site representative logs into the electronic/computerized system so the CRA could verify the entries in the system against the printouts. The CRA does not need to perform these activities for all participants but at least for some of them and for key data (e.g., eligibility criteria and primary endpoints) as per the sponsor/CRO instructions.

Paper source data will be collected by paper sheets:

- By trained and delegated site staff for clinical outcome assessments (SLEDAI-2K, SFI, PGA, BILAG, CLASI, and tender/swollen joint count) and supportive data from physical examination, weight, clinical symptoms, and medical evaluation of the participants.

10.6 Data handling

10.6.1 Data collection, data transfer procedure, and data access

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timely reporting of participants' data.

Electronic data capture will be used to collect eCRF data. The investigator and site personnel 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. The investigator/delegate will approve the data (i.e., confirm the accuracy and completeness of the data recorded) using an electronic signature (as per US 21 CFR Part 11).

Participant recruitment and enrollment data will be completed for all participants (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each participant recruited, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those participants who fail to complete the study.

The investigator and site personnel will be trained on the use of the paper sheets [see Section 7.2.2]. The data on the paper sheets will be considered source documents.

10.6.2 Database management and quality control

The eCRF must be completed in a timely manner as per eCRF completion guidelines.

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 personnel or delegate on an ongoing basis to look for unexpected patterns in data and for study monitoring. Should discrepant data be detected, a query specifying the matter 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 event of health authority queries, it is also necessary to have access to the complete study records, provided that participant data confidentiality is protected.

This process will continue until database lock.

Laboratory samples and 12-lead ECGs will be processed through a central vendor and the results of the enrolled participants will be electronically sent to the sponsor at pre-specified

intervals with a final transfer prior to database lock. During the study, the site staff and sponsor representatives can access the data in view-only mode on the central server of the respective vendor [see also Section 10.6.1].

AEs and medical history are coded with MedDRA version 26.0 or later. Medications are coded with the WHO Drug Dictionary.

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/CRO Quality System documents. The sponsor is responsible for ensuring that the investigator/delegate will have permanent access (either "write" access or "read-only" access) to the site eCRF participant data, until receipt of an electronic copy of the site eCRFs (including the audit trail).

10.7 Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. A protocol deviation code list will be available to provide guidance on protocol deviations recording.

Prospective approvals of protocol deviations, also known as protocol waivers or exemptions, are not permitted.

The investigator must conduct the study in compliance with the IEC/IRB-approved and/or the regulatory authority-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 participant.

Protocol deviations must be reported to the IEC/IRB and regulatory authorities according to local requirements.

10.8 Clinical monitoring

Prior to study start at a site, all required approvals must be obtained. A site initiation visit will be performed after 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 investigator must ensure that all key site personnel involved in the study are present/available during the site initiation visit and will dedicate sufficient time to it.

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

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study 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. Monitoring activities will be performed according to the study-specific monitoring guidelines. The methodology and the frequency of the monitoring visits will be mainly based on participant recruitment rate and critical data collection times.

The investigator/delegate must ensure that the eCRF is completed as per the eCRF completion guidelines and that all requested participant 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 to ensure that any issues detected during these monitoring visits are resolved.

A close-out visit will be performed for any initiated site when there are no more active participants and all follow-up issues have been resolved. If a site does not screen any participants, the close-out visit may be performed prior to study closure at the discretion of the sponsor.

10.9 Study safety oversight

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study specific- examinations, as required) is monitored and reviewed on a continuous basis by the sponsor.

The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values) for the purpose of monitoring safety. Such additional data may be shared with external experts.

10.10 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 suspended or prematurely 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 recruited participants and ensure

their appropriate treatment and follow-up, as described in Section 6.3. 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 participants' 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 CDE does not approve the continuation of the study or the continued treatment of the participants enrolled in the study, the study will be terminated. The investigators and IECs/IRBs will be informed promptly of the CDE's decision.

10.11 Audit

The sponsor 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 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 site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., participant records) and facilities.

10.12 Inspections

Health authorities and/or the IEC/IRB may also conduct an inspection of this study at the site (during the study or after its completion).

Should an inspection be announced by a health authority and/or the IEC/IRB, the investigator must immediately inform the sponsor that such a request has been made.

The investigator and site personnel must cooperate with the sponsor to handle the inspection related to sponsor studies. The investigator and site personnel must also cooperate with the inspector(s) to ensure proper performance of the inspection and allow access to all study documentation (e.g., participant records) and study facilities.

10.13 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), 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 as outlined in internationally recognized guidance documents (e.g., European Medical Writers Association, American Medical Writers Association, International Society for Medical Publication Professionals), 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 submission to a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Medical 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 60 days prior to submission for publication or presentation at a congress. 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 is permitted to write a publication during such a review period.

11 REFERENCES

[Cenerimod IB] Investigator's Brochure for cenerimod (ACT-334441), version 15. Idorsia Pharmaceuticals, Ltd, December 2024.

[Albrecht 2005] Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, et al. The CLASI (Cutaneous SLE Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005;125(5):889–894.

[Aringer 2019] Aringer M, Costenbader KH, Daikh DI, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 EULAR/ACR classification criteria for systemic lupus erythomatosus. Arthritis Rheumatol. 2019;71(9):1400.

[Bertoglio 2021] Bertoglio IM, de Lucena Valim JM, Daffre D, Aikawa NE, Silva CA, Bonfa E, et al. Poor prognosis of COVID-19 acute respiratory distress syndrome in

lupus erythematosus: nationwide cross-sectional population study of 252119 patients. ACR Open Rheumatol. 2021;3(11):804–11.

[Buyon 2005] Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial. Ann Internal Med. 2005;142(12 Pt 1):953–62.

[Carroll 2004] Carroll MC. A protective role for innate immunity in systemic lupus erythematosus. Nat Rev Immunol. 2004; 4(10):825–31.

[CTCAE 2017] Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services; National Institutes of Health; National Cancer Institute. 27 November 2017 [accessed on 26 January 2022]. Available from:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[Dhillon 2021] Dhillon S. Telitacicept: First Approval. Drugs, 2021, 1671–1675.

[Durkan 2019] Durkan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. Lancet. 2019;393(10188):2332–43.

[FDA 2009] US Food and Drug Administration. Guidance for industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009 [accessed on 26 January 2022]. Available from: https://www.fda.gov/media/116737/download

[FDA 2014] US Food and Drug Administration. Draft guidance for industry: Analgesic Indications: Developing Drug and Biological Products. February 2014 [accessed 9 November 2023]. Available from: https://www.fdanews.com/ext/resources/files/02/02-05-14-Analgesic.pdf

[FDA 2014b] US Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations. March 2014 [accessed 19 March 2025]. Available from: https://www.fda.gov/media/88254/download

[Felten 2021] Felten R, Kawka L, Dubois M, Ugarte-Gil MF, Fuentes-Silva Y, Piga M, et al. Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study. Lancet Rheumatol. 2021;3(4):e2435.

[Furie 2019] Furie RA, Morand EF, Bruce IN, Kalunian KC, Vital EM, Ford TL, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus

(TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatology. 2019;1(4);e20819.

[Gilenya® SmPC] Gilenya® 0.25 mg and 0.5 mg hard capsules. Summary of product characteristics. European Medicines Agency [accessed on 17 November 2020]. Available from :
https ://www.ema.europa.eu/en/documents/product-information/gilenya-epar-product-information_en.pdf

[Ginsberg 1983] Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of Single Voided Urine Samples to Estimate Quantitative Proteinuria. N Engl J Med. 1983;309(25):1543–6.

[He 2023] He X, Lloyd E, Cooper S, Li L, Chauhan D, Juliao P, Quasny H, Chunde Bao C,. Healthcare Costs and Utilization for Patients With Systemic Lupus Erythematosus in China: A National Claims Database Study. VALUE HEALTH REG ISSUES. 2023; 37:88–96

[Hermann 2019] Hermann V, Batalov A, Smakotina S, Juif PE, Cornelisse P. First use of cenerimod, a selective $S1P_1$ receptor modulator, for the treatment of SLE: a double-blind, randomised, placebo-controlled, proof-of-concept study. Lupus Sci Med. 2019;6(1). Erratum in: Lupus Sci Med. 2020;7(1 Suppl 1):11–8.

[Juif 2016] Juif PE, Kraehenbuehl S, Dingemanse J. Clinical pharmacology, efficacy, and safety aspects of sphingosine-1-phosphate receptor modulators. Expert Opin Drug Metab Toxicol. 2016;12(8):879–95.

[Juif 2017] Juif PE, Baldoni D, Reyes M, Wilbraham D, Febbraro AV, Hoch M, et al. Pharmacokinetics, Pharmacodynamics, Tolerability, and Food Effect of Cenerimod, a Selective S1P1 Receptor Modulator in Healthy Subjects. Int J Mol Sci. 2017;18(2636):1–15.

[Julious 2000] Julious SA, Debarnot CA. Why are pharmacokinetic data summarized by arithmetic means? J Biopharm Stat. 2000 Feb;10(1):55-71.

[Kaul 2016] Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, Van Vollenhoven R, et al. Systemic lupus erythematosus. Nat Rev Disease Primers. 2016;2:1–21.

[KDIGO 2012] Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Evaluation and Management of Chronic Kidney Disease. Chapter 1: Definition and classification of CKD. Kidney International Supplements. 2013;3(1):19–63. [accessed on 17 November 2020]. Available from:
https ://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

[Kirou 2004] Kirou KA, Lee C, George S, Louca K, Papagiannis IG, Peterson MGE, et al. Coordinate Overexpression of Interferon-α–Induced Genes in Systemic Lupus Erythematosus. Arthritis Rheum. 2004;50(12):3958–67.

[Lateef 2012] Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther. 2012;14(Suppl 4):S4.

[Li 2020] Li M, Zhao Y, Zhang Z, Huang C, Liu Y, Gu J, Zhang X et al. 2020 Chinese guidelines for the diagnosis and treatment of systemic lupus erythematosus Rheumatol Immunol Res 2020;1(1):5–23

[Mayzent® SmPC] Mayzent® 0.25 mg, 1 mg, and 2 mg film-coated tablets. Summary of product characteristics. European Medicines Agency [accessed on 13 January 2020]. Available from: https://www.ema.europa.eu/en/documents/product-information/mayzent-epar-product-information_en.pdf

[Morand 2020] Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 2020;382(3):21121.

[Moyon 2021] Moyon Q, Sterlin D, Makoto M, Anna F, Mathian A, Lhote R, et al. BNT162b2 vaccine-induced humoral and cellular responses against SARS-CoV-2 variants in systemic lupus erythematosus. Ann Rheum Dis. 2021;0:19.

[Navarra 2011] Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):72131.

[Northcott 2022] Northcott M, Jones S, Koelmeyer R, Bonin J, Vincent F, Kandane-Rathnayake R, et al. Type 1 interferon status in systemic lupus erythematosus: a longitudinal analysis. Lupus Sci Med. 2022;9(1):e000625.

[Oke 2019] Oke V, Gunnarsson I, Dorschner J, Eketjall S, Zickert A, Niewold TB, et al. High levels of circulating interferons type I, type II and type III associate with distinct clinical features of active systemic lupus erythematosus. Arthritis Res Ther. 2019;21(1):107.

[Petri 2001] Petri M. Long-Term Outcomes in Lupus. Am J Manag Care. 2001;7(16 Suppl):S4805.

[Petri 2005] Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al; OC-SELENA Trial. Combined Oral Contraceptives in Women with Systemic Lupus Erythematosus. N Engl J Med. 2005;353(24):2550–8.

[Piali 2017] Piali L, Birker-Robaczewska M, Lescop C, Froidevaux S, Schmitz N, Morrison K, et al. Cenerimod, a novel S1P1 receptor modulator with unique signaling properties. Pharmacol Res Perspect. 2017;e00370:1–12.

[Ponvory® SmPC] Ponvory® film-coated tablets. Summary of product characteristics. European Medicines Agency [accessed on 6 February 2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/ponvory-epar-product-information_en.pdf

[Price 2005] Price CP, Newall RG, Boyd JC. Use of Protein:Creatinine Ratio Measurements on Random Urine Samples for Prediction of Significant Proteinuria: A Systematic Review. Clinical Chemistry. 2005;51(9):1577–86.

[Ronnblom 2019] Ronnblom L, Leonard D. Interferon pathway in SLE: one key to unlocking the mystery of the disease. Lupus Sci Med. 2019;6:e000270.

[Ruggenenti 1998] Ruggenenti P, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. BMJ. 1998;316(7130):504–9. Erratum in BMJ 1998;317(7171):1491.

[Tian 2022] Tian X, Li M, Wang Q, Zhao J, Zeng X. The challenges and future perspective for the Management of systemic lupus erythematosus in China: A concise annual report of 2020. Rheumatol Immunol Res 2022;3(1):38–44

[ukkidney.org] UK Kidney Association [Internet]. Bristol (UK): The UK eCKD Guide for Proteinuria [cited 29 November 2023]. Available from: https://ukkidney.org/health-professionals/information-resources/uk-eckd-guide/proteinuria#sthash.jdT5cPIP.dpbs

[Urowitz 1976] Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med. 1976;60(2):221–5.

[Xiong 2014] Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. Nat Rev Rheumatol. 2014;10(2):97–107.

[Zeposia® SmPC] Zeposia® hard capsules. Summary of product characteristics. European Medicines Agency [accessed on 20 May 2020]. Available from: https://www.ema.europa.eu/en/documents/product-information/zeposia-epar-product-information_en.pdf

12 APPENDICES

Appendix 1 Clinical laboratory tests

Laboratory assessment	Variables		
Hematology	Platelet count	Erythrocyte indices:	Leukocyte count with differential counts:
	Erythrocyte count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	Reticulocytes	Monocytes
			Eosinophils
			Basophils
Clinical chemistry	Blood urea nitrogen or urea urea (mg/dL) = urea nitrogen (mg/dL) * 2.14	AST	Bilirubin (total and direct)
	Creatinine	ALT	Total protein
	eGFR using the CKD-EPI formulae	ALP	Albumin
	Glucose	LDH	GGT
		CK	
	Aldolase	Lipid profile: total cholesterol, triglycerides, LDL, HDL	HbA1c
	Uric acid	Electrolytes: sodium, potassium, chloride, calcium	
Coagulation tests	Prothrombin time and INR	aPTT	
Test for tuberculosis[1]	IFN gamma release assay		
Virus serology[2]	Anti-HAV IgM, hepatitis B surface antigen, hepatitis C antibodies (anti-HCV IgG/IgM, HCV-RNA PCR if positive anti-HCV IgM or IgG)	Varicella-zoster virus IgG antibodies	Anti-HEV IgG, anti-HEV IgM, HEV-RNA PCR (if positive anti-HEV IgM and/or IgG)
	HIV1 and HIV2 antibodies		

Laboratory assessment	**Variables**		
Immunology lupus related	ANA, Anti-dsDNA	C3, C4, CH50, Anti-Sm, IFN alpha	Anti-cardiolipin IgA anti-cardiolipin IgG, anti-cardiolipin IgM, antiglobulin (Coombs), haptoglobin, anti beta-2 glycoprotein 1 (anti b2GP1), lupus anticoagulant
Urinalysis (spot urine)	Protein (protein/creatine ratio) Albumin (albumin-to-creatinine ratio) *Creatinine*		Dipstick analysis: e.g. pH, glucose, protein; blood (hemoglobin, white blood cells), ketones, nitrite Microscopic examination – sediment (red blood cells, white blood cells, casts)
Pregnancy test serum			Beta hCG
Pregnancy test urine	Dipstick (performed locally)		

1 An IFN gamma release assay will be performed at Visit 1 (Screening) to screen for active or latent TB [see Sections 5.3 and 7.2.3.8].

2 Virus serology 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]).

ANA = antinuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; anti-Sm = anti-Smith; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CK = creatine (phospho) kinase; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; GGT= gamma glutamyl transferase; HAV = hepatitis A virus; HbA1c = glycated hemoglobin; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high-density lipoprotein; HEV = hepatitis E virus; HIV = human immunodeficiency virus; IFN = interferon; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PCR = polymerase chain reaction; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell count.

Appendix 2 2019 EULAR/ACR Classification criteria for SLE

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Figure 2.
Classification criteria for systemic lupus erythematosus
Note: * In an assay with ≥ 90% specificity against relevant disease controls § Additional criteria items within the same domain will not be counted.

ACR = American College of Rheumatology; ANA = antinuclear antibodies; anti-Sm = anti-Smith; ECG = electrocardiogram/graphy; EULAR = European League Against Rheumatism; Ig = immunoglobulin; SLE = systemic lupus erythematosus.
Source: [Aringer 2019].

The actual assessment to be used will prevail.

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 6.2.3]:

- Adenosine
- Acebutolol
- Ajmaline
- Amiodarone
- Aprindine
- Atenolol
- Azimilide
- Bepridil
- Betaxolol
- Bisoprolol
- Bretylium
- Bunaftine
- Cibenzoline
- Digoxin
- Diltiazem
- Disopyramide
- Dofetilide
- Dronedarone
- Encainide
- Esmolol
- Flecainide
- Ibutilide
- Ivabradine
- Lidocaine
- Lorajmine
- Lorcainide
- Metoprolol
- Mexiletine
- Moracizine
- Nadolol
- Phenytoin
- Pilocarpin
- Prajmalium
- Procainamide
- Propafenone
- Propranolol
- Quinidine
- Sparteine
- Tedisamil
- Timolol
- Tocainide
- Verapamil
- Vernakalant

If, in the judgment of the investigator, it is in the best interests of the participant to receive any of the drugs listed above, study treatment must be permanently discontinued. It is recommended to wait for 6 months (i.e., 5 half-lives of cenerimod) to initiate any treatment with the drug listed above.

Topically applied therapies are allowed.

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 6.2.3]:

- Amifampridine
- Amiodarone
- Amisulpride
- Anagrelide
- Apomorphine
- Arsenic trioxide
- Artenimol
- Astemizole
- Azithromycin
- Bedaquiline
- Bepridil
- Chlorpromazine
- Ciprofloxacin
- Citalopram
- Clomipramine
- Clarithromycin
- Cocaine
- Disopyramide
- Dolasetron
- Domperidone
- Dronedarone
- Droperidol
- Flecainide
- Fluconazole
- Erythromycin
- Escitalopram
- Halofantrine
- Haloperidol
- Ketoconazole
- Levofloxacin
- Levomethadyl
- Mesoridazine
- Methadone
- Moxifloxacin
- Ondansetron
- Pentamidine
- Pimozide
- Procainamide
- Probucol
- Quinidine
- Sevoflurane
- Sildenafil
- Sotalol
- Sparfloxacin
- Sulpiride
- Terfenadine
- Thioridazine
- Voriconazole
- Vandetanib
- Ziprasidone

If, in the judgment of the investigator, it is in the best interests of the participant to receive any of the drugs listed above, study treatment must be permanently discontinued. It is recommended to wait for 6 months (i.e., 5 half-lives of cenerimod) to initiate any treatment with the drug listed above.

Appendix 5 Criteria for discharge from monitored setting on Day 1 and on the first day of re-initiation following treatment interruptions

At the 12 hours post-dose on Day 1 and on the first day of re-initiation of study treatment following treatment interruptions lasting for at least 7 days in the first 14 days of treatment, all the following criteria must be met:

- ECG-derived resting HR > 45 bpm; *and* if HR < 50 bpm it must not be the lowest value measured post-dose;
- SBP ≥ 90 mmHg;
- For participants 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 newly occurred persistent clinically significant ECG abnormality (e.g., AV block second-degree or higher) or ongoing AE requiring continued hospitalization;
- No other clinically significant symptoms, signs or abnormalities as per judgment of the investigator.

If at 12 h post-dose the participant does not meet discharge criteria, he/she must be permanently discontinued from study treatment. Participants who are permanently discontinued should not be discharged from the monitored setting before the HR abnormalities and BP 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 6 SLEDAI-2K: Data collection sheet

Study No.:_____ Patient name:_____ Visit name:_____ _____ _____

d m yr

Enter weight in SLEDAI-2K score column if descriptor is present at the time of the visit or in the **preceding 10 days.**

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

4	_____	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	> 0.5 gram/24 hours.
4	_____	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	> 38 ◦C. Exclude infectious cause.
1	_____	Thrombocytopenia	< 100,000 platelets / × 10^9/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / × 10^9/L, exclude drug causes.

TOTAL SCORE: _____

The actual scale to be used will prevail

Note that leukopenia will not be evaluated due to the mechanism of action of cenerimod.

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 7 BILAG-2004 index

BILAG-2004 INDEX **Centre:** **Date:** **Initials/Hosp No:**

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

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

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

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

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

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

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

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

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

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

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

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

Revision: 1/Sep/2009

The actual scale to be used will prevail
Total white blood cell count and lymphocyte count will not be evaluated due to the mechanism of action of cenerimod.

Appendix 8 SLE Flare Index

Mild or Moderate Flare ☐

- ☐ Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)
- ☐ New/worse:
  - Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus
  - Nasopharyngeal ulcers
  - Pleuritis
  - Pericarditis
  - Arthritis
  - Fever (SLE)
- ☐ Increase in prednisone, but not to >0.5 mg/kg/day
- ☐ Added NSAID or hydroxychloroquine for SLE activity
- ☐ ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare ☐

- ☐ Change in SELENA-SLEDAI instrument score to greater than 12
- ☐ New/worse:
  - CNS-SLE
  - Vasculitis
  - Nephritis
  - Myositis
  - Plt <60,000
  - Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L

  Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization
- ☐ Increase in prednisone to >0.5 mg/kg/day
- ☐ New cyclophosphamide, azathioprine, methotrexate for SLE activity
- ☐ Hospitalization for SLE activity
- ☐ Increase in Physician's Global Assessment score to >2.5

Source: [Petri 2005].
The actual scale to be used will prevail

Appendix 9 Physician's Global Assessment Visual Analog Scale

Physician's Global Assessment (PGA)
Visual Analog Scale

Rate your assessment of SLE disease activity since the last visit:

Completion instructions:
- Rate your assessment of SLE disease activity since the last visit by placing a vertical mark across the horizontal line of the scale to indicate your answer
*- Use a metric ruler to measure the length beginning from the left side of the scale (i.e., from the 0 "None" mark) to the middle of your vertical mark and record the result in the below data field in mm**
- Enter the result in the database to get the corresponding PGA score calculated

Length measured ☐☐☐ mm

**Measure the length and round to the nearest millimeter. The following rounding rules are to be followed:*
Up to .4 mm = round down to the nearest millimeter (e.g., 71.4 = 71 mm)
.5 to .9 mm = round up to the nearest millimeter (e.g., 71.5 = 72 mm)

The actual scale to be used will prevail

Appendix 10 CLASI

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

activity **damage**

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

Mucous membrane

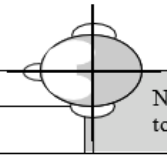
Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)
☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)
☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

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



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

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

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

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Appendix 11 Tender/swollen joints count

Assessment date: ☐☐ / ☐☐☐ / ☐☐☐☐ Time: ☐☐ : ☐☐

Joint Position		Reason Not Evaluable
Shoulder Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Elbow Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Wrist Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Metacarpophalangeal (MCP) I Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Metacarpophalangeal (MCP) II Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Metacarpophalangeal (MCP) III Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Metacarpophalangeal (MCP) IV Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	

Joint Position		Reason Not Evaluable
Metacarpophalangeal (MCP) V Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Finger Proximal Interphalangeal (Finger PIP) I Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Finger Proximal Interphalangeal (Finger PIP) II Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Finger Proximal Interphalangeal (Finger PIP) III Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Finger Proximal Interphalangeal (Finger PIP) IV Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Finger Proximal Interphalangeal (Finger PIP) V Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Knee Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	

Total number of tender joints: Total number of swollen joints: Total number of tender and swollen joints:

The actual assessment to be used will prevail

Appendix 12 Conversion table from glucocorticoids to Prednisone

Glucocorticoid	Approximate equivalent dose (mg)	Conversion factor to Prednisone	Half - life (hs)
Cortisone	**25**	**0.2**	**<12 (short)**
Hydrocortisone	**20**	**0.25**	**<12 (short)**
Deflazacort	**7.5**	**0.67**	**<12 (short)**
Prednisolone	**5**	**1**	**12–36 (medium)**
Prednisone	**5**	**1**	**12–36 (medium)**
Methylprednisolone	**4**	**1.25**	**12–36 (medium)**
Triamcinolone	**4**	**1.25**	**12–36 (medium)**
Betamethasone	**0.75**	**6.67**	**36–72 (long)**
Dexamethasone	**0.75**	**6.67**	**36–72 (long)**

Conversion: any glucocorticoid x Conversion factor to Prednisone = Prednisone dose

Example: Triamcinolone 8 mg x 1.25 = Prednisone 10 mg

Reference: Goodman & Gilman's The Pharmacological Basis of Therapeutics (2023), chapter 50, page 1013

Clarifications

- These dose relationships only apply to oral or IV administration. Glucocorticoid potencies may differ greatly following intramuscular or intra-articular administration.
  - Methylprednisolone (MEDROL) → oral
  - Methylprednisolone Succinate (SOLU-MEDROL) → IV (FDA label mentions the same conversion factor than methylprednisolone)
  - Methylprednisolone Acetate (DEPO-MEDROL) → IM, intra-articular or intra-lesional (FDA label mentions the same conversion factor than methylprednisolone)
- Fludrocortisone, even though is a glucocorticoid, it is used for its mineralocorticoid activity, the anti-inflammatory activity is negligible at normal therapeutic doses (1/10 that of hydrocortisone)

Appendix 13 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 grading system (2017 v5.0) and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known PD effect of the study treatments (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 treatment) 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.

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	n/a	n/a	n/a	n/a
MCV	n/a	n/a	n/a	n/a
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 (leukocytes) total count	ND	< 1.9 × 10 e9/L	> 20.0 × 10 e9/L (> 20,000/mm^3)	CTCAE (grade 3) > 100.0 × 10 e9/L (>100,000/mm^3)
Lymphocyte total	ND	< 0.2 × 10 e9/L (< 200/mm^3) **ALERT*** **< 0.2 × 10 e9/L** **(< 200/mm^3)**	> 4.0 × 10 e9/L (> 4000/mm^3)	≥ 8 × 10 e9/L (> 8000/mm^3)
Neutrophils total	< 1.5 × 10 e9/L (< 1500/mm^3)	< 1.0 × 10 e9/L (< 1000/mm^3)	ND	ND
Eosinophils total	ND	ND	> 5.0 × 10 e9/L or > 5% (> 5000 cells/mm^3)	ND
Monocytes total	ND	ND	ND	ND
Basophils total	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells	ND	ND	> 90%	> 95%
AST	ND	ND	≥ 3 ULN **ALERT** **≥ 3 ULN**	⩾ 5 ULN **ALERT** **⩾ 5 ULN** **⩾ 8 ULN**
ALT	ND	ND	⩾ 3 ULN **ALERT** **⩾ 3 ULN**	⩾ 5 ULN **ALERT** **⩾ 5 ULN** **⩾ 8 ULN**
GGT	ND	ND	≥ 2 ULN	≥ 5 ULN
Total bilirubin	ND	ND	≥ 2 ULN **ALERT** **≥ 2 ULN** **combined with**	≥ 5 ULN

Parameter	**LL**	**LLL**	**HH**	**HHH**
			ALT or AST ≥ 3 ULN	
Alkaline Phosphatase	ND	ND	> 2.5 ULN	> 5 ULN
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 or > 1.5 × baseline	> 3 ULN 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	> 5 ULN
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
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)
Creatin (phospho) kinase (CK, CPK)	ND	ND	>5 × ULN	>10 × ULN
IgG	Na	ND	ND	ND
IgM	ND	ND	ND	ND

Parameter	LL	LLL	HH	HHH
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-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**

GENERAL note: this table displays safety alerts for possible drug induced liver disease (DILI), lymphocytopenia as per protocol and serum pregnancy test. Additional alerts may be applicable, details are described in a respective section of laboratory manual.

*The ALERT will provide the exact lymphocyte count. In addition, if lymphocyte count < 500 cells/µl at FSV, 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 the FDA [FDA 2009].

*** Source for protein/creatinine ratio thresholds: [ukkidney.org].

ALT = alanine aminotransferase; ANA = antinuclear 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; FDA = Food and Drug Administration; FSV = Final Study Visit; GGT- gamma glutamyl transferase; 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 14 New York Heart Association Classes of Heart Failure

Class	Description	Symptoms	
Class I	No limitation of physical activity	Ordinary physical activity does not cause symptoms	
Class II	Slight limitation of physical activity	Comfortable at rest, but ordinary physical activity results in HF symptoms as:	• Palpitations • Fatigue • Shortness of breath
Class III	Marked limitation of physical activity	Comfortable at rest, but less than ordinary activity results in HF symptoms Common symptoms include:	• Shortness of breath • Fatigue • Pain
Class IV	HF symptoms present, even at rest	Discomfort with any physical activity. Unable to carry on any physical activity without symptoms of HF Symptoms increase during any activity including:	• Persistent cough • PND • Swelling • Cognitive change

Adapted from the American Heart Association.