Official Study 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*

NCT Number: *NCT07266090*

Date: *16 sep.2025*

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.):	[redacted]

The information contained in this document, especially unpublished data, is the property of the sponsor of this study, Viatris Innovation GmbH. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an independent ethics committee(s) or institutional review board(s). It is understood that this information will not be disclosed to others without written authorization from Viatris Innovation GmbH, except to the extent necessary to obtain informed consent from those persons to whom the study treatment(s) may be administered.

SPONSOR CONTACT DETAILS

Sponsor	Viatris Innovation GmbH
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.
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.

[redacted]

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.

[redacted]

[redacted]

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	[redacted]

AMENDMENT DETAILS

Current Amendment

Amendment Number	ID-064A204	
Version No.	V3.0	
Version Date	16 Sep. 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: 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**	**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
Summary of the Amendment	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;	

	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**	

[redacted]

Summary of Changes in the Amendment Version 2.0

[redacted]

[redacted]

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS 19

1 PROTOCOL SUMMARY 23

1.1 Protocol synopsis ID-064A204 23
1.2 Schema 41
1.3 Schedule of activities 42

2 INTRODUCTION 51

2.1 Indication 51
2.2 Investigational treatment 52
2.3 Study rationale 53
2.4 Benefit/risk assessment of cenerimod 54
2.4.1 Potential benefits 54
2.4.2 Known and potential risks 55
2.4.3 Study procedures and associated potential risks 57
2.4.4 Assessment of benefit -risk 57

3 STUDY OBJECTIVES AND ENDPOINTS 58

3.1 List of objectives and endpoints – 58
3.2 Appropriateness of endpoints 60

4 STUDY DESIGN AND PLAN 61

4.1 Study design 61
4.1.1 Study periods for an individual participant 61
4.2 Study duration and End-of-Study definition 62
4.3 Study design rationale 62
4.4 Study committees 63

5 STUDY POPULATION 63

5.1 Participant population description 63
5.2 Inclusion criteria 63
5.3 Exclusion criteria 65
5.4 Rationale for the selection of the study population 70
5.5 Contraception requirements for women of childbearing potential 70
5.5.1 Definition of childbearing potential 70
5.5.2 Methods of contraception 71

5.6 Contraception for male participants with a partner who is of childbearing potential 72
5.7 Screen failures and re-screening 73
5.8 Criteria for withdrawal of participants 73
5.8.1 Study treatment interruption and permanent discontinuation of study treatment 73
5.8.1.1 Principles 73
5.8.1.2 Pregnancy 74
5.8.1.3 Lack of compliance with methods of contraception 74
5.8.1.4 Cardiovascular 75
5.8.1.5 Infections 75
5.8.1.6 Lymphocyte count monitoring 76
5.8.1.7 Liver enzyme abnormalities 77
5.8.1.8 Ocular abnormalities 79
5.8.1.9 Initiation of forbidden concomitant medication during the study 79
5.8.1.10 Other potential permanent treatment discontinuation 79
5.8.1.11 Other study-specific criteria for re-initiation after temporary treatment interruption 79
5.8.2 Measures for participant retention 80
5.8.3 Withdrawal from the study 80
5.8.4 Lost to follow-up 81

6 TREATMENTS 81

6.1 Study treatment 81
6.1.1 Investigational treatment 81
6.1.2 Study treatment dosing and administration 82
6.1.2.1 Study treatment dose adjustments 82
6.1.3 Justification for dose 82
6.1.4 Treatment assignment 82
6.1.5 Study treatment handling/preparation/storage/accountability 82
6.1.5.1 Study treatment packaging and labeling 83
6.1.5.2 Study treatment distribution and storage 83
6.1.5.3 Study treatment dispensing 83
6.1.5.4 Study treatment accountability 83
6.1.5.5 Study treatment return and destruction 84
6.1.6 Study treatment compliance 84
6.2 Previous and concomitant medications 84
6.2.1 Auxiliary medicinal products 85
6.2.1.1 SLE background therapy (except OCS background therapy) conditions of use 85

6.2.1.2 OCS background therapy conditions of use 86
6.2.2 Allowed concomitant therapy 89
6.2.2.1 CS burst conditions of use 89
6.2.2.2 NSAIDs conditions of use 90
6.2.3 Forbidden concomitant therapy 90
6.3 Medical care of participants after study completion / withdrawal from study 91

7 VISIT SCHEDULE AND STUDY ASSESSMENTS AND PROCEDURES 91

7.1 General information 91
7.1.1 Screening 92
7.1.2 Unscheduled visits 93
7.1.3 Study completion 93
7.2 Study assessments and procedures 93
7.2.1 Demographics / baseline characteristics 93
7.2.2 Disease activity assessments 94
7.2.2.1 Systemic Lupus Erythematosus Disease Activity Index-2000 95
7.2.2.2 British Isles Lupus Assessment Group 95
7.2.2.3 SLE Flare Index 97
7.2.2.4 Physician's Global Assessment of disease 98
7.2.2.5 Cutaneous Lupus Erythematosus Disease Area and Severity Index 98
7.2.2.6 Tender/swollen joints count 98
7.2.3 Safety assessments 99
7.2.3.1 Physical examination 99
7.2.3.2 Weight and height 100
7.2.3.3 Electrocardiograms 100
7.2.3.4 Clinical laboratory assessments 102
7.2.3.5 Ophthalmological examination 104
7.2.3.6 Optical coherence tomography 105
7.2.3.7 Chest X-ray or CT scan 105
7.2.3.8 Test for tuberculosis 105
7.2.3.9 Skin examination 106
7.2.4 Blood pressure assessments 106
7.2.5 Pharmacokinetic and pharmacodynamic assessments 106
7.2.5.1 Pharmacokinetic assessments 106
7.2.5.2 Pharmacodynamic assessments 107
7.2.6 Biomarker assessments 107
7.2.6.1 Disease activity biomarkers 107

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS 107
8.1 Safety definitions 107
8.1.1 Definition of adverse events 107
8.1.2 Definition of adverse events of specific interest 108
8.1.3 Definition of serious adverse events 109
8.1.4 Intensity of adverse events 109
8.1.5 Relationship to study treatment 110
8.1.6 Relationship to study design or protocol-mandated procedure 110
8.1.7 Definition of study treatment overdose, misuse, and abuse 110
8.2 Reporting procedures 110
8.2.1 Reporting adverse events 110
8.2.2 Reporting serious adverse events 111
8.2.3 Reporting procedure for SUSARs 112
8.2.4 Reporting medical or surgical intervention 112
8.3 Pregnancy 112
8.3.1 Reporting of pregnancy 112
8.3.2 Follow-up of pregnancy 113

9 STATISTICAL METHODS 113
9.1 Analysis sets 113
9.1.1 Screened set 113
9.1.2 Safety Analysis Set (SS) 113
9.1.3 Pharmacokinetic Analysis Set (PKS) 113
9.1.4 Pharmacodynamic Analysis Set (PDS) 113
9.2 Description of statistical analyses 113
9.2.1 Analysis of safety endpoints 114
9.2.2 Analysis of pharmacokinetic endpoints 115
9.2.3 Analysis of PD endpoints 116
9.2.4 Analysis of efficacy endpoints 116
9.3 Planned analyses 117
9.4 Sample size 117

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 117
10.1 Regulatory and ethical considerations 117
10.2 Informed consent process 118
10.3 Data protection and privacy 119
10.4 Indemnification, compensation, and refund of expenses to participants and investigators 120
10.5 Essential documents and retention of documents 120

10.5.1 Investigator Site File 120
10.5.2 Source documents 121
10.6 Data handling 122
10.6.1 Data collection, data transfer procedure, and data access 122
10.6.2 Database management and quality control 122
10.7 Protocol deviations 123
10.8 Clinical monitoring 123
10.9 Study safety oversight 124
10.10 Premature termination or suspension of the study 124
10.11 Audit 125
10.12 Inspections 125
10.13 Reporting of study results and publication 125

11 REFERENCES 126

12 APPENDICES 131

LIST OF TABLES

Table 1 Schedule of activities at Screening 42
Table 2 Schedule of activities after Screening 44
Table 3 Schedule of activities: PTOP (applicable to participants who permanently discontinue study treatment 49
Table 4 Study procedures and associated potential risks 57
Table 5 Objectives and endpoints 58
Table 6 Example of background OCS therapy forced tapering schedule 88
Table 7 Relationship among laboratory tests for proteinuria 102

LIST OF FIGURES

Figure 1 Study design 41
Figure 2 Guidance for re-test results of lymphocytes < 200 cells/µL 77
Figure 3 Guidance for monitoring liver test abnormalities 78
Figure 4 OCS management overview 86

[redacted]

LIST OF APPENDICES

Appendix 1 Clinical laboratory tests 131
Appendix 2 2019 EULAR/ACR Classification criteria for SLE 133
Appendix 3 Forbidden anti-arrhythmic or heart rate lowering medications 134
Appendix 4 Forbidden medications with risk of torsade de pointes 135
Appendix 5 Criteria for discharge from monitored setting on Day 1 and on the first day of re-initiation following treatment interruptions 136
Appendix 6 SLEDAI-2K: Data collection sheet 137
Appendix 7 BILAG-2004 index 139
Appendix 8 SLE Flare Index 140
Appendix 9 Physician's Global Assessment Visual Analog Scale 141
Appendix 10 CLASI 142
Appendix 11 Tender/swollen joints count 143
Appendix 12 Conversion table from glucocorticoids to Prednisone 145
Appendix 13 Notable abnormalities for ECG, BP, and laboratory variables 146
Appendix 14 New York Heart Association Classes of Heart Failure 150

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:** **Post-treatment observation period** • • **Follow-up period:**

	The study design is depicted in Figure 1.
PLANNED DURATION	[redacted]
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	[redacted]
CONCOMITANT THERAPY	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]
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	[redacted]

1.2 Schema

The study design is depicted in Figure 1.

[redacted]

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

[redacted]

[redacted]

[redacted]

Table 2 Schedule of activities after Screening

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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



[redacted]

2.3 Study rationale

[redacted]

[redacted]

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

[redacted]

2.4.2 Known and potential risks

[redacted]

Identified risks:

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

2.4.4 Assessment of benefit -risk

[redacted]

[redacted]

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

[redacted]



[redacted]

3.2 Appropriateness of endpoints

[redacted]

[redacted]

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.

[redacted]

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

4.1.1 Study periods for an individual participant

[redacted]

The study design is depicted in Figure 1.

4.2 Study duration and End-of-Study definition

[redacted]

4.3 Study design rationale

[redacted]

4.4 Study committees

[redacted]

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

[redacted]

5.5 Contraception requirements for women of childbearing potential

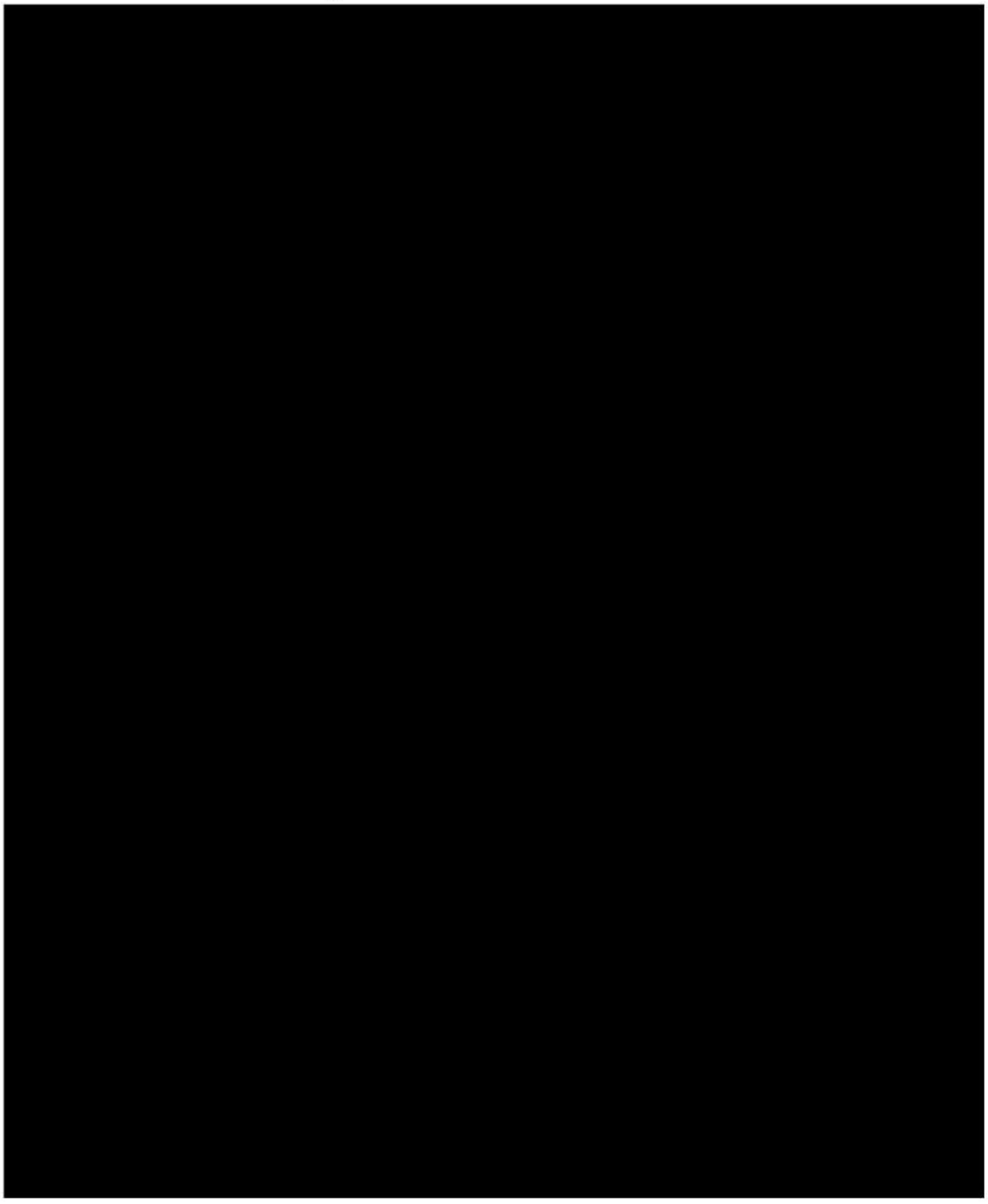
5.5.1 Definition of childbearing potential

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



[redacted]

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

[redacted]

[redacted]

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.



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.

[redacted]

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

[redacted]

5.8.1.4.2 Other cardiovascular stopping criteria

[redacted]

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.

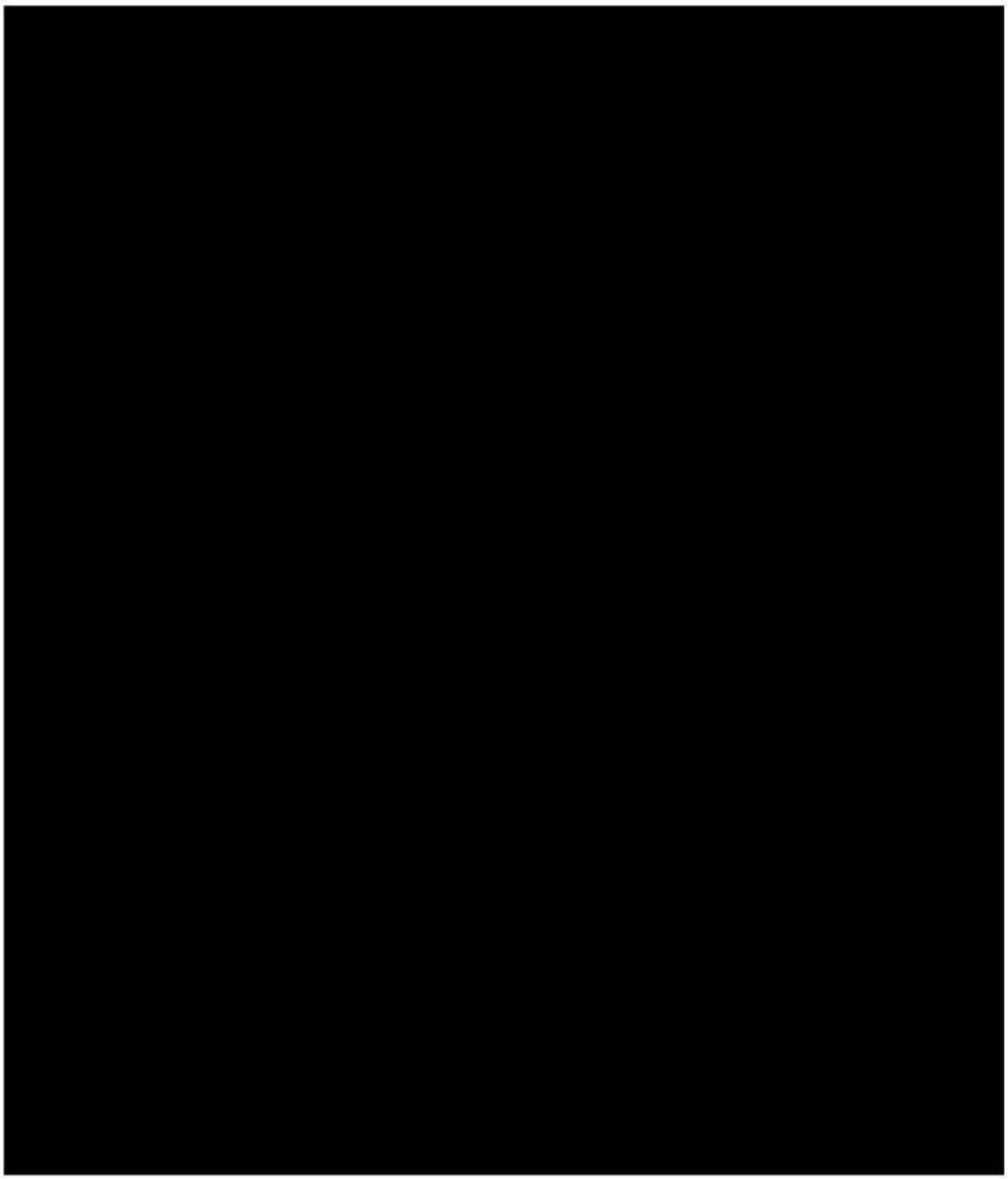
5.8.1.6 Lymphocyte count monitoring

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

[redacted]

5.8.1.7 Liver enzyme abnormalities

[redacted]



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

[redacted]

or locally according to the scheme illustrated in Figure 3. [redacted]

[redacted]

[redacted]

5.8.1.8 Ocular abnormalities

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

[redacted]

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.

[redacted]

- 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.

[redacted]

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.

[redacted]

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.
- [redacted]
- 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.

[redacted]

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.

[redacted]

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

[redacted]

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

[redacted]

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.

[redacted]

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:

6.2 Previous and concomitant medications

[redacted]

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

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7 VISIT SCHEDULE AND STUDY ASSESSMENTS AND PROCEDURES

7.1 General information

[redacted]

[redacted]

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

[redacted]

[redacted]

7.1.2 Unscheduled visits

[redacted]

7.1.3 Study completion

[redacted]

7.2 Study assessments and procedures

[redacted]

7.2.1 Demographics / baseline characteristics

[redacted]

[redacted]

7.2.2 Disease activity assessments

[redacted]

[redacted]

7.2.2.1 Systemic Lupus Erythematosus Disease Activity Index-2000

[redacted]

Notes:

[redacted]

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].

[redacted]

[redacted]

7.2.2.3 SLE Flare Index

[redacted]

7.2.2.4 Physician's Global Assessment of disease

[redacted]

7.2.2.5 Cutaneous Lupus Erythematosus Disease Area and Severity Index

[redacted]

7.2.2.6 Tender/swollen joints count

[redacted]

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

[redacted]

7.2.3.2 Weight and height

[redacted]

7.2.3.3 Electrocardiograms

7.2.3.3.1 Cardiac monitoring applicable to all participants

[redacted]

[redacted]

7.2.3.3.2 Additional cardiac monitoring on Day 1

[redacted]

7.2.3.4 Clinical laboratory assessments

[redacted]

[redacted]

[redacted]

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

[redacted]

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).

[redacted]

7.2.3.6 Optical coherence tomography

[redacted]

[redacted]

7.2.5 Pharmacokinetic and pharmacodynamic assessments

7.2.5.1 Pharmacokinetic assessments

[redacted]

[redacted]

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

[redacted]

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:

[redacted]

8.1.2 Definition of adverse events of specific interest

[redacted]

[redacted]

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

[redacted]

[redacted]

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

[redacted]

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.

[redacted]

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.

[redacted]

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

[redacted]

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)

[redacted]

9.1.4 Pharmacodynamic Analysis Set (PDS)

[redacted]

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

[redacted]

Adverse events

[redacted]

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

[redacted]

Vital signs and body weight

[redacted]

Electrocardiograms

[redacted]

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.

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

[redacted]

- Observed BICLA response.

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

[redacted]

[redacted]

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 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.



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:

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.

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

[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

[redacted]

[redacted]

[redacted]

Appendix 2 2019 EULAR/ACR Classification criteria for SLE

[redacted]

Appendix 3 Forbidden anti-arrhythmic or heart rate lowering medications

[redacted]

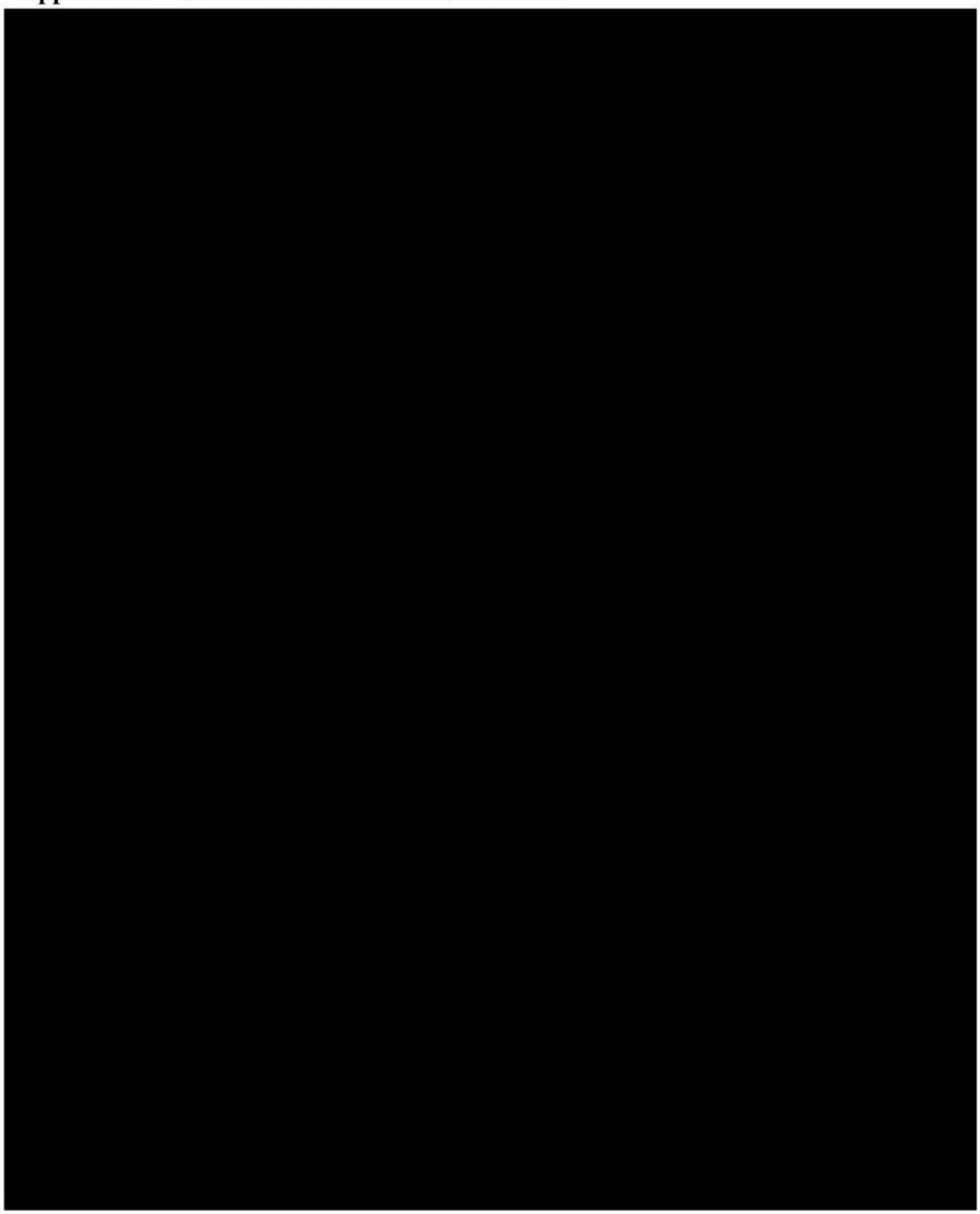
Appendix 4 Forbidden medications with risk of torsade de pointes

[redacted]

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

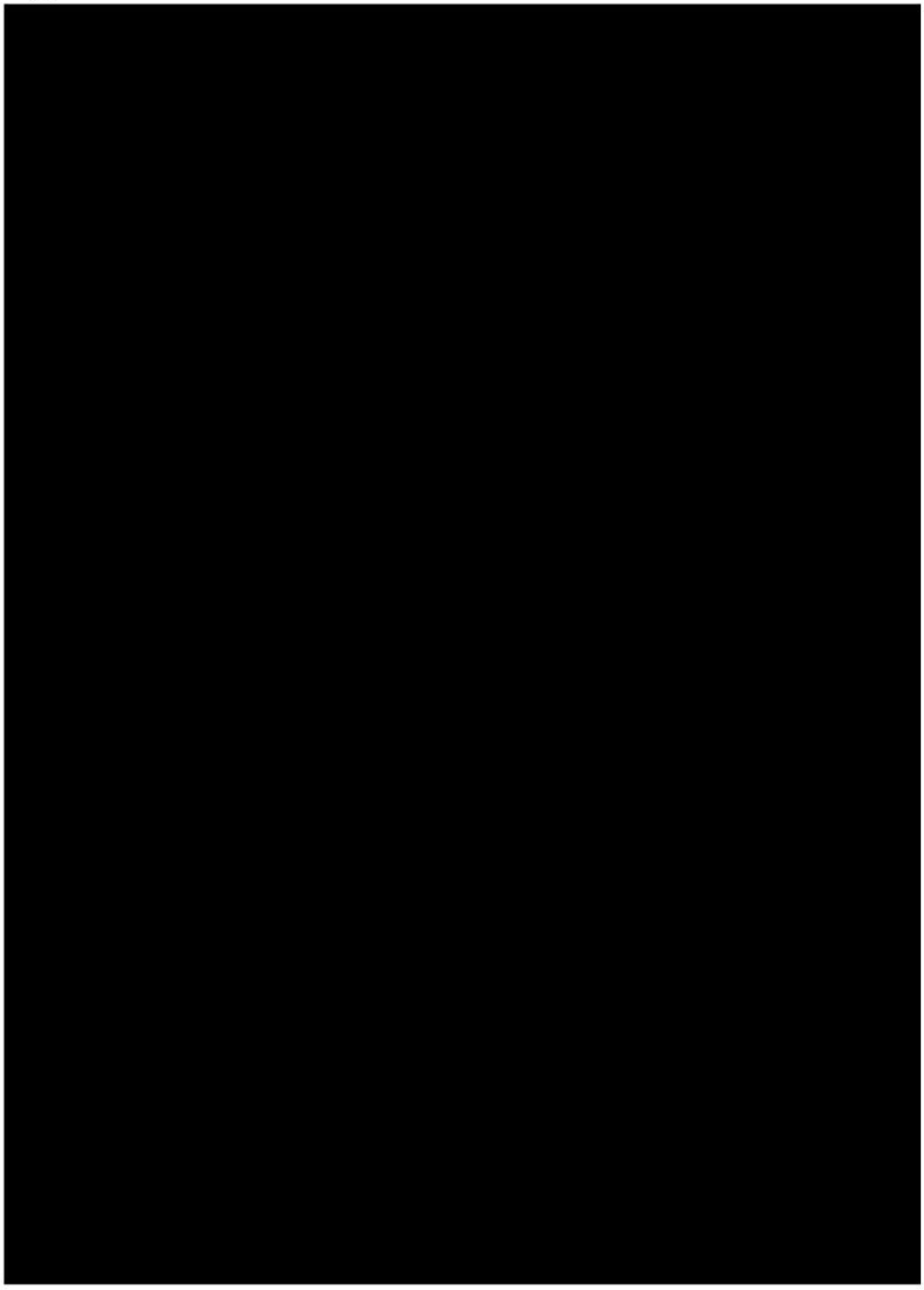


Appendix 6 SLEDAI-2K: Data collection sheet



[redacted]

Appendix 7 BILAG-2004 index



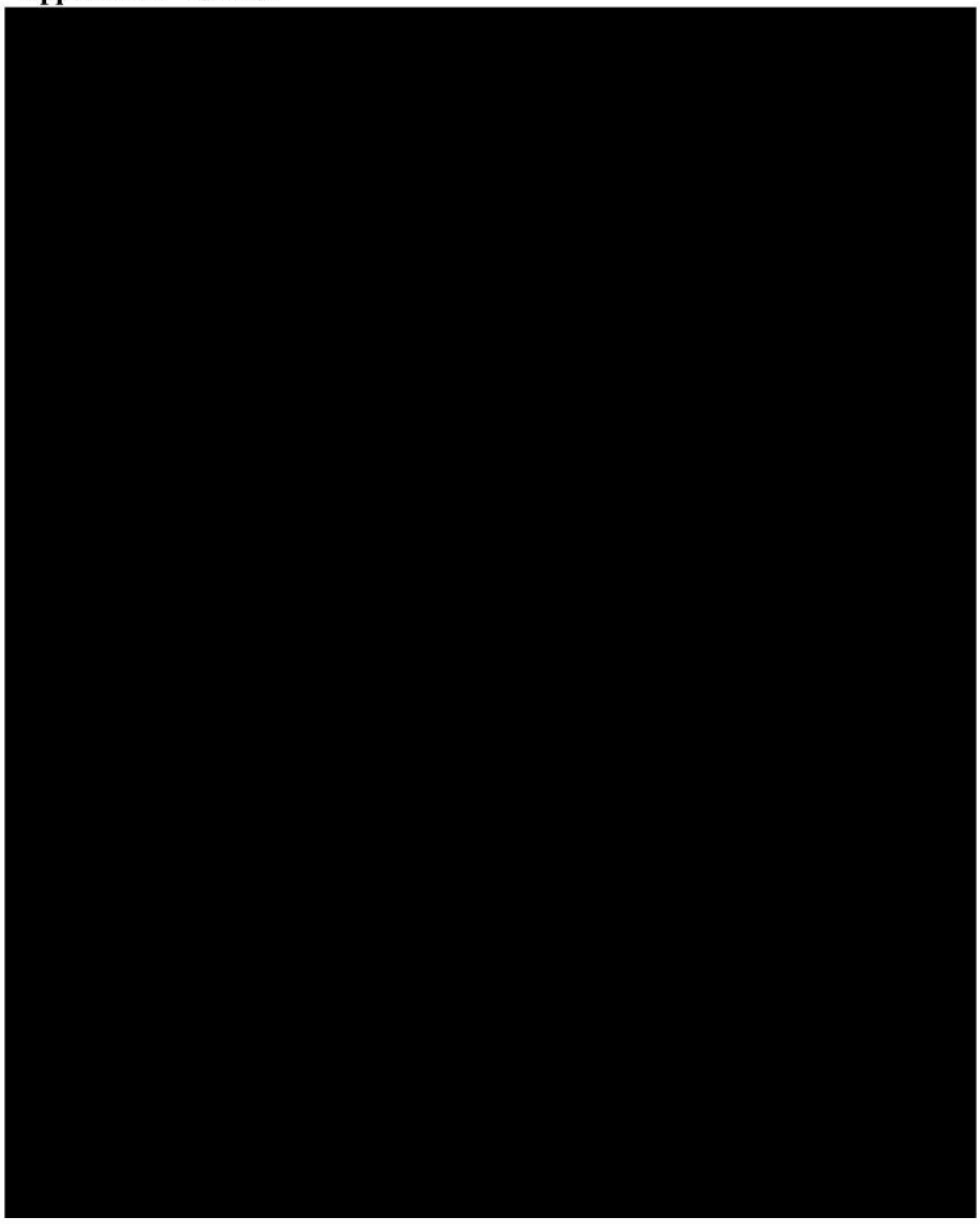
Appendix 8 SLE Flare Index

[redacted]

Appendix 9 Physician's Global Assessment Visual Analog Scale



Appendix 10 CLASI



Appendix 11 Tender/swollen joints count

[redacted]

[redacted]

Appendix 12 Conversion table from glucocorticoids to Prednisone

[redacted]

Appendix 13 Notable abnormalities for ECG, BP, and laboratory variables

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 14 New York Heart Association Classes of Heart Failure

